ISSN (ON-LINE): 1806-3756

JBP
Jornal Brasileiro de **Pneumologia**

PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 51, Number 4
July | August
2025

Volume 51, Number 4 July | August 2025

HIGHLIGHT

Influence of ADRB2 variants on bronchodilator response and asthma control in a mixed population

Clinical and imaging features of IIM-associated interstitial lung disease: a retrospective study

Maximal dynamic inspiratory pressure: S-Index prediction values and diagnosis accuracy

ISSN (ON-LINE): 1806-3756

JBP Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 51, n. 4 July/August 2025

Associação Brasileira de Editores Científicos

ABEC

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

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

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Expediente

BRAZILIAN THORACIC SOCIETY

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

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Address: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 08000 616218.
Editorial Manager: Luana Maria Bernardes Campos.
E-mail: jbp@jbp.org.br | jbp@sbpt.org.br
Distribution: Free to members of the BTS and libraries

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ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 51, n. 4 July/August 2025

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ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

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https://dx.doi.org/10.36416/1806-3756/e20250207

Bronchoscopy and interventional radiology: a strategic alliance in thoracic disease management

Bianca Fidelix Espindula[1], Iunis Suzuki[1], Altair da Silva Costa Junior[1], Priscila Mina Falsarella[1], Rodrigo Gobbo Garcia[1]

The Latin word *mederi*, which means to heal or to treat, originated the term *medicus*, used in Ancient Rome to describe those who cared for human health through observation and empirical methods. Interestingly, *mederi* can also be translated as "to choose the best path," a definition that metaphorically anticipates the modern interdisciplinary cooperation among medical specialties, an approach potentially capable of defining the most appropriate diagnostic and therapeutic route for each patient.

Medicine has witnessed significant evolution in recent decades, marked by the advent and rapid expansion of minimally invasive specialties. With the exponential growth of knowledge, specialization has become inevitable. The volume of information and the sophistication of diagnostic and therapeutic tools have surpassed the capacity of any single professional to master them all. Traditionally, hospitals organize their departments on the basis of technological or operational affinity, not always prioritizing the clinical journey of patients. This dynamic has led to the grouping of services based on structural convenience: respiratory endoscopy is integrated with digestive endoscopy because of equipment similarity, and interventional radiology is placed within imaging departments because of shared infrastructure. However, such an organization rarely aligns with the best clinical interest of patients.

In response to this structural mismatch, our institution has adopted an innovative model in which bronchoscopy and interventional radiology share the same department and physical space. Although at first glance these might seem like incompatible fields because of differences in instruments, workflows, and team training, experience has shown that this strategic partnership, by placing the patient at the center of decision-making, promotes more accurate and personalized clinical approaches. Daily collaboration and physical proximity facilitate real-time discussion of cases, an especially valuable interaction in complex clinical scenarios in which isolated approaches often fail to provide satisfactory diagnostic or therapeutic solutions.

Bronchoscopy and interventional radiology are complementary pillars in the investigation of mediastinal, hilar, and pulmonary lesions. Both disciplines share the fundamental goal of providing effective and less morbid alternatives to traditional surgical procedures. In many cases, bronchoscopy may rely on interventional radiology to reach a diagnostic or therapeutic target, and, conversely, interventional radiology can benefit from the expertise of bronchoscopy in airway management or for complementary diagnostic approaches.

Real-time interdisciplinary dialogue helps identify the best access route to challenging targets, evaluating, for example, whether advanced bronchoscopy, combining radial EBUS, fluoroscopy, or cone-beam CT, offers advantages over CT-guided transthoracic biopsy (Figure 1). This decision becomes especially relevant in patients at high risk for pneumothorax, such as those with emphysema, those with pulmonary fibrosis, and those with a single lung, or when nodules are located deep within the lung parenchyma. Similarly, for mediastinal lesions, the choice between EBUS-TBNA and CT-guided transthoracic biopsy is carefully considered, with lesion location, proximity to vital structures, and patient risk profile being taken into consideration. The goal remains the same: to maximize diagnostic yield while minimizing morbidity.[1,2]

The integration of bronchoscopy and interventional radiology also brings significant logistical benefits for the patient. By combining these specialties in a shared environment, diagnostic tests and staging procedures can be performed during a single anesthetic session, a principle known as the one-stop shop. This approach significantly reduces the time to reach a definitive diagnosis; prevents repeated hospital admissions and multiple anesthetic exposures; and accelerates treatment initiation.

In addition to diagnosis, airway management during interventional procedures represents another point of convergence between these specialties. Bronchoscopy allows intubation of difficult airways and placement of double-lumen tubes during percutaneous interventions (Figure 2). It also plays a role in managing hemoptysis resulting from transthoracic biopsies, assisting with the placement of endobronchial blockers and the application of other hemostatic measures, thus ensuring rapid and effective bleeding control. In turn, interventional radiology promptly detects and treats pneumothorax following transbronchial biopsy by performing image-guided chest tube drainage. This synergy and immediate response enhance safety standards and ensure timely management of adverse events.[3]

Although differences in workflow, team training, and equipment logistics may pose initial challenges, the incorporation of bronchoscopy into interventional radiology units or broader interventional medicine departments has shown clear benefits. Shared protocols, joint training, and integrated procedure rooms foster a

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ISSN 1806-3756

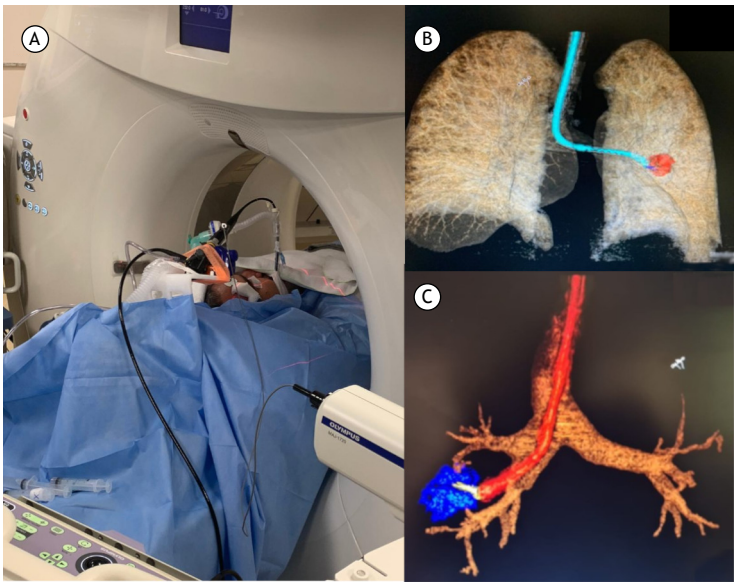

Figure 1. Combination of bronchoscopy techniques using radial EBUS and CT for the diagnosis of a pulmonary nodule. In A, patient in the procedure room, undergoing simultaneous bronchoscopy with radial EBUS and CT. In B and C, three-dimensional CT reconstruction to guide the biopsy procedure.

Figure 2. Placement of a double-lumen endotracheal tube for a CT-guided biopsy of a peripheral nodule with a high risk of bleeding. In A, patient undergoing intubation in the procedure room. In B and C, bronchoscopic view of the intubation procedure with a double-lumen endotracheal tube.

culture of safety, improve outcomes, and accelerate the learning curve for all professionals involved. This promotes an optimized approach with interdisciplinary discussions focused on selecting the best diagnostic and therapeutic strategy for each patient.[4]

Our experience illustrates a fundamental transformation in modern medicine: the shift from a fragmented, infrastructure-centered model to a patient-centered approach supported by multidisciplinary collaboration, diagnostic optimization, and risk mitigation. This redirection not only improves clinical outcomes but also promotes innovation, strengthens professional training, and drives the development of new therapeutic strategies.

The traditional separation between bronchoscopy and interventional radiology, historically driven by logistical convenience, no longer meets current demands. Integrating these practices has proven to be feasible, safe, and, above all, superior in addressing the increasingly complex landscape of thoracic diseases, in which diagnostic and therapeutic approaches transcend the boundaries of a single specialty. We invite the medical community to consider this collaborative model as a paradigm for the future of interventional pulmonary medicine.

We would like to highlight that the activities described in this editorial were performed at the *Hospital Israelita Albert Einstein* Center for Interventional Medicine, located in the city of São Paulo, Brazil.

FINANCIAL SUPPORT

None.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the following: study conception; manuscript preparation; and critical revision of the manuscript for important intellectual content.

CONFLICTS OF INTEREST

None declared.

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Household air pollution: another threat to Indigenous people in Brazil

Rafael Futoshi Mizutani[1], Ubiratan de Paula Santos[1]

Household air pollution (HAP) is a significant health risk worldwide. According to the 2021 Global Burden of Disease study, 33.8% of the global population is exposed to high levels of HAP, contributing to 111 million disability-adjusted life years—or 3.9% of all disability-adjusted life years—and resulting in 3.11 million deaths.[1] The impact of HAP is disproportionate, with the greatest burden falling on the lowest socioeconomic regions of Africa, Asia, and Latin America, especially in remote communities.[1,2]

HAP is primarily caused by the burning of materials such as wood, coal, charcoal, crop residues, and animal feces for cooking and heating.[3] Vulnerable groups such as women, children, and the elderly are the most affected because they spend more time indoors than do men.[4] These groups are also more susceptible to the adverse health effects of air pollution. In pregnant women, HAP increases the risk of preterm births and low birth weight.[1] Children exposed to HAP are at a heightened risk of respiratory infections, asthma, impaired lung development, and even death. In 2021, HAP was responsible for 500,000 deaths among children under five years of age, accounting for 11% of global under-five mortality.[1] Among the elderly, HAP is a major risk factor for COPD, cardiovascular disease, lung cancer, diabetes, and premature death.[1]

Despite extensive research on the morbidity and mortality of HAP, directly measuring exposure remains a challenge, as highlighted by Gioda[5] in a recent study published in the *Jornal Brasileiro de Pneumologia*. In the study, Gioda measured fine particulate matter levels inside traditional Indigenous dwellings (*malocas*) in various Amazonian communities over short periods (of 20-60 min), comparing the indoor measurements with those taken outdoors. Limited access to power sources restricted the duration of the measurements. Although the mean fine particulate matter levels during firewood burning were recorded at 203 ± 261 μg/m^3, it is likely that mean daily exposure is lower, given the intermittent nature of fire use. Nevertheless, the study demonstrates that Indigenous people are regularly exposed to high levels of HAP.

Indigenous populations in Brazil face numerous socioeconomic challenges in comparison with non-Indigenous groups. They experience limited access to education, health care, electricity, and nutritious food, leading to higher childhood mortality rates and lower life expectancy.[6] In addition, record-breaking wildfires in the Amazon have compounded their exposure to outdoor air pollution, further threatening their health.[7,8] Deforestation, illegal mining, and the shifting weather patterns caused by climate change have led to more frequent famines, further exacerbating their vulnerability.[9]

Addressing these health disparities requires concerted efforts from governmental bodies. It is essential that the government provide full support to improve the living conditions of Indigenous communities, improving housing ventilation and stove exhaust; providing cleaner energy sources (such as gas); and expanding access to health services. Protecting Indigenous territories from deforestation, forest burning, illegal occupation, and mining is also critical, as is improving food security for these communities. The Brazilian society owes a significant debt to its Indigenous peoples. Closing the gap in these inequalities is vital to building a more just and equitable society for all.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

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  ◄ Voltar ao sumário ISSN 1806-3756

J Bras Pneumol. 2025;51(4):e20250344
https://dx.doi.org/10.36416/1806-3756/e20250344

Lung cancer screening: an urgent necessity

Gustavo Faibischew Prado[1,2], Thiago Lins Fagundes de Sousa[1,3], Isabele Alves Chirichela[2]

Lung cancer screening (LCS) was brought back to the center of the debate in Brazil after a public hearing on a bill proposing the implementation of LCS in the country. The hearing was held in the House of Representatives on August 19, 2025, and on August 20, the Senate's Social Affairs Committee approved a proposal to make August National Month of Lung Cancer Awareness and Prevention, an initiative known as *Agosto Branco* (White August). However, despite this timely alignment, health leaders and decision-makers remain adamant, arguing that the Brazilian Unified Health Care System currently struggles to diagnose and treat patients presenting with symptoms or incidental findings, and that adding screening would overburden a network that "cannot meet" the existing demand.

It is essential to reinforce and expand prevention policies, which have made Brazil a global leader in tobacco control.[1] It is equally urgent to structure integrated and assertive care pathways for symptomatic patients and patients with incidental imaging findings, thus ensuring swift and definitive routes to diagnosis and treatment. Nevertheless, a significant reduction in lung cancer mortality cannot be achieved without taking further steps.

The problem is that when symptoms are present, the disease is almost invariably locally advanced or metastatic, and even with an excellent fast-track system the impact on survival and quality of life remains limited. This is not a play on words: "rapid diagnosis of advanced disease is not early diagnosis." It would be equivalent to abandoning breast cancer screening and waiting for patients to present with palpable masses, ulcerations, or bone pain, or to abandoning cervical cancer screening and intervening only when cases involve genital bleeding or urinary obstruction.

LCS shifts diagnosis to earlier stages, offering more patients a real chance of cure. For health care systems, LCS also translates to less costly treatments and greater return on investment. Not screening would be akin to treating myocardial infarctions only when patients develop cardiogenic shock, instead of investing in prevention and early diagnosis of coronary disease. Medicine should not wait for a catastrophe to act, and lung cancer should not be an exception.

It is worth recalling that when a study by the U.S. National Lung Screening Trial Research Team was published in 2011,[2] many experts were skeptical about LCS.[3,4] Many questioned whether the results would be reproducible in other scenarios; whether benefits would extend to different populations; how to cope with overdiagnosis[5]; and whether it would be justifiable to propose an expensive screening program in countries with profound inequalities in primary health care. In Brazil, skepticism also included concerns about the fact that Brazil is a vast country in which specialized professionals are unevenly distributed.[6] However, technological advances now allow CT scans to be remotely reviewed by radiologists and specialists anywhere in the country, helping to mitigate barriers related to misdiagnosis and disparities in expertise. Many of the aforementioned questions have therefore been answered. We now have robust evidence of mortality reduction in different scenarios,[7,8] as well as practical experience showing feasibility in the national context, with questions regarding the high prevalence of tuberculosis in Brazil being answered.[9,10] More recently, low-dose CT screening has been shown to be cost-effective in the Brazilian Unified Health Care System.[11]

This is not a matter of choosing screening, prevention (including regulatory measures addressing the increasing use of electronic nicotine delivery systems),[12] or improving the diagnostic journey: we need all three in a complementary and integrated manner if we truly want to change the landscape of lung cancer in Brazil. Complex, multifactorial problems require comprehensive solutions. Refusing to implement LCS at this point is simply accepting preventable deaths. According to the International Agency for Research on Cancer, lung cancer cases and lung cancer mortality in Brazil will have increased by 65% and 74%, respectively, by the year 2040.[13]

Ultimately, this discussion is not about statistics; it is about the profound human cost of delayed diagnosis. It concerns the lives of people who could still be at home, working, and spending time with their families, as well as those who are diagnosed too late because they were denied the opportunity for early detection. LCS is not just an option; it has become an urgent necessity. To forgo this critical intervention is to abdicate the responsibility of saving lives and betray the promise of a healthier future.

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J Bras Pneumol. 2025;51(4):e20250321
https://dx.doi.org/10.36416/1806-3756/e20250321

Electronic cigarettes: emerging challenges in cessation and dependence management. A call for evidence-based guidelines to address a growing epidemic among Brazilian youth

Maria Enedina Claudino Aquino Scuarcialupi[1,2,3], Carlos Leonardo Carvalho Pessôa[3,4], Ramiro Dourado-Maranhão[3,5,6]

The use of electronic cigarettes (vapes), a relatively recent form of nicotine consumption, has been consolidated into a global epidemic, with rising prevalence particularly among young people—including adolescents aged 13 to 24 years.[1] Created by Chinese pharmacist Hon Lik in 2003,[2,3] the device initially failed to gain widespread acceptance. The patent was later transferred to the tobacco industry, which heavily invested in marketing strategies emphasizing aesthetic appeal, a variety of flavors, attractive colors, innovative design, and the misleading claim that the product contained only water vapor and was harmless to health.[4-6]

These claims were swiftly refuted by scientific evidence and clinical experience, as reports have accumulated significant respiratory, cardiovascular, and mental health damage.[7-11] In 2019, an outbreak of a previously undescribed pulmonary condition—E-cigarette or Vaping product use-Associated Lung Injury (EVALI)—was recorded, causing 68 deaths among young people in the United States, with cases and fatalities subsequently reported in other countries, including Brazil.[12]

In Brazil, the sales, transportation, and advertising of electronic cigarettes have been prohibited since 2009 by the Brazilian Health Regulatory Agency,[13] a policy mirrored in countries such as Mexico, India, and Argentina. Conversely, nations such as Canada, the United States, and the United Kingdom have implemented additional restrictive measures, including raising the minimum purchase age, banning certain flavors, and limiting nicotine content.[6,14,15]

The appeal of electronic cigarettes has been heightened by the constant technological evolution of their devices. in 2024, data from the Brazilian national Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases indicated that the average age of experimentation was around 13 years; that consumption was higher among boys; and that overall smoking prevalence increased from 9% in 2023 to 11.6% in 2024, possibly driven by vape use among youth.[16,17] This scenario raises pressing questions: Has there been a relaxation in communication with the public and the medical community? Were there failures in enforcement and product seizures? Was there underestimation of the severity of the problem? Meanwhile, the tobacco industry's lobbying power continues to influence the public and policymakers.

Structurally, e-cigarettes have four main components: a lithium battery, a tank, an atomizer, and a mouthpiece. Heating above 350°C produces an aerosol containing ultrafine particles and a complex mixture of chemicals—propylene glycol, glycerin, nitrites, heavy metals (such as lead and nickel),[8,10,18] diacetyl, benzoic acid, and flavorings. Additionally, synthetic nicotine, nicotine salts, cannabis derivatives (CBD, THC), and amphetamines have been identified—all of which capable of inducing strong dependence—as shown in recent studies, including research conducted in Brazil by two important Brazilian universities.[18,19]

These devices primarily attract individuals who had never smoked, along with a smaller proportion of combustible cigarette smokers seeking, often mistakenly, to reduce health risks. However, national and international data show that dual use (conventional + electronic cigarettes) remains frequent and is increasing.[20,21]

The narrative review published by Martins et al.[22] in this issue of the *Jornal Brasileiro de Pneumologia* provides health professionals with a broad approach to vape cessation, including behavioral support, nicotine replacement therapy (NRT), and non-nicotine pharmacological treatments. While this review is both relevant and timely, it is important to note that the scientific literature on vape cessation is still limited, frequently relying on studies with small sample sizes. Consequently, the review article featured in this issue makes a valuable contribution, highlighting the necessity for further research that specifies sample sizes and confidence intervals. On the other hand, it is important to stress that some studies referred in this review involve medications unavailable in Brazil, such as varenicline and cytisine, which could mislead clinical practice.

Another important aspect that warrants attention is that NRT has yet to be specifically validated for e-cigarette dependence. This is not unexpected, given the only

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recent rise in electronic cigarette use. However, caution is advised when applying the findings from NRT studies focused on traditional cigarette smokers to those who use electronic cigarettes.

Cognitive behavioral therapy, delivered individually or in groups, plays a central role in managing this population, composed mainly of young people undergoing physical and psychological maturation, with greater neuroplasticity and vulnerability to social influences.[14,23] Cognitive-behavioral strategies that encourage reflection on self-image ("How do I see myself? How do I see the world? How do I think the world sees me?"), world perception, and social integration can help develop coping strategies for chemical and behavioral dependence. Complementary resources include physical, cultural, artistic, and manual activities, support apps, peer networks, and vape-free environments.

Applying theoretical models such as the stages of change,[24,25] and validated instruments for dependence assessment (Penn State Nicotine Dependence Index, Modified Fagerström for e-cigs) can refine therapeutic planning. However, the high nicotine levels in vapes—often exceeding those in conventional cigarettes—pose challenges for simply adapting usual NRT regimens. Continuous NRT combined with rapid-release forms during peak cravings may be considered, always alongside intensive behavioral support.

It is important to note that the recommendations discussed here do not constitute formal guidelines, but rather provisional guidance. As with conventional smoking, pharmacological treatment in adolescents must be used with extreme caution and close follow-up, with behavioral therapy as the first-line approach.

To sum up, medical societies and health authorities must invest in continuing education, provide educational materials, and consolidate clinical protocols to ensure safe and effective professional practice in addressing e-cigarette dependence.

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J Bras Pneumol. 2025;51(4):e20250329
https://dx.doi.org/10.36416/1806-3756/e20250329

Lateral flow urine lipoarabinomannan assay for tuberculosis diagnosis in people living with HIV: a step in the right direction, but we need more

Ana Paula Santos[1,2], Fernanda Carvalho Queiroz Mello[2]

Rapid diagnosis of tuberculosis is one of the most important pillars of the WHO End TB Strategy.[1] This is especially crucial for paucibacillary forms—including extrapulmonary tuberculosis, tuberculosis in children, and in people living with HIV (PLHIV)—which remain major challenges.

Since 2019, the WHO has recommended the lateral flow urine lipoarabinomannan assay (LF-LAM) to assist in diagnosing active tuberculosis in HIV-positive inpatients and outpatients who meet specific criteria, most of which are related to disease severity and the degree of immunosuppression as measured by CD4 cell counts.[2] Following these recommendations, the Brazilian National Ministry of Health incorporated LF-LAM into the public health system. PLHIV presenting with clinical manifestations of pulmonary or extrapulmonary tuberculosis (regardless of CD4 cell counts) and those who are severely ill should undergo LF-LAM. Asymptomatic patients should be tested on the basis of their CD4 cell counts, i.e., < 200 cells/mm^3 for inpatients and < 100 cells/mm^3 for outpatients.[3]

Lipoarabinomannan is the most extensively studied immunomodulatory lipid in the mycobacterial cell wall and contributes to the pathogenicity of virulent mycobacteria by reducing the host protective response and evading immunity.[4] Following the degradation of *Mycobacterium tuberculosis*, the remaining free lipoarabinomannan in the bloodstream is filtered through the glomerular basement membrane into the urine. Using an immunochromatographic test, antibodies against lipoarabinomannan on a strip react with this antigen, producing a colored line that is interpreted as reactive.

In this issue of the *Jornal Brasileiro de Pneumologia*, Pereira et al.[5] present the results of LF-LAM (DETERMINE™ TB LAM Ag test; Abott Laboratories, Abott Park, IL, USA) for tuberculosis diagnosis in PLHIV in southern Brazil. In their study,[5] LF-LAM detected an additional 8.6% of tuberculosis cases in comparison with rapid molecular tests on sputum. LF-LAM–positive patients were younger and had lower CD4 counts, whereas smoking was more common among LF-LAM–negative patients.[5]

The literature, however, shows inconsistent results regarding the performance of LF-LAM for tuberculosis diagnosis. One systematic review and meta-analysis showed a wide range of sensitivities (from 8% to 80%), whereas specificity ranged from 88% to 99%.[6] More recently, a diagnostic yield of 41% was reported for LF-LAM, being 61% for rapid molecular tests and 32% for sputum smear microscopy.[7]

Despite its suboptimal sensitivity for routine clinical use, LF-LAM has several characteristics that make it attractive for tuberculosis diagnosis. The easier availability of urine in comparison with that of sputum or other biological specimens, the reasonable cost of the test, and its use as a point-of-care test are some of the advantages. These characteristics have led to a reduction in eight-week mortality in a study conducted in Africa,[8] where patients were often severely ill, had advanced immunosuppression, were unable to produce sputum, and were living in settings with scarce diagnostic resources. In such patients, the speed of tuberculosis diagnosis can be the difference between a favorable and an unfavorable outcome.

Although LF-LAM shows benefits in reducing mortality among PLHIV, the occurrence of false-positive and invalid results should be taken into account by clinicians. In a recent study,[9] approximately 20% of LF-LAM–positive results were attributed to nontuberculous mycobacterial disease, nocardiosis, and cryptococcosis—conditions that must be included in the differential diagnosis of PLHIV. Another 7% of cases showed invalid results in patients with chronic kidney disease.[9]

Importantly, molecular and/or microbiological tuberculosis investigations must continue in order to identify the mycobacteria and determine *M. tuberculosis* drug susceptibility, given that LF-LAM has shown comparable sensitivity for diagnosing tuberculosis and nontuberculous mycobacterial disease,[10] and cannot detect drug-resistant tuberculosis.

The first commercial LF-LAM was the DETERMINE™ TB LAM Ag test (Alere, Waltham, MA, USA). The next-generation LF-LAM, SILVAMP TB LAM (Fujifilm, Tokyo, Japan) promises increased sensitivity as a result of its ability to detect lower lipoarabinomannan concentrations. Despite this improvement, variability in accuracy between SILVAMP TB LAM lot numbers, as identified by Huerga et al.,[11] has reduced its reliability. For this reason, the next-generation LF-LAM has yet to be endorsed for clinical use by the WHO.

Research is ongoing to develop and evaluate other lipoarabinomannan-based tests for tuberculosis diagnosis in PLHIV and non-HIV patients, as well as using specimens other than urine. Another potential application that is currently being studied is the use of lipoarabinomannan

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ISSN 1806-3756

tests to monitor tuberculosis patients during treatment. The electrochemiluminescence lipoarabinomannan research assay has been used in order to measure this antigen in the urine of HIV-negative individuals with pulmonary tuberculosis and to monitor antituberculosis treatment.[12] The results suggest that there is a strong possibility of meeting the WHO target product profile for tuberculosis diagnosis in the near future.

Although LF-LAM can be very helpful in PLHIV, particularly those who are hospitalized, as shown by Pereira et al,[5] it still requires careful interpretation in a clinical context.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(4):e20250278
https://dx.doi.org/10.36416/1806-3756/e20250278

Intrapulmonary lymph nodes

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

A 64-year-old man undergoing treatment for colon adenocarcinoma underwent imaging tests n for metastasis screening. A chest CT scan revealed a small, triangular nodule in the left lung, closely related to the oblique fissure (Figure 1).

Solitary pulmonary nodules (SPNs) remain a major diagnostic challenge for radiologists and pulmonologists. Recent technological advances in imaging techniques and the widespread use of CT have increased the frequency of pulmonary nodule detection. Small nodules (up to 5 mm in diameter) are commonly detected on CT images, and their clinical significance appears to differ significantly from that of larger nodules. However, this increased detection rate has not affected the basic issue of determining the nodule's status—benign (no need for specific treatment) or indeterminate (potentially malignant). Most nodules are resected for diagnosis and definition of appropriate treatment.

Pulmonary lymph nodes are a common and underrecognized cause of SPN. These lymph nodes are usually found at the bifurcation of the bronchi, before the fourth branch, where they are called peribronchial lymph nodes. Occasionally, lymph nodes are present in the lung parenchyma, where they are called intrapulmonary lymph nodes (IPLN) or perifissural nodes. Differentiating IPLN from other small lung nodules on CT scans can be difficult, although clinically important. In particular, erroneous evaluation of an IPLN that is interpreted radiologically as a tumor nodule leads to overstaging and possible exclusion of surgical treatment in patients with primary lung cancer. Several CT features can aid in the differential diagnosis of IPLN. These lymph nodes can be oval, round, triangular, or trapezoidal, with well-defined borders, predominating in the subpleural regions of the lower lobes. They are frequently attached to the pleura or separated from the pleural surface by a few millimeters. IPLNs have thin, linear adhesions that extend from the nodule to the pleura. These linear densities have been shown to represent normal or thickened interlobular septa.[1-3]

It is important to emphasize that typical IPLNs, although generally benign, may show growth, without this indicating malignancy. Since they are lymph node-related, their growth may be due to reactive changes, especially inflammatory ones.[1-3]

In conclusion, IPLNs present imaging characteristics suggestive of benignity, which should be considered in the differential diagnosis of SPN. Correct identification of these lesions can reduce the number of unnecessary surgeries and follow-up examinations.

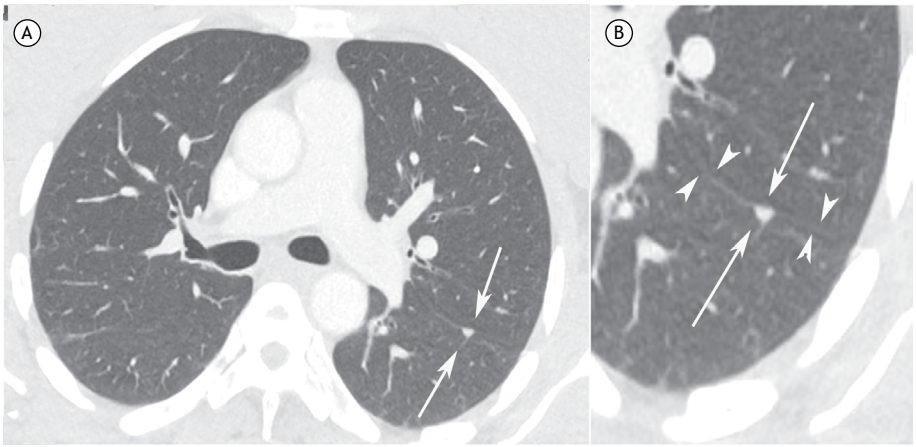

Figure 1. In A, axial CT image of the chest (lung window) showing a small triangular-shaped nodule in the posterior region of the left lung, closely related to the pleural fissure. In B, detail at higher magnification of the aforementioned nodule, clearly characterizing the triangular shape of the intrapulmonary lymph node (arrows) and its close relationship with the oblique fissure (arrowheads).

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ISSN 1806-3756

Prospective cohort studies and their contribution to public health end evidence-based medicine

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PRACTICAL SCENARIO

In the first half of the XX century, the observation that lung cancer cases appeared to be much more common among smokers led to the suspicion that smoking caused lung cancer. The health consequences of increase prevalence of smoking became a public issue, sparking a scientific controversy over whether the statistical link between smoking and lung cancer was a causal relationship or a mere coincidence.

A cohort study was the decisive factor in resolving the issue.[1] Some experts argued that a simple correlation did not prove causation, but a carefully designed observational study provided overwhelming evidence that, in this case, it did. The British Doctors Study,[1] a landmark prospective cohort study that followed over 40,000 male doctors for several decades was crucial for several reasons:

- Temporal sequence: The study established a clear temporal sequence, showing that heavy smoking consistently preceded the diagnosis of lung cancer.
- Strength of association: The study revealed a powerful statistical association. For example, heavy smokers had a risk of developing lung cancer over 20 times that of non-smokers, an effect too large to be easily dismissed as random chance.
- Dose-response relationship: It demonstrated a strong dose-response relationship, proving that the more an individual smoked, the higher the risk became. This systematic increase in risk with increased exposure is a powerful indicator of a causal relationship.

The first scientific publication from the cohort study, published in 1954, was a turning point.[1] It presented such compelling evidence that it shifted the scientific community from skepticism to a consensus that smoking was a direct and primary cause of lung cancer.

WHAT ARE PROSPECTIVE COHORTS?

A cohort study is an observational, longitudinal research design that follows a group of people, or a cohort, over time to see how a specific exposure affects their health outcomes. The core of this design is to compare the risk—the incidence of events—between an exposed group and an unexposed group. Therefore, researchers may calculate the relative risk (RR), which reflects the strength of the association. When the duration of observation is also considered, the incidence rate ratio (IRR) is used to describe the relationship between events and time.[2]

The key feature of this design is that exposure status is established before the disease occurs. A cohort study is called prospective when investigators plan the study and define the variables of interest before enrolling patients and follow them over time.[3] This method is particularly strong to establish a clear temporal relationship—the exposure is known to have occurred *before* the outcome—and is less prone to bias (Table 1). A retrospective cohort study uses existing records, such as medical records or employment information, to define a cohort and assess past exposure to risk factors. This design is faster and less costly than prospective studies but may suffer from incomplete data and biases such as misclassification of exposure or outcomes.[2]

The methodology involves:

1. Defining the study population: The cohort should be a representative sample of the population of interest.
2. Defining and measuring the exposure: Researchers accurately define and measure the exposure of interest in all participants at baseline. This may involve surveys, biological markers, or environmental measurements.
3. Follow-up: The cohort is followed over a specified period to monitor the development of the disease. This is typically done through regular check-ups, questionnaires, or linkage to national health databases.
4. Measuring the outcome: The occurrence of the disease or health outcome is systematically and reliably measured in both the exposed and unexposed groups.

MODERN APPLICATIONS AND FUTURE DIRECTIONS

Cohort studies remain a cornerstone of modern epidemiology. They are used in order to study a wide range of exposures and outcomes, including:

- The long-term effects of environmental pollutants on respiratory health.
- The relationship between dietary patterns and cardiovascular disease.
- The impact of new drug therapies on patient outcomes over time.

Future directions for cohort studies include the integration of advanced technologies, such as genetic

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ISSN 1806-3756

Table 1. Strengths and limitations.

Strengths	Limitations
Temporal Relationship: Establishes the direction of causality (exposure precedes outcome).	Time-Consuming and Expensive: Especially for prospective studies, as they can span many years.
Multiple Outcomes: Can examine the effect of a single exposure on multiple different outcomes (e.g., smoking and lung cancer, heart disease, stroke).	Inefficient for Rare Diseases: Requires a very large cohort and long follow-up period to observe enough cases of a rare disease.
Incidence Rates: Allows for the direct calculation of incidence rates and relative risks.	Potential for Loss to Follow-up: Participants may drop out of the study, which can introduce selection bias if lost individuals differ from those who remain.
Reduces Bias: Less prone to recall bias than case-control studies.	Potential for Confounding Factors: Although confounding variables can be controlled during the analysis, there is always a risk of unmeasured or residual confounding.

and genomic data, to explore the interplay between environmental factors and genetic predispositions. The use of large-scale electronic health records and data linkage will also make it possible to conduct more efficient and comprehensive retrospective cohort studies.

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Technical aspects and interpretation of oscillometry

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Oscillometry is a noninvasive pulmonary function test that measures respiratory system impedance during tidal breathing. It does not require forced maneuvers, and by using a low-amplitude oscillatory signal, it assesses respiratory resistance and reactance.[1]

Resistance reflects opposition to airflow. Low-frequency measurements (e.g., resistance at 5 Hz—R5—and resistance at 6 Hz—R6) represent total airway resistance, whereas high-frequency measurements (e.g., resistance at 19 Hz—R19—and resistance at 20 Hz—R20) reflect central airway resistance. The difference between low and high frequencies (e.g., R5—R20) offers insight into distal airway involvement. Reactance encompasses two components: elastance, which quantifies the pressure required to overcome the resistance of the lung to volume change, thereby reflecting its stiffness or decreased compliance; and inertance, which mainly reflects pressure losses from gas acceleration in the central airways. More negative values of reactance at 5 Hz (X5) indicate increased elastance. The resonant frequency (Fres), where total reactance equals zero, increases with decreased lung compliance. The area of reactance (AX), which is defined as the area under the X5-Fres curve, quantifies the reactive load of the respiratory system and is a sensitive indicator of peripheral airway obstruction.[2]

Reference equations developed with the same device must be used in order to ensure accurate interpretation because results are not interchangeable between devices. It is also important to confirm that the equation covers the age range of the study population in order to avoid misclassification of patterns (Table 1).

Oscillometry has shown clinical value across several respiratory conditions. In asthma, it can detect small airway dysfunction even when FEV_1 is normal. Abnormal R5-R20, X5, and AX values are common and correlate with disease control. In bronchopulmonary dysplasia, preterm individuals often present with elevated resistance and AX, as well as more negative reactance values, suggesting persistent mechanical impairment. In neuromuscular disorders, increased R5, Fres, and AX values, as well as more negative reactance values, reflect a restrictive pattern caused by reduced lung volumes and increased elastic load from respiratory muscle weakness.[3]

In acute respiratory failure, AX is often the most affected parameter, indicating elevated elastance and heterogeneous tissue mechanics. Reactance becomes more negative, reflecting increased lung stiffness, whereas resistance may remain within normal limits. These values typically improve with recovery, making oscillometry a useful tool for monitoring disease progression and therapeutic response.[4]

Regarding bronchodilator response, King et al.[2] proposed the following thresholds: ≥ 40% reduction in low-frequency resistance (R5 and resistance at 6 Hz); a ≥ 50% increase in X5; or a ≥ 80% decrease in AX. Bickel et al.[1] suggested more conservative cutoffs based on ROC analysis: a ≥ 30-35% reduction in R5; a ≥ 8.6% reduction in resistance at 10 Hz; or ≥ 29.1% reduction in AX.

Although no specific oscillometry phenotype for restrictive lung disease has been defined, findings in a veteran cohort suggest that more negative values of X5, an increased AX, and a higher Fres are associated with a restrictive pattern, likely reflecting increased lung stiffness.[5]

In conclusion, oscillometry is a sensitive and versatile technique that complements spirometry in a wide range of clinical contexts. However, further standardization—particularly in the interpretation of parameters associated with restrictive patterns—is required to enhance its diagnostic accuracy and clinical integration.

Table 1. Oscillometric patterns of lung function.

Functional pattern	R5	R20	R5-R20	X5	AX	Fres
Normal	Normal	Normal	Normal	Normal or less negative	Normal	Normal
Peripheral obstruction	Normal or increased	Normal or increased	Increased	Normal or Increased (more negative)	Increased	Normal or increased
Central obstruction	Increased	Increased	Normal	Normal	Normal	Normal
Probable restriction	Normal	Normal	Normal	Increased (more negative)	Increased	Normal or increased

ULN: upper limit of normal; LLN: lower limit of normal; R5: resistance at 5 Hz; R20: resistance at 20 Hz; R5-R20: difference between R5 and R20; X5: reactance at 5 Hz; AX: area of reactance; and Fres: resonant frequency. Resistances, AX and Fres are considered normal if the value is ≤ULN. Reactances are considered normal if the value is ≥LLN.

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AUTHOR CONTRIBUTIONS

IAA: searched, selected, and synthesized the relevant literature, wrote the initial and final versions of the manuscript, and structured the overall narrative. MAFV: reviewed the manuscript and provided critical feedback throughout the process. LGR: coordinated the development process, contributed to the interpretation of the technical and clinical aspects of oscillometry, and reviewed the final version with expert input to ensure clarity and consistency.

CONFLICTS OF INTEREST

LGR has served as a speaker for Chiesi, Thorasys, and Pulmone, and as a member of the advisory board for Sunvou. IAA has served as a speaker for AstraZeneca and GlaxoSmithKline.

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Inhalation therapy: current and emerging devices in pediatrics

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INTRODUCTION

Inhalation therapy remains a cornerstone in the management of pediatric respiratory diseases, providing targeted drug delivery with rapid onset and reduced systemic exposure. However, the pediatric population presents unique challenges related to lung anatomy and physiology, breathing patterns, cognitive development, and treatment adherence, as well as the characteristics of pulmonary disease, which can significantly influence drug deposition and therapeutic outcomes.[1]

Pediatric conditions such as asthma, cystic fibrosis, croup, and recurrent wheezing often require chronic or intermittent inhaled therapies to control symptoms and prevent exacerbations. These respiratory diseases are among the leading causes of morbidity and mortality in childhood, contributing significantly to the high number of pediatric visits to emergency departments.[2]

Given the critical role of inhalation therapy in pediatric respiratory care, a comprehensive understanding of the available delivery systems, their clinical applications, and their limitations are essential to optimizing treatment outcomes. This review aims to examine current modalities of inhalation therapy, discuss emerging technologies, and evaluate their advantages and limitations in the context of pediatric care.

MODALITIES OF INHALATION THERAPY

Inhalation therapy in children encompasses several modalities, each with distinct advantages and considerations. The primary devices used for delivering inhaled medications include nebulizers, pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs).

Regular nebulizers

Jet nebulizers convert liquid medication into a fine mist, which is inhaled through a mask or mouthpiece. They are reserved for the minority of children who cannot be effectively trained to use a spacer device.[3,4]

Ultrasonic/vibrating-mesh nebulizers

These newer nebulizer technologies have gained increasing attention in clinical practice. Ultrasonic nebulizers offer quieter operation and shorter administration times compared with jet devices, but their use is limited by potential drug degradation and incompatibility with certain formulations. In contrast, vibrating-mesh nebulizers combine high efficiency, consistent aerosol generation, shorter administration times, and superior portability, making them especially valuable in pediatric care.

pMDIs

pMDIs deliver a fixed dose of medication with each actuation. When used with a spacer, they are the preferred delivery system for young children, particularly those ≤ 5 years, with a face mask recommended for infants and toddlers and a mouthpiece for older preschool children.[3,4]

DPIs

DPIs are typically shaped like a tube or disk and include a mouthpiece. Depending on the model, the powder formulation may be preloaded or inserted by the patient, consisting of micronized drug particles alone or blended with larger carrier particles, usually lactose. DPIs are breath-actuated and therefore do not require coordination between actuation and inhalation; however, they demand a rapid and forceful inspiratory maneuver. As a result, they are suitable only for children older than 5-6 years who can generate sufficient inspiratory flow, while younger children usually require alternative delivery systems.[4]

SMIs

SMIs generate a slow-moving mist that enhances pulmonary deposition. They are propellant-free and are easier to use than pMDIs, but they remain limited for pediatric populations.[4]

The choice of an inhalation device in children must account for developmental stage, coordination ability, and inspiratory capacity. Clinical guidelines emphasize that pMDIs with spacers represent the first-line option in most pediatric age groups, while nebulizers, DPIs, and breath-actuated pMDIs may serve as alternatives depending on the child's age and clinical condition. Table 1 summarizes age-specific recommendations and suitable alternatives for pediatric patients.

INNOVATIONS IN INHALATION DEVICES AND ADVANCES IN TECHNOLOGY AND DRUG DELIVERY SYSTEMS

Recent innovations in inhalation devices and drug delivery systems for pediatric patients have focused on enhancing the efficiency and usability of DPIs and

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ISSN 1806-3756

Table 1. Recommended inhalation devices by age group in pediatric patients.

Inhaler device	Age group			
	< 3 years	3-4 years	5-7 years	8-11 years
Nebulizer	Possible	Possible for acute asthma or croup		
MDI, small volume spacer & mask	Yes	May transition to no mask		
MDI & spacer; no mask		Possible	Yes	Yes
Dry powder device			Possible	Yes

MDI: metered-dose inhaler. Observation: Pressurized metered-dose inhalers (pMDIs) with spacers are the preferred option across most age groups, while nebulizers, dry powder inhalers, and breath-actuated pMDIs serve as alternatives depending on the child's age and ability to use the device properly.

nebulizers, using through approach specifically tailored for children.

Advances in nebulizer technology, such as vibrating-mesh nebulizers or mesh nebulizers, have markedly improved delivery efficiency. These devices can be adapted to individual patient needs, improving adherence and optimizing pulmonary drug delivery.[5] Technologies that aimed at improving the use of DPIs by infants include the Infant Air-Jet Dry Powder Aerosol Delivery System (iDP-ADS), which employs a bifurcated two-prong nasal interface and enables consistent monitoring and control of lung pressures and ventilatory parameters, thereby enhancing aerosol delivery.[6]

CLINICAL AND PRACTICAL ADVANTAGES AND LIMITATIONS OF PEDIATRIC INHALATION THERAPY

Each inhalation device presents distinct advantages and limitations that determine its suitability in pediatric care. Recognizing these differences is essential for individualized tailoring treatment and promoting adherence.

Nebulizers enable aerosol delivery independently of patient coordination or inspiratory effort, making them particularly useful in infants, young children, or patients in respiratory distress. They are frequently employed in emergency settings and for patients with limited cooperation. However, conventional jet nebulizers are associated with prolonged administration times, reduced portability, and the need for meticulous cleaning to prevent microbial contamination.[1,4]

pMDIs offer efficient pulmonary deposition, reduced oropharyngeal deposition, and improved safety profiles, especially when used in conjunction with spacers. However, their effectiveness depends on correct inhalation technique, and misuse remains a common barrier to optimal outcomes.[1,4]

DPIs are environmentally advantageous and well accepted by older children. However, their effectiveness depends on the generation of adequate inspiratory flow, which may be compromised during acute exacerbations or by children younger than 6 years of age, limiting their applicability in some clinical scenarios.[1,4]

SMIs require minimal coordination and no propellants, aligning with environmentally sustainable practices. Despite these advantages, SMIs remain limited in pediatric populations due to their higher cost and restricted availability.[1,4]

Overall, inhalation therapy remains a cornerstone in the management of pediatric respiratory diseases, providing targeted, rapid, and minimally invasive drug delivery. However, the effectiveness of this approach depends on the selection and correct use of inhalation devices, which must be tailored to the child's age, developmental stage, and clinical condition. While pMDIs with spacers remain the mainstay across most pediatric age groups, newer technologies—such as mesh nebulizers and advanced DPI systems—are expanding therapeutic options, particularly for patients with anatomical or functional limitations.

Understanding the strengths and limitations of each device is essential to optimizing treatment, supporting adherence, and improving clinical outcomes. As inhalation technology continues to evolve, integrating these advances into pediatric care will be essential to delivering safe, effective, and individualized respiratory therapy for children.

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J Bras Pneumol. 2025;51(4):e20250066
https://dx.doi.org/10.36416/1806-3756/e20250066

ORIGINAL ARTICLE

Influence of *ADRB2* variants on bronchodilator response and asthma control in a mixed population

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Submitted: 17 February 2025.
Accepted: 19 May 2025.

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

ABSTRACT

Objective: Given that β_2 agonists constitute the primary treatment for asthma and that treatment response varies as a result of polymorphisms in the *ADRB2* gene, we sought to investigate the associations between *ADRB2* gene variants and bronchodilator response (BDR) in asthma patients. **Methods:** A genetic database comprising 813 individuals was analyzed for variants in the *ADRB2* gene. A longitudinal analysis of severe asthma patients was performed to evaluate changes in BDR over time. **Results:** The rs1042713, rs1042714, and rs1042717 variants were associated with age-related changes in BDR in patients with severe asthma. The G allele (rs1042714) and the A allele (rs1042717) were associated with uncontrolled asthma, with carriers of the G46/G79/A252 alleles showing a higher risk of difficult-to-control asthma. Notably, no association was found between these variants and *ADRB2* expression levels. **Conclusions:** Our findings suggest that a genetic panel including *ADRB2* variants, as well as age-related differences in BDR, is a useful complementary tool in asthma management.

Keywords: Bronchodilator agents; Beta-2 adrenergic receptor; Genetic variation;; Asthma; Ethnic groups.

INTRODUCTION

Asthma is a chronic disease that affects more than 339.4 million individuals worldwide[1] and approximately 20 million people in Brazil.[2] The main features of asthma are lower airway respiratory symptoms associated with recurrent and typically local inflammation and airflow limitation that can be reversed with the use of a bronchodilator.[3,4]

The goal of asthma treatment is to control asthma symptoms and prevent disease progression with the use of inhaled corticosteroids (ICS) in combination with long-acting β_2 agonists (LABAs) and short-acting β_2 agonists (SABAs).[5,6] SABAs are also used in spirometry, which is useful for diagnosing, monitoring, and assessing asthma severity and treatment effectiveness.[2] The bronchodilator action of β_2 agonists occurs through the activation of the β_2-adrenergic receptor coupled to a G protein, which stimulates the adenylate cyclase and cyclic adenosine 3',5'-monophosphate pathways, promoting airway smooth muscle relaxation.[7]

Approximately 39% of asthma patients have poor disease control, persistent symptoms, and exacerbations, which may be associated with the individual genetic background.[8] Inadequate clinical control and decreased bronchodilation (tachyphylaxis) have both been linked to the chronic use of β_2-adrenergic bronchodilators.[9] Immediate removal of agonists may promote recycling of receptors back to membrane; however, persistent activation can lead to degradation and reduced synthesis of new receptors.[10] Furthermore, studies indicate that aging is associated not only with a reduced acute response to bronchodilators but also with a chronic loss of reversibility.[11]

Single nucleotide polymorphisms (SNPs) are the main types of genetic variations associated with changes in bronchodilator response (BDR) phenotypes in individuals with asthma,[8] which can lead to altered structure of proteins and the rate of protein or gene expression, contributing to a variety of responses to treatments.[12] Polymorphisms of the *ADRB2* gene, which encodes the β_2-adrenergic receptor, are related to changes in function and coupling of agonists, particularly the rs1042713 (G46A) and rs1042714 (G79C) variants, which result in the alteration of the amino acid glycine at codon 16 to arginine and from the glutamic acid at codon 27 to glutamine, respectively.[13]

Such variations have been associated with changes in respiratory function and response to β_2 agonists in previous studies in Brazil and worldwide.[14,15] However,

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Financial support: This study received financial support from the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; PRONEX Mandate no. 020/2009; Grant no. 6353 PNX 0018/200) and the *Fundação de Amparo à Pesquisa do Estado da Bahia* (FAPESB, Foundation for the Support of Research in the State of Bahia).

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ISSN 1806-3756

there are divergences in the literature regarding the effect of *ADRB2* polymorphisms on BDR.[16] The conclusions of previous studies may have been influenced by variables such as the number of participants and heterogeneity of populations, highlighting the need for further studies. Therefore, the present study sought to assess the influence of *ADRB2* gene variants on the response to asthma treatment in a sample of urban adults in Brazil.

METHODS

Characterization of the study population

The present study included 401 individuals who had a diagnosis of severe asthma[4] as confirmed by two experts and who were followed under the auspices of the *Programa para o Controle da Asma na Bahia* (ProAR, Bahia State Program for the Control of Asthma). All 401 patients were classified as having severe asthma in accordance with international criteria, as described in detail elsewhere.[3] An additional 412 patients followed under the auspices of the ProAR were classified as having mild to moderate asthma and were also included in the study. The inclusion criteria were being > 18 years of age and living in the city of Salvador, Brazil. The exclusion criterion was having other chronic or acute diseases of the lower airways or lungs.

The present study was approved by the Research Ethics Committee of the Climério de Oliveira Maternity Hospital (Ruling no. 099/2010), located in the city of Salvador, Brazil. A subpopulation of asthma patients was recruited for gene expression assays, and this subproject was approved by the Research Ethics Committee of the Federal University of Bahia School of Medicine (Protocol no. CAAE 82928818.9.0000.5577/2.549.881). All participating patients gave written informed consent.

Symptom control was assessed by the six-item Asthma Control Questionnaire, previously validated for use in Brazil.[17] Scores of < 1.5 indicate controlled/partially controlled asthma, whereas scores ≥ 1.5 indicate uncontrolled asthma. All participating patients underwent spirometry before and 15 min after bronchodilator (albuterol) administration, as recommended by the American Thoracic Society/European Respiratory Society.[18] A KoKo spirometer (KoKo PFT, Longmont, CO, USA) was used, with predicted values for the Brazilian population being used as reference; a 12% (and ≥ 200 mL) increase in FEV_1 was considered significant for a β_2 agonist response, as follows (BDR = 100 × ((post-FEV_1 – pre-FEV_1)/pre-FEV_1)).[19]

We performed a retrospective longitudinal analysis of spirometry data from 309 severe asthma patients in the 18- to 88-year age bracket (2,349 observations, with intervals of 3-15 years [mean, 11 ± 2 years] and a mean of 8 BDR measurements per patient) to evaluate BDRs. This approach was used in order to capture temporal changes in BDR and assess the influence of genetic factors and aging.

Blood samples, genotyping, and gene expression

Peripheral blood samples were collected for DNA extraction in accordance with the manufacturer instructions (Gentra Puregene blood kit; QIAGEN, Hilden, Germany). Genotyping of the DNA samples was performed with the Infinium® Multi-Ethnic AMR/AFR BeadChip microarray (Illumina, Inc., San Diego, CA, USA). Data for the *ADRB2* gene were extracted from the Genome Reference Consortium Human Build 37 (available at www.ncbi.nlm.nih.gov) with a ± 10,000 bp margin.

Two SNPs with a minor allele frequency of < 5% and 64 individuals with < 90% genotyping rates were excluded, a total of 749 individuals remaining for association analyses. A subset of 31 individuals, selected by genotype, was used for functional studies, peripheral blood mononuclear cells being isolated with HisTopaque®-1077 (Sigma-Aldrich, Burlington, MA, USA). The Invitrogen™ PureLink™ RNA Mini Kit (Thermo Fisher Scientific, Waltham, MA, USA) was used for the extraction of RNA to be used in the expression assay, and reverse transcription was performed with the SuperScript™ IV First-Strand Synthesis System (Thermo Fisher Scientific).

Real-time PCR was carried out on the QuantStudio 12K Flex Real-Time PCR System (Thermo Fisher Scientific) using *ADRB2* TaqMan® Gene Expression Assays (Thermo Fisher Scientific), with *ACTB* as the normalization gene and non-risk genotypes serving as reference for relative expression calculations.

Platforms, databases, and statistical analysis

Genetic data for the SNPs were obtained from the U.S. National Center for Biotechnology Information SNP database (available at https://www.ncbi.nlm.nih.gov/snp/) and the Ensembl genome browser (available at https://www.ensembl.org/index.html), and SNPStats and PLINK 1.9 were used in order to assess the impact of multiple SNPs on the evaluated phenotypes.[20] Linkage disequilibrium between markers was analyzed with Haploview, version 4.2.[21]

The IBM SPSS Statistics software package, version 22 (IBM Corporation, Armonk, NY, USA) was used for preliminary analyses, including assessment of covariates and variables through mean comparisons (by means of the Kruskal-Wallis test or ANOVA, depending on group distribution) and chi-square tests. Association analyses between phenotypes and variants were performed with PLINK 1.9 and R software, version 4.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) under additive, recessive, and dominant models. Logistic regressions adjusted for sex, age, BMI, smoking exposure (primary, secondary, current, or former), and a major ancestry marker component were conducted; only SNP associations

with $p < 0.05$ were considered significant, with permutation procedures used in order to reduce false-positive results.[22]

With the use of R software, version 4.0.2, linear mixed fixed- and random-effects models—with age, additive genotype effects, an age × genotype interaction, and subject-specific intercepts and slopes as random effects—were performed with the *lmerTest* package. Additionally, a generalized additive mixed model via the *gamm4* package was used in order to assess the impact of age on longitudinal BDR by genotype, with genotype-specific smooth and density plots created with *ggplot2*. All analyses were adjusted for sex, smoking exposure, BMI, and an ancestry marker.

Centered smoothing plots were generated, and the 95% confidence intervals around the smoothed curves were depicted as shaded areas. Results were adjusted for covariates. R software packages were used in order to draw a correlation plot between BDR (BDR = 100 × ((post-FEV_1 − pre-FEV_1)/pre-FEV_1)) and age (in years) in the study population.

Other graphics and linear regression analyses, as well as expression analyses, were performed with GraphPad Prism, version 5 (GraphPad Software, Inc., San Diego, CA, USA), the Mann-Whitney test or the Student's t-test being used depending on group distribution.

RESULTS

In the severe asthma group, there was a higher proportion of females, older individuals, smokers, and individuals with a higher BMI. All individuals with severe asthma regularly used ICS + LABAs (Table 1).

The *ADRB2* gene variants investigated in the present study were characterized in terms of the polymorphic allele (A1), the reference allele (A2), the potential functional role, and the minor allele frequency in the ProAR population (Table 2). The SNPs included in the analyses are located in coding regions of the *ADRB2* gene (Figure S1) and showed a low level of linkage disequilibrium (Figure S2).

We found no significant associations of asthma severity with SNPs or sets of SNPs, a finding that suggests that there is no relationship between the genetic profile evaluated in the present study and the phenotype in question. None of the variants were associated with a lack of BDR in the cross-sectional analysis, even when the population was stratified by disease severity.

The linear mixed fixed- and random-effects models revealed no significant associations between the main effects (age and genotype) or their interactions and BDR. In contrast, comparative analyses with generalized additive mixed models allowed us to visualize, through smoothing, significant trends in the longitudinal variation of BDR as a function of age by genotype. An independent analysis of genotype showed that BDR decreases over time ($F = 11.79$; $p < 0.001$; Figure S3).

The presence of the A (A46) allele of rs1042713 in heterozygous form ($F = 4.16$; $p = 0.04$) and in homozygous form ($F = 2.98$; $p = 0.03$) was related to a greater variation in acute BDR with age (Figure 1). The presence of the reference G (G79) allele of rs1042714 in homozygous form characterized the absence of C79 polymorphic alleles ($F = 8.56$; $p < 0.01$; Figure 2). The reference G (G252) allele of rs1042717 in homozygous form ($F = 8.28$; $p < 0.01$) and heterozygous form ($F = 4.26$; $p = 0.04$) was also related to a greater variation in BDR with age in comparison with the standard response (Figure S4).

A joint longitudinal analysis of the rs1042713 and rs1042714 variants showed that individuals with four

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

	Mild to moderate asthma (n = 383)	Severe asthma (n = 366)	p
Sex			0.02
Female	297 (77.5%)	297 (81.1%)	
Male	86 (22.5%)	69 (18.9%)	
Age, years	36 ± 13	51 ± 14	< 0.01
Exposure to smoking			< 0.01
No	278 (72.6%)	233 (63.7%)	
Yes	105 (27.4%)	133 (36.3%)	
BMI, kg/m^2	26.99 ± 5.78	29.11 ± 5.60	< 0.01
Use of ICS + LABAs	0 (0.0%)	366 (100.0%)	< 0.01

ICS: inhaled corticosteroids; and LABAs: long-acting β_2 agonists. [a]Data expressed as n (%) or mean ± SD.

Table 2. Single nucleotide polymorphisms included in the analysis.

SNP	A1	A2	MAF	Function
rs1042713	A	G	0.44	Missense
rs1042714	C	G	0.24	Missense
rs1042717	A	G	0.32	Synonymous
rs1800888	A	G	0.01	Missense
rs3729943	G	C	0.01	Missense

SNP: single nucleotide polymorphism; A1: polymorphic allele; A2: reference allele; and MAF: minor allele frequency.

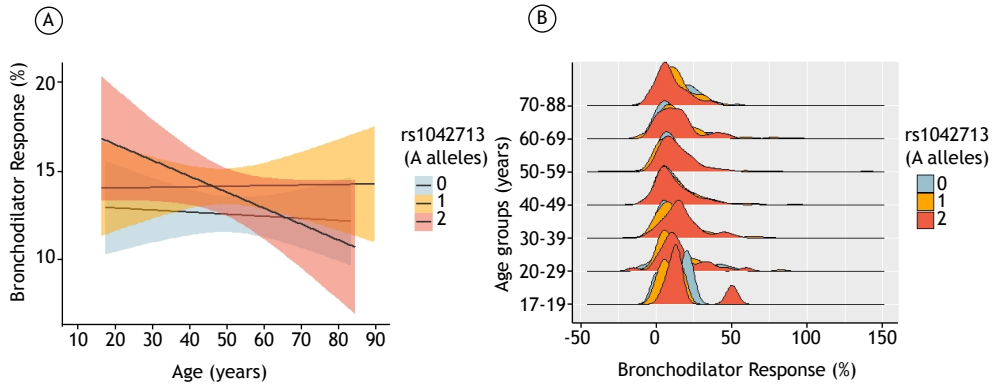

Figure 1. Correlation between rs1042713 and variations in longitudinal bronchodilator response. In A, overlaid smooths with a shaded area stratified by the number of A alleles—0, 1, or 2—and bronchodilator response adjusted for covariates. In B, density graphs for individuals stratified by bronchodilator response, grouped by number of A alleles and age.

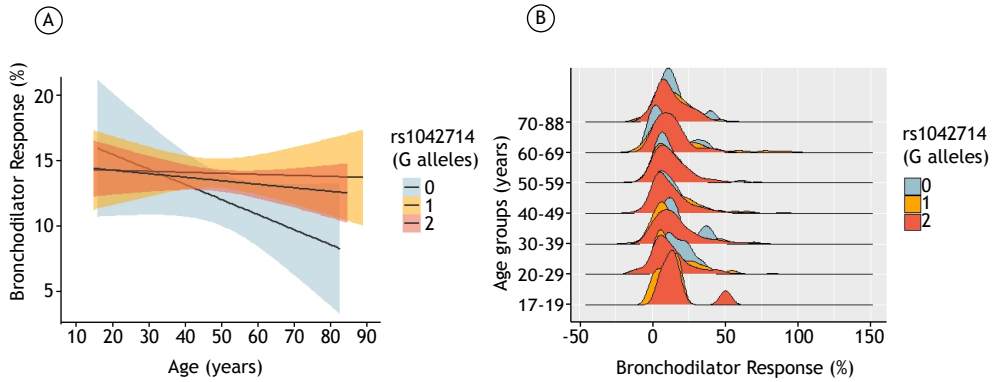

Figure 2. Correlation between rs1042714 and variations in longitudinal bronchodilator response. In A, overlaid smooths with a shaded area stratified by the number of G alleles—0, 1, or 2—and bronchodilator response adjusted for covariates. In B, density graphs for individuals stratified by bronchodilator response, grouped by number of A alleles and age.

risk alleles (A46A46-G79G79) had a more pronounced variation in acute BDR with increasing age (F = 3.01; p = 0.03; data not shown). The other combinations of risk alleles showed no significant results.

In recessive models, the G (G79) allele of rs1042714 was found to be associated with severe uncontrolled asthma (OR = 1.75; permutation p = 0.02). Similarly, the A (A252) allele of rs1042717 showed an association with a lack of disease control in patients with severe asthma (OR = 2.06; permutation p = 0.04). No other SNP in the *ADRB2* gene was associated with asthma control in any genetic model for individuals with severe asthma (p > 0.05; Table 3). Our allelic analysis showed that a specific combination of genotypes formed by the evaluated SNPs was associated with a lack of disease control in individuals with severe asthma. The set containing the G (G46) allele of rs1042713, the G (G79) allele of rs1042714, and the A (A252) allele of rs1042717 showed a different outcome in comparison with that in individuals with other genotypic combinations (OR = 3.2; p = 0.02). In addition, the presence of one of the genotype sets formed among the evaluated SNPs was associated with a lack of disease control in individuals with severe asthma. The set of genotypes containing the G (G46) allele of rs1042713, the G (G79) allele of rs1042714, and the A (A252) allele of rs1042717 showed a significantly different outcome when compared with that in individuals with other sets of genotypes (OR = 3.2; p = 0.02; Table 4). No other combination of alleles was found to be statistically significant. The genotypes of rs1042713, rs1042714, and rs1042717 did not affect the relative quantification of *ADRB2* gene expression between the groups of patients with severe asthma (Figure S5).

DISCUSSION

Missense variants of the *ADRB2* gene, such as rs1042713 (G46A) and rs1042714 (G79C), which promote amino acid changes and affect receptor structure and function,[23,24] were associated with SNP rs1042717 and genotype sets linked to asthma control and a lack of acute response to short-acting bronchodilators in severe asthma patients evaluated longitudinally. However, we cannot determine whether these variants alter gene expression, given that exon variants are less often implicated in regulatory effects than are non-coding ones.[25,26] This finding

Table 3. Associations of rs1042714 and rs1042717 with asthma control in individuals with severe asthma.

Genotype	Severe controlled/partially controlled asthma - n (%)	Severe uncontrolled asthma - n (%)	OR (95% CI) Permutation p*
rs1042714			
CC/CG	115 (46.6%)	38 (32.8%)	1.75 (1.10-2.86) Permutation p = 0.02
GG	132 (53.4%)	78 (67.2%)	
rs1042717			
AG/GG	224 (90.1%)	96 (82.8%)	2.06 (1.06-4.01) Permutation p = 0.04
AA	23 (9.9%)	20 (17.2%)	

A: adenine; C: cytosine; and G: guanine. *Only significant results (permutation p < 0.05) are presented.

Table 4. Associations of sets of rs1042713 (G46), rs1042714 (G79), and rs1042717 (A252) genotypes of the *ADRB2* gene with severe asthma control.

Allele set	Severe controlled/partially controlled asthma - n (%)	Severe uncontrolled asthma - n (%)	OR (95% CI)	p*
Ref.	107 (43.3%)	39 (33.7%)	3.2 (1.21-8.47)	0.02
G46/G79/A252	140 (56.7%)	77 (66.3%)		

*Only significant results (p < 0.05) are presented.

suggests that the observed clinical impact is likely due to structural changes in the receptor rather than to alterations in gene expression, indicating that the effect of these variants occurs through a mechanism other than transcriptional regulation.

No significant differences in acute BDR were found among patients with asthma. Importantly, all individuals diagnosed with severe asthma were using continuous LABAs. It is known that chronic exposure to β_2 agonists results in downregulation of β_2 receptors,[9,15] with reduced responsiveness and consequent tachyphylaxis to LABAs.[15] Our finding corroborates those of a meta-analysis[27] in which the authors analyzed five studies of the A46G polymorphism and concluded that it was not associated with BDR in asthma patients who chronically used ICS + LABAs.[27] Furthermore, it is known that age is an important modifying factor of genetic predisposition.

In our longitudinal analysis, we identified correlations between different genotypes and changes in BDR over time. Unlike what we found in our cross-sectional analysis, our longitudinal analysis showed a significant implication of the A46 allele in BDR variation with age. This result may indicate a possible reversal of the effect of that allele on asthma patients, given that the results indicate greater reversibility at ages closer to 18 years, different from what was found in older individuals, in whom reversibility levels were lowest among the different genotypes of rs1042713. This inversion of effects might explain why cross-sectional analyses failed to detect significant associations with that SNP.

One cohort study showed that individuals homozygous for A46 using LABAs regularly experienced a marked reduction in BDR in comparison with A46 homozygotes using SABAs sporadically and individuals homozygous for G46 using LABAs.[15] Furthermore, the A46 allele was associated with tachyphylaxis,[28] supporting the notion that A46 isoforms undergo increased downregulation and decreased cyclic adenosine 3',5'-monophosphate response after repeated bronchodilator use, suggesting a link between that allele, receptor efficiency, and alterations in the lysosomal degradation process of the β2-adrenergic receptor.[9]

We found that individuals with the G79 allele show a stable BDR over time, whereas those with the C79C79 genotype show a reduced response; this finding is consistent with those of an in vitro study showing that the G79G79 genotype confers greater resistance to downregulation following prolonged β_2 agonist stimulation in fibroblast cultures.[29] In a case-control study, the presence of the C79 allele was linked to tachyphylaxis, whereas the G79 allele acted as a protective factor, promoting a favorable BDR.[28]

We also analyzed the impact of different sets of rs1042713 and rs1042714 genotypes on the reversibility of asthma with age. The results corroborated other findings of ours, indicating that individuals with the A46A46-G79G79 genotype show a greater change in BDR with age in comparison with those with other genotypes (data not shown).

We then evaluated the influence of these genetic variants on severe asthma control under regular therapy. Our results indicate that the G79G79 and A252A252 genotypes correlate with poor control despite treatment with LABAs and ICS, whereas rs1042713 showed no association with a lack of asthma control. These findings are consistent with those of previous studies using the six-item Asthma Control Questionnaire [30] and studies involving pediatric populations,[31] although Sood et al.[31] reported an association of rs1042714 with exacerbation risk via the C allele, a discrepancy that may be partly explained by population stratification.

In order to assess the joint effect of rs1042713, rs1042714, and rs1042717, we analyzed all possible genotypic combinations. We found that the presence of the G46 and G79 alleles (in block with A252) had a greater impact on severe asthma control than did the individual genotypes. Collectively, these results

demonstrate that these variants influence respiratory disease monitoring, given that spirometry, which is used for asthma diagnosis, severity assessment, and treatment effectiveness assessment, is based on the individual response to short-acting β_2 agonists, a response that has been shown to be affected by these variants.[32,33]

It is important to consider that the lack of individuals with three or more polymorphic alleles in our population represents a limitation of our study, given that these data could better characterize all the possibilities of genotypic combinations among the studied variants. It was also not possible to recruit a larger number of individuals for gene expression analysis. The present study did not assess the effects of socioeconomic factors,[34] housing,[35] working conditions,[36] the airway microbiome,[37] epigenetic data,[38] or other factors that have been shown to modify asthma phenotypes.[39,40]

In summary, the rs1042713, rs1042714, and rs1042717 variants are associated with BDR changes with age in asthma patients, and asthma control is significantly linked to these SNPs; furthermore, continued LABA exposure may interfere with the acute response to β_2-adrenergic drugs, suggesting that chronic bronchodilator use may modify the genetic effect. These findings enhance our understanding of the mechanisms behind β_2 agonist-induced bronchodilation and its impact on spirometry, paving the way for personalized asthma therapy based on individual genetic profiles. Although challenges such as cost and accessibility persist, the continuous improvement of a genetic panel shows promising potential.

AUTHOR CONTRIBUTIONS

PASSR and RSC: data analysis and manuscript preparation. PASSR, AASCF, HMPT, LGSG, HSS, JLR, ALO, CVNS, GPPC, CAVF, and RSC: clinical data acquisition and management. PASSR, HMPT, HSS, JLR, ALO, CAVF, and RSC: laboratory analyses and interpretation. AASCF, CAVF, and RSC: study concept and supervision. PASSR, CAVF, and RSC: research, statistical analysis, and data interpretation. PASSR, CAVF, AASCF, GPPC, and RSC: writing—original draft. All authors read, reviewed, revised, and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(4):e20250123
https://dx.doi.org/10.36416/1806-3756/e20250123

ORIGINAL ARTICLE

Clinical, functional, and computed tomographic characterization of idiopathic inflammatory myopathy-associated interstitial lung disease: a retrospective cohort study

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Submitted: 7 April 2025.
Accepted: 14 May 2025.

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ABSTRACT

Objective: To evaluate clinical, functional, and CT characteristics, as well as disease progression, in patients with idiopathic inflammatory myopathy-associated interstitial lung disease (IIM-ILD) treated at a referral center in Brazil. **Methods:** This was a retrospective cohort study analyzing demographic characteristics, clinical variables, pulmonary function test results, HRCT findings, serological profiles, treatments, and outcomes. **Results:** Seventy-nine IIM-ILD patients were included in the present study. The mean follow-up period was 8.7 ± 4.7 years. The most common diagnosis was antisynthetase syndrome, observed in 51 (64.5%) of the 79 patients. The most common symptoms were dyspnea (in 94.9%), arthralgia (in 82.2%), and muscle weakness (in 75.9%). Mean baseline FVC was 2.19 ± 0.75 L, corresponding to 62.5% of the predicted value. During follow-up, FVC showed significant improvement. The most common CT patterns were indeterminate (in 44.4%) and nonspecific interstitial pneumonia (in 35.4%). Treatment most frequently included prednisone (in 98.7%), azathioprine (in 92.3%), or methotrexate (in 57.7%). Overall survival was 84.8%. Mortality was higher among patients who developed pulmonary hypertension and those who required intravenous methylprednisolone pulse therapy. **Conclusions:** Most patients with IIM-ILD progress well with immunosuppressive therapy. Pulmonary hypertension and the need for methylprednisolone pulse therapy appear to be associated with higher mortality.

Keywords: Lung diseases, interstitial; Myositis; Antisynthetase syndrome; Tomography; Spirometry.

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are systemic autoimmune disorders that primarily affect skeletal muscle and often involve interstitial lung disease (ILD), a major contributor to morbidity and mortality. Antisynthetase syndrome (ASyS) is a rare IIM subtype that is defined by anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies and features such as myositis, ILD, arthritis, Raynaud's phenomenon, and mechanic's hands.[1] Although ASyS was initially classified as an IIM subtype, it may present as isolated ILD, especially in patients with anti-PL-7 or anti-PL-12 antibodies.[2] Several IIM-related autoantibodies aid in diagnosis and stratification. Among anti-ARS antibodies, anti-Jo-1 is the most common and is strongly associated with ILD, which may precede myositis in up to 20% of cases.[3] ILD affects 23-65% of IIM patients and is the leading cause of mortality in this group.[1,4] The pathogenesis of IIM-associated ILD (IIM-ILD) is unclear but likely shares initial immune mechanisms with muscle involvement.[5] IIM-ILD has a highly variable course, from stable disease to rapidly progressive forms with marked lung function decline and reduced quality of life.[6] The Bohan and Peter classification, established in 1975, remains a cornerstone in the diagnosis of IIM. It proposes five key criteria: symmetric proximal muscle weakness; elevated serum muscle enzymes; myopathic changes on electromyography; characteristic muscle biopsy findings; and typical skin rash (heliotrope rash or Gottron's papules) for dermatomyositis. A diagnosis is categorized as definite, probable, or possible polymyositis or dermatomyositis depending on the number and combination of criteria met. Despite limitations related to specificity and overlap syndromes, the Bohan and Peter framework continues to be widely referenced in clinical and research settings.[1,4] Early diagnosis and treatment are critical for improved outcomes, but management remains a challenge because of the limited data available from clinical trials and the lack of specific ILD guidelines for IIM/ASyS.[7] The objective of the present study was

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Financial support: None.

to evaluate clinical, functional, and CT characteristics, as well as disease progression, in patients with IIM/ASyS treated at a referral center in Brazil.

METHODS

This was a retrospective observational cohort study including IIM/ASyS patients followed at an ILD referral center in Brazil between 1986 and 2020. Diagnosis was based on Bohan and Peter criteria (≥ 2 for probable myositis) or positive anti-ARS antibodies. Adults with ≥ 2 pulmonary function tests were included to allow longitudinal analysis. Data from 79 of 132 IIM patients were analyzed; the remaining patients had missing information and were therefore excluded from the analysis. Demographic, clinical, radiological, functional, and laboratory data were collected via a thorough review of electronic and paper medical records. Variables included age, sex, time to diagnosis, extramuscular features, serology (for anti-ARS antibodies), and treatments. Primary outcomes were functional decline, as assessed by pulmonary function tests, and overall survival. Patients were followed from the diagnosis of ILD until death or their last documented visit. Treatment-related adverse events were also recorded. Because of the noninterventional nature of our study, with no additional risk to patients and no intervention other than routine outpatient follow-up care, a waiver of written informed consent was requested on the basis of Brazilian National Health Council Resolution no. 466/2012. The study was approved by the local research ethics committee (Protocol no. 2.827.565).

Categorical variables were reported as frequencies, whereas continuous variables were reported as mean ± SD or median [IQR], depending on their distribution. Values of FVC and percent predicted FVC (FVC%) were described as mean ± SD and median [min-max]. Paired t-tests were used in order to compare baseline and final FVC values. Survival was analyzed by the Kaplan-Meier method. The level of significance was set at $p < 0.05$. All analyses were performed with the IBM SPSS Statistics software package for Windows, version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Of a total of 132 IIM patients, 79 (59.8%) met the inclusion criteria. Most (75.9%) were female, with a mean age of 45.2 ± 13.2 years (range, 18-82) and a mean follow-up of 8.7 ± 4.7 years. ASyS was the most common phenotype, in 51 (64.5%) of the 79 patients included in the study (Table 1).

The mean time from symptom onset to diagnosis was 17.7 ± 28.9 months; n = 67). Dyspnea was the most common symptom (in 94.9% of the 79 patients included in the study). In most cases, dyspnea was classified as severe (a modified Medical Research Council scale score of 3 in 24 patients [30.3%] and of 4 in 23 [29.3%]). Symptomatic improvement in dyspnea was seen in 59 of 70 patients (84.2%), most commonly after initiation of pharmacological treatment. Cough was present in 56 (70.8%) of the 79 patients, and 38 (48.2%) reported an improvement in their cough after treatment, whereas 10 (12.6%) had no improvement. The most common extrapulmonary manifestations were arthralgia (in 82.2%), muscle weakness (in 75.9%), and mechanic's hands (in 69.6%); symptoms such as fever, weight loss, and Raynaud's phenomenon were also common. When available, data were analyzed and, in general, immunosuppressive treatment led to an improvement in the symptoms of arthralgia in 44 patients (77.2%; n = 57); muscle weakness in 54 patients (100%; n = 54); and mechanic's hands in 46 patients (88.4%; n = 52).

Antinuclear antibody was positive in 65.8% (50/76), with titers ≥ 1/320 in 44%; the cytoplasmic pattern was the most common (50%; n = 76). Rheumatoid factor was positive in 20.8% (14/67), and anti-cyclic citrullinated peptide antibody was positive in 28.5% (4/14). Anti-SSA was found in 30.4% (21/69), and anti-SSB was found in 4.3% (3/69). Among anti-ARS antibodies, anti-Jo-1 was the most common (in 55.3%), followed by anti-PL-12 (in 9.1%) and anti-PL-7 (in 3.9%; Table 1). Corticosteroids were used in 98.7% (n = 78) of patients, typically combined with azathioprine or methotrexate. Treatment was individualized and adjusted on the basis of clinical response and adverse events. Intravenous methylprednisolone was given to 42.9%, and intravenous cyclophosphamide was given to 37.2%. Mycophenolate mofetil was used in 40.7%, and methotrexate was used in 57.7%. Azathioprine was associated with adverse events (including nausea, cytopenia, and liver enzymes) in 63.8%, and methotrexate was associated with adverse events in 26.6%, with one case of interstitial reaction (Table 1).

Patients underwent a mean of 5.9 spirometry tests (n = 79). As can be seen in Table 2, initial FVC was 2.19 ± 0.75 L, and FVC% was 62.6 ± 20.3%. DL_{CO} (in % of predicted) was available for 27 patients, averaging 50.6 ± 19.3%. FVC decreased by ≥ 10% in 25.3%, improved by ≥ 10% in 35.4%, and remained stable in 39.3% (Figure 1). Overall, FVC% improved

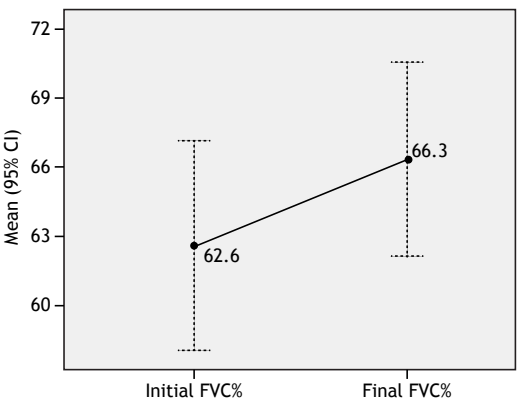

Figure 1. Comparison of percent predicted FVC (FVC%) values between the first and last assessment in 79 patients with idiopathic inflammatory myopathies.

Table 1. Clinical, demographic, laboratory, and functional variables in patients with idiopathic inflammatory myopathies.[a]

Variable	N = 79
Age at diagnosis	
Age, years	45.2 ± 13.2
Sex	
Female	60 (75.9)
Diagnosis	
Antisynthetase syndrome	51 (64.5)
Amyopathic dermatomyositis	12 (15.1)
Dermatomyositis	08 (10.2)
Polymyositis	06 (7.6)
Anti-MDA5 syndrome	01 (1.4)
Anti-PM/Scl syndrome	01 (1.4)
Positivity for IIM-related autoantibodies	
Anti-Jo-1	46 (58.2)
Anti-PL-12	02 (2.5)
Anti-PL-7	02 (2.5)
Anti-PL-12 and anti-Jo-1	01 (1.2)
Anti-PM/Scl	01 (1.2)
Anti-MDA5	01 (1.2)
Time from symptom onset to diagnosis (n = 67)	
Time elapsed, months	17.7 ± 28.9
Dyspnea at diagnosis (n = 79)	75 (94.9)
mMRC scale score	
0	2 (2.5)
1	13 (16.4)
2	17 (21.5)
3	24 (30.3)
4	23 (29.3)
Clinical manifestations (n = 79)	
Arthralgia	65 (82.2)
Proximal muscle weakness	60 (75.9)
Cough	56 (70.8)
Mechanic's hands	55 (69.6)
Myalgia	49 (62.0)
Raynaud's phenomenon	48 (60.7)
Weight loss	48 (60.7)
Gastroesophageal reflux disease	47 (59.4)
Fever	37 (46.8)
Dysphagia	33 (41.7)
Drugs	
Oral prednisone	77/78 (98.7)
Oral azathioprine	72/78 (92.3)
Oral methotrexate	45/78 (57.7)
Intravenous methylprednisolone pulse therapy	33/77 (42.9)
Oral cyclosporine	32/78 (41.0)
Oral mycophenolate mofetil	31/76 (40.8)
Intravenous cyclophosphamide pulse therapy	29/78 (37.2)
Rituximab	19/77 (24.7)
Primary cancer	
Lung	02 (16.7%)
Cervix	02 (16.7%)
Stomach	02 (16.7%)
Salivary gland	1 (8.3%)
Leukemia	1 (8.3%)
Lymphoma	1 (8.3%)
Breast	1 (8.3%)
Melanoma	1 (8.3%)
Prostate	1 (8.3%)

IIM: idiopathic inflammatory myopathy; and mMRC: modified Medical Research Council. [a]Data expressed as n (%) or mean ± SD.

Table 2. Comparison of FVC values (in L and % of predicted) between the first and last assessment in 79 patients with idiopathic inflammatory myopathies.[a]

Variable	Initial	Final
FVC, L	2.19 ± 0.75	2.26 ± 0.79
FVC, % predicted	62.6 ± 20.3	66.3 ± 18.3

[a]Data expressed as mean ± SD.

over time, with no association between outcomes and antibody subtype or treatment.

All 79 patients underwent HRCT. Initial scans showed minimal changes, with interstitial lung abnormalities in only one patient (1.3%). As can be seen in Table 3, the most common CT pattern was indeterminate (in 44.4%), followed by nonspecific interstitial pneumonia (in 35.4%) and nonspecific interstitial pneumonia + organizing pneumonia (in 13.9%). Mean pulmonary artery trunk diameter was 2.78 ± 0.37 cm, and the pulmonary artery trunk/aorta ratio was 0.91 ± 0.11 (i.e., not suggestive of pulmonary hypertension).

The most common comorbidities were hypertension (in 41.7%), dyslipidemia (in 39.2%), and diabetes (in 17.7%). Malignancy was reported in 15.1% (n = 12), with the lungs, cervix, and stomach being the most common primary sites (two cases each; Table 1). Echocardiograms were performed in 79.7% (n = 63); 23.8% showed pulmonary artery systolic pressure > 35 mmHg or tricuspid regurgitant jet velocity > 2.7 m/s, being suggestive of pulmonary hypertension. Right ventricular dysfunction was found in only 1 patient, who required high-flow oxygen at initial evaluation.

Mean overall survival was 25.9 years (95% CI, 20.6-31.1), with 84.8% surviving at the end of follow-up (a total of 12 deaths; Figure 2). Survival did not differ by malignancy status (p = 0.624). Patients with echocardiographic signs of pulmonary hypertension (a tricuspid regurgitant jet velocity > 2.7 m/s) had lower survival (68.4% vs. 90.9%; p = 0.012; Figure 3). No survival difference was found regarding the use of methotrexate, mycophenolate mofetil, cyclosporine, rituximab, or cyclophosphamide. Intravenous methylprednisolone pulse therapy was associated with worse survival (75.8% vs. 90.9%; p = 0.02), likely reflecting more severe disease. A trend toward lower survival was seen in those with a > 10% decline in FVC (p = 0.06).

DISCUSSION

The present retrospective study of IIM-ILD patients followed at a referral center in Brazil found that females in the 50- to 59-year age bracket predominated, their diagnosis being delayed; dyspnea was the most common symptom—improving with treatment in most cases—together with extrapulmonary features such as muscle weakness and arthralgia; despite immunosuppression, 25.3% of the patients in the present study had a decline in FVC, whereas others remained stable or improved; echocardiographic signs of pulmonary hypertension were associated

Table 3. CT patterns observed in patients with idiopathic inflammatory myopathies.[a]

CT pattern	N = 79
INDETERMINATE	35 (44.4%)
NSIP	28 (35.4%)
NSIP + OP	11 (13.9%)
UIP	2 (2.5%)
OP	2 (2.5%)
ILAs	1 (1.3%)

ILAs: interstitial lung abnormalities; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; and UIP: usual interstitial pneumonia. [a]Data expressed as n (%).

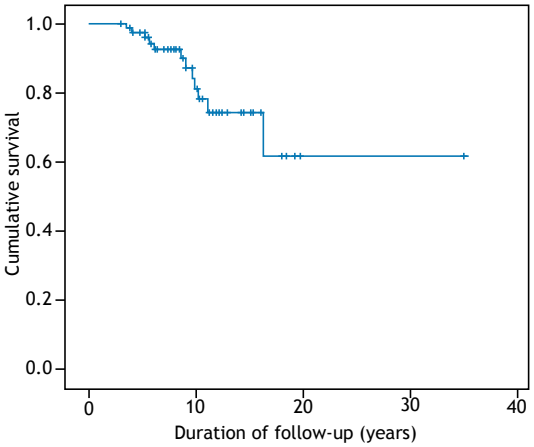

Figure 2. Cumulative survival in 79 patients with idiopathic inflammatory myopathies and interstitial lung disease.

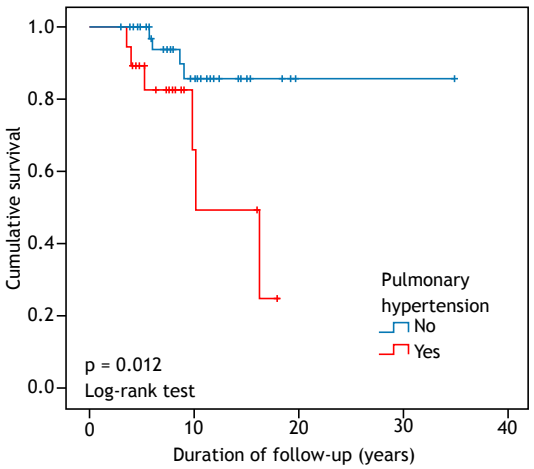

Figure 3. Survival curves according to the presence or absence of pulmonary hypertension on echocardiography.

with worse prognosis; and methylprednisolone pulse therapy was associated with reduced survival, likely reflecting more severe disease.

IIM has a global incidence of 5-10 per 100,000 adults and a prevalence of 14-17 per 100,000 adults.[7] Polymyositis and dermatomyositis show a bimodal incidence peak: in childhood (at the age of 7 years, approximately) and adulthood (in the 30- to 50-year age bracket).[8] IIM-ILD shows a clear female predominance, with 70-80% of cases occurring in women.[9] In our study, 75.9% of the patients were women, with a mean age at diagnosis of 45.2 years, reflecting the typical profile of middle-aged female predominance reported in the literature.[10] This pattern supports a role for hormonal, genetic, and immunological factors in female predisposition to IIM-ILD.[11]

Arthritis, mechanic's hands and positivity for anti-ARS antibody (anti-Jo-1) have been identified as risk factors for a higher incidence of ILD.[3,12] Our results highlight a high frequency of positivity for anti-Jo-1, which is a classic marker of ASyS and which is strongly associated with ILD. In our cohort, anti-Jo-1 was the most common of all anti-ARS antibodies, being found in 42 of 76 patients (55.3%), followed by anti-PL-12, in 7 of 77 (9.1%), and anti-PL-7, in 3 of 77 (3.9%). This finding is consistent with the literature, which shows that anti-Jo-1 is the most common autoantibody in this setting, followed by other, less common anti-ARS antibodies such as anti-PL-7 and anti-PL-12.[4,13] These autoantibodies influence lung phenotype, disease severity, and treatment response, underscoring the role of serology in prognosis and risk stratification.[4,6]

The negative impact of ILD on survival is well documented in the literature, and the progression of ILD is represented functionally by a decrease in lung capacity.[14-16] ILD is the main pulmonary manifestation of IIM/ASyS, contributing to morbidity and mortality, and may precede myositis in up to 20% of cases; early detection and treatment can be critical factors in patient prognosis.[17] In our study, patients had a mean 17-month delay to diagnosis, potentially impacting ILD progression because of delayed treatment, and approximately 25% of patients had evidence of functional decline, with a decrease of > 10% in FVC.

Initial IIM symptoms reflect the systemic inflammatory nature of IIM.[8] Clinical severity closely correlates with autoantibody profile, aiding in guiding IIM/ASyS management.[18] Non-muscular features such as fever, weight loss, skin involvement, gastrointestinal symptoms, ILD, arthritis, and Raynaud's phenomenon are more common in patients who are positive for anti-ARS antibodies,[3] and dyspnea, cough, hypoxemia, and reduced exercise capacity suggest pulmonary involvement.[19-21] Dyspnea (in 94.9%), cough (in 70.8%), arthralgia (in 82.2%), and Raynaud's phenomenon (60.7%) were common symptoms among our patients. These findings reinforce that respiratory symptoms, particularly dyspnea and cough, should prompt evaluation for pulmonary involvement in patients with rheumatologic diseases.

Our study demonstrated spirometric stability or improvement in most patients, being consistent with prior studies. Correia et al. reported FVC stability/improvement in 60% of patients.[22] Conticini et al. reported FVC stability/improvement in 100% of patients on mycophenolate mofetil/rituximab.[23] González-Pérez et al. found > 10% increase in FVC in 67% of patients, especially with early treatment

(< 6 months).[24] These findings support the potential for functional improvement in IIM-ILD with timely and appropriate therapy.

Pulmonary hypertension was suspected in 23.8% of patients. Right ventricular dysfunction was seen in only 1 patient, who required high-flow oxygen because of advanced parenchymal disease. Pulmonary hypertension was uncommon, and given that the ability of transthoracic echocardiography to estimate systolic pulmonary artery pressure accurately is often compromised in patients with fibrotic lung disease,[25] this number of suspects is probably inaccurate. Current evidence supports the concept that although pulmonary hypertension is rare in IIM, it is linked to a worse prognosis when present.[26] In the French pulmonary hypertension registry (n = 5,223), only 34 had IIM, with only three cases of IIM-associated pulmonary arterial hypertension.[27] Most of those patients had pulmonary hypertension caused by parenchymal lung disease or overlap autoimmune syndromes.[27] The findings of the present study are consistent with current evidence showing that pulmonary hypertension appears to be an indicator of advanced disease and carries a poor prognosis. We found no cases of pulmonary arterial hypertension in the present study.

Initial IIM treatment typically includes oral or intravenous corticosteroid pulse therapy, although strong evidence of benefit is lacking.[28] In our cohort, 98.7% received treatment with corticosteroids. Treatment generally involves corticosteroids, with or without immunosuppressants.[29-31] However, the evidence for immunosuppressant use in IIM is based mainly on small open-label prospective studies and retrospective observational studies, which focus primarily on muscle strength, skin lesions, and functionality scales. Although the evidence for treating ILD in IIM is limited, the available evidence suggests a benefit from combining immunosuppressive drugs with corticosteroids in patients with IIM-ILD.[32-37] Azathioprine, methotrexate, and mycophenolate mofetil were commonly used immunosuppressants, with no differences in outcomes. Intravenous methylprednisolone pulse therapy was reserved for severe cases, likely explaining their poorer prognosis.

Bronchiectasis, reticulation, and honeycombing on CT suggest fibrosis and may occur in some IIM/ASyS patients.[38,39] Antifibrotic agents such as nintedanib and pirfenidone are aimed at reducing the progression of the fibrotic component of ILD.[40] In our study, none of the patients received treatment with antifibrotic agents, given that this class of drugs is not available for use in the Brazilian public health care system.

The present study has limitations that are inherent to its retrospective design and its single-center nature, which may limit the generalization of the findings. The exclusion of 53 patients because of missing data was a significant loss and may have affected the results of the study, as well as having an impact on the frequency of missing data in the patients analyzed. Our study recruited patients with a diagnosis of IIM/ASyS and pulmonary involvement confirmed by chest CT. Because an extended antisynthetase antibody panel was not performed in all patients, it is possible that we missed some positive autoantibodies in our population. In patients in whom there was a high level of suspicion, the extended panel included antibodies such as anti-PL-7 and anti-PL-12. The fact that we had a convenience sample and that anti-Jo-1 is the most easily measured of all IIM-related autoantibodies makes the frequency of its positivity highly subject to selection bias. Additionally, the lack of pulmonary biopsy in most cases precludes a precise histopathological characterization of ILD, although HRCT scans were evaluated by experienced radiologists with expertise in ILD and, in clinical practice, lung biopsy is rarely performed in the context of autoimmune ILD. Plethysmography and DL_{CO} measurements were rarely performed in our patients, although they could have led to a better understanding of the physiological data during the follow-up period. Methylprednisolone pulse therapy was given to patients with greater initial severity; this probably explains the worse outcomes observed in those patients and represents a confounding bias. In addition, this association most likely does not represent a causal effect. However, the inclusion of a well-characterized cohort with a long follow-up period and serial functional data adds robustness to the analyses performed in the present study and enhances the clinical relevance of our results.

The data from the present study are consistent with the literature in terms of epidemiology, serological profile of autoantibodies, clinical manifestations, frequency of CT findings, and survival outcomes. The analysis of functional behavior showed stability of or increase in FVC in most of the study participants with the combined use of immunosuppressants and oral corticosteroids, with no evidence of superiority of any drug. Mortality was higher in patients who received methylprednisolone pulse therapy and in those who had signs of pulmonary hypertension.

AUTHOR CONTRIBUTIONS

JRBOF, ANC, and RAK designed the study. JRBOF collected the data. JRBOF, MW, and MVYS analyzed and interpreted the data and statistical results. RAK and ANC provided study material. JRBOF, ANC, and RAK interpreted the results and wrote the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(4):e20250039
https://dx.doi.org/10.36416/1806-3756/e20250039

Sequential versus massively parallel strategies for molecular characterization of non-small cell lung cancer samples obtained by endobronchial ultrasound-guided transbronchial needle aspiration

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Submitted: 16 April 2025.
Accepted: 28 April 2025.

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ABSTRACT

Objectives: The advent of massively parallel next-generation sequencing (MP-NGS) offers potential advantages over sequential molecular profiling (SMP) in the management of non-small cell lung cancer (NSCLC). This study compares the two methodologies using samples obtained through endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), focusing on actionable mutation detection, turnaround time (TAT), and clinical outcomes. **Methods:** A retrospective analysis was conducted on NSCLC patients who underwent EBUS-TBNA and molecular characterization between January 2020 and December 2023. SMP and MP-NGS were compared in terms of actionable mutation detection rates, TAT, and impact on overall survival (OS). **Results:** Among 106 patients, MP-NGS demonstrated a significantly higher detection rate of actionable mutations compared to SMP (40.9% vs. 22.2%, p=0.042). The median TAT was slightly shorter with SMP than with externally outsourced MP-NGS (17 days vs. 23 days, p=0.076). Patients diagnosed via MP-NGS were more frequently allocated to targeted therapies (44.26% vs. 22.2%, p=0.038), which may have positively influenced overall survival (672 days vs. 138 days, p=0.053). **Conclusion:** MP-NGS provided superior diagnostic and clinical advantages over SMP in NSCLC, supporting its adoption as a standard diagnostic approach to enhance personalized therapy and improve patient outcomes.

Keywords: Non-Small Cell Lung Cancer, Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration, Sequential Molecular Profiling, Massively Parallel Next-Generation Sequencing, Actionable Mutations, Personalized Therapy.

INTRODUCTION

Lung cancer (LC) currently ranks first in both incidence and mortality among all types of cancer worldwide,[1] and is closely associated with tobacco epidemics.[2] Non-small cell lung cancer (NSCLC), which accounts for over 85% of all LC cases,[3] remains a diagnostic challenge, as it often presents asymptomatically until advanced stages, when surgery is no longer a viable option.[4] At this point, understanding its subcellular characteristics becomes critical, as this can unveil therapeutic pathways with significantly improved efficacy and safety profiles.[5,6] Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) plays a key role in this context by enabling both the diagnosis and staging of NSCLC[7,8,9] in a minimally invasive manner. The main challenge, however, lies in obtaining adequate samples to meet the requirements of both pathologists and molecular geneticists—fulfilling the threefold goal outlined in clinical guidelines: diagnosis, staging, and molecular characterization in a single procedure.[10]

While EBUS-TBNA is a safe and effective tool for diagnosis and staging,[8,9] its reported yield for molecular profiling is variable, likely due to methodological heterogeneity.[11,12] In a previous study, we found that 89.5% of samples obtained via EBUS-TBNA were satisfactory for *EGFR* testing, but only 81.3% were suitable for *ALK* assessment.[13] In that investigation, the *EGFR* status was determined by real-time polymerase chain reaction (RT-PCR); if the results were negative, *ALK* gene rearrangements were subsequently assessed using fluorescence *in situ*

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ISSN 1806-3756

hybridization (FISH). Despite encouraging results, a key limitation of sequential testing strategies became apparent: depletion of EBUS-TBNA-collected material between tests, particularly affecting downstream markers. With the growing number of clinically relevant molecular markers, a decline in sample utility can be expected when using sequential methods.[14] Therefore, evaluating the potential of massively parallel (MP) molecular analysis—particularly through next-generation sequencing (NGS)—is increasingly relevant.[15] Emerging data support the feasibility of MP-NGS in EBUS-TBNA samples, with reported yields ranging from 86.1% to 98%, depending on the gene panel size.[16,17] However, some variability persists.

Building on these findings, the present study aimed to compare sequential molecular profiling (SMP) with massively parallel next-generation sequencing (MP-NGS) in NSCLC samples obtained via EBUS-TBNA, evaluating feasibility, turnaround time (TAT), treatment strategies, and overall survival (OS). The objective was to clarify the differences between these methods and determine which approach better enhances diagnostic accuracy, reduces TAT, and supports personalized treatment decisions.

METHODS

A cross-sectional cohort study was conducted including patients with stage IV NSCLC, as defined by the 8th edition of the TNM classification,[18] diagnosed between January 2020 and December 2023 at the Francisco Gentil Portuguese Institute of Oncology of Coimbra (IPOC-FG). The cohort was retrospectively established by identifying eligible patients who underwent simultaneous EBUS-TBNA and molecular characterization of NSCLC during this period. Patients were divided into two groups based on the molecular profiling strategy adopted. Between January 2020 and December 2021, SMP was performed in-house, whereas from January 2022 onward, molecular characterization was conducted using outsourced MP-NGS. The two strategies were compared in terms of sample adequacy, mutation detection rates, actionable mutations, and TAT. Additionally, treatment modalities and OS were evaluated.

All patients provided written informed consent, and the study was conducted as part of a PhD project approved by the Ethics Committee of the IPOC-FG (approval No. 23-2022).

EBUS procedures were performed using a BF-UC180F bronchoscope (Olympus, Tokyo, Japan) under general anesthesia, with airway secured via a laryngeal mask. TBNA was carried out using 21G needles (ViziShot 2, Olympus, Tokyo, Japan). In accordance with institutional protocol, at least three needle passages were performed per lesion. Suction use was guided by lymph node vascular patterns[19] and was withheld in cases of grade III/IV vascularity.

Collected specimens were fixed in a 4% aqueous formaldehyde solution, centrifuged at 400×g for 15 min for cell block preparation from the pellet, and subsequently embedded in paraffin for histopathological examination.

SMP followed a stepwise strategy that was performed after immunohistochemistry, including PD-L1 assessment, as previously described by our group.[13] Briefly, the workflow involved RT-PCR for *EGFR* mutation analysis using the Cobas® EGFR Mutation Test v2 (Roche Diagnostics, Mannheim, Germany), a CE-IVD assay designed to detect 42 mutations across exons 18, 19, 20, and 21, including exon 19 deletions, L858R, T790M, G719X, S768I, and exon 20 insertions. Formalin-fixed paraffin-embedded (FFPE) tumor sections (5 µm) were reviewed by a pathologist, and manual microdissection was conducted for samples containing fewer than 10% tumor cells. DNA was extracted using the Cobas® DNA Sample Preparation Kit (Roche Diagnostics, Mannheim, Germany), and amplification/detection was carried out on a Cobas® z480 analyzer (Roche Diagnostics, Mannheim, Germany), according to the manufacturer's instructions.

ALK and *ROS1* rearrangements were evaluated by FISH using 3-µm FFPE tissue sections. Samples with fewer than 100 viable tumor cells were excluded from the analysis. Following standard pretreatment, slides were incubated overnight with SPEC ALK (Z-2124, ZytoVision GmbH, Bremerhaven, Germany) or SPEC ROS1 (Z-2144, ZytoVision GmbH, Bremerhaven, Germany) dual-color break-apart probes. After post-hybridization washing, the slides were analyzed using a Leica DMI6000 B fluorescence microscope (Leica Microsystems GmbH, Wetzlar, Germany).

For MP-NGS, FFPE tumor blocks with ≥10% tumor content were selected. Genomic DNA/RNA was extracted using the MagMAX™ FFPE DNA/RNA Ultra Kit (Thermo Fisher Scientific, USA), and nucleic acids were quantified with a Qubit® 3.0 fluorometer. Sequencing was performed on the Genexus platform (Thermo Fisher Scientific, USA) using the Oncomine Precision Assay GX, which detects mutations, copy number variations, and fusion variants across 50 cancer-related genes. The results were interpreted using the Oncomine Reporter to identify associated therapies.

To ensure comparability, actionable mutations were defined as *EGFR* mutations, as well as *ALK* and *ROS1* rearrangements, which were consistently tested in both approaches and align with international guidelines for targeted therapies.[6]

Data analysis was performed using IBM SPSS Statistics software (v27.0; IBM Corp., USA). Continuous variables were presented as medians and ranges, while categorical variables were reported as frequencies (n) and percentages (%). The Shapiro-Wilk test was used to assess the normality of continuous variables. Since the variables did not follow a normal distribution, non-parametric methods were employed. Pearson's Chi-Square test was used to compare operational

characteristics between the SMP and MP-NGS groups. TAT, defined as the interval from sample collection to final diagnosis (in days), was analyzed using the Mann-Whitney U test. Kaplan-Meier curves were used to estimate median survival times, and survival distributions were compared using the log-rank test. Multivariate Cox regression analysis was applied to identify independent predictors of survival. Collinearity diagnostics, including the variance inflation factor (VIF), were conducted to confirm the absence of significant multicollinearity. All statistical tests were two-sided, with p-values < 0.05 considered statistically significant.

RESULTS

During the four-year study period, 106 patients with stage IV NSCLC underwent molecular testing on samples obtained via EBUS-TBNA. Of these, 45 were tested using SMP and 61 using MP-NGS.

Patients in both the SMP and MP-NGS groups were predominantly male (62.2% and 60.7%, respectively), with median ages of 67 and 69 years. Adenocarcinoma was the most common histological subtype (SMP: 91.1%; MP-NGS: 88.5%), and the majority of patients were classified as stage IVB (SMP: 68.9%; MP-NGS: 65.57%). No significant epidemiological or clinicopathological differences were observed between groups. Detailed results are presented in Table 1.

Regarding molecular profiling outcomes, adequate samples were obtained in the SMP group for *EGFR* analysis in 93.3% of cases, for *ALK* in 78.4%, and for *ROS1* in 75%, resulting in an overall success rate of 62.2%. Actionable mutations were identified in 22.2% (*EGFR*: 15.6%; *ALK*: 6.7%), while no *ROS1* rearrangements were detected.

In the MP-NGS group, all samples were adequate for molecular analysis. Mutations were detected in 88.5% of cases, with actionable mutations identified in 40.9% (*EGFR*: 32.8%; *ALK*: 8.2%). Similarly, no *ROS1* rearrangements were observed. However, additional relevant mutations were detected, including *HER2* (8.2%), *RET* (1.6%), and *BRAF* (1.6%). *KRAS* mutations were found in 21.3% of cases, with the G12C variant accounting for 8.2%. Details of the mutations are presented in Figure 1.

Table 1. Epidemiological and clinicopathological characteristics of the included patients.

Variable	SMP (n = 45)	MP-NGS (n = 61)	p-value
Sex, n (%)			
Male	28 (62.2)	37 (60.7)	
Female	17 (37.8)	24 (39.3)	0.870*
Age, median (min; max)	67 (38; 84)	69 (42; 86)	0.933#
Smoking history, n (%)			
Never smoker	11 (24.4)	21 (34.4)	
Former smoker	15 (33.3)	19 (31.1)	
Current smoker	19 (42.2)	21 (34.4)	0.519*
ECOG performance status			
0	17 (37.8)	34 (55.7)	
1	18 (40)	19 (31.1)	
2	7 (15.5)	7 (11.5)	
3	3 (6.7)	1 (1.6)	0.223*
Diagnostic procedure			
EBUS alone	28 (62.2)	40 (65.6)	
EBUS and EUS-b	17 (37.8)	21 (34.4)	0.722*
Type of sample			
Lymph node	32 (71.1)	39 (63.9)	
Tumor	11 (24.4)	20 (32.8)	
Left adrenal gland	2 (4.4)	2 (3.3)	0.635*
Histology, n (%)			
Adenocarcinoma	41 (91.1)	54 (88.5)	
Adenosquamous carcinoma† Combined	2 (4.4)	4 (6.6)	
adenocarcinoma and NE carcinoma†	1 (2.2)	3 (4.9)	
Squamous cell carcinoma	1 (2.2)	0	0.556*
Stage, n (%)			
IVA	14 (31.1)	21(34.4)	
IVB	31 (68.9)	40 (65.6)	0.720*

Legend: SMP, Sequential molecular profiling; MP-NGS, Massively parallel–Next generation sequencing; ECOG, Eastern Cooperative Oncology Group; EBUS, Endobronchial Ultrasound; EUS-b, Endoscopic Ultrasound (trans-esophageal) with the echobronchoscope; NE, neuroendocrine; *Pearson's Chi-square test; #Mann-Whitney U test. †In cases classified as adenosquamous carcinoma (n=6) and combined adenocarcinoma with neuroendocrine features (n=4), the diagnosis was suggested based on morphology and immunohistochemistry, performed on FFPE cell blocks obtained by EBUS-TBNA. In five of these cases (3 adenosquamous, 2 combined adenocarcinoma/NE carcinoma), the diagnosis was later confirmed using surgical biopsies from the primary tumor (n=2) or metastatic sites (pleura, n=1; subcutaneous tissue, n=2).

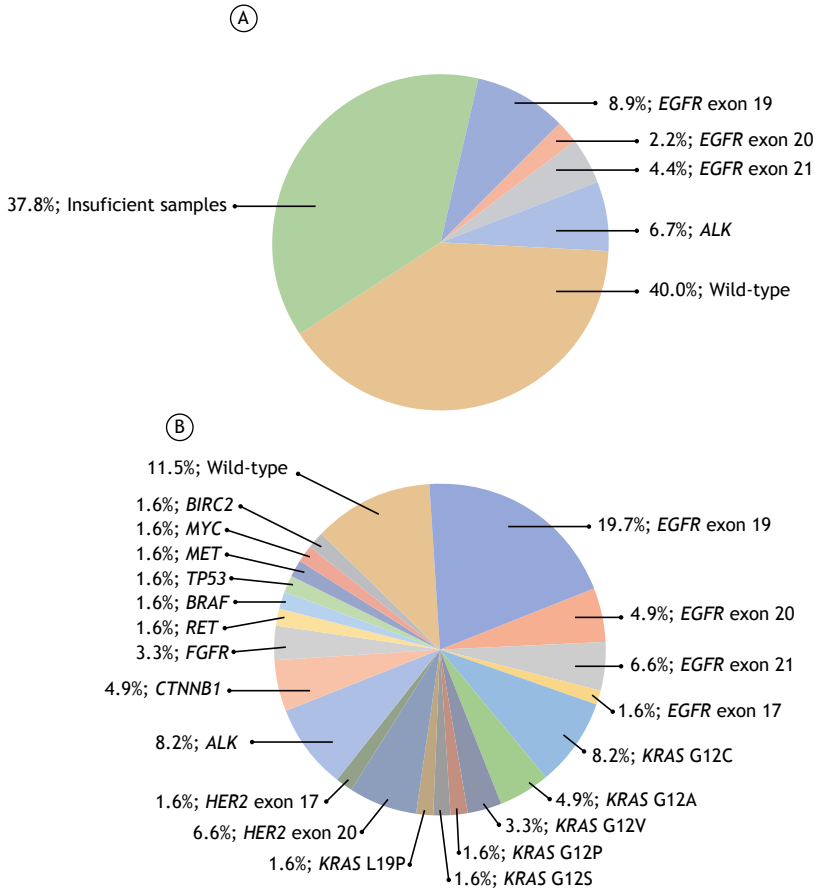

Figure 1. Pie charts illustrating the molecular profiling results in stage IV NSCLC samples using (A) sequential molecular profiling (SMP) and (B) massively parallel–next generation sequencing (MP-NGS). Legend: Aside from the data presented in the charts, 9 patients (14.7%) from the MP-NGS group exhibited complex molecular patterns: 1 harbored three mutations (*EGFR* exon 19, *CDKN2A*, and *PTEN*); 4 combined *EGFR* mutations with a second mutation (2 with *CTNNB1*; 1 with *TP53*; 1 with *PIK3CA*); 4 combined *KRAS* mutations with a second mutation (2 with *FGFR*; 1 with *TP53*; 1 with *BRAF*). These data highlight the superior discriminative power of MP-NGS, the absence of insufficient samples when using this method, and the reduced proportion of cases classified as wild-type.

MP-NGS demonstrated significantly higher success in obtaining sufficient samples for molecular analysis ($p=2 \times 10^{-5}$) and enabled the identification of a significantly greater number of actionable mutations compared to SMP (p=0.042). A comparative summary of the operational characteristics of both methods is shown in Table 2.

The median TAT for positive results was significantly shorter with SMP than with MP-NGS (11 vs. 24 days; p=0.002). Although the overall TAT for SMP was also shorter than that of MP-NGS (17 vs. 23 days), this difference was not statistically significant (p=0.076). Detailed results for these measures are presented in Table 2.

Considering therapeutic options, targeted therapy was administered to 44.3% of patients in the MP-NGS group, compared to 22.2% in the SMP group. Conversely, best supportive care was significantly less frequent in the MP-NGS group (13.1%) than in the SMP group (37.8%).

The differences between the SMP and MP-NGS methods were statistically significant regarding the increased use of targeted therapy (p=0.026) and the reduced utilization of best supportive care (p=0.019). Therapeutic allocation by profiling method (SMP vs. MP-NGS) and the relationship between detected actionable mutations and corresponding targeted therapies are detailed in Figure 2.

The Kaplan-Meier survival analysis revealed significant differences in OS based on the presence of actionable mutations (log-rank p=0.002) and first-line therapy (log-rank p<0.001). Patients with actionable mutations had a median OS of 1128 days, compared to 138 days for those without mutations. First-line targeted therapy was associated with the longest median survival (1128 days), whereas best supportive care was linked to the shortest survival (46 days). Overall, patients in the MP-NGS group exhibited a trend toward improved survival compared to those in the SMP group, with a median OS of 672 days versus 138 days, respectively (log-rank

Table 2. Comparison of molecular profiling techniques: SMP vs. MP-NGS.

Variable	SMP step 1 RT-PCR (*EGFR*)	SMP step 2 FISH (*ALK*)	SMP step 3 FISH (*ROS1*)	SMP Overall results	MP-NGS Overall results	p-value
Patients tested, n (%)	45 (100)	37 (82.2)	24 (53.3)	45 (100)	61 (100)	NA
Adequate samples, n (%)	42 (93.3)	29 (78.4)	18 (75)	28[a] (62.2)	61 (100)	2×10^{-5}*
Samples with actionable[b] mutations, n (%)	7 (15.6)	3 (6.7)	0	10 (22.2)	25 (41)	0.042*$
Time to positive result[c], median (max; min)	8 (3; 34)	15 (9; 33)	NA	11 (3; 34)	24 (3; 57)	0.002#
Time to final molecular result[c], median (max; min)	15 (9; 33)	17 (3; 58)	23 (3; 58)	17 (3; 58)	23 (3; 57)	0.076#

Legend: SMP, Sequential molecular profiling; RT-PCR, Real-time polymerase chain reaction; *EGRF*, Epidermal growth factor receptor; FISH, Fluorescence *in situ* hybridization; *ALK*, Anaplastic lymphoma kinase; *ROS1*, Proto-oncogene receptor tyrosine kinase; MP-NGS, Massively parallel–Next generation sequencing; NA, not applicable. [a]Overall SMP: combines the positive results of *EGFR* (deemed complete, and that did not require further profiling) and the 18 additional cases where both *ALK* and *ROS1* could be tested, reflecting the sample sufficiency for all tests required to complete the molecular characterization of individual samples. [b]Actionable Mutations: mutations assessed by all three diagnostic methods—*EGFR*, *ALK*, and *ROS1*—were considered actionable. [c]Time to Result: the time, measured in days, from the completion of histopathological evaluation, including PD-L1 staining, to the final result of the molecular study. *Pearson's Chi-square test; *$ Fisher's Exact test; # Mann-Whitney U test.

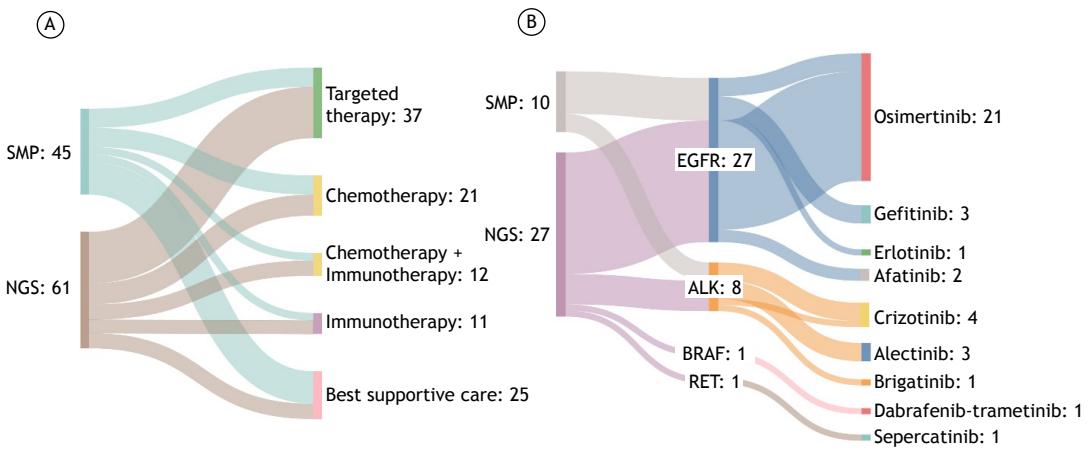

Figure 2. Relationship between molecular profiling strategies and first-line therapeutic choices with detailed targeted therapy selection. Legend: (A) Sankey diagram illustrating the distribution of first-line therapeutic strategies based on the molecular diagnostic method. The figure highlights a significant increase in the use of targeted therapies with MP-NGS compared to SMP (44.3% vs. 22.2%; p=0.026; Pearson's Chi-square test) and a notable reduction in the use of best supportive care strategies with MP-NGS compared to SMP (13.1% vs. 37.8%; p=0.019, Pearson's Chi-square test). (B) Sankey diagram detailing the targetable mutations identified by each method and their corresponding therapies. This panel underscores the superior discriminatory capacity of MP-NGS, which identified more actionable mutations and facilitated greater use of targeted therapies.

p=0.053). According to the Cox proportional hazards model, the presence of actionable mutations remained an independent predictor of improved survival (HR: 0.48; 95% CI: 0.25–0.96; p=0.027), whereas the molecular diagnostic method (MP-NGS vs. SMP; HR: 0.99; p=0.924) and first-line therapy (HR: 1.13 across therapy types; p=0.588) were not statistically significant. All VIF values were below 5, indicating acceptable multicollinearity. Full details are available in Supplementary Tables 1 and 2 and Supplementary Figure 1.

DISCUSSION

The present study offers a detailed comparative analysis of two molecular profiling strategies—SMP and MP-NGS—using minimally invasive EBUS-TBNA-derived samples from patients with stage IV NSCLC. Our findings highlight the superior performance of MP-NGS in identifying actionable mutations, detecting a wider array of genetic alterations, and facilitating access to personalized therapies, which may contribute to improved clinical outcomes, including a potential survival benefit.

The clinical and epidemiological characteristics of our cohort are consistent with those reported in similar patient populations,[20,21] supporting the representativeness of our findings. While the retrospective nature of this study limited control over participant inclusion and group allocation, the comparative analysis of clinical and epidemiological variables revealed no significant differences between the two groups (Table 1), further reinforcing the internal validity of our results.

When comparing the performance of both methodologies, our findings highlight the superiority of MP-NGS over SMP in optimizing the use of EBUS-TBNA-derived samples. MP-NGS achieved a significantly higher sample adequacy rate (100% vs. 62.2%; $p=2 \times 10^{-5}$; Table 2) and identified more actionable mutations in *EGFR* (32.8%) and *ALK* (8.2%) compared to SMP (15.5% and 6.7%, respectively) (Table 2; Figure 1). Moreover, MP-NGS detected a broader spectrum of mutations in 88.5% of patients, with 14.7% harboring more than one, underscoring its enhanced sensitivity and efficiency in identifying emerging actionable targets.[22,23,24]

In order to directly compare the two methods, this study restricted the definition of actionable mutations to *EGRF*, *ALK*, and *ROS1*, in accordance with the minimum requirements outlined in international guidelines.[6] However, the field of targeted therapy for NSCLC continues to evolve, with new actionable mutations being identified regularly.[25] For instance, *RET* rearrangements and *BRAF* mutations—assessed only through MP-NGS in our sample—are already targetable,[26,27,28] as observed in our cohort (Figure 2). Additionally, MP-NGS identified *KRAS* mutations, including the G12C variant in 8.2% of patients, which are increasingly actionable with inhibitors such as sotorasib, showing promising clinical outcomes.[29,30] Furthermore, the simultaneous mutations identified via MP-NGS in several patients (Figure 1) highlight the heterogeneity of NSCLC and open possibilities for sequentially targeting multiple pathways, reinforcing the value of this profiling method.[31]

One notable finding in our study was the progressive decline in sample adequacy throughout the sequential steps of the SMP method, with the lowest adequacy observed for *ROS1* testing (62.2%) (Table 2). This trend aligns with previous reports[11,13] and underscores the critical challenge of sample exhaustion, which is particularly relevant when dealing with limited material such as EBUS-TBNA-derived specimens. Sample depletion often results from the hierarchical testing order, in which IHC, PD-L1 assessment, and *EGFR* analysis are prioritized, frequently leaving insufficient material for FISH-based *ALK* and *ROS1* evaluations.[32] An indirect indicator of this limitation is the discrepancy in *ALK* mutation detection rates between MP-NGS (8.2%) and SMP (6.7%). Similar findings have been reported in other studies, particularly when *ALK* is assessed by IHC, which is prone to false negatives.[25,33] FISH, on the other hand, is generally highly sensitive and specific, provided that samples have adequate tumor content.[25] Although the lower detection rate observed in the SMP group may partly reflect random heterogeneity inherent to the study's retrospective design, we hypothesize that it also stems from the intrinsic limitations of EBUS-TBNA's sampling capacity, compounded by the issue of sample exhaustion discussed above. Notably, MP-NGS effectively overcame these challenges, achieving a sample adequacy rate of 100%.

The median TAT was 17 days for SMP and 23 days for MP-NGS. Although this difference was not statistically significant, the shorter TAT for SMP likely reflects cases in which positive *EGFR* results concluded testing early, eliminating the need for further molecular analyses (Table 2). Additionally, unlike SMP, which was performed in-house, MP-NGS was outsourced, leading to longer processing times due to shipping and external handling—an issue previously documented in the literature.[34] When compared with international guidelines and published benchmarks,[35] these differences become more pronounced. Most studies report median TATs for NGS of around 10 days,[36] which is substantially shorter than the values observed in our cohort. These discrepancies highlight real-world challenges in the timely diagnosis and treatment of NSCLC, especially in institutions where advanced molecular platforms are either not fully integrated or rely on external laboratories. Addressing these limitations will require coordinated strategies to optimize molecular workflows, including wider adoption of in-house MP-NGS platforms and reflex testing protocols to accelerate result turnaround times.[37] In parallel, the development of ultra-rapid multiplex PCR platforms represents a promising complementary approach.[38] These emerging technologies may enable broader genomic profiling—in some cases using existing RT-PCR infrastructure[38]—with the potential to deliver clinically actionable results within a markedly reduced TAT.

The treatment data revealed distinct patterns between the two profiling methods. The MP-NGS group received more targeted therapies (44.26% vs. 22.2%; p=0.038), suggesting that MP-NGS may facilitate more personalized treatment strategies by identifying a broader range of actionable mutations (Figure 2), which may have influenced survival outcomes. Indeed, the Kaplan-Meier analysis showed a trend toward improved survival in the MP-NGS group (median OS: 672 vs. 138 days; log-rank p=0.053). Although this difference did not remain significant in the multivariable Cox model (HR: 0.99; p=0.924), the presence of actionable mutations was independently associated with OS in both models. As previously documented,[39,40] this finding suggests that the survival advantage associated with MP-NGS is primarily mediated by factors such as the identification of actionable mutations and improved access to targeted therapies (Supplementary Tables 1 and 2; Supplementary Figure 1), ultimately reinforcing the clinical value of this method.

This study has some limitations inherent to its retrospective and uncontrolled design. Additionally, the relatively small sample size and the evolving treatment landscape of NSCLC—particularly the growing use of targeted therapies—may have influenced the outcomes.[39,40]

In spite of these constraints, the real-world nature of this study provides valuable insights into the clinical management of advanced NSCLC. Specifically, our findings highlight the superior performance of MP-NGS over SMP in detecting actionable mutations and facilitating access to personalized treatments. Although MP-NGS was associated with a longer TAT due to external processing requirements, its broader mutation coverage and greater sensitivity underscore its clinical utility in the evolving field of personalized NSCLC therapy. Moreover, the observed trend toward improved survival in the MP-NGS group further supports the potential advantages of this method over SMP, particularly in scenarios where only limited samples are available from minimally invasive procedures such as EBUS-TBNA.

Future research should focus on evaluating the cost-effectiveness and accessibility of MP-NGS, particularly in less specialized centers, to guide strategies for its broader and more effective implementation. Additionally, as molecular diagnostics continue to evolve, future studies should explore the comparative performance, feasibility, and clinical impact of emerging genomic technologies alongside MP-NGS.

AUTHOR CONTRIBUTIONS

Study conceptualization, formulation of the research questions, and writing of the manuscript: LVR, RC, LTB, and VS. Execution of EBUS-TBNA procedures and collection of data from clinical files: LVR. Supervision of the sequential molecular profiling protocol, assistance with data collection, and critical review of the database: MV. Development of the MP-NGS protocol, data review, and assurance of database completeness: AA, AFL, and VS. Critical review of the results, statistical analysis, and final content of the manuscript: LVR and LTB. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the research.

FINANCIAL SUPPORT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST

The authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.

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J Bras Pneumol. 2025;51(4):e20240409
https://dx.doi.org/10.36416/1806-3756/e20240409

Maximal dynamic inspiratory pressure: S-Index prediction values and diagnosis accuracy

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Submitted: 13 December 2024.
Accepted: 25 May 2025.

ABSTRACT

Objective: To establish reference values and prediction equations for the strength index (S-Index), in order to meet the growing demand for clinical application and diagnostic understanding of maximal dynamic inspiratory pressure. **Methods:** This was a prospective study of 120 healthy subjects between 18 and 80 years of age. The S-Index, measured from RV to TLC after at least eight reproducible maximal maneuvers with a < 10% difference, was obtained. The MIP was also measured, and differences between S-Index and MIP values were analyzed. A multiple linear regression model estimating the S-Index value was based on clinically significant independent variables. For model cross-validation and diagnostic accuracy, we used a separate sample of COVID-19 survivors to compare the observed and predicted S-Index values. **Results:** The S-Index strongly correlated with the FEV_1 and FVC. However, sex, age, weight, and height retained their significance in all final models, collectively explaining 62% of the variation in the observed values. The performance of the prediction equation was satisfactory in suggesting differences between COVID-19 survivors with an MIP < 80 cmH_2O and those with an MIP ≥ 80 cmH_2O. For both sexes, the S-Index exhibited the potential for ruling out, rather than confirming, inspiratory muscle weakness. If below the lower limit of normal, further evaluation is important, especially in men. **Conclusions:** To our knowledge, this is the first set of reference equations for the S-Index based on a healthy adult population across various age groups in Brazil. Its potential as an adjunct index in evaluating inspiratory muscle strength was also explored for the first time.

Keywords: Maximal respiratory pressures; Muscle strength; Respiratory muscles.

INTRODUCTION

In assessing the respiratory system, the inspiratory muscles serve as the primary pump for effective ventilation.[1] In clinical settings, the maximal static inspiratory pressure (MIP) has traditionally been measured to estimate inspiratory muscle strength, given that gold-standard invasive techniques are often impractical to implement outside of research environments.[2] However, advances in device technology have introduced alternative methods for assessing inspiratory muscle strength, such as the maximal dynamic pressure, the application of which has now expanded beyond healthy individuals[3-6] to include patients with heart failure,[7] stroke survivors,[8] and children with asthma.[9] For that test, the subject performs a forceful inspiration, from RV to TLC, through an open valve, while the dynamic inspiratory pressure is plotted continuously for each lung volume during inspiration, creating a timeline.[10] The peak value is known as the strength index (S-Index), which is believed to reveal valuable information about the inspiratory muscle capacity to generate volume and its impact on overall performance in patients and athletes.[11]

The S-Index is an adjunct index provided by an inspiratory training device (POWERbreathe KH2; HaB International, Southam, UK); it has been well established that the S-Index cannot replace the MIP.[10,11] Amid the growing popularity of the S-Index,[5] some studies have erroneously treated this dynamic parameter as equivalent to the MIP.[8,12,13] During the COVID-19 outbreak, more patients underwent evaluation of inspiratory muscle strength due to the acute and long-term effects of the disease, which extend beyond the respiratory system.[14] This underscores the importance of clearly distinguishing the S-Index from the MIP to ensure accurate assessment and interpretation.

The S-Index and the MIP are different technical measurements and do not represent the same physiological information or muscle recruitment, because the S-Index, unlike the MIP, is flow-dependent.[7] On that basis, the S-Index is believed to be a functional parameter, mimicking the normal, resistance-free contraction of inspiratory muscles.[5,11] Despite studies demonstrating a strong correlation between the S-Index and the MIP, given that both measure the same property, there is wide variability between their values.[10,11] This could be

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Financial support: None.

ISSN 1806-3756

related to static and dynamic contractions, reflecting the contrast between the generality of the MIP and the specificity of the S-Index for the same task.[15]

It has long been recognized that individual measurements hold limited significance unless they can be compared to a reference value.[16] A 2021 study proposed a set of equations predicting the S-Index on the basis of a sample of 92 healthy, fit elderly volunteers, mostly women, although those equations are not generalizable to other age groups.[6] Despite some progress, there have been, to our knowledge, no studies providing reference values for the S-Index in differing age groups.

The aim of this study was to generate S-Index prediction equations for males and females, as well as to understand their accuracy in determining inspiratory muscle weakness, using MIP as a reference. A separate sample of COVID-19 survivors was used in order to compare the observed S-Index values with those predicted by the equations.

METHODS

Study design and participants

This was a cross-sectional study in which we evaluated healthy subjects between 18 and 80 years of age. Participants were recruited through verbal, online, and printed invitations during the 2018-2020 period. The inclusion criteria were being a nonsmoker and having a BMI ≤ 30 kg/m^2. Individuals with abnormal spirometry results—values under the lower limit of normal (LLN)—were excluded, as were those who used illicit drugs, those who were athletes, those with self-reported respiratory or heart disease, neuromuscular or thoracic orthopedic conditions, history of thoracic or abdominal surgery, or pregnancy, and those who were incapable of understanding the proposed tests, as well as those with inspiratory muscle weakness, according to the predictive values published previously.[17] Subsequently, we analyzed data from COVID-19 survivors, collected at a later stage, to compare the observed S-Index values with the values predicted by the equations derived in the present study.

Although a formal sample size calculation was not performed, this convenience sample was intended to offer preliminary insights into the differences between the MIP and S-Index and to develop a prediction equation for the latter. The study was approved by the Research Ethics Committee of the Federal University of São Paulo (Reference no. 2.410.123/2017), and all participants gave written informed consent.

Procedures

Data related to demographics, current health status, past illnesses, history of surgery, and smoking habits were obtained. To evaluate physical activity levels, we used the modified Baecke Index questionnaire.[18] To measure body weight and height, we used a calibrated scale and a stadiometer with subjects in light clothing and standing barefoot.

None of the subjects were habituated to the test or had ever undergone this assessment. The protocol was explained, and all techniques were demonstrated before each of the tests, all of which were performed by the same evaluator. Volunteers were submitted to a warm-up and familiarization stage.[3] To qualify for the familiarization stage, the individuals were evaluated by a trained physiotherapist to determine whether they could follow the previously established guidelines. Volunteers who failed the familiarization stage were excluded from the study.

Pulmonary function

Pulmonary function was assessed with a spirometer (CareFusion Microloop; Becton, Dickinson and Company, Franklin Lakes, NJ, USA), in accordance with the recommendations of the American Thoracic Society.[19] We selected the FVC (in L) and FEV$_1$ (in L) obtained after at least three forceful expiration maneuvers, subsequently comparing those with the values predicted for the population of healthy adults in Brazil.[20]

Inspiratory muscle strength assessment

All tests involved the use of the same handheld POWERBreathe device, which was connected to a computer running software specific to the device (BREATHELINK; HaB International). A rubber-flanged mouthpiece originally designed for the device was used.

The mouth MIP (in cmH$_2$O) was obtained after at least five acceptable maximal maneuvers (forceful inspirations from RV to TLC), with three of them having a difference of less than 10%. An inspiratory effort of at least 1.5 s was maintained so that a plateau pressure sustained for 1 s could be recorded. Subjects were advised to rest for one minute between efforts.[21,22]

After the MIP value had been obtained, the dynamic inspiratory pressure was determined by identifying the greatest S-Index value (cmH$_2$O) in maneuvers performed from RV to TLC. At least eight maximal maneuvers that were reproducible (with a < 10% difference) were performed to avoid interpretive errors associated with learning effects.[3] During each S-Index test, flow (L/s) and volume (L) are also provided and recorded for analysis. The operational differences between static and dynamic assessments of inspiratory muscle strength, in terms of the mechanisms of the device valve, are shown in the supplementary online videos.

The highest value from an acceptable inspiratory curve was selected unless it was reached in the final maneuver.[21,22] Tests were repeated after 30 min of rest to confirm the results obtained. Each volunteer then completed a minimum of ten MIP maneuvers and sixteen S-Index maneuvers.

As illustrated in Figure S1, subjects remained seated with their back resting against the chair back, wearing

a nose clip, with their lips tightly closed around the mouthpiece to avoid air leaks. The maximal effort was encouraged in the form of standardized vigorous verbal stimulation, and closer attention was given to avoiding the use of facial muscles and compensatory movements of the head and trunk.[21,22]

Comparison among COVID-19 survivors

We used data from COVID-19 survivors to compare observed and predicted S-Index values, employing the equations derived in the present study. Using a different validation sample yields a measure of the future performance of the model that is more unbiased and less optimistic, because the magnitude of the residual is less likely to be impacted.[23] The same protocol for evaluating inspiratory muscle strength was used in the collection of these data, which was performed by the same investigators. Subjects were recruited from the post-COVID-19 outpatient clinic of São Paulo Hospital, operated by the Federal University of São Paulo in the city of São Paulo, Brazil. The protocol mentioned is part of a larger study assessing respiratory muscle strength, pulmonary function, exercise capacity, and dyspnea. It was approved by the Institutional Review Board of São Paulo Hospital (Reference no. 4.346.971, from 19 October 2020). Other papers analyzing this sample of COVID-19 survivors have been published.[24,25] From that large sample of COVID-19 survivors (N = 361), we analyzed the diagnostic accuracy of the S-Index as a surrogate parameter for identifying inspiratory muscle weakness. To determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), we used the LLN for the S-Index and a cutoff of 80 cmH_2O for the MIP. The age-specific LLN was calculated by using z-scores, with the following formula[26]:

LLN = age-specific mean − (1.645 × *standard error of the estimate*)

Statistical analysis

A visual curve analysis was performed before the final inclusion of the data, which were subsequently analyzed with the IBM SPSS Statistics software package, version 21.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism, version 9 (GraphPad Software, Inc., San Diego, CA, USA). Normality tests and visual data inspection revealed variable normality distribution. The data were stratified by sex and age group (20-39, 40-59, and 60-80 years), and the descriptive statistics were compared by using the Student's t-test. After correlating MIP values against the S-Index, the Bland-Altman method was employed to investigate the agreement between them, for all sample sizes and for males and females separately.[27]

To investigate the relationships among them using demographic, anthropometric, and clinical data, we performed correlation analyses. Using multiple linear regression with least-squares minimization, we included independent variables with significant clinical relevance and statistical significance in a model to estimate the S-Index value, with sex and age serving as adjustment factors. Variables were included in order of decreasing correlation coefficient, and the F probability was used to add or remove variables.

For all data, the coefficient of determination (R^2) is reported with the residual standard error, the equation of the regression line, and the partial coefficients with their standard errors. For all analyses, values of $p < 0.05$ were considered statistically significant.

RESULTS

A total of 153 subjects were recruited. Of those, 15 were considered ineligible. Of the 138 remaining individuals, 18 were excluded: 15 because they presented with altered pulmonary function; and 3 because they were unable to perform respiratory tests properly. Therefore, the final sample comprised 120 individuals (50 men and 70 women), stratified by age into three groups (Figure S2).

Because the S-Index is a flow-dependent measure derived from a non-occluded valve, it is important to determine the correlation between the S-Index and inspiratory flow; Figure 1 illustrates their perfect positive correlation ($r = 0.99$; $p < 0.0001$). The figure also shows a moderate positive correlation between the S-Index and the inspiratory VC generated during each maneuver from RV to TLC ($r = 0.68$; $p < 0.0001$), which was found to decrease with age (Figure S3).

Baseline characteristics and parameters are summarized in Table 1. For the total sample size, the mean MIP value showed no significant difference in comparison with the mean S-Index (102 ± 27 vs. 100 ± 31 cmH_2O, $p = 0.43$), a finding that was consistent across all age groups. Figure 2 shows a moderate correlation between the S-Index and the MIP ($r = 0.61$, $p < 0.0001$), and a Bland-Altman plot reveals a narrow, not significant bias (+1.9 cmH_2O, 95% CI: −2.8 to 6.6) with large variability (range, −49.4 to 53.2 cmH_2O).

The increasing variance toward higher values implies troubled agreement and an equivalence problem. In a sub-analysis considering sex, the bias between the S-Index and the MIP was significant for the women (6.4 cmH_2O, 95% CI: 2.4 to 10.3) but not for the men (−4.4 cmH_2O, 95% CI: −1.0 to 9.8).

Males had higher S-Index values than did their age-matched female counterparts. The S-Index decreased with advancing age, which presented a significant negative effect ($r = -0.42$, $p < 0.0001$ for men and $r = -0.44$, $p < 0.0001$ for women), as illustrated in Table 2 and Figure S4. As depicted in Figure S5, height had the strongest correlation with the S-Index ($r = 0.72$, $p < 0.0001$). In addition, FEV_1 and FVC showed significant positive correlations with the S-Index.

In the multiple linear regression analysis, age, height, and weight remained in all final models, collectively explaining 62% of the S-Index variation (Table 3).

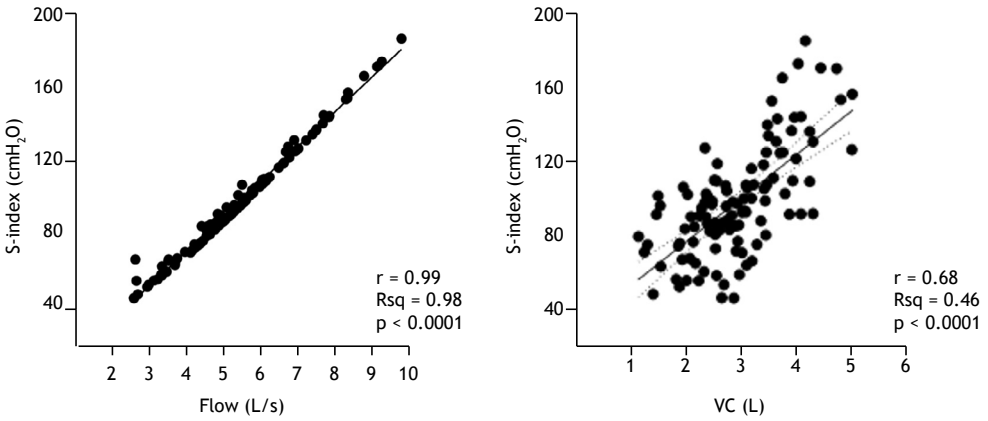

Figure 1. The graph on the left shows the positive correlation between the strength index (S-Index) and inspiratory flow—*S-Index* = (18.78 × *flow*) − 3.85, estimated R^2 (Rsq): 0.98, p < 0.0001. The graph on the right shows the correlation between the S-Index and the inspiratory VC for the sample as a whole—*VC* = (0.02 × *S-Index*) + 0.99 (standard error of the estimate: 0.63), Rsq: 0.46, p < 0.0001. Regression lines are presented with the corresponding 95% confidence intervals.

Table 1. Anthropometric, spirometry, and inspiratory muscle strength data, by sex and age group.[a]

Variable	Men (n = 50) Age group (years)			Women (n = 70) Age group (years)		
	20-39 (n = 27)	40-59 (n = 15)	60-80 (n = 8)	20-39 (n = 26)	40-59 (n = 23)	60-80 (n = 21)
Anthropometric data						
Age, years	28 ± 6	49 ± 7	70 ± 7	29 ± 5	52 ± 6	73 ± 16
Height, cm	179 ± 8	170 ± 5	170 ± 6	164 ± 5	160 ± 7	157 ± 6
Weight, kg	78 ± 13	71 ± 8	74 ± 9	60 ± 7	70 ± 6	60 ± 8
BMI, kg/cm^2	24 ± 3	24 ± 2	25 ± 3	22 ± 3	25 ± 3	24 ± 3
Physical activity score	6 ± 4	6 ± 3	7 ± 2	6 ± 1	6 ± 1	7 ± 2
Spirometry parameters						
FEV_1, L	3.6 ± 1.6	3.2 ± 1	3.1 ± 0.5	3.1 ± 0.3	2.6 ± 0.3	2.0 ± 0.4
FEV_1, % of predicted	81.8 ± 36.1	88.7 ± 27.4	99.2 ± 11.1	94.6 ± 9.7	100.1 ± 9.7	99.6 ± 13.5
FVC, L	4.2 ± 1.9	3.9 ± 1.1	3.9 ± 0.7	3.4 ± 0.4	3.0 ± 0.4	2.4 ± 0.5
FVC, % of predicted	80.0 ± 35.2	89.6 ± 26.3	96.2 ± 15.6	92.4 ± 10.3	96.3 ± 9.1	89.8 ± 11.5
FEV_1/FVC ratio	85.7 ± 38.6	76.8 ± 21.9	80.7 ± 9.9	90.5 ± 6.4	87.6 ± 6.6	86.9 ± 9.0
Inspiratory muscle strength						
MIP, cmH_2O	127 ± 30*	114 ± 17*	109 ± 25*	100 ± 16	89 ± 17	75 ± 15
S-Index, cmH_2O	137 ± 28*	113 ± 21*	105 ± 23*	92 ± 14	80 ± 17	73 ± 16
MIP – S-Index	−10 ± 33	1 ± 27	4 ± 27	8 ± 24	9 ± 21	2 ± 22
MIP – S-Index, p-value	0.12	0.86	0.62	0.10	0.51	0.7

S-Index: strength index. [a]All data, except statistical data, expressed as mean ± SD. *p < 0.01 vs. women (t-test).

Spirometric variables lost their independent predictive power after those basic anthropometric variables were considered in the multiple regression, with a lower adjusted R^2 and R^2 change when compared with the previous model of prediction. After the predicted residual sum of squares method was applied to the model equations, the original values of R^2 and standard error of the estimate were found to have only a mild effect.

Table S1 shows the mean difference between the expected and observed S-Index values among the 361 COVID-19 survivors evaluated. For men and women with an MIP ≥ 80 cmH_2O, the observed S-Index values closely matched the predicted values, indicating good agreement. Conversely, in patients with an MIP < 80 cmH_2O, the observed S-Index values were significantly lower than were the predicted values, statistically and clinically, demonstrating the ability of the equation to distinguish among different clinical profiles in terms of inspiratory muscle performance.

For each patient, we analyzed the LLN derived from the S-Index z-score and classified it by the presence of inspiratory muscle weakness, using the same MIP

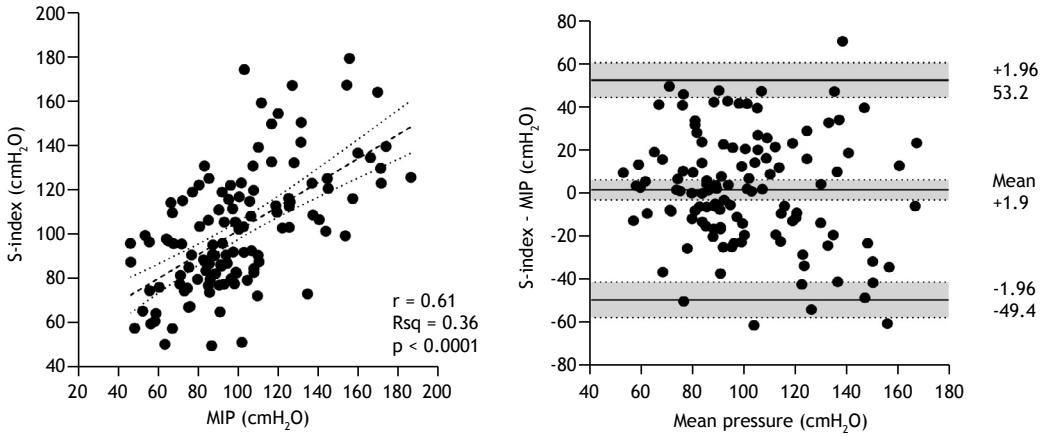

Figure 2. On the left, the strength index (S-Index) values compared with the MIP values in 120 healthy subjects. Linear regression analysis generated an equation—*S-Index* = (0.67 × *MIP*) + 30 (standard error of the estimate: 24), estimated R^2 (Rsq): 0.36. On the right, a Bland-Altman plot of differences between the S-Index and MIP. Shaded areas represent 95% confidence intervals.

Table 2. Correlation matrix.[a]

Variable	Variable						
	Age	Weight	Height	BMI	FEV_1	FVC	S-Index
Age	1						
Weight	−0.14	1					
Height	−0.46*	0.69*	1				
BMI	0.26*	0.67*	−0.06	1			
FEV_1	−0.44*	0.31*	0.46*	−0.03	1		
FVC	−0.35*	0.38*	0.50*	0.02	0.96*	1	
S-Index	−0.45*	0.59*	0.72*	0.07	0.41*	0.43*	1

S-Index: strength index. [a]Values represent the Pearson correlation coefficient between variables. *p < 0.01.

Table 3. Prediction equation for the strength index in healthy subjects.

	Constant	Age (years) CE ± SEE	Weight (kg) CE ± SEE	Height (cm) CE ± SEE	R^2	RSE
S-Index (cmH_2O)						
Male	− 32.3	−0.39 ± 0.11	0.47 ± 0.22	0.79 ± 0.32	0.62	19.27
Female	− 54.0	−0.39 ± 0.11	0.47 ± 0.22	0.79 ± 0.32	0.62	19.27

S-Index: strength index; CE: coefficient estimate; SEE: standard error of the estimate; R^2: coefficient of determination; and RSE: residual standard error.

cutoff (Table S2). The sensitivity of the S-Index for detecting true inspiratory muscle weakness was 76% for men and 18% for women. In terms of specificity, the S-Index correctly identified patients without muscle weakness at a rate of 75% for men and 95% for women. In our study sample, the PPV—the probability of having inspiratory muscle weakness when the result was positive—was 31% for men and 75% for women. The NPV was 95% for men and 64% for women.

DISCUSSION

To our knowledge, this is the first study to provide a set of S-Index prediction equations derived from healthy adults of different ages by using a standardized methodology according to established guidelines.[21,22] One study published S-Index reference equations specific to an elderly population (mean age of 72 ± 5 years), based on 92 subjects, mostly women, incorporating FEV_1, six-minute walk distance, age, and height in the prediction models.[6] Those equations incorporate tests that are more sophisticated as independent variables to predict the S-Index, transforming a straightforward task into a complex investigation. By using simple demographics and anthropometric data in the prediction model, we increase the likelihood of achieving large populations, generalizing the applicability from large hospitals and research centers to home-based care.[28,29]

Given the aspects mentioned above, our comparison is limited. When tested on a sample of 361 COVID-19 survivors to evaluate prediction accuracy, the S-Index showed a small mean difference of only 5 cmH_2O between the expected and observed values (95% of the predicted value) among women without inspiratory muscle weakness. Although statistically significant, that difference is unlikely to have a notable clinical impact when studying subjects without muscle weakness. For the 173 men without muscle weakness, a significant difference of 13 cmH_2O was observed between expected and observed values. However, when looking at the percentage of the predicted value, reaching a mean of 90% is generally considered a good indication of normality in clinical terms.

The distinction between normality and disease becomes more apparent when COVID-19 survivors with inspiratory muscle weakness, as suggested by lower MIP, are examined. In our sample of such individuals, the difference between the expected and observed values for men was significant at 36 cmH_2O, representing 70% of the predicted value, and at 14 cmH_2O for women, corresponding to 84% of the predicted value. Patients with muscle impairment can produce a lower mean inspiratory flow,[30] which could lead to a markedly lower S-Index than that observed in those without it.

One original finding of this study is the capability of the S-Index to serve as a potential surrogate parameter for detecting impaired inspiratory muscle strength. Although we have used MIP values as the reference standard, previous studies, acknowledging that MIP is not the gold standard for diagnosing specific diaphragm weaknesses,[31] have demonstrated its potential in various applications,[32] such as in the early detection of intensive care unit-acquired weakness, for which it has been shown to have 88% sensitivity and 76% specificity.[33]

Among the COVID-19 survivors evaluated in the present study, the S-Index exhibited greater potential for ruling out inspiratory muscle weakness than for confirming it, regardless of the sex of the patient. When the S-Index falls below the LLN, further evaluation is warranted, especially in men. When the result was positive, the test was more reliable in confirming weakness in women than in men, whereas, when the result was negative, it was better at excluding weakness in men than in women.

The choice of using a cutoff pressure of 80 cmH_2O to categorize groups is a limitation that may have affected our results. It is generally agreed that values above 80 cmH_2O are not indicative of significant weakness.[21] The use of the 80 cmH_2O cutoff risks misdiagnosis this condition in women, given that a recent study involving 610 healthy subjects in Europe suggested that the threshold is lower (62 cmH_2O) for women.[34] After all, a fixed cutoff fails to account for variations in sex and age, which significantly influence strength values.

To our knowledge, there have been no studies evaluating the S-Index in different age groups. That is why we partitioned our comparison. In a study of 43 healthy adults with a mean age of 37 ± 9 years,[3] the S-Index for the inspiratory muscle warm-up group was 123 cmH_2O, with no sex-based differences.[3] In contrast, we found a significant difference between males and females in the 20- to 39-year age group (137 ± 28 cmH_2O vs. 92 ± 14 cmH_2O). Similarly, a recent survey of 597 young athletes with a mean age of 21.4-22.0 years reported a mean S-Index of 145 ± 30 cmH_2O for the men, compared with 101 ± 28 cmH_2O for the women.[5] This highlights notable sex-based differences in S-Index values. For older age groups, our S-Index values showed significant variation in comparison with those published in a previous study.[6]

Among the variables evaluated in the present study, height exhibited the strongest predictive ability. In the literature (old and new), it has consistently been shown that there is a correlation between height and lung capacity, with taller individuals generally having larger lungs and therefore a greater ability to store air.[35-37] During a dynamic strength test, the open valve enables passage of inspiratory volume, detecting flow and resulting in the S-Index pressure. That relationship is further supported by the fact that the S-Index correlates significantly with the inspiratory vital capacity and with spirometric variables.

An additional aim of the present study was to analyze the differences between the MIP and S-Index values. Although both assess inspiratory muscle strength and demonstrate a moderate correlation, they show significant variability. That variability highlights their distinct mechanisms and emphasizes the idea that they should not be used interchangeably. This is confirmed by the large standard deviations compared to the small mean values, along with notable discrepancies in the agreement analysis, which align with previous studies reporting differences greater than 50 cmH_2O.[7,10,11] This significant variability introduces a level of unpredictability, making it unwise to use bias as a correction factor to interchange values between the two measures.

Our study has some strengths. To better understand the behavior of the S-Index as a clinical parameter, we made efforts to collect data from individuals of different ages and sexes, as well as with different BMIs, activity levels, and exercise habits, representing the general population. In contrast with previous studies, which used three, five, or ten maximal inspiratory maneuvers, we conducted a minimum of sixteen assessments to obtain reliable maximum S-Index values preceding inspiratory muscle warm-up, as previously described.[3]

Our study also has some notable limitations, including the fact that we employed a convenience sample and that the sample included relatively few elderly men. Despite our efforts to recruit participants through verbal, printed, and online invitations and to conduct

data collection at an elderly community center, this limitation remains a concern and should be carefully addressed when testing such individuals.

To our knowledge, this study provides the first S-Index prediction equations for healthy adults in Brazil. It incorporated age, weight, and height as explanatory variables, and, because of their simplicity, these equations have broad applicability in various clinical settings.

ACKNOWLEDGMENTS

We thank the elderly community center at Parque da Água Branca - São Paulo for the assistance in recruiting subjects.

AUTHOR CONTRIBUTIONS

VCS: study design; data acquisition, analysis, and interpretation; and writing—original draft. MFLSS: data acquisition and interpretation; and writing—review and editing. EVMF: data interpretation; and writing—review and editing. LEN: data interpretation; and writing—review and editing. PCAS: study conception and design; data interpretation; and writing—review and editing. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(4):e20250159
https://dx.doi.org/10.36416/1806-3756/e20250159

ORIGINAL ARTICLE

Patient-reported outcomes in tuberculosis: a qualitative exploration of psychosocial, economic, and treatment-related challenges

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Submitted: 15 May 2025.
Accepted: 9 June 2025.

Study carried out at the Tuberculosis Outpatient Clinic, Vila Nova de Gaia, Portugal.

ABSTRACT

Objective: Personal experiences, perceptions, and views of patients are crucial in understanding the subjective impacts of diseases. The complexity and duration of tuberculosis treatment impose significant physical, emotional, social, and economic burdens, highlighting the need for person-centered, integrated care strategies that address stigma, fatigue, and accessibility to support well-being. Patient-reported outcomes (PROs) are essential for capturing patient perspectives and improving health care strategies. In this study we explored the multifaceted experiences of patients with tuberculosis, seeking to understand their values and priorities during treatment. **Methods:** Semistructured interviews with adult tuberculosis patients were conducted at a referral center for tuberculosis diagnosis and management in northern Portugal. After verbatim transcription and anonymization, thematic analysis was performed. **Results:** Seventeen interviews were conducted. Most (58.8%) of the study participants were male, and most had pulmonary tuberculosis. Our thematic analysis identified five PROs: treatment experiences; health-related quality of life; functional status; symptoms and symptom burden; and health behaviors. People with tuberculosis acknowledged the impact of multiple factors on their overall health, particularly the psychological and physical burdens of tuberculosis and its treatment. Several areas for improvement and opportunities for enhanced support were identified, particularly in communication, emotional support, and management of treatment burden. **Conclusions:** Our findings highlight the need for tailored PRO measures (PROMs) addressing treatment burden, psychosocial distress, and functional limitations in tuberculosis care. Enhancing communication, psychological support, and multidisciplinary approaches in tuberculosis management could improve patient outcomes and overall well-being. Addressing tuberculosis-related stigma and providing targeted interventions may contribute to a more people-centered approach to care.

Keywords: Patient reported outcome measures; Qualitative research; Quality of life; Tuberculosis.

INTRODUCTION

Tuberculosis remains a significant global health challenge, affecting approximately 10.8 million individuals worldwide.[1] Despite concerted efforts to mitigate its impact, tuberculosis continues to impose a substantial physical, emotional, and social burden on those affected.[2,3] In Portugal, although tuberculosis incidence has gradually declined over recent decades, it remains a pressing public health concern, with an incidence rate of 13.7 cases per 100,000 population in 2023,[4] underscoring the need for effective and person-centered care strategies.

Although research on the impact of tuberculosis on quality of life is growing, the specific concerns most valued by people with tuberculosis remain underexplored. The prolonged and complex nature of tuberculosis treatment[5] often leads to significant emotional and physical fatigue, disrupting daily life.[3] Although video-observed therapy (VOT) has demonstrated higher patient acceptability than directly observed therapy (DOT),[6] the treatment burden persists, affecting adherence and overall well-being.

The social implications of tuberculosis are equally significant, with stigma and discrimination driven by the contagious nature of the disease frequently leading to social isolation and mental health challenges.[7] The economic burden is also considerable, affecting not only individuals but entire communities.[8] To ensure equitable access to tuberculosis care and support, a person-centered and integrated approach is essential.[1]

Patient-reported outcomes (PROs) are increasingly recognized as valuable in tuberculosis research.[9] Defined as "any report of the status of a patient's health

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Financial support: This study received financial support from the Foundation for Science and Technology (Grant nos. UIDB/04750/2020 [DOI: https://doi.org/10.54499/UIDB/04750/2020] and LA/P/0064/2020 [DOI: https://doi.org/10.54499/LA/P/0064/2020]). João P Ramos and Mariana Vieira are recipients of doctoral grants from the Foundation for Science and Technology and the *Fundo Social Europeu Mais* (FSE, European Social Fund Plus; Grant nos. 2024.00492.BD [JPR] and 2024.03947.BD [MV]).

condition that comes directly from the patient, without interpretation by a clinician or anyone else,"[10] PROs provide critical insights into patient experiences. Although PROs are widely studied in chronic diseases such as cancer, diabetes, and HIV,[11] their application in tuberculosis remains limited. A systematic review of cancer-related PROs identified symptom control, physical function, and emotional well-being as key patient concerns.[12] Similarly, tuberculosis research has highlighted the importance of PROs in tailoring treatment and improving patient care.[2] However, existing patient-reported outcome measures (PROMs) are not specifically designed for tuberculosis, limiting their applicability.

Despite progress in qualitative tuberculosis research,[13] most studies on PROs originate from low- or middle-income countries,[14] where findings are often assessed in isolation. Variability in experiences across different phases of treatment remains underexplored, particularly in high-income settings. The present study addressed this gap by examining the experiences of people living with tuberculosis in Portugal, assessing their values and priorities during treatment. By understanding their perspectives, the present study sought to enhance clinical care, develop person-centered strategies, and improve health outcomes for people with tuberculosis.

METHODS

This was a qualitative study conducted from May of 2023 to August of 2024 at the Tuberculosis Outpatient Clinic in Vila Nova de Gaia, Portugal. Located in the largest municipality in northern Portugal, the clinic serves as a referral center for confirmed and probable tuberculosis cases in the region. It also manages cases of multidrug-resistant and extensively drug-resistant tuberculosis in the northern and central regions of Portugal. Ethical approval was obtained from the Northern Regional Health Administration in Portugal (Protocol no. CE/2023/77).

People ≥ 18 years of age with a confirmed diagnosis of any type of tuberculosis and currently undergoing treatment were recruited through convenience sampling. Eligible participants were contacted by telephone and invited to participate in an interview, either on a prescheduled date or during their routine follow-up visits. All participants received an information sheet detailing the objectives of the study and how the research team intended to use the results. Before data collection, a male health care professional at the clinic provided a thorough explanation of the study, ensuring that participants had the opportunity to ask questions and clarify any concerns. Written informed consent was obtained from all participants. Those who were unable to provide consent or who declined to participate were excluded.

The semistructured interviews followed a script that was developed by the research team and that was informed by prior studies in the field (see Supplementary material). The script allowed flexibility to explore emerging themes and was pilot tested with five participants, with no subsequent changes thereafter. Participants were asked about various aspects of tuberculosis from their perspective, beginning with their diagnosis, symptoms, and knowledge of the disease. The interviews also explored treatment experiences, including psychosocial implications, challenges related to adherence, and the impact of tuberculosis and its treatment on mental well-being and social interactions. Additionally, participants were asked about their interactions with health care providers, particularly regarding communication patterns and their perceived significance in tuberculosis care.

All interviews were conducted in person at the clinic by the first author (PV), with no other members of the research team present in the room. The first author received training in qualitative research methods from experienced members of the research team (JPR, MV, and PB). Each session lasted approximately 50 minutes.

The interviews were audio-recorded (with participant informed consent) and transcribed verbatim into Portuguese. To ensure confidentiality, all transcripts underwent anonymization, with names, geographic data, and other identifiers being removed in order to prevent data triangulation and patient identification.

A combined inductive and deductive thematic analysis[15] was conducted by two independent researchers (PV and LLF) until meaning saturation was achieved; that is, when no new themes or subthemes (and their underlying relation) emerged.[16] Initially, each transcript was independently reviewed, and a preliminary set of themes and subthemes was developed for each transcript. These were subsequently cross-checked and validated by the research team. The analysis was aimed at identifying commonly reported PROs, including treatment experience, health-related quality of life (HRQoL), functional status, symptoms and symptom burden, and health behaviors, while also allowing room for themes outside this framework. The study was conducted in accordance with the Consolidated Criteria for Reporting Qualitative Research (see Supplementary material).[17]

RESULTS

A total of 17 participants were interviewed. Of those, 58.8% were male, with a mean age of 57.8 ± 14.2 years. Most of the study participants had pulmonary tuberculosis (n = 8), although other forms of tuberculosis, such as pleural, cutaneous, intestinal, bone, and lymph node tuberculosis, were also present. Eight participants were professionally active, and all resided in the Vila Nova de Gaia municipality. Findings were categorized into five main PROs: treatment experience; HRQoL; functional status; symptoms and symptom burden; and health behaviors. Table 1 shows a detailed description of the sociodemographic characteristics of the study participants.

Table 1. Sociodemographic characteristics of the study participants.

Patient	Sex	Age, years	Occupation	Type of tuberculosis
1	Male	70	Retired	Pulmonary
2	Female	67	Retired	Lymph node
3	Male	60	Security guard	Pulmonary
4	Male	78	Retired	Pleural
5	Male	57	Salesman	Pulmonary
6	Female	63	Fishmonger	Cutaneous
7	Male	58	Retired	Pulmonary
8	Male	49	Building contractor	Pleural
9	Male	74	Retired	Lymph node
10	Male	58	Private chauffeur	Gastrointestinal
11	Female	26	Student	Pulmonary
12	Male	45	Street food vendor	Pulmonary
13	Female	76	Retired	Pulmonary, lymph node
14	Female	54	Administrative assistant	Lymph node
15	Female	36	Kitchen assistant	Bone
16	Female	66	Retired	Pulmonary
17	Male	45	Forest ranger	Pulmonary

Participants generally expressed satisfaction with the health care that they received, particularly valuing clear communication from health care professionals (Table 2). Many of the respondents appreciated the support and detailed information provided (see quote number [Q] 1 and Q2; Table 2); however, a subset of patients reported feelings of fear or hesitancy when engaging with health care providers (Q3). The recurring need for more targeted and tuberculosis-specific information was a prominent theme. Diagnostic delays, often attributed to limited awareness among health care professionals, negatively impacted treatment experiences (Q4, Q5, and Q6). Additionally, the burden associated with treatment modalities, particularly in the context of DOT/VOT, was reported to affect adherence and quality of life (Q7 and Q8).

Many of the study participants described significant strain on interpersonal relationships, primarily due to fears surrounding the transmission of tuberculosis. Concerns about infecting loved ones, especially vulnerable individuals such as children and the elderly, led to feelings of isolation, loneliness, and even social exclusion (Q9 and Q10). These experiences reinforced internalized stigma and, in several cases, resulted in self-imposed isolation (Q11 and Q12). Although a few of the study participants managed to resume some of the routines of their daily life, most remained fearful of transmitting the disease, which in turn heightened emotional distress (Q13). The reduction in social interactions was compounded by financial instability, with some participants reporting job loss or diminished economic independence (Q14 and Q15). Furthermore, experiences of discrimination and stigma significantly contributed to psychological distress, thereby reducing HRQoL (Q16).

Tuberculosis symptoms and the treatment process had a tangible impact on participant functional status. Many reported difficulties in performing daily tasks, with a notable perception of lost autonomy (Q17). Concerns regarding the potential impact of tuberculosis on existing comorbid conditions were also voiced (Q18 and Q19). Despite the considerable challenges presented by the disease and its treatment, most of the study participants acknowledged the critical importance of treatment adherence in eventually improving their functional status and alleviating symptoms.

Participants widely acknowledged the severity of tuberculosis and the considerable difficulty associated with its treatment. Uncertainty regarding treatment outcomes, coupled with the fear of medication side effects, further compounded these challenges (Q20 and Q21). The historical association of tuberculosis with high morbidity added to the emotional distress experienced (Q22 and Q23). Many of the study participants expressed concern that adverse side effects could necessitate treatment discontinuation (Q24 and Q25), thereby prolonging the overall recovery process and exacerbating physical and emotional burdens.

Participants changed their health habits because of the disease, exhibiting knowledge regarding transmission routes and the need for personal protective equipment to prevent disease spread (including the use of masks and social distancing as protective measures) and emphasizing adaptation to the new context of social interactions. Although these measures were deemed necessary, they often disrupted the spontaneity of social interactions (Q26), contributing to feelings of isolation (Q27). A proactive approach to seeking tuberculosis-related information was common among participants (Q28 and Q29), and many believed that greater knowledge could help alleviate some of the distress associated with the disease. Notably, although participants expressed a desire for guidance on managing lifestyle changes, particularly regarding nutrition, there was a prevailing sentiment that support from health care professionals in this area was insufficient.

Table 2. Themes and subthemes with illustrative quotes.

Theme	Subtheme	Category	Quote number	Quote
Treatment experience	Health care communication	Patient-doctor relationship	1	I think I'm with people who are from the field. I believe in them. I'm going to do what they're asking and telling me to do. Because ultimately I'm a layman. And what they're doing I always believe it's the best for me. (Patient 3)
			2	They've explained everything to me very well and I'm always asking questions when I have doubts. (Patient 14)
			3	Neither outside nor here. I don't talk to anyone. I deal with it as I can/the best way I can. (Patient 9)
		Limited tuberculosis awareness among health care professionals	4	I was sadder when I sought help from the family doctors. [. . .] When people have a history, they [family doctors] go on the computer and see this and that. I went to the family doctor, and I told him that I'd already had a problem eight years ago. What was I told to do? An expectorant, plus this, plus that. An X-ray and an analysis of the expectoration. In fact, I asked for that myself. And then they gave me the tests to do, and I asked if I could come directly to the tuberculosis outpatient clinic. (Patient 3)
			5	After having clues, let's say, signs. I think they devalued the signs. And I'm sad because that's two months I've lost. And it's been two months that aggravated my health. (Patient 3)
			6	It's not a disease that's . . . Although it's being talked about more now. Even in hospitals, staff are tested for tuberculosis and everything. But I think it's still a bit of a taboo because it's more closely associated with the lungs. (Patient 14)
	Real-world barriers	Logistical constraints	7	Coming here every day from one end of Gaia to the other, right? In terms of transport, I don't have my own car. That's why it takes me two, two and a half hours just to get from here to work and from work to here. And that's the most painful part. (Patient 14)
			8	It's tiring. I mean, it's not tiring, but sometimes my phone runs out of space. As I was saying the day before yesterday, I didn't do it. I took the medication, but I didn't get around to making the video. (Patient 15)
Health-related quality of life	Psychosocial impact	Emotional distress	9	I thought everyone in my house was already infected. And I said, oh my God. I said, oh my God, I just got sick, and now I've spread the disease to everyone. And I felt sad, I cried and everything. [. . .] I isolated myself from people. I thought that, with this illness, I couldn't even be around other people. I could only watch them passing through. I'd rather die alone. I don't know where I got it from, where it came from. But I don't want to pass it on to someone else. Because it's too much suffering. (Patient 15)
			10	The only reason I don't go to my sister-in-law's house is because of my niece. My niece is ill. I've stopped going. I don't want my little girl to die. (Patient 12)
		Social isolation	11	I wouldn't be able to socialize with the people I live with at home either. My daughter, my son-in-law, my granddaughter, my wife. And I couldn't live with them. I had to live in isolation. (Patient 9)
			12	Three months without contact with people. I couldn't even be with my children or grandchildren. (Patient 13)
			13	It's a boring phase. Avoiding people. Having to wear a mask. I'm also afraid of passing it on to someone else. And then it never ends. (Patient 5)
	Socioeconomic impact	Financial burden	14	When I was told I had tuberculosis, my work contract had ended, I had no money for the next month, and suddenly I had six months of treatment ahead of me. It was the worst part, but we'll have to manage with patience. (Patient 11)
		Employment challenges	15	They started to get scared. My colleague, the boss of the van, started to get scared. Go away. Go away, you can't be here. Go away, you can't be here. You can't be here. (Patient 12)
			16	For example, my boss immediately made the comment, "Oh, that's increasing now because people are living in the neighborhood," and she immediately asked, "Do Brazilians live in your building?" and I don't know, what if they do? But they don't live in the neighborhood. Because I don't exactly live in a social housing block. (Patient 5)

Continue...▶

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Table 2. Themes and subthemes with illustrative quotes. (Continued...)

Theme	Subtheme	Category	Quote number	Quote
Functional status	Perceived limitations	Restrictions on daily life and autonomy	17	There's nothing we can do. We're trapped. And it's like being in prison. A prisoner has more freedom. (Patient 3)
	Treatment fatigue	Medication overload	18	I didn't want to, because of my kidney. I started to think, if they told me to avoid antibiotics, avoid anti-inflammatories, antibiotics, and drink lots of water, and I don't know what else, and I say, it's going to finish me off. (Patient 16)
			19	It must be, it must be. Then they were saying, "Oh, so many pills, are you going to take everything?" If you must, you must. (Patient 6)
Symptoms and symptom burden	Psycho-emotional burden	Fear and uncertainty	20	The worry is that I don't know, I'm going to die. I'm already going to die. I had tuberculosis, and tuberculosis is a disease, isn't it? It's not very easy to cure, is it? (Patient 1)
			21	I don't know if I'm getting better or worse, I don't know. I take the pills, I go home. (Patient 2)
		Coping with emotional and mental struggles	22	I mean, sometimes I feel really down, don't I? I feel sad to be here with this, and I don't know how I got it, you know? (Patient 8)
			23	With the treatment I sometimes thought I'd rather die of the disease than be cured. But then it fell into place, fortunately. (Patient 4)
	Adverse events		24	I'd take them now, and after an hour or an hour and a half I'd go and eat. After a while I'd be vomiting, and I'd throw it all up. (Patient 9)
			25	Then I had to stop because it was damaging my liver. (Patient 13)
Health behaviors	Behavioral adjustments	Precautionary	26	Also, my wife, who didn't understand, you know? I didn't have any intimacy with her for almost a month, because I was afraid that I might transmit something. And I'd say to her, we're not going to be intimate for a while. Until I know the answers, we won't do anything. (Patient 10)
			27	It was a normal thing. At the time I thought I wouldn't get too close to people. And always put on a mask if I'm talking to someone. If it's in the street, for example, I try to steer clear of where there are a lot of people. (Patient 11)
	Health-related decision-making	Health information seeking	28	Yes, I started researching the medication, I started researching certain things, and fortunately the one I got isn't transmissible. (Patient 4)
			29	And then sometimes you don't know exactly what's bad for you and what's not. Or what's good for it. Regarding the liver, even on the internet, there isn't anything . . . There are contradictory things; for example, one website says that oranges cleanse the liver. There's another that says it's the worst. The public health lady said that oranges and citrus fruits are not good for you. There's a problem with food. Information about food. (Patient 5)

DISCUSSION

Our qualitative analysis revealed key insights into psychosocial and health care experiences of people undergoing tuberculosis treatment, highlighting their understanding of tuberculosis and its social and economic impacts, as well as the psychological burden of tuberculosis treatment.

A major PRO identified in the present study centered on treatment experiences, highlighting essential factors for people with tuberculosis, with the need for clear communication playing a crucial role. Although many of the study participants valued the information and support provided by health care professionals—which reassured them throughout the treatment process[18]—others expressed hesitancy or fear in communicating openly, leading to gaps in understanding and emotional distress. This underscores the need for person-centered communication strategies that address medical and psychological needs. Tuberculosis awareness also significantly influenced the overall treatment experience. The literature reiterates that although tuberculosis knowledge is adequate in several health care professional groups, continued efforts are needed to keep this knowledge updated.[19] Our findings suggest that a lack of awareness among health care professionals contributes to diagnostic delay,[20] emphasizing the importance of continued training and education for improved PROs.

Tuberculosis had a profound impact on HRQoL, a dimension known to be deeply affected in people with tuberculosis.[21] Many of the study participants reported anxiety, fear, and emotional distress, which persisted even after starting adequate treatment. The most significant impact stemmed from limitations in social relationships, particularly with close family members. Many of the study participants isolated themselves from loved ones to prevent transmission, particularly to vulnerable individuals such as children and the elderly, with the sense of isolation—both physical (as a result of mandatory isolation) and social (from stigma and reduced social contact)—worsening emotional distress.

Tuberculosis treatment also imposed a loss of freedom, restricting their ability to work, travel, or engage in daily activities, further affecting HRQoL. Combined with the physical and psychological burden, these factors had a profound impact on the overall well-being of the study participants, highlighting the need for targeted interventions to enhance patient care.[22]

Financial instability was a major concern, given that prolonged treatment led to loss of employment or income. This financial stress added another layer of difficulty to an already challenging situation, with improved social support and the involvement of family and community members in tuberculosis treatment emerging as critical in addressing this issue.[18]

Stigma and discrimination emerged as another significant factor influencing social interactions and HRQoL, with participants experiencing discrimination from peers, coworkers, and even family members due to misconceptions about tuberculosis transmission. These findings are consistent with those of previous studies highlighting the persistent stigma associated with tuberculosis and its detrimental effects on social well-being.[7]

Functional status was widely recognized as an important outcome, with tuberculosis and its treatment significantly affecting physical abilities. Although the functional impact of tuberculosis sequelae is well documented,[23] the impact of active tuberculosis on daily living remains underrepresented in the literature. Participants highlighted the burden of symptoms on daily activities, contributing to psychological and physical distress. Despite these challenges, most remained adherent to treatment, recognizing its necessity. Providing adequate support and education on the impact of tuberculosis on daily function could enhance PROs.

The perception of tuberculosis as a difficult-to-treat disease with a demanding treatment regimen emerged as a key determinant of outcomes, with participants expressing frustration over its complexity and duration. Concerns over medication side effects and uncertainty regarding treatment effectiveness contributed to emotional fatigue, further exacerbating mental health challenges. Although DOT and VOT remain essential for tuberculosis management,[24,25] they impose social, financial, and occupational burdens, for which more patient-friendly approaches should be explored.[26]

Although participants recognized the importance of adherence, fear of potential side effects had a profound impact on their well-being. A structured support network focusing on early identification and management of side effects could ease concerns. Multidisciplinary care, involving physicians, nurses, and social workers,[27] and, as suggested by our data, the need for nutritional support were highlighted as essential for comprehensive tuberculosis management.

Changes in health behaviors were also noted, with participants demonstrating increased awareness and understanding of tuberculosis transmission and preventive measures, including mask wearing and social distancing. Although these behaviors are necessary for infection control, they exacerbated feelings of isolation and psychological distress. Knowledge gaps regarding tuberculosis persisted,[28] with some of the study participants attempting to self-educate, emphasizing the need for structured education and accessible information to improve support and understanding during tuberculosis treatment.

Our study provides valuable insights into the experiences of people with tuberculosis, capturing multiple dimensions of their health outcomes. Given that most of the studies on similar topics have been conducted in low- or middle-income countries, our findings contribute perspectives from different health care settings, allowing broader comparisons. The wide

range of themes explored enabled a comprehensive assessment of participant experiences and needs. However, some limitations must be acknowledged. We were unable to conduct member checking to validate participant responses; this could have strengthened the reliability of our findings. Additionally, because we used convenience sampling, selection bias may have excluded individuals with lower engagement in their treatment, limiting the diversity of perspectives. Recall bias and the self-reported nature of the data may also have influenced responses, as participants may have omitted or emphasized certain experiences.

The findings of the present study have several important implications for health care providers and policymakers. Each of the identified domains had a significant impact on the overall well-being of patients and could serve as key areas for a more personalized treatment approach targeting enhanced patient outcomes and satisfaction. Improving tuberculosis-related information is crucial not only for people with tuberculosis, given that increased knowledge may ease disease burden, but also for health care professionals, given that enhanced training could increase awareness and lead to improved care. Strengthening patient-provider communication and multidisciplinary support—including nutritional support and psychological support to help patients cope with the emotional distress—could further enhance integrated care. Social determinants must also be considered. Financial assistance and employment protection could help alleviate economic strain, while public health campaigns aimed at reducing tuberculosis-related stigma could foster a more supportive environment. Further research on PROs in tuberculosis care, particularly in high-income settings, is needed. Developing tuberculosis-specific PROMs can promote a person-centered approach, ensuring that treatment aligns with the lived experiences and priorities of people with tuberculosis.

AUTHOR CONTRIBUTIONS

PV: conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing—original draft, and writing—review and editing; LL: formal analysis, visualization, writing—original draft, and writing—review and editing; MV and JPR: conceptualization, formal analysis, methodology, resources, supervision, validation, visualization, and writing—review and editing; PB: conceptualization, methodology, visualization, and writing—review and editing; and RD: conceptualization, project administration, supervision, validation, and writing—review and editing. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Treatment completion and challenges in rolling out 12-dose weekly rifapentine plus isoniazid to prevent tuberculosis among people living with HIV and pediatric household contacts in Brazil

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Submitted: 8 April 2025.
Accepted: 14 June 2025.

Study carried out at the Centro Municipal de Saúde Píndaro de Carvalho Rodrigues, the Centro Municipal de Saúde João Barros Barreto, the Clínica da Família Rinaldo de Lamare, all located in Rio de Janeiro (RJ) Brasil, as well as at the Fundação de Medicina Tropical Doutor Heitor Vieira Dourado, located in Manaus (AM) Brasil.

ABSTRACT

Objective: In July of 2021, the Brazilian National Ministry of Health integrated three months of once-weekly isoniazid plus rifapentine (3HP) into the National Guidelines for Tuberculosis Control as a first-line tuberculosis preventive therapy (TPT) option for people living with HIV (PLHIV) and tuberculosis household contacts (HHCs). As part of the Unitaid-sponsored Increasing Market and Public Health Outcomes through Scaling up Affordable Access Models of Short Course Preventive Therapy for TB project to implement short-course TPT, we evaluated 3HP uptake, completion, and tolerability among PLHIV and pediatric HHCs in Brazil. **Methods:** We conducted a multicenter single-arm pragmatic project to roll out 3HP for PLHIV and HHCs in the 2- to 14-year age bracket in the cities of Rio de Janeiro and Manaus, Brazil. Participants were identified, treated, and monitored in accordance with Brazilian national tuberculosis guidelines. De-identified patient-level data on treatment initiation, adverse events, and completion were collected and analyzed. **Results:** From October of 2021 to March of 2023, 380 PLHIV (77.6% of whom were male; median age, 40 years [IQR, 31-51]) and 74 HHCs (54.1% of whom were male; median age, 8.6 years [IQR, 5.1-11.8]) were enrolled in the study. Treatment completion rates were 83.7% among PLHIV and 82.4% among HHCs. Completion rates were higher in Rio de Janeiro than in Manaus (PLHIV: 86.0% vs. 79.6%; HHCs: 85.2% vs. 80.9%), although completion of 10 doses was similar (PLHIV: 86.4% vs. 86.1%). Adverse event-related discontinuation was low (PLHIV: 2.4%; HHCs: 2.7%). One person living with HIV developed active tuberculosis during treatment. At six months of follow-up, 99.6% of the PLHIV remained free of tuberculosis. **Conclusions:** The 3HP regimen was successfully introduced, had high treatment completion rates, and was well tolerated. Widespread use of 3HP for TPT may accelerate tuberculosis elimination in Brazil.

Keywords: Tuberculosis; Latent tuberculosis; HIV infections; Isoniazid; Rifapentine; Treatment adherence and compliance.

INTRODUCTION

Tuberculosis remains a global health crisis and reclaimed its position as the leading cause of death by an infectious agent in 2024, surpassing COVID-19.[1] Despite relative stability in case numbers over the past two years, 2023 saw 10.8 million tuberculosis cases and 1.25 million deaths, with nearly 13% occurring among people living with HIV (PLHIV). Brazil, one of the 30 high tuberculosis burden countries and among the top 10% globally for tuberculosis/HIV coinfection burden,[2] reported an estimated 80,012 tuberculosis cases in 2023, with a 9.3% tuberculosis/HIV coinfection rate.[3] The situation is critical in children under 15 years of age, with 3,409 new cases in 2023, reflecting a rising trend since 2020.[3]

Tuberculosis prevention in PLHIV and pediatric household contacts (HHCs) is crucial for reducing transmission and mortality in these vulnerable populations, given

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Financial support: This study received financial support from Unitaid (the Increasing Market and Public Health Outcomes through Scaling up Affordable Access Models of Short Course Preventive Therapy for TB [IMPAACT4TB] project; Grant no. 2017-20-IMPAACT4TB).

◄ Voltar ao sumário

their increased susceptibility to disease progression and the complex diagnostic and treatment challenges that they face.[1,4-8]

Despite the proven effectiveness of tuberculosis preventive therapy (TPT) in reducing progression of tuberculosis infection to active tuberculosis disease,[9] fewer than 46% of the nearly 39 million PLHIV, 37% of the 1.56 million eligible HHCs under 5 years of age, and only 15% of the estimated 13 million HHCs of all ages globally received TPT in 2022.[10] Preventing the progression of tuberculosis infection to active tuberculosis disease is crucial for reducing disease burden and mortality, while assuring progress towards the 2030/2035 targets set by the United Nations General Assembly High-Level Meeting on the Fight against Tuberculosis and the End TB Strategy.[1]

The challenge in scaling up TPT coverage is compounded by adherence issues, particularly with longer treatment regimens. Adherence to longer TPT regimens such as preventive therapy with six months of daily isoniazid has proven challenging.[11] Isoniazid preventive therapy completion rates are frequently low, with studies indicating that up to 50% of individuals who initiate TPT fail to complete it.[11-13] Nonadherence to isoniazid preventive therapy has been observed to increase over time since TPT initiation.[12] Short-course TPT regimens, such as three months of once-weekly isoniazid plus rifapentine (3HP), are a promising alternative, with shorter duration and low toxicity levels as incentives for treatment completion, highlighting the relationship between shorter duration and improved adherence.[14-16]

Since 2018, the WHO has recommended 3HP consisting of 12 once-weekly doses of rifapentine and isoniazid for children over 2 years of age and adults, including those with HIV, as an alternative to longer regimens.[17] The Brazilian National Ministry of Health sanctioned the inclusion of the 3HP regimen at the end of 2020.[18] In July of 2021, the Brazilian National Ministry of Health integrated 3HP into the National Guidelines for Tuberculosis Control as a first-line TPT option for PLHIV and tuberculosis contacts, with free distribution in the Brazilian Unified Health Care System starting in the last quarter of 2021. As part of the Unitaid-sponsored Increasing Market and Public Health Outcomes through Scaling up Affordable Access Models of Short Course Preventive Therapy for TB (IMPAACT4TB) project to implement short-course TPT, we evaluated 3HP uptake, treatment completion, and tolerability in PLHIV and pediatric HHCs in Brazil during its nationwide rollout.

METHODS

We conducted a multicenter single-arm pragmatic project to roll out 3HP for PLHIV and pediatric HHCs in the cities of Rio de Janeiro and Manaus, Brazil. Although 3HP was incorporated into the National Guidelines for Tuberculosis Control as a frontline TPT choice in July of 2021, regulatory delays slowed the importation of rifapentine, postponing 3HP implementation. Rifapentine (Priftin®; Sanofi S.A., Paris, France) arrived in Brazil in September of 2021, and study enrollment began in October of 2021 with the incorporation of 3HP into the Brazilian Unified Health Care System.

Eligible participants were identified, treated, and monitored in accordance with Brazilian national tuberculosis guidelines (Figures 1 and 2) at four public-sector health clinics. In the city of Rio de Janeiro, enrollment took place at three primary health care facilities: *Centro Municipal de Saúde Píndaro de Carvalho Rodrigues*, *Centro Municipal de Saúde João Barros Barreto*, and *Clínica da Família Rinaldo de Lamare*. In the city of Manaus, enrollment was overseen by the *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado*, a tertiary health care facility specializing in infectious diseases. Inclusion and exclusion criteria were applied uniformly across sites. However, because of the clinical profile of the patients, the tertiary health care facility in Manaus may have enrolled participants with more advanced HIV or complex comorbidities.

Adult PLHIV (≥ 18 years of age) were eligible if they were enrolled in public-sector HIV care; had no active tuberculosis; had not received tuberculosis treatment in the last two years; had never received TPT (unless newly exposed); and provided written informed consent. Exclusion criteria included inability to take oral medication; body weight < 30 kg; drug-resistant tuberculosis exposure in the last 12 months; isoniazid intolerance; grade 3/4 peripheral neuropathy; pregnancy/breastfeeding; substance abuse; and antiretroviral therapy with protease inhibitors, nevirapine, tenofovir alafenamide, or cobicistat. Pediatric HHCs (in the 2- to 14-year age bracket) were eligible if they were pulmonary tuberculosis contacts; had no history of current or past active tuberculosis disease; and had never received TPT (unless newly exposed and HIV positive). Exclusion criteria included inability to take oral medication; body weight < 10 kg; drug-resistant tuberculosis exposure; isoniazid intolerance; and antiretroviral therapy with dolutegravir, raltegravir, protease inhibitors, or nevirapine.

According to Brazilian national tuberculosis guidelines, PLHIV with a CD4 count of ≤ 350 cells/mm^3 or an unknown CD4 count are eligible for TPT after exclusion of active tuberculosis. For individuals with a CD4 count > 350 cells/mm^3, TPT is recommended following exclusion of active tuberculosis and a positive result on either a tuberculin skin test or interferon-gamma release assay (Figure 1).

In the present study, participants in the 10- to 18-year age bracket were considered to be adolescents. Asymptomatic HHCs ≥ 10 years of age are eligible for TPT after active tuberculosis is excluded; a positive tuberculin skin test result; and a normal chest X-ray. Symptomatic individuals undergo further evaluation: those with evidence of active tuberculosis are treated accordingly, whereas those with persistent symptoms

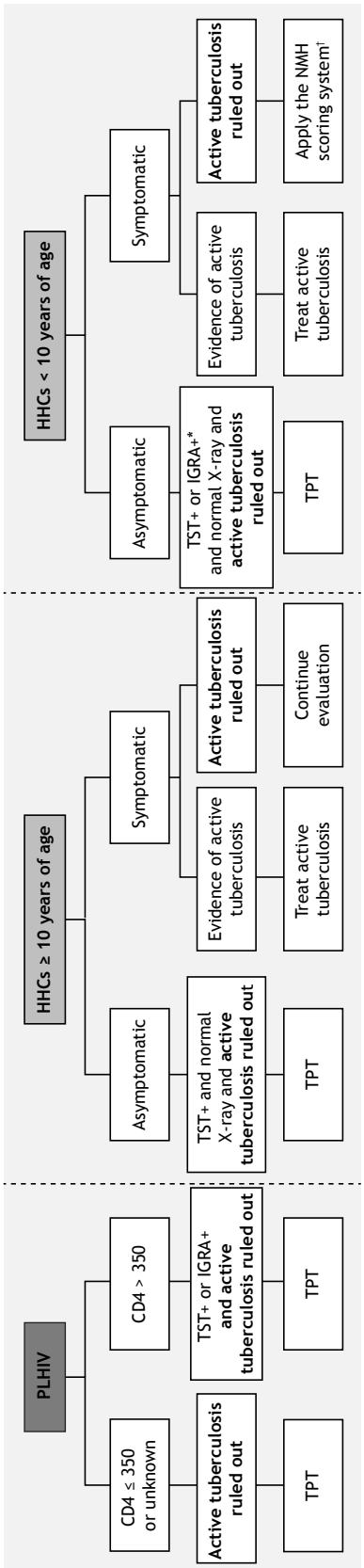

Figure 1. Brazilian national guidelines on tuberculosis preventive therapy (TPT) for people living with HIV (PLHIV) and household contacts (HHCs). TST: tuberculin skin test; and IGRA: interferon-gamma release assay. *Only in those ≥ 2 years of age and < 10 years of age. †Scoring system developed by the Brazilian National Ministry of Health (NMH) for diagnosing tuberculosis in children.

without evidence of active tuberculosis require further investigation (Figure 1).

For HHCs < 10 years of age, asymptomatic individuals are eligible for TPT after exclusion of active tuberculosis; a positive tuberculin skin test or interferon-gamma release assay; and a normal chest X-ray. Symptomatic children with evidence of active tuberculosis are treated for active disease, whereas those without active tuberculosis are further investigated using the Brazilian National Ministry of Health scoring system to guide management (Figure 1).

PLHIV ≥ 18 years of age and HHCs in the 2- to 14-year age bracket who met eligibility criteria in accordance with Brazilian national guidelines were eligible for enrollment. Enrolled participants were prescribed 3HP at monthly clinic visits and monitored for tuberculosis signs and symptoms, adherence, and adverse events over the three-month treatment course. Vitamin B6 was concomitantly prescribed to reduce the risk of peripheral neuropathy. For adult PLHIV, the 3HP regimen consisted of 900 mg of isoniazid (three 300 mg tablets) and 900 mg of rifapentine (six 150 mg tablets), taken once weekly for 12 weeks with vitamin B6, totaling 10 tablets per dose. For pediatric HHCs, weight-based dosing was used. Rifapentine was prescribed at 300-750 mg (2-5 150 mg tablets) and isoniazid at 300-700 mg (via combinations of 100 mg and/or 300 mg tablets), administered once weekly for 12 weeks. To ascertain adherence, participants were provided with blister packs containing the exact number of doses required for the month. At each monthly visit, they were instructed to return the blister packs, allowing providers to verify the number of doses taken. Treatment completion was defined in accordance with national guidelines, as 12 weekly doses of 3HP taken in 12-15 weeks. Treatment interruption was defined as three missed doses (i.e., having taken ≤ 9 doses). Treatment discontinuation was categorized as being related to adverse events or patient choice.

Follow-up of adult PLHIV was conducted at six months after treatment completion to assess tuberculosis outcomes through medical record reviews and data from the Brazilian National Ministry of Health Case Registry Database.

De-identified patient-level data on treatment initiation, adverse events, and treatment completion were entered into a secure Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN, USA) database. Data were analyzed with Stata software, version 18.0 (StataCorp LLC, College Station, TX, USA). Data are presented as frequencies (percentages) for categorical variables and medians (interquartile ranges) for continuous variables.

All study participants provided written informed consent. HHCs provided assent in addition to the written informed consent provided by their legal guardians. The study was conducted under a common protocol approved by the WHO Ethics Review Committee

and was approved by the Johns Hopkins Medicine Institutional Review Board (Protocol no. IRB00258322), the Brazilian National Research Ethics Committee, and relevant local institutional review boards.

RESULTS

From October of 2021 to March of 2023, 380 PLHIV and 74 HHCs were enrolled in the study and initiated TPT with 3HP (Figure 2).

Demographics of study participants

PLHIV

A total of 380 PLHIV were enrolled: 243 in the city of Rio de Janeiro and 137 in the city of Manaus (Table 1). Most of the study participants were male, accounting for 77.6% of the sample, with similar proportions observed in Rio de Janeiro (78.2%) and Manaus (76.6%). The median age of PLHIV was 40 years (IQR, 31-51), with slightly higher median ages in Rio de Janeiro (41 years; IQR, 32-52) than in Manaus (36 years; IQR, 28-47). The median BMI was 25.4 kg/m^2 (IQR, 22.7-28.6), with comparable values in Rio de Janeiro (25.7 kg/m^2; IQR, 23.2-28.8) and Manaus (24.6 kg/m^2; IQR, 21.9-27.6). Most (80.8%) of the PLHIV were on dolutegravir-based antiretroviral therapy at enrollment (83.5% in Rio de Janeiro and 75.9% in Manaus).

HHCs in the 2- to 14-year age bracket

Seventy-four HHCs were enrolled: 27 in Rio de Janeiro and 47 in Manaus. Of those, 54.1% were male, with similar proportions in Rio de Janeiro (55.6%) and Manaus (53.2%). The median age of HHCs was 8.6 years (IQR, 5.1-11.8), being 8.6 years in Rio de Janeiro (IQR, 4.9-12.6) and 9.1 years in Manaus (IQR, 5.1-11.8). All of the participants in Rio de Janeiro had normal weight; undernutrition or stunting was present in 19.1% of the participants in Manaus.

Treatment outcomes

PLHIV

The treatment completion rate in accordance with Brazilian national tuberculosis guidelines was 83.7%, with Rio de Janeiro achieving a slightly higher completion rate of 86.0%, in comparison with 79.6% in Manaus (Table 2). Of the study participants, 86.0% completed 10 doses within an 11 to 15-week time frame, with comparable completion rates in Rio de Janeiro (86.4%) and Manaus (86.1%).

Treatment discontinuation due to patient choice occurred in 3.4% of participants, with a higher discontinuation rate in Manaus (5.8%) than in Rio de Janeiro (2.1%). Adverse events led to treatment discontinuation in 2.4% of participants, with most cases occurring in Rio de Janeiro (3.3%) and one case in Manaus (0.7%).

Treatment was changed for 1.1% of participants, with two participants each in Rio de Janeiro (0.8%) and Manaus (1.5%). Treatment interruption occurred in 6.6% of participants, being slightly higher in Rio de Janeiro (7.4%) than in Manaus (5.1%).

Active tuberculosis was diagnosed in one participant (0.3%) during 3HP treatment in Manaus, where one death unrelated to 3HP was also reported (0.7%). No active tuberculosis diagnoses or deaths were recorded among participants in Rio de Janeiro.

HHCs in the 2- to 14-year age bracket

Of the HHCs in the present study, 82.4% completed treatment, with a slightly higher completion rate in Rio de Janeiro (85.2%) than in Manaus (80.9%). In addition, 87.8% of participants completed 11 doses within an 11 to 15-week period, with a higher rate in Rio de Janeiro (92.6%) than in Manaus (85.1%).

Treatment was discontinued by patient choice in 4.1%, with one participant in Rio de Janeiro (3.7%) and two in Manaus (4.3%). Adverse events led to treatment discontinuation in 2.7% of HHCs, with one case each in Rio de Janeiro (3.7%) and Manaus (2.1%).

Treatment was changed for 1.4% of HHCs, all of whom were in Manaus (2.1%), whereas no changes were recorded in Rio de Janeiro. Additionally, treatment interruption occurred in 4.1% of cases, exclusively in Manaus (6.4%), with no occurrences in Rio de Janeiro.

No active tuberculosis diagnoses occurred among the HHCs while on treatment.

Tolerability

Treatment discontinuation because of toxicity was uncommon in both groups of participants (Table 3). Among PLHIV, systemic hypersensitivity affected 0.8%, all of whom were in Rio de Janeiro (1.2%). Mild hepatotoxicity and flu-like reactions accounted for discontinuation in 0.5% of participants, again limited to those in Rio de Janeiro (0.8%). Additionally, one participant in Rio de Janeiro discontinued treatment because of peripheral neuropathy (0.3% overall; 0.4% in Rio de Janeiro). In Manaus, one participant discontinued treatment because of nausea and vomiting (0.7%).

Peripheral neuropathy led to discontinuation in one HHC in Manaus (2.1%), whereas vomiting was the cause of discontinuation for one HHC in Rio de Janeiro (0.4%).

Follow-up

Six-month follow-up after treatment completion was performed for 271 of the 380 PLHIV enrolled in the present study. At six months, 99.6% of the 271 PLHIV remained free of tuberculosis, with all of the participants in Rio de Janeiro (100%) and most of those in Manaus (98.7%) showing no signs of active tuberculosis. There was one reported death unrelated to tuberculosis or 3HP in Manaus (1.3%), whereas no deaths were recorded among the participants in Rio de Janeiro (Table 4).

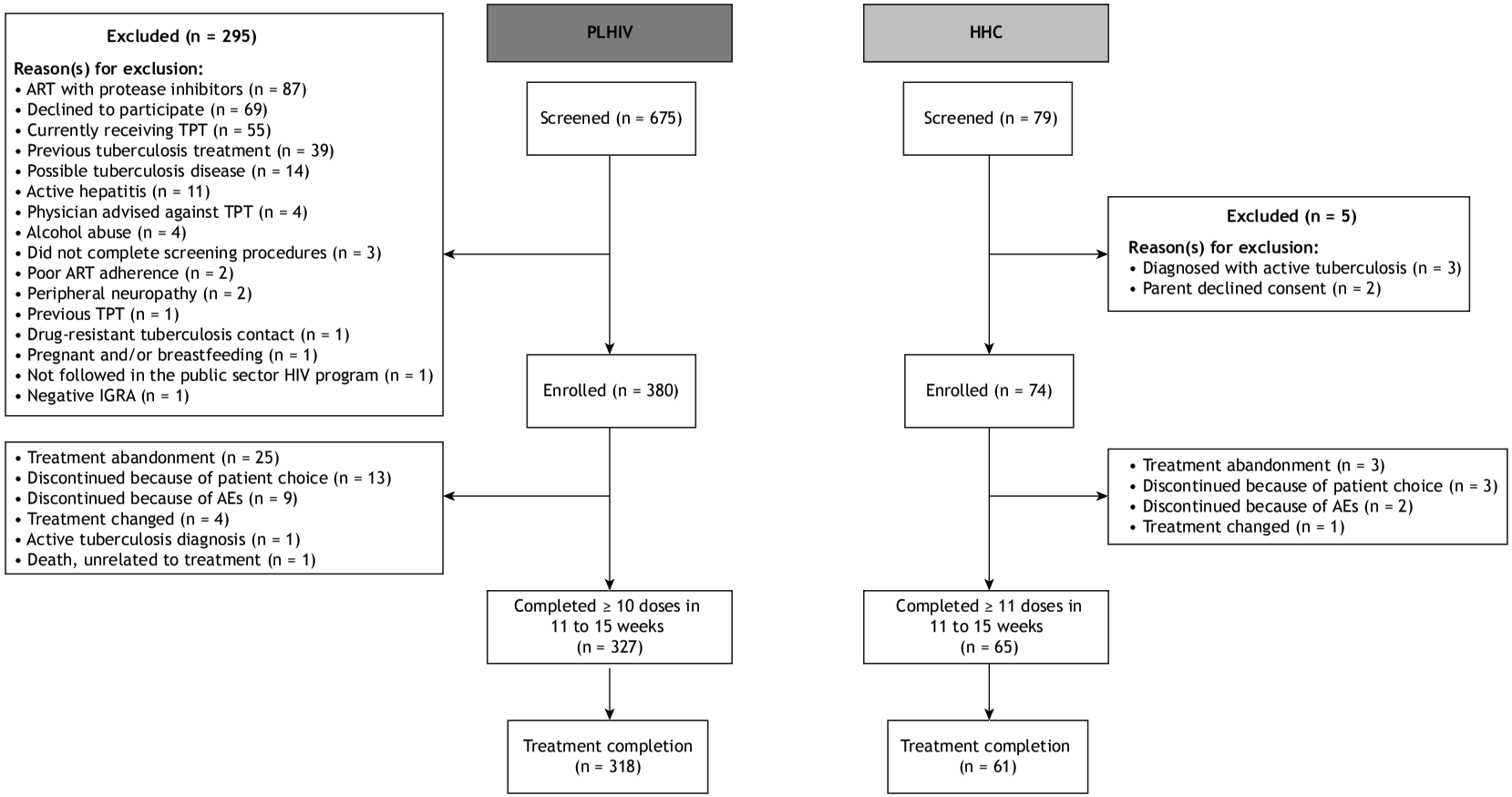

Figure 2. Study flow diagram. PLHIV: people living with HIV; HHCs: household contacts; TPT: tuberculosis preventive therapy; ART: antiretroviral therapy; IGRA: interferon-gamma release assay; and AEs: adverse events.

Table 1. Baseline characteristics of patients receiving tuberculosis preventive therapy with three months of once-weekly isoniazid plus rifapentine.[a]

	Overall	Rio de Janeiro	Manaus
	PLHIV (N = 380)	PLHIV (n = 243)	PLHIV (n = 137)
Male	295 (77.6)	190 (78.2)	105 (76.6)
Age, years	40 [31-51]	41 [32-52]	36 [28-47]
BMI, kg/m^2	25.4 [22.7-28.6]	25.7 [23.2-28.8]	24.6 [21.9-27.6]
Dolutegravir-based ART	307 (80.8)	203 (83.5)	104 (75.9)
	HHCs (N = 74)	HHCs (n = 27)	HHCs (n = 47)
Male	40 (54.1)	15 (55.6)	25 (53.2)
Age, years	8.6 [5.1-11.8]	8.6 [4.9-12.6]	9.1 [5.1-11.8]
Normal weight	65 (87.8)	27 (100)	38 (80.9)
Weight-for-age Z-score < −2	9 (12.2)	0	9 (19.1)

PLHIV: people living with HIV; ART: antiretroviral therapy; and HHCs: household contacts. [a]Data presented as n (%) or median [IQR].

Table 2. Treatment outcomes in people living with HIV and household contacts in the 2- to 14-year age bracket receiving tuberculosis preventive therapy with three months of once-weekly isoniazid plus rifapentine.[a]

	Overall	Rio de Janeiro	Manaus
	PLHIV (N = 380)	PLHIV (n = 243)	PLHIV (n = 137)
Treatment completion in accordance with Brazilian national tuberculosis guidelines	318 (83.7)	209 (86.0)	109 (79.6)
Completed ≥ 11 doses in 11 to 15 weeks	324 (85.3)	210 (86.4)	114 (83.2)
Completed ≥ 10 doses in 11 to 15 weeks	327 (86.0)	210 (86.4)	118 (86.1)
Discontinued because of patient choice	13 (3.4)	5 (2.1)	8 (5.8)
Discontinued because of adverse events	9 (2.4)	8 (3.3)	1 (0.7)
Treatment changed	4 (1.1)	2 (0.8)	2 (1.5)
Treatment interruption	25 (6.6)	18 (7.4)	7 (5.1)
Active tuberculosis diagnosis	1 (0.3)	0	1 (0.7)
Death[b]	1 (0.3)	0	1 (0.7)
	HHCs (N = 74)	HHCs (n = 27)	HHCs (n = 47)
Treatment completion in accordance with Brazilian national tuberculosis guidelines	61 (82.4)	23 (85.2)	38 (80.9)
Completed ≥ 11 doses in 11 to 15 weeks	65 (87.8)	25 (92.6)	40 (85.1)
Discontinued because of patient choice	3 (4.1)	1 (3.7)	2 (4.3)
Discontinued because of adverse events	2 (2.7)	1 (3.7)	1 (2.1)
Treatment changed	1 (1.4)	0	1 (2.1)
Treatment interruption	3 (4.1)	0	3 (6.4)
Active tuberculosis diagnosis	0	0	0

PLHIV: people living with HIV; and HHCs: household contacts. [a]Data presented as n (%). [b]Death unrelated to treatment, caused by disseminated cryptococcosis.

Table 3. Treatment-discontinuing adverse events in people living with HIV and household contacts in the 2- to 14-year age bracket receiving tuberculosis preventive therapy with three months of once-weekly isoniazid plus rifapentine.[a]

Treatment-discontinuing AEs	Overall	Rio de Janeiro	Manaus
	PLHIV (N = 380)	PLHIV (n = 243)	PLHIV (n = 137)
Flu-like reaction	2 (0.5)	2 (0.8)	0
Mild hepatotoxicity	2 (0.5)	2 (0.8)	0
Systemic hypersensitivity	3 (0.8)	3 (1.2)	0
Peripheral neuropathy	1 (0.3)	1 (0.4)	0
Other[b]	1 (0.3)	0	1 (0.7)
	HHCs (N = 74)	HHCs (n = 27)	HHCs (n = 47)
Peripheral neuropathy	1 (0.1)	0	1 (2.1)
Other[c]	1 (0.1)	1 (0.4)	0

AEs: adverse events; PLHIV: people living with HIV; and HHCs: household contacts. [a]Data presented as n (%). [b]Nausea and vomiting. [c]Vomiting.

Table 4. Six-month follow-up outcomes in people living with HIV and receiving tuberculosis preventive therapy with three months of once-weekly isoniazid plus rifapentine.[a]

Outcome at follow-up	Overall	Rio de Janeiro	Manaus
	N = 271	n = 194	n = 77
Free of tuberculosis	270 (99.6)	194 (100)	76 (98.7)
Death[b]	1 (3.7)	0	1 (1.3)

[a]Data presented as n (%). [b]Death caused by dissecting aortic aneurysm.

DISCUSSION

The implementation of the 3HP regimen for TPT in Brazil, specifically among PLHIV and HHCs, has shown promising results in terms of treatment completion rates and overall tolerability. The high completion rates in our study—83.7% among PLHIV and 82.4% among HHCs—demonstrate that the 3HP regimen is both feasible and acceptable in real-world settings, supporting its broader implementation in tuberculosis control programs. Adverse events leading to treatment discontinuation were minimal, emphasizing the overall tolerability of 3HP (PLHIV: 2.4%; HHCs: 2.7%). These outcomes are consistent with the literature regarding the robust safety profile of 3HP, underscoring that 3HP is a feasible and well-tolerated option for tuberculosis prevention in these vulnerable populations. However, differences in outcomes between Rio de Janeiro and Manaus highlight contextual factors that may influence TPT completion and tolerability across different settings. The higher completion rates observed in Rio de Janeiro, particularly among PLHIV (PLHIV: 86.0% vs. 79.6%; HHCs: 85.2% vs. 80.9%), may reflect differences in health care infrastructure and participant complexity between the two types of health care settings. In Rio de Janeiro, care was provided at primary health care facilities, offering more geographically accessible, community-based routine and preventive care. In Manaus, however, care was provided at a tertiary health care facility, serving a larger, geographically dispersed population possibly facing greater barriers to accessing care—including longer travel times for medical care and follow-up—and more complex conditions, such as lower CD4 counts.[19] Poor transportation infrastructure, particularly in northern Brazil, where Manaus is located, amplifies health care access challenges. Studies show that geographic and systemic inequities within the Brazilian public health care system drive regional disparities in health care access and quality across various services.[20,21] Although contextual factors likely influenced site differences in the present study, small sample sizes could exaggerate percentage differences in treatment discontinuation and interruption, requiring cautious interpretation.

Although the completion rates for ≥ 10 doses among PLHIV in Rio de Janeiro and Manaus were similar (86.4% vs. 86.1%), they do not represent the complete 12-dose regimen. This means that although many patients were close to completing the entire course, a gap remains to be addressed. If patients drop out after 10 or 11 doses, they may not receive the full protective benefit of the regimen, potentially leaving them at risk for developing active tuberculosis. Although adherence to 10 or more doses is not categorized as treatment interruption by Brazilian national or WHO guidelines, the data suggest that additional efforts should be made to ensure that patients complete the 12-dose regimen. This might involve improved follow-up, patient education, and support services to address barriers that might prevent patients from completing the regimen and reduce the risk of developing active tuberculosis. The high pill burden of the 10-tablet weekly dose may have contributed to decreased adherence, underscoring the importance of considering fixed-dose combination formulations during scale-up. Notably, Brazil began distributing the fixed-dose combination formulation of 3HP in February of 2024,[22] possibly enhancing tolerability and adherence among those receiving 3HP and ultimately supporting better treatment completion and maximizing the protective benefits of the regimen.

Pediatric populations face unique challenges. The use of nondispersible tablets presents challenges such as difficulty swallowing, poor palatability, and caregiver burden, all of which may affect adherence and limit scale-up in children.[23,24] Although 74 pediatric HHCs were included in the present study, further studies are warranted to assess 3HP performance in larger cohorts of children and adolescents and to evaluate child-friendly regimens, such as dispersible tablets, to ensure equitable access to TPT across age groups.

The findings from the six-month follow-up of PLHIV in the present study underscore the high efficacy of the intervention in preventing tuberculosis among PLHIV, with all but one participant who died of causes unrelated to tuberculosis maintaining a tuberculosis-free status at the six-month mark.

Brazilian national reports indicate that 71.6% of patients completed 3HP from rollout to April of 2022, and 1.3% discontinued 3HP because of adverse events.[3] The national data are consistent with the trends observed in our study, reinforcing the importance of ongoing support and monitoring to maintain high adherence levels and minimize treatment interruption. The agreement between our findings and national reports strengthens the case for a broader implementation of the 3HP regimen, with an emphasis on overcoming regional disparities.

The strengths of the present study include its multicenter design and the use of a standardized regimen across diverse settings, allowing a comparison of outcomes between different regions. However, our study is not without limitations. The observational

nature of the study and the lack of a control group limit the ability to draw causal inferences about the factors contributing to the differences in outcomes between sites. Local factors, such as health care infrastructure, environmental conditions, and patient demographics, may play a significant role in influencing outcomes, and these factors should be further explored in future studies. The six-month follow-up period may not have captured long-term protection; extended monitoring could improve evaluation of outcomes and recurrence risk.

Despite the positive intent of the policy change, regulatory delays in the importation of rifapentine emerged as a critical barrier to the timely implementation of 3HP. The challenges during this period shed light on the bureaucracy involved in translating policy change into effective practice. Understanding and addressing such barriers are essential for future policy implementations.

In April of 2023, the Brazilian government introduced the Interministerial Committee for the Elimination of Tuberculosis and Other Socially Determined Diseases, which is aimed at fostering multisectoral collaboration to eliminate tuberculosis in Brazil.[25,26] This initiative, including the Brazilian National Ministry of Health and the eight other federal ministries, set ambitious targets to reduce the incidence of tuberculosis to fewer than 10 cases per 100,000 population and the annual number of tuberculosis deaths to fewer than 230 by 2023. Our findings support the ongoing implementation of the 3HP regimen as a vital component in achieving these goals, emphasizing the need for continued efforts to overcome regulatory and logistical barriers that could hinder progress.

The findings of the present study provide valuable insights into the practical aspects of translating policy changes into effective tuberculosis control strategies. Despite initial regulatory delays, 3HP was successfully introduced, showed high treatment completion rates, and was well tolerated, constituting a promising strategy for accelerating tuberculosis elimination in Brazil. The present study demonstrates that short-course TPT can be effectively integrated into national tuberculosis control programs, achieving high rates of treatment completion and low rates of treatment-discontinuing adverse events. As Brazil continues its efforts to combat tuberculosis, the success of 3HP implementation provides a compelling case for a broader adoption of short-course TPT regimens to accelerate progress toward tuberculosis elimination.

ACKNOWLEDGMENTS

This work was supported by Unitaid. We would like to thank the Aurum Institute, in Johannesburg, South Africa, for being our technical partner in this project. We would also like to thank the staff at the *Centro Municipal de Saúde Píndaro de Carvalho Rodrigues*, the *Centro Municipal de Saúde João Barros Barreto*, the *Clínica da Família Rinaldo de Lamare*, and the *Fundação de Medicina Tropical Doutor Heitor Vieira Dourado*. Finally, we would like to thank all of those who consented to participate in the study for their contribution to the successful implementation of the project.

AUTHOR CONTRIBUTIONS

VS, SCC, JW, VC, GC, REC, MCS, and BD: conceptualization. IS: formal analysis; visualization; and writing—original draft. JGO, ABS, RSG, SDA, and MCS: investigation. IS and SC: data curation. VS, SCC, JW, MG, VC, GC, REC, MCS, and BD: methodology. IS, JGO, ABS, SC, RSG, SDA, VS, SCC, JW, MG, VC, GC, REC, MCS, and BD: project administration and writing—review and editing. GC and REC: funding acquisition. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(4):e20250152
https://dx.doi.org/10.36416/1806-3756/e20250152

ORIGINAL ARTICLE

Lateral flow urine lipoarabinomannan assay for tuberculosis diagnosis in HIV-positive inpatients and outpatients

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Submitted: 4 May 2025.
Accepted: 16 May 2025.

Study carried out under the auspices of the Programa de Pós-Graduação em Ciências Pneumológicas, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To evaluate tuberculosis diagnosis with the use of the lateral flow urine lipoarabinomannan assay (LF-LAM) in addition to the Xpert® MTB/RIF Ultra assay on sputum in HIV-positive inpatients and outpatients. **Methods:** This was a prospective cross-sectional study including HIV-positive patients ≥ 18 years of age with an indication for LF-LAM in accordance with Brazilian National Ministry of Health criteria. **Results:** A total of 140 patients were included in the study. LF-LAM was positive in 23 (16.4%). An additional 12 (8.6%) were diagnosed with the aid of LF-LAM, this increase in tuberculosis detection being statistically significant. LF-LAM–positive patients were younger and had lower CD4 counts in comparison with LF-LAM–negative patients. Smoking was more common among LF-LAM–negative patients than among LF-LAM–positive patients. **Conclusions:** The use of LF-LAM significantly increases the detection of tuberculosis in HIV-positive patients, mostly in those who are hospitalized. These findings highlight the utility of LF-LAM, especially in regions with high tuberculosis and HIV infection incidence.

Keywords: Tuberculosis; Mycobacterium tuberculosis; HIV infections; Diagnosis.

INTRODUCTION

The likelihood of developing active tuberculosis increases in proportion to the presence of certain risk factors or comorbidities such as HIV infection. According to the WHO, people living with HIV have an 18-fold higher risk of developing active tuberculosis than the rest of the world population. In 2019, of an estimated 815,000 HIV-associated tuberculosis cases worldwide, only 56% were reported, possibly in part due to underdiagnosis and suboptimal access to health care services. Therefore, improving access to early and rapid tuberculosis diagnosis is a fundamental principle of the fight against tuberculosis and a pillar of the WHO End TB strategy.[1]

Although molecular assays such as Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) have helped in the diagnosis of tuberculosis by enabling faster and more sensitive results, especially in people living with HIV, there are still challenges in using such tests for tuberculosis diagnosis in some populations. In HIV-positive patients, the paucibacillary nature of tuberculosis, as well as scarce sputum production, makes it difficult to use molecular tests based on sputum samples.[1]

Lipoarabinomannan is an immunogenic virulence factor that is released by metabolically active or degrading bacterial cells and that is specific to mycobacterial species. Lipoarabinomannan was first characterized in 1980 as a potential marker of active tuberculosis and is the most studied biological marker for tuberculosis to date.[2] Several studies have shown that, in tuberculosis patients, lipoarabinomannan is found in urine,[3,4] as well as in blood and sputum.[5,6] Urinary lipoarabinomannan levels are known to be elevated in individuals with tuberculosis-HIV coinfection and to increase with decreasing CD4 cell counts.[7] The lateral flow urine lipoarabinomannan assay (LF-LAM) has been commercially available as a rapid point-of-care test that allows detection of mycobacterial lipoarabinomannan in urine samples.[8,9] LF-LAM has a sensitivity of 42% for diagnosing tuberculosis in HIV-positive individuals with tuberculosis symptoms and of 35% for diagnosing tuberculosis in HIV-positive individuals who have not been evaluated for tuberculosis symptoms. As a simple point-of-care test that does not rely on sputum evaluation, LF-LAM can aid in the diagnosis of tuberculosis, particularly when a sputum sample cannot be produced.[10]

The objective of the present study was to evaluate tuberculosis diagnosis with the use of LF-LAM in addition to the Xpert® MTB/RIF Ultra assay on sputum in HIV-positive inpatients and outpatients.

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Financial support: None.

◄ Voltar ao sumário
ISSN 1806-3756

METHODS

Study design and setting

A prospective cross-sectional study was conducted to evaluate LF-LAM for the diagnosis of tuberculosis in the routine care of HIV patients. The study was conducted in the city of Alvorada, in southern Brazil.

Patients and data collection

The study included HIV-positive inpatients and outpatients ≥ 18 years of age with an indication for LF-LAM in accordance with Brazilian National Ministry of Health criteria, as follows: having a CD4 count of < 100 cells/mm^3, regardless of symptoms; showing signs and/or symptoms of pulmonary or extrapulmonary tuberculosis, regardless of CD4 count; and being severely ill, regardless of CD4 count. An adult was defined as being severely ill when presenting with any of the following: an RR ≥ 30 breaths/minute; an HR ≥ 120 bpm; inability to walk without assistance; and a body temperature ≥ 39°C, with local epidemiology and clinical judgment being taken into consideration. Patients who declined to participate in the study were excluded.

Patients provided urine samples for LF-LAM, and the DETERMINE™ TB LAM Ag test (Abbott Laboratories, Abbott Park, IL, USA) was performed in accordance with the manufacturer instructions. The following data were recorded: demographic data (including sex, age, and race); symptoms (including cough, fever, night sweats, hemoptysis, weight loss, dyspnea, and chest pain); smoking status; alcohol use; CD4 cell count; sputum AFB smear and culture results; and Xpert® MTB/RIF Ultra assay results.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics software package for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA). Data were presented as number of cases, mean ± standard deviation, or median [interquartile range]. Categorical comparisons were performed with the chi-square test and Yates' correction or Fisher's exact test, as appropriate. Continuous variables were compared by means of the t-test or the Wilcoxon test. A two-sided value of $p < 0.05$ was considered significant for all analyses.

RESULTS

A total of 140 patients were included in the present study. The characteristics of the study population are shown in Table 1. The mean age was 30.3 ± 9.6 years, and 42.1% were male. Smoking, alcohol abuse, and drug use were reported by 71 (50.7%), 35 (25.0%), and 22 (15.7%), respectively. The mean CD4 count was 117.2 ± 25.9 cells/mm^3. Thirty-seven (26.4%) were inpatients, and 103 (73.6%) were outpatients.

The Xpert® MTB/RIF Ultra assay on sputum was positive in 11 (7.9%) of the 140 patients included in the study, and resistance to rifampin was detected in 2 (1.4%). LF-LAM was positive in 23 (16.4%). An additional 12 patients (8.6%) were diagnosed with the aid of LF-LAM. This increase in tuberculosis detection was statistically significant ($p = 0.0041$).

Table 2 shows the characteristics of patients with positive and negative LF-LAM results. LF-LAM–positive patients were younger than LF-LAM–negative patients (21.4 ± 3.8 years vs. 32.0 ± 9.5 years; $p < 0.0001$). Smoking was more common among LF-LAM–negative patients (n = 66; 56.4%; $p = 0.005$) than among LF-LAM–positive patients (n = 5; 21.7%). LF-LAM–positive patients had a lower CD4 count than did LF-LAM–negative patients (76.5 ± 8.1 cells/mm^3 vs. 125.2 ± 20.1 cells/mm^3; $p < 0.0001$). All of the patients with a positive LF-LAM result were inpatients, and 14 (12.0%) of those with a negative LF-LAM result were inpatients.

DISCUSSION

In the present study, we found that LF-LAM was positive in 16.4% of HIV patients in a region of Brazil in which the prevalence of tuberculosis and HIV infection is high. An additional 12 patients (8.6%) were diagnosed with the aid of LF-LAM. All of the patients with a positive LF-LAM result were inpatients. LF-LAM–positive patients were younger and had a lower CD4 count than LF-LAM–negative patients. In addition, smoking was more common among LF-LAM–negative patients than among LF-LAM–positive patients.

People living with HIV have an increased risk of tuberculosis, which accounts for approximately

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

Characteristic	N = 140
Demographic characteristic	
Age, years	30.3 ± 9.6
Male	81 (42.1)
White	119 (85.0)
Symptom	
Cough	83 (59.3)
Weight loss	132 (94.3)
Dyspnea	10 (7.1)
Fever	11 (7.9)
Night sweats	13 (9.3)
Hemoptysis	1 (0.7)
Smoking	71 (50.7)
Alcohol abuse	35 (25.0)
Drug use	22 (15.7)
CD4 count	117.2 ± 25.9
Inpatient	37 (26.4)
Outpatient	103 (73.6)
Xpert® MTB/RIF positivity (detected)	11 (7.9)
Rifampin resistance	2 (1.4)
LF-LAM	23 (16.4)

LF-LAM: lateral flow urine lipoarabinomannan assay. [a]Data presented as mean ± SD or n/N (%).

Table 2. Comparison between patients with positive flow urine lipoarabinomannan assay results and those with negative results.[a]

Characteristic	LF-LAM–positive (n = 23)	LF-LAM–negative (n = 117)	p
Demographic characteristic			
Age, years	21.4 ± 3.8	32.0 ± 9.5	< 0.0001
Male	12 (52.2)	69 (59.0)	0.709
White	22 (95.7)	97 (82.9)	0.198
Symptom			
Cough	14 (60.9)	69 (59.0)	0.999
Weight loss	23 (100)	109 (93.2)	0.353
Dyspnea	0	10 (8.5)	0.368
Fever	1 (4.3)	10 (8.5)	0.692
Night sweats	1 (4.3)	12 (10.3)	0.694
Hemoptysis	0	1 (0.9)	0.999
Smoking	5 (21.7)	66 (56.4)	0.005
Alcohol abuse	4 (17.4)	31 (26.5)	0.510
Drug use	5 (21.7)	17 (14.5)	0.362
CD4 count	76.5 ± 8.1	125.2 ± 20.1	< 0.0001
Inpatient	23 (100)	14 (12.0)	< 0.0001
Xpert® MTB/RIF positivity (detected)	3 (75.0)	8 (57.1)	0.999

LF-LAM: lateral flow urine lipoarabinomannan assay. [a]Data presented as mean ± SD or n/N (%).

one third of all deaths in HIV patients.[1] Therefore, among people living with HIV, systematic screening for tuberculosis disease should be conducted at each visit to a health care facility, according to the WHO.[11] However, because there is often no sputum sample available for an Xpert MTB/RIF assay, LF-LAM has emerged as a diagnostic aid. Tuberculosis detection significantly increased from 11 (7.9%) with the use of the Xpert® MTB/RIF Ultra assay alone to 23 (16.4%) when LF-LAM was added. This finding is in agreement with previous studies.[12,13] In a prospective cohort of 98 HIV patients in Tanzania,[12] the combination of the Xpert® MTB/RIF assay and LF-LAM increased tuberculosis diagnosis from 24% to 37%. In a prospective cohort of 84 patients from three referral hospitals in Kilimanjaro,[13] LF-LAM increased tuberculosis detection from 31% with the use of Xpert® MTB/RIF alone to 55% with the use of both assays. In a systematic review and individual patient meta-analysis,[14] the diagnostic yield of sputum Xpert in HIV-associated *Mycobacterium tuberculosis* bloodstream infection was 77% and increased to 89% when combined with LF-LAM. These findings are important because there is often no sputum sample available for testing with the Xpert® MTB/RIF assay, especially in immunosuppressed patients.

Although we evaluated outpatients and inpatients in our study, all positive results for LF-LAM were from hospitalized patients. Some studies[15,16] have previously demonstrated that the use of LF-LAM may have a role in reducing mortality in hospitalized patients because of an increase in the number of tuberculosis diagnoses. In a pragmatic, randomized, parallel-group, multicenter trial[15] conducted in ten hospitals in Africa, the authors evaluated the effect on mortality of a strategy including the use of LF-LAM. They found that this strategy was associated with reduced eight-week mortality. In another multicenter, double-blind, randomized controlled trial[16] conducted in two hospitals in Malawi and South Africa, the use of LF-LAM in tuberculosis screening in HIV-positive inpatients did not reduce overall mortality in all patients, but it might have had benefits in some subgroups, such as those with low CD4 cell counts, those with severe anemia, or those with clinically suspected tuberculosis. Unfortunately, because we did not evaluate mortality in the present study, we were unable to evaluate the impact of those in-hospital diagnoses made with the aid of LF-LAM.

In the present study, LF-LAM–positive patients had lower CD4 cell counts. In fact, it has been demonstrated that the estimated sensitivity of LF-LAM is greater in patients with lower CD4 cell counts.[17] In a prospective, observational study including adult HIV patients hospitalized in a public district hospital in Malawi, LF-LAM was more likely to be positive in people with CD4 counts below 200 cell/mm^3.[18]

An interesting finding of our study was that there was a lower frequency of smoking among patients with a positive LF-LAM result. Although it is possible that smoking can somehow hinder the detection of LAM, we found no other studies reporting a similar finding. Therefore, larger studies are needed to confirm this finding.

Our study has limitations, given that we recruited patients from a single setting; however, we do not think that this prevents the generalization of the results. On the other hand, this is the first study in Brazil to evaluate the use of LF-LAM in outpatients and inpatients, in conjunction with the Xpert® MTB/RIF Ultra assay on sputum.

In conclusion, in the present pragmatic study we demonstrated that the use of LF-LAM significantly increases the detection of tuberculosis in HIV-positive patients, mostly in those who are hospitalized. These findings highlight the utility of LF-LAM, especially in regions with high tuberculosis and HIV infection incidence. Future multicenter studies involving a larger number of patients may help to confirm our findings.

AUTHOR CONTRIBUTIONS

GRP: conceptualization; methodology; investigation; data curation; project administration; and writing—original draft. MSB, CS, MPP, AKS, RSLB, MSS, GSR, and JVVD: conceptualization; methodology; investigation; and writing—review and editing. DRS: conceptualization; methodology; investigation; data curation; project administration; supervision; and writing—original draft. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(4):e20250061
https://dx.doi.org/10.36416/1806-3756/e20250061

Vaping cessation: how to treat nicotine dependence and tailor the nicotine replacement dose. A narrative review

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

ABSTRACT

Electronic nicotine delivery systems, electronic cigarettes, or vapes have been extensively marketed as a safer alternative to combustible cigarettes and as aids for smoking cessation. However, electronic cigarettes often deliver more potent forms of nicotine, such as nicotine salts and synthetic nicotine, which are masked by appealing aromas and flavors, thereby attracting nonsmoking children and adolescents. On the other hand, adults dependent on freebase nicotine (found in conventional cigarettes) often become addicted to these new forms of nicotine in electronic cigarettes. Dual use is common and poses significant health risks, potentially exceeding those of using either product alone. Dual users experience increased odds of COPD, lung cancer, cardiovascular disease, and stroke. Electronic cigarettes represent a new challenge for global public health and health professionals. There are currently no specific guidelines for vaping cessation treatment. This study sought to provide health professionals with a comprehensive vaping cessation approach, including effective strategies such as behavioral support, nicotine replacement therapy, and the use of nicotine-free medications.

Keywords: Vaping; Cessation Guidance, Electronic nicotine delivery systems; nicotine replacement therapy, E-cigarette; Addiction medicine.

INTRODUCTION

Electronic cigarettes (ECs), also known as e-cigarettes, e-cigs, or vapes, are types of electronic nicotine delivery systems. ECs consist of a lithium battery, e-liquids, propylene glycol, vegetable glycerin, nicotine (most often), additives, and other substances that are harmful to health. The act of using ECs is known as "vaping," and EC users do not identify themselves as smokers; rather, they call themselves "vapers."[1,2]

Social media plays a key role in the illegal sale and promotion of ECs, creating a false sense of security with misleading information delivered through influencers and hashtag campaigns sponsored by the tobacco industry. These strategies lead EC users to believe that they are simply inhaling water vapor or a less harmful product.[2] In reality, ECs contain several toxic and carcinogenic substances, such as heavy metals and different types of additives with attractive aromas and flavors, such as kiwi or peach, which facilitate the absorption of countless harmful substances, as well as new forms of nicotine, which are more addictive and which are not used in combustible cigarettes.[1]

Dual use of combustible cigarettes and ECs is a prevalent behavior associated with a significantly increased risk of cardiovascular, cerebrovascular, and pulmonary diseases such as COPD and lung cancer, thereby contributing to elevated rates of premature mortality.[3-5]

In 2021, The WHO estimated that there were 82 million EC users worldwide, EC use being more prevalent among children in the 13- to 15-year age bracket than among people in older age groups, as well as being more prevalent among boys than among girls.[6] Therefore, ECs are a new and major challenge for global public health.

In the present study, we sought to investigate issues such as the wide variety of electronic nicotine delivery systems; the breadth of nicotine products currently available on the market; and the patterns of EC use. We also examined approaches to vaping cessation; pharmacological treatment with or without nicotine replacement; and how to tailor the nicotine replacement dose.

PHYSICAL, PSYCHOLOGICAL, AND BEHAVIORAL ASPECTS OF ADDICTION

In childhood and adolescence, the brain is still developing; nicotine affects areas responsible for memory, feelings, thoughts, and decision-making processes and

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Financial support: None.

◄ Voltar ao sumário
ISSN 1806-3756

can cause serious damage to mental and physical health, leading to nicotine addiction.[7] Addiction is characterized by a failure to control drug use. In other words, physical, psychological, and behavioral disorders occur in the absence of the drug, including insomnia, cramps, dizziness, anxiety, irritability, craving, and agitation.[7]

The psychological aspect of dependence encompasses the meaning or function that smoking has for the user. The device itself can be used in order to deal with feelings and emotions, as well as for relaxation or coping with stressful situations.[7] There is also the behavioral component of addiction: several associations of behaviors linked to rituals and pairing of habits via implicit memory are obstacles to quitting smoking.[7]

ECs have a pleasant smell and taste, and the packaging has beautiful colors, evoking affective memories of smells, tastes, and colors; in addition, associations of EC use with pleasurable social experiences can lead to cognitive distortions that cloud the understanding of the risks of EC use.[8,9]

TREATMENT OF NICOTINE ADDICTION

Motivational interviewing and cognitive behavioral therapy

Addiction to ECs and dual use are emerging public health challenges that require evidence-based and tailored therapeutic approaches. Although strategies used for conventional smoking cessation are applicable, EC addiction management requires adaptations to address unique patterns of nicotine use and a younger population of users.

Communication skills are essential for establishing a therapeutic relationship and encouraging patient engagement in treatment. Miller and Rollnick's motivational interviewing is widely recognized as an important therapeutic approach in clinical settings. It is a patient-centered approach that incorporates core principles such as asking open-ended questions, active listening, providing affirmation (praise, recognition, and understanding), and summarizing the contents mentioned back to the patient. The main goal is to elicit the person's own reasons for change in an atmosphere of empathy and acceptance.[10] It can be combined with other therapeutic methods such as cognitive behavioral therapy (CBT).[11]

In CBT for addictive disorders, five critical components of a therapy session are structure (including mood assessment, setting the agenda, action planning, and gathering patient feedback); collaboration; case conceptualization; psychoeducation; and the use of standardized techniques. By collaboratively exploring emotions, behaviors, thoughts, and beliefs with the patient, a more feasible and effective plan for behavior change can be developed. Addiction-related thoughts and beliefs are pivotal for the addiction process. Other specific cognitive processes in addiction include self-efficacy, positive outcome expectancies, negative outcome expectancies, and permissive beliefs (i.e., "I will just use it today.") Instrumental thoughts, which guide the logistics of addictive behaviors (such as how to obtain the substance), also need to be assessed.[12]

Some cognitive behavioral techniques have shown promise in the treatment of drug addiction and, consequently, can be useful for the nonpharmacological treatment of EC addiction. For example, cognitive restructuring consists of helping patients question their distorted thoughts and beliefs on the basis of more realistic evidence, including evidence on the role that substance use plays in the physical and mental health of users. When these cognitive distortions are altered and made more flexible, it becomes possible to change the emotional state and, consequently, the behavior of users. The development of coping and problem-solving strategies can also improve the response to treatment.[13]

Behavioral support plays a pivotal role in the treatment of EC addiction. Counseling programs assist users in developing strategies for cessation and have been shown to enhance the efficacy of pharmacological and behavioral interventions.[14] The combined use of psychological support and medication can improve outcomes and adherence to treatment protocols.

Although there is limited evidence for structured therapeutic interventions for EC addiction, tools such as smartphone applications are currently being developed and investigated. Although further studies are needed to evaluate their quality, content, user acceptance, and effectiveness, these tools can support EC cessation through text messages that target cognitive aspects and promote behavior change.

In a randomized controlled trial for vaping cessation, 2,588 participants in the 18- to 24-year age bracket were recruited for a fully automated text message intervention delivering social support, as well as cognitive and behavioral coping skills training, with the control arm receiving assessment only. The content included self-efficacy exercises, coping strategies, information about the risks of vaping, the benefits of quitting, how to cut down to quit, and distraction and substitution tips. Thirty-day abstinence rates after 7 months of follow-up were 24.1% (95% CI, 21.8-26.5) in the intervention group and 18.6% (95% CI, 16.7-20.8) in the control group (OR, 1.39; 95% CI, 1.15-1.68; $p < 0.001$).[15] However, in a recent systematic review of interventions for quitting vaping, evidence for text message-based interventions were considered of low certainty for vaping cessation in comparison with control in participants in the 13- to 24-year age bracket (two studies, 4,091 participants).[16]

How to decide when pharmacological treatment is necessary

The decision to initiate pharmacological treatment for nicotine dependence, including vaping, should be based on a comprehensive assessment of patient history, prior cessation attempts, level of nicotine dependence,

and severity of withdrawal symptoms.[13] Given the amplified health risks of dual EC and combustible cigarette use, complete cessation of all tobacco and nicotine products is the major therapeutic goal.[17]

Nicotine replacement therapy (NRT), bupropion, varenicline, and cytisine (also known as cytisinicline), when used in combination with CBT, can reduce withdrawal symptoms and cravings, aiding in overcoming nicotine dependence, regardless of the delivery method.[13] Extrapolating from the established success of evidence-based pharmacological treatment for smoking cessation, similar strategies are reasonably applicable to EC users, even as specific guidelines evolve.

Early studies support this approach, with varenicline demonstrating a 40% continuous abstinence rate in comparison with 20% with placebo[18] and cytisinicline showing efficacy for EC cessation (31.8% vs 15.1% with placebo), suggesting potential pharmacological options for adults seeking to quit vaping.[19]

NRT for vapers

NRT is available in a variety of ways to suit different needs and levels of addiction. There is fast-acting nicotine (e.g., 2 or 4 mg gums or lozenges, sprays, and inhalers), which can be used in order to manage sudden cravings. Another form of NRT is slow-acting nicotine patches, which provide constant support throughout the day (e.g., 21, 14, and 7 mg transdermal patches).[20]

The maximum dose of NRT depends on the form used. For patches, it is usually not recommended to exceed a dose of 42 mg/day, but individual assessments are necessary. For gums and lozenges, the dose should be limited to approximately 15 to 20 gums or lozenges per day. Higher doses are recommended for heavier nicotine users.[20]

For early-stage treatment regimens, it is recommended to start with a higher dose (e.g., 21 mg patches). As patients wean themselves from ECs (i.e., in the maintenance phase of treatment), gradual reductions in NRT are recommended. After 6 to 12 weeks, lower doses should be prescribed (e.g., 14 mg patches and then 7 mg patches).[20]

In the weaning phase, a gradual reduction in dose over 8 to 12 weeks is recommended. Patients should be supported throughout the treatment with behavioral counseling to increase efficacy.[20]

Special attention should be paid to nicotine overdose situations, in which symptoms such as nausea, vomiting, increased heart rate, and dizziness may occur. Health care professionals should inform users of these signs of toxicity.[20]

Contraindications such as cardiovascular disease (e.g., recent myocardial infarction and unstable angina) and being pregnant or breastfeeding should be considered by health care professionals during treatment planning.[20]

How to tailor the nicotine replacement dose for EC users

The wide variety of ECs and liquid nicotine products available on the market has made it challenging for health care professionals to tailor the nicotine replacement dose.

Clinically relevant measures of EC use include the number of times the device is used/day; the number of puffs/day; the volume of liquid nicotine consumed/day; the concentration and type of liquid nicotine in ECs; EC generation; and EC electrical power (in watts). However, there are several limitations. First, one distinctive characteristic of EC use is automatic use throughout the day—a behavior known as "grazing"—whereas, with tobacco cigarette smoking, there is a clear start and a clear end to smoking each cigarette.[21,22] Second, EC users are not always able to provide correct information on the device characteristics, such as power, nicotine content, and composition.[23-28]

Very few trials on vaping cessation have been conducted. To our knowledge, there are currently no evidence-based guidelines regarding pharmacological interventions for vaping cessation. In a review of vaping cessation interventions available to former smokers, the authors investigated ECs as a smoking cessation method.[29] Given that EC users worldwide are increasingly seeking vaping cessation treatment, a reasonable approach is to use the scientific evidence available for combustible cigarette smoking cessation, including the use of NRT and other first-line medications in combination with CBT.

The correct use of NRT for EC users is challenging and of paramount importance.[1] Specialists or clinicians aiding EC users in vaping cessation should collect data on three parameters in order to measure EC use:

- device features—EC type (mod or pod); rechargeable or disposable; brand/brands used; and number of puffs the device delivers
- e-liquid characteristics: type of nicotine (freebase nicotine, nicotine salt, or synthetic nicotine); amount of e-liquid (mg/mL) per refill or per tank; and nicotine concentration (%; mg/mL) per refill
- EC use characteristics: refill frequency or time until next purchase of a disposable pod; number of e-liquids used in the tank; final concentration of nicotine in the e-liquid after filling the tank with more than one e-liquid; and dual use of combustible cigarettes and ECs

If a health care professional chooses to use NRT for vaping cessation, they must calculate the approximate nicotine dose. To that end, the following information is required: nicotine type and concentration (in % or mg/mL); tank/device capacity (in mL); and the time it takes to consume all of the e-liquid. Brazilian legislation determines that the maximum nicotine concentration in firsthand smoke must be 1 mg per cigarette.[30] The idea is to use NRT to replace the amount of nicotine consumed per day.

Hypothetical clinical case

A 20-year-old male seeks vaping cessation treatment. He reports using the following: nicotine salts at a concentration of 2%; an EC the total capacity of which is 10 mL of e-liquid; and 10 mL of e-liquid in 4 days. How can the health professional aiding in vaping cessation calculate the approximate amount of nicotine consumed, the equivalence between EC use and combustible cigarette use, and a safe nicotine replacement dose (Figure 1)? Among pharmacological treatments for smoking cessation, bupropion, varenicline, and cytisinicline stand out (Figure 2).

Bupropion, an antagonist of nicotinic receptors and dopamine reuptake inhibitor, helps alleviate withdrawal symptoms and reduces cravings for ECs. This pharmacological approach can be combined with behavioral support to optimize treatment outcomes.[17] Bupropion reduces seizure threshold and should not be used in patients who are at an increased risk of seizures.[17]

Varenicline, a partial agonist of the α4β2 nicotinic receptors, has proven efficacy in aiding EC cessation by reducing cravings and the reinforcing effects associated with nicotine consumption. Studies suggest that varenicline is preferable as a cessation strategy because of its safety and efficacy profile.[31,32]

In a randomized clinical trial, the efficacy of varenicline (1 mg twice daily for 12 weeks) combined with counseling was evaluated in daily EC users seeking to quit. The results demonstrated significantly higher continuous abstinence rates with varenicline in comparison with placebo: 40% vs. 20% at weeks 4 to 12 and 34.3% vs. 17.2% at weeks 4 to 24. Although these findings reinforce the effectiveness of varenicline, they also indicate a low incidence of serious adverse events unrelated to the medication.[18]

In a recently published randomized clinical trial, the effectiveness of varenicline for nicotine vaping cessation was evaluated among individuals in the 16- to 25-year age bracket who vaped daily or near daily but did not regularly smoke tobacco. Participants were assigned to three groups: 12 weeks of double-blind varenicline with behavioral counseling and text messaging support (n = 88), identical placebo with counseling and support (n = 87), or referral to support only (enhanced usual care, n = 86). The primary outcome was biochemically verified continuous vaping abstinence during the last 4 weeks of treatment. Results showed that abstinence was 51% with varenicline vs. 14% with placebo during weeks 9-12 and 28% vs. 7% during weeks 9-24, indicating a significant benefit of varenicline. Varenicline also outperformed enhanced usual care, with higher abstinence rates. The authors of the study concluded that varenicline significantly improved vaping cessation in that population.[33]

Cytisinicline is an alkaloid that occurs naturally in several plant genera. Its molecular structure has some similarity to that of nicotine and varenicline, and it has the same pharmacological effects: it is a partial agonist of brain nicotinic acetylcholine receptors. It

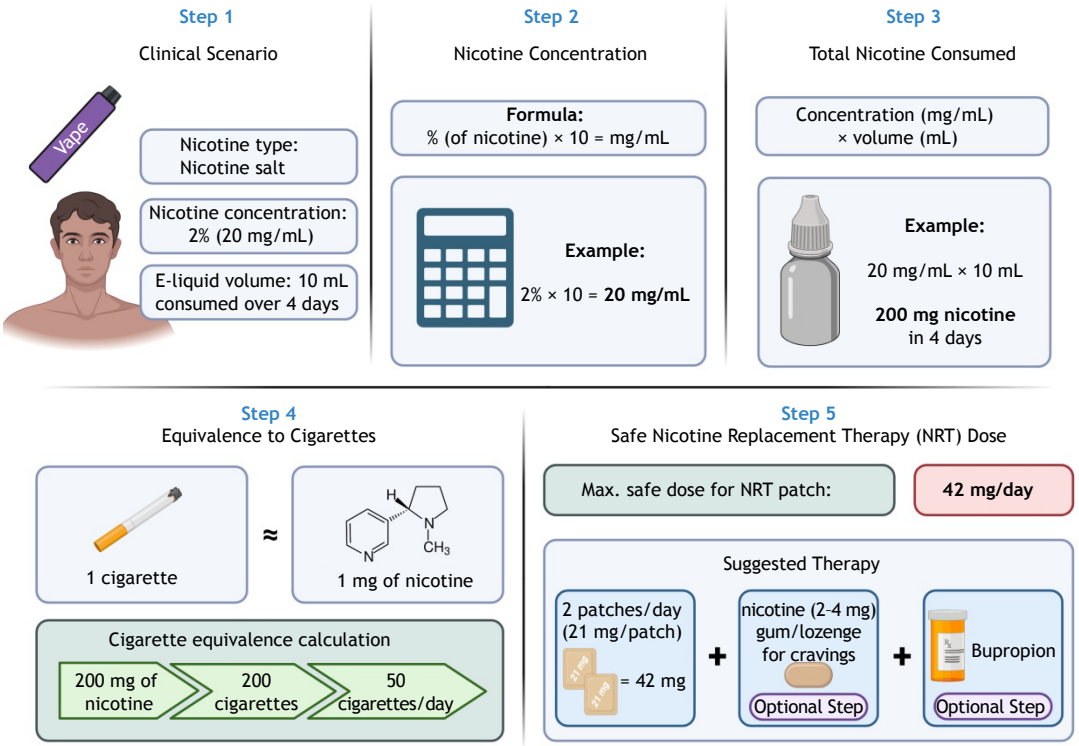

Figure 1. Example of approximate calculation of nicotine equivalence.

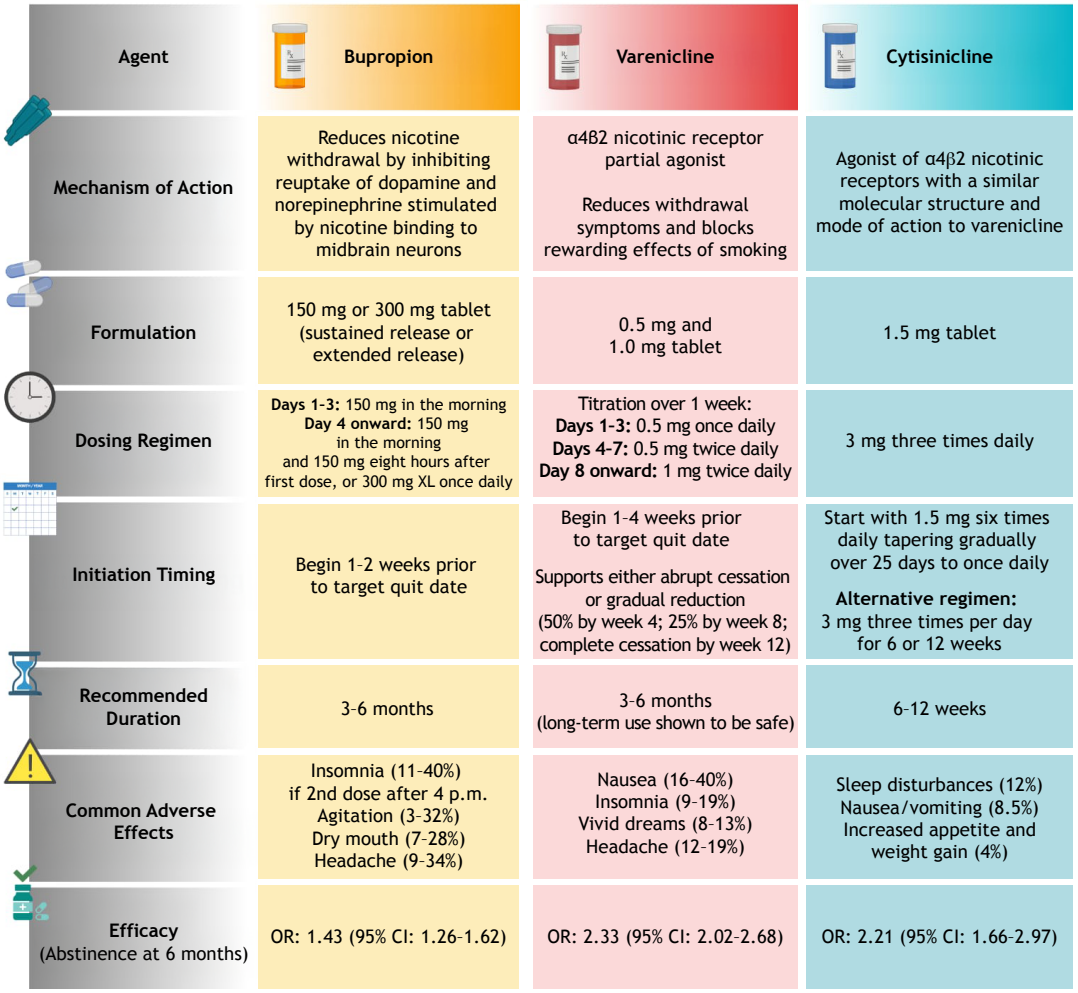

Figure 2. Non-nicotine pharmacological treatment for smoking cessation and smoking abstinence at 6 months. Adapted from Barua et al. and Lindson et al.[17,34]

decreases the urge to use tobacco and reduces the severity of nicotine withdrawal symptoms, while also reducing the reward experience of using tobacco.[34]

FINAL CONSIDERATIONS

The treatment of EC dependence requires an integrated approach combining behavioral interventions and pharmacotherapy, with the ultimate goal being complete nicotine cessation.

The present study provides health care professionals with a comprehensive cessation framework, including strategies for behavioral support; safe and effective use of NRT; and non-nicotine pharmacological alternatives. A key contribution of our study is the methodology for calculating nicotine equivalence, which facilitates accurate NRT dosing and supports clinical decision-making in the management of nicotine addiction. Further studies are needed to strengthen the evidence base and inform best practices in the treatment of EC dependence.

ACKNOWLEDGMENTS

We sincerely thank Felipe M. Berg for his valuable assistance in creating the two figures in this article, both of which were created with BioRender software (available at https://www.biorender.com/).

AUTHOR CONTRIBUTIONS

SRM and PCRPC: conceptualization (lead), methodology (equal), project administration (lead), writing—original draft (equal), and writing—review and editing (equal). CC, MS, CAPT, and VLGB: conceptualization (equal), methodology (equal), project administration (supporting), writing—original draft (equal), and writing—review and editing (equal). All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Pulmonary function estimation using smartphone audio and deep learning

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TO THE EDITOR:

Respiratory diseases are on the rise globally, and COPD now ranks as the fourth leading cause of death worldwide. In 2021 alone, COPD claimed approximately 3.5 million lives, and 90% of deaths were in people under 70 years of age living in low- and middle-income countries.

While spirometry remains the gold standard for diagnosing COPD and monitoring pulmonary diseases, conventional spirometers cost over $2,000, limiting their availability in resource-constrained settings. Even portable alternatives may be too expensive for routine use. Mobile phones offer a promising solution to this accessibility challenge. With their widespread availability, they present an opportunity to implement cost-effective spirometry using the phone's embedded microphone. Previous research has demonstrated the feasibility of measuring pulmonary function through breath sounds,[1-3] although many approaches required additional equipment such as external microphones or instrumented blowpipes.[4-6]

Our approach advances this concept by analyzing the sound of a patient's forced breathing without any external equipment, making it more accessible to health care professionals and patients alike. This shift toward equipment-free measurements opens opportunities for applying advanced analytical techniques, particularly neural networks. These computational models excel at pattern recognition, making them ideal for analyzing complex audio signals from breathing.[7,8]

It's important to note that spirometry and audio recordings measure fundamentally different phenomena. Traditional spirometry directly measures airflow and volume, while our approach analyzes acoustic signals indirectly related to airflow. These acoustic patterns are influenced by airway anatomy, ambient acoustics, and microphone characteristics. Our objective is to establish whether these distinct techniques can derive comparable functional values, creating a reliable mapping between acoustic patterns of forced expiration and corresponding pulmonary function metrics.

The authors obtained ethical approval from two Brazilian universities: *Universidade Estadual de Campinas* and *Universidade Federal de São Paulo* research ethics committees (CAAE 65695422.4.0000.5404). We collected recordings from consenting patients undergoing routine spirometry in the Pulmonary Function Laboratory of the Pulmonology Division at the *Escola Paulista de Medicina/Universidade Federal de São Paulo*. For each participant, a single post-bronchodilator spirometry reading was performed using conventional equipment, providing reference values for FVC, FEV_1, and PEF. Immediately after the standard spirometry procedure, each participant performed a single forced expiration maneuver under a standardized positioning protocol. Volunteers held a Samsung Galaxy J500M/DS (Samsung Electronics; Suwon, South Korea) smartphone upright with the screen facing them at approximately 30 cm, directing their expiratory flow toward the center of the screen. To optimize signal quality and ensure reproducibility, a nose clip was applied, and a tube was placed in the mouth, as shown in Figure 1. A certified respiratory technician supervised all maneuvers to ensure proper technique, and recordings were made using the free app Audio Recorder (Samsung Electronics).

This one-to-one approach allowed for direct comparison between the clinically measured spirometry values and the audio-derived estimates for each patient. The analysis covered three key spirometry parameters: FVC, FEV_1, and PEF. In total, we gathered 25 recordings: 7 from healthy patients, 14 from patients with obstructive diseases, and 4 from patients with restrictive disorders. The study cohort consisted of 9 males and 16 females with a mean age of 58.8 ± 13.6 years. All data was anonymized for further processing.

Audio samples were processed using the Torch Audio library, standardized to mono-channel at 48 kHz, and adjusted to a uniform duration of five seconds. To address the limited dataset size, we implemented a comprehensive three-stage data augmentation pipeline to improve model generalization and robustness. In the first stage, we applied Additive White Gaussian Noise with a controlled signal-to-noise ratio between 0 and 0.3, simulating various real-world recording conditions. The second augmentation stage involved random gain adjustment, multiplying the audio signal by a random factor between 0 and 60, helping the model become invariant to volume differences. For the third stage, we transformed each augmented audio sample into a set of three mel spectrograms with different time-frequency resolutions (window sizes: 512, 1,024, and 2,048 samples), all with a 25% frame overlap and 64 mel frequency bins. These three spectrograms were combined as channels in a single image, providing a rich multi-resolution input to the convolutional neural networks. Finally, we applied SpecAugment techniques to the spectrograms, randomly masking frequency bands and time segments to enhance model generalization.[9] This augmentation strategy dynamically expanded the dataset, generating endless training examples from the original 25 recordings during model training.

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ISSN 1806-3756

Two convolutional neural network models were compared as regressors. The baseline architecture consisted of four consecutive blocks, each with a feature detection layer, a Rectified Linear Unit (known as ReLU) activation function, and a normalization layer. We also utilized the more advanced residual network (know as ResNet) architecture with 152 layers (ResNet152), which was pre-trained on the ImageNet database containing over 14 million images across 20,000 categories, providing a robust foundation for transfer learning to our specific task. Transfer learning was applied to the ResNet152 using three strategies: (1) Freezing—all layers were kept fixed, except the final classification layer; (2) Unfreezing—all layers were fine-tuned; and (3) Partial freezing—only the last 50 layers were fine-tuned, preserving the general feature extraction capabilities of the earlier layers while allowing the deeper layers to adapt to the specific application.

The performance of our deep learning models is quantified using the root mean squared error (RMSE) reported in Table 1. For FVC, the best-performing model was the ResNet152 with the freezing strategy, yielding an RMSE of 0.66 ± 0.27 L. For FEV_1 and PEF, the RMSE values are approximately 0.5 L and 1.32 L/min, respectively. When compared to the average clinical values (FVC = 2.92 ± 0.89 L, FEV_1 = 2.02 ± 0.63 L, PEF = 5.88 ± 1.94 L/min), they represent rough deviations of 28% for FVC, 35% for FEV_1, and 20% for PEF. Although these deviations are larger than those typically seen in conventional spirometry, it is important to note that our method employs only the built-in microphone of a smartphone—without any additional hardware—to capture respiratory sounds under real-world conditions. In contrast, many existing smartphone-based or low-cost spirometry tools rely on external devices to achieve lower prediction errors. Our approach prioritizes accessibility and cost-effectiveness, making it particularly suitable for resource-limited settings.

Figure 1. Figure diagram illustrating the standardized positioning used for smartphone spirometry. The participant performs a forced expiratory maneuver while holding a smartphone approximately 30 cm away, with the screen facing him/her, similar to taking a selfie. A nose clip and a mouth tube are used to ensure proper technique and optimize signal quality.

In conclusion, this study demonstrates the potential of using smartphone microphones as a cost-effective and accessible alternative to traditional spirometry equipment, with deep learning models showing a promising correlation between forced expiration audio and pulmonary function parameters. While the current error margins (20-35%) are higher than clinical standards for conventional spirometry, this approach represents a significant step toward more accessible respiratory assessment tools, especially in resource-limited settings where conventional spirometers are scarce. By leveraging widely available technology and advanced machine learning techniques, we hope to contribute to more accessible respiratory health care screening worldwide.

We acknowledge the fact that the small dataset (25 samples) limits generalizability, reflecting the study's exploratory nature. Future work should expand the dataset, refine regression models, and test advanced techniques such as recurrent neural networks or transformers to better capture temporal audio patterns. We also recognize that the current implementation does not meet established clinical pulmonary function testing accuracy standards, which typically require error margins below 5-10%. Future research will focus on reducing prediction errors to approach clinically acceptable levels for diagnostic use. Using a single device model is another limitation, as its outdated hardware may not reflect current technology. Yet, this choice serves as a "worst-case scenario," showing that even older devices can provide valuable data. Results will likely improve

Table 1. RMSE results of the tested architectures and fine-tuning techniques. RMSE measures the average magnitude of prediction errors compared to actual spirometry values. Lower values indicate better performance.

Network		RMSE		
Architecture	Fine-tuning Strategies	FVC (L)	FEV_1 (L)	PEF (L/min)
Classic CNN	-	0.82 ± 0.15	0.49 ± 0.17	1.25 ± 0.22
ResNet152	Unfreezing	0.78 ± 0.17	0.48 ± 0.28	1.56 ± 0.51
	Partial Freezing	0.74 ± 0.23	0.52 ± 0.19	1.46 ± 0.69
	Freezing	0.66 ± 0.27	0.50 ± 0.23	1.32 ± 0.37

RMSE: root mean squared error; CNN: convolutional neural network; and ResNet152: residual network architecture with 152 layers.

with newer models featuring better microphones, and future research should include various smartphones to enhance generalizability and develop calibration protocols to manage hardware differences.

ACKNOWLEDGMENTS

We thank Marta Amorim and Julio Pacheco Carlstrom for their technical assistance.

AUTHOR CONTRIBUTIONS

GSR, BSM, and JBM: study conception and design; GSR: data curation and investigation; GSR: software development; GSR and BSM: project administration and supervision; GSR, BSM: resource management; GSR, BSM, and JBM: analysis and interpretation of results. GSR wrote the original draft of the manuscript, and all authors (GSR, BSM, and JBM) contributed to reviewing and editing subsequent versions. All authors reviewed the results and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Trends in clinical and pharmacological profiles of severe asthma in the era of biologics in the Brazilian public health system: real-world evidence from a tertiary outpatient clinic

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TO THE EDITOR:

Protocolos Clínicos e Diretrizes Terapêuticas (PCDT, Clinical Protocols and Therapeutic Guidelines) are documents that are issued by the Brazilian National Ministry of Health and that must be followed by *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System) managers. Before the PCDT for asthma were updated in 2021,[1] patients with severe asthma treated in the SUS did not have access to biologics and experienced a high disease burden. In 2012, we published data describing the characteristics of our outpatient population with severe asthma, highlighting this significant disease burden.[2]

Omalizumab has been available for the treatment of severe asthma for more than a decade; however, in 2016 the Brazilian National Committee for Technology Incorporation decided against the provision of treatment with omalizumab within the scope of the SUS.[3] In response, we at the Pulmonology and Allergy/Immunology Outpatient Clinic of the University of São Paulo School of Medicine *Hospital das Clínicas*, located in the city of São Paulo, Brazil, developed a protocol to enable patient access to omalizumab treatment.[4] We also sought to develop researcher-initiated projects designed prior to the incorporation of biologics and presented our findings at a number of conferences, sharing our clinical experience.[5,6]

Biologics can reduce exacerbation rates, decrease oral corticosteroid (OCS) use, and improve asthma control. However, after treatment initiation, it is important to evaluate patient response within 6-12 months with the goal of reducing maintenance therapy, especially those associated with significant side effects. In this context, tapering OCS and high-dose inhaled corticosteroid (ICS) doses is particularly relevant.[7,8]

There are several ways to assess clinical response to biologic therapy, including a reduction in exacerbation frequency; improvement in symptom control and lung function; reduction in maintenance therapy; prevention of adverse effects; and enhanced patient satisfaction. [7,8] When a satisfactory clinical response is achieved, it is recommended to reduce maintenance therapy to the lowest dose required to maintain disease control. In this context, strategies to minimize OCS use are especially important, given the potential for significant adverse effects.[7]

Since the 2021 update of the PCDT for asthma,[1] patients with severe asthma treated in the SUS have had access to two biologics, namely, omalizumab and mepolizumab. Here, we present real-life outcomes in patients followed at our asthma outpatient clinic after the inclusion of omalizumab and mepolizumab in the SUS, as outlined in the updated PCDT for asthma. This was a retrospective observational study, the primary objective of which was to evaluate the clinical and pharmacological profiles of severe asthma patients treated at a tertiary outpatient clinic in the SUS. The study was approved by the local institutional review board (Protocol no. 7.058.172).

The statistical analysis was descriptive in nature. Categorical variables were presented as absolute numbers and percentages. Numerical variables were expressed as mean ± standard deviation, depending on the distribution of the data. In the present study, handling of missing data was not applicable because data on the outcomes assessed (Asthma Control Test [ACT] scores, Asthma Control Questionnaire [ACQ] scores, exacerbations, and prescribed medications) are regularly collected through standardized procedures during each visit, and no data were missing.

This was a convenience sample. Of a total of 60 severe asthma patients receiving omalizumab or mepolizumab for at least six months in accordance with the 2021 PCDT for asthma,[1] 45 were included. Of those, 11 (18.3%) were excluded because of prior use of another biologic agent, and 4 (6.7%) declined to participate. After patients gave written informed consent, patient medical records and our electronic prescription system were retrospectively reviewed in order to collect data at baseline and at 24 and 48 weeks after initiation of biologic therapy, as well as to assess medical prescriptions. A total of 45 patients were evaluated at baseline and at 24 weeks, whereas 30 patients were evaluated at 48 weeks. This was due to the fact that 15 patients either discontinued therapy because of treatment failure or had an insufficient follow-up period. The data were entered into a Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN, USA) database. The use of other medications was

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ascertained from previous prescriptions, and short-acting β_2 agonist (SABA) doses were recorded from our electronic prescribing system. Adherence to treatment with biologics was assessed on the basis of outpatient clinic attendance.

Our patient population was predominantly female (77.8%) with uncontrolled asthma (mean ACT score, 14.5 ± 5.3; mean ACQ score, 2.5 ± 1.2). Most were using a high-dose ICS combined with a long-acting β_2 agonist (LABA), except for one patient who was intolerant to LABAs. Approximately 67% had childhood onset asthma, and 55.6% were atopic. Patients experienced an average of 3.3 exacerbations in the preceding year and had impaired lung function (prebronchodilator percent predicted FEV_1, 62 ± 22). The mean age at initiation of biologic therapy was 50 years, and 17.8% were former smokers. One third of the study participants were receiving maintenance OCS therapy, and 60% received mepolizumab. The mean number of comorbidities was 4.4. Adherence to biologic therapy was demonstrated by the fact that 71% and 80% of the study participants attended all scheduled appointments at weeks 24 and 48, respectively.

We observed an improvement in asthma control following biologic therapy. At baseline, the mean ACT score was 14.5 ± 4.8 and the mean ACQ score was 2.5 ± 1.3, indicating uncontrolled asthma. At week 48, those scores improved to 17.8 ± 5.1 (a 3.3-point increase) and 1.5 ± 1.0 (a 1.0-point decrease), respectively (Table 1). Given that a change of 3 points in the ACT score and 0.5 points in the ACQ score is considered clinically significant,[1,8] our results demonstrate a clinically significant improvement in asthma control.

There have been few real-life studies evaluating the response to biologics in patients with severe asthma in Brazil. In a study evaluating severe asthma patients in a public hospital in the state of Paraná,[9] there was an ACT score improvement of 4.8 points, which is comparable to the results observed in our study. In addition, the frequency of exacerbations decreased from an average of 3 per year to 0 per year, despite a reduction in the proportion of patients using OCSs (Table 1).

At baseline, approximately 35% of patients were receiving maintenance OCS therapy. As can be seen in Table 1 and Figure 1, there was a relative reduction of approximately 49% in the proportion of patients using OCSs by week 48, decreasing from 35.5% to 17.8%.

No significant changes were observed in the use of maintenance ICS-LABA therapy during follow-up, and more than 50% of the patients remained on additional ICS therapy alongside ICS + LABA throughout the evaluation period (Table 1). The lack of evidence supporting ICS step-down approaches in patients with severe asthma likely explains the more conservative approach to this intervention. The first evidence for ICS reduction in this context emerged in early 2024 with the use of benralizumab.[10] Given that our patients

Table 1. Evaluation of severe asthma patients during follow-up.[a]

Variable	Baseline (n = 45)	Week 24 (n = 45)	Week 48 (n = 30)
No. of exacerbations	3 [0-11]	0 [0-5]	0 [0-4]
ACT score	14.5 ± 4.8	17.3 ± 5.5	17.8 ± 5.1
ACQ score	2.5 ± 1.3	1.7 ± 1.2	1.5 ± 1.0
ICS-LABA maintenance therapy	44 (97.8)	44 (97.8)	28 (93.3)
Mean daily dose of ICS + LABA, µg[b]	1,382 ± 341	1,350 ± 412	1,418 ± 409
ICS	26 (57.8)	23 (51.1)	17 (56.7)
Mean daily dose of ICS, µg[b]	2,227 ±1352	2,117 ± 1,388	2,276 ± 1,428
Total daily dose of ICS, µg[b]	1,696 ± 950	1,547 ± 775	1,742 ± 1,010
OCS	16 (35.5)	14 (31.1)	8 (17.8)
Total daily dose of OCS, mg[c]	21 ± 14	21 ± 14	17 ± 11
Rescue ICS + LABA	16 (35.6)	17 (37.8)	7 (23.3)
Mean daily dose of rescue ICS + LABA, µg	700	623	485
SABA	27 (60)	23 (51)	18 (60)
Mean daily dose of SABA, µg	625	543	522
Antibiotic therapy[d]	9 (20)	8 (17.8)	4 (13.3)
H1 antihistamines	19 (42.2)	19 (42.2)	14 (46.7)
Antileukotrienes	17 (37.8)	17 (62.2)	11 (36.7)
Proton pump inhibitor	39 (86.7)	38 (84.4)	25 (83.3)
Prokinetics	28 (62.2)	25 (55.6)	14 (46.7)
Nasal corticosteroid	34 (75.6)	35 (77.8)	23 (76.7)
Ipratropium bromide	17 (37.8)	19 (42.2)	9 (30)
Tiotropium bromide	11 (24.4)	7 (15.6)	8 (26.7)

ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; ICS: inhaled corticosteroid; OCS: oral corticosteroid; LABA: long-acting β_2 agonist; and SABA: short-acting β_2 agonist. [a]Data presented as n (%), mean ± SD, or median [IQR]. [b]ICS dose equivalent to budesonide. [c]OCS dose refers to prednisone or equivalent. [d]Azithromycin (3 times/week).

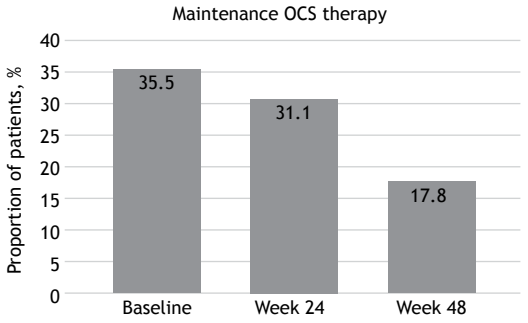

Figure 1. Proportion of patients receiving maintenance oral corticosteroid (OCS) therapy during follow-up.

were evaluated by the same medical team prior to each biologic dose, we can infer that adjustments to maintenance ICS-LABA therapy, OCSs, and other medications were tailored to each patient, even with the constraints of real-life clinical practice.

To assess the use of therapy (ICS-LABA therapy or SABA therapy), we considered the total daily dose because it was not feasible to estimate the actual individual dose used, given that the evaluation was based on electronic prescription data. A reduction was observed in the proportion of patients who were prescribed ICS-LABA therapy for relief and in the mean ICS dose within this combination, decreasing from 700 µg at baseline to 485 µg at week 48. Similarly, the mean SABA dose decreased throughout the study period. (Table 1)

Each of the study participants used an average of eight medications, some of which were prescribed for comorbidities related to asthma. It is important to consider the potential impact of those comorbidities, as well as other factors, on treatment response. However, because data were collected exclusively from our electronic prescribing system, we were unable to capture information on treatments outside our facility.

Our study has some limitations. First, it was a single-center study conducted at a tertiary university hospital; therefore, caution is recommended when generalizing the data. Second, the small sample size and the descriptive and retrospective design of the study may also be subject to information gaps. Nonetheless, this was a real-life study conducted in a complex clinical setting and evaluating severe asthma patients treated by the same medical team while receiving biologic therapy. This approach reflects a personalized, patient-centered model of care, underscoring the importance of appropriate patient selection and close follow-up when prescribing high-cost treatments, especially in the context of limited financial resources.

Our data describe the clinical and pharmacological profiles of severe asthma patients treated with biologics at a tertiary outpatient clinic in the Brazilian public health system. This real-life study demonstrates significant improvements in clinical control and exacerbation rates, despite a reduction in the proportion of patients using OCSs. However, our findings also suggest that a longer follow-up period may be required to reduce maintenance therapy further. The presence of comorbidities often leads to polypharmacy and increases the risk of self-medication, potentially complicating disease control. Our results underscore the importance of pharmacist involvement in patient care to identify treatment-related problems, optimize therapeutic management, and prevent inappropriate or irrational medication use.

AUTHOR CONTRIBUTIONS

CFOST, PCMH, VBP, AC, RAA, and RMCP conceived the study and reviewed the manuscript. CFOST, PCMH, and RMCP planned the collection and contributed to the analysis of data. CFOST performed the collection of data and submitted the manuscript. All authors are responsible for the overall content of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Evaluation of screening methods for preclinical interstitial lung disease associated with rheumatoid arthritis

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TO THE EDITOR,

The early diagnosis of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) remains a challenge in clinical practice, and the development of individualized screening criteria using measurable indicators is still an unmet need that warrants further investigation.[1] The most recent guidance on the subject—the 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Screening and Monitoring of Interstitial Lung Disease (ILD) in People with Systemic Autoimmune Rheumatic Diseases—recommends screening all patients considered at high risk for RA-ILD using high-resolution computed tomography (HRCT) and spirometry with lung volumes and diffusing capacity of carbon monoxide (DLCO). A conditional recommendation against the use of the six-minute walk test (6MWT) was issued due to the lack of studies evaluating its efficacy as a screening tool.[2]

In order to evaluate the association between the 6MWT, serum levels of Krebs von den Lungen-6 (KL-6), and spirometry parameters, including lung volumes and DLCO, with HRCT findings suggestive of ILD in RA, we conducted a cross-sectional observational study at a tertiary rheumatology center in Brazil. All included participants were adults, with a confirmed diagnosis of RA according to the 2010 ACR/EULAR criteria,[3] without respiratory symptoms or a prior diagnosis of ILD, and had been on stable treatment for at least 8 weeks. All RA diagnoses were reviewed and confirmed, and data were collected through clinical evaluations and medical record reviews.

The study participants underwent HRCT to identify ILD findings, including the presence of reticulation with or without ground-glass opacities, traction bronchiectasis, honeycombing, or isolated ground-glass opacities. Two independent, qualified readers, who were not blinded to the clinical data, evaluated the HRCT scans. Serum KL-6 levels were measured using the ELISA technique. Pulmonary function tests (PFTs), including the 6MWT, were performed according to international guidelines.[4,5] Although all assessments were intended to be conducted on the same day, eleven patients had an interval of more than 100 days between tests due to team or patient unavailability. Nevertheless, this was deemed acceptable, as no significant clinical events occurred during this period. Overall, the time intervals between tests were short: the median interval between HRCT and PFTs was 20 days; between KL-6 and PFTs, 35 days; and between HRCT and KL-6, 0 days. Association and concurrent validity analyses were performed using Pearson's correlation coefficient, biserial correlation, and point-biserial correlation tests. Receiver operating characteristic (ROC) curves were constructed to determine cutoff values. Data were analyzed using SPSS (version 23.0), JASP (version 0.18.3.0), and Jamovi (version 2.5.3).

This study was approved by the local ethics committee, and all patients provided informed consent.

Initially, a non-probability sample of 44 patients was selected. However, 7 were unable to complete all the required assessments, resulting in a final cohort of 37 patients. The majority were female (86.5%), and 81% had elevated levels of rheumatoid factor and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies. The mean age of the patients was 54.4 years (SD=13.75), with a median disease duration of 4.6 years. Additionally, 37.8% were current or former smokers (Table 1).

The HRCT scans revealed mild findings, affecting less than 5% of the lung parenchymal volume according to the semi-quantitative evaluation by the readers, with no evidence of honeycombing. Only 29.8% of the scans were normal. Interstitial changes were observed in 32.4% of the scans, with one case (2.7%) showing overlap with airway alterations. Non-specific and airway-related changes—such as nodules, cysts, emphysema, and air trapping—were identified in 35.1% of the scans.

On average, the patients exhibited a forced vital capacity (FVC) of 1.96 ± 0.69 L (88.8 ± 18.77% of predicted), a forced expiratory volume in the first second (FEV_1) of 2.38 ± 0.59 L (89.92 ± 12.54% of predicted), and an FEV_1/FVC ratio of 80.0 ± 7.64—all values above the lower limit of normal. Two tests indicated a mild restrictive pattern, six showed a mild-to-moderate obstructive pattern, and one revealed a combined ventilatory defect. The mean DLCO was 19.02 ± 4.0 mL/min/mmHg (96.53 ± 16.18% of predicted), with 10.8% of patients showing a mild reduction. The mean serum KL-6 level was 606 ± 362.64 U/mL.

The mean 6MWT distance (6MWTD) was 451.08 ± 105.58 meters and was moderately correlated with preclinical ILD changes on HRCT ($r_p b$=0.547; p=0.001). In our study, a 6MWTD cutoff of 462.55 m demonstrated good accuracy in distinguishing patients with HRCT findings suggestive of RA-ILD from those without (AUC=0.813; 95% CI: 0.665 – 0.960; p=0.003) (Figure 1). Serum KL-6 levels were also correlated with HRCT findings suggestive of ILD ($r_p b$=0.33;

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  ◄ Voltar ao sumário ISSN 1806-3756

Table 1. Clinical characteristics of the study sample (n=37).

Variables	Descriptive Statistics
Age, years	54.41 (13.75)
Female sex, n / %	32 / 86.5
Smoking, n / %	
Ex-smoker	12 / 32.4
Current smoker	2 / 5.4
Never smoked	23 / 62.2
Tobacco load, pack-years	18.87 (30.98)
Disease duration, years*	4.60 (0.56–50.56)
Rheumatoid factor, n / %	
Low: <3x ULN	7 / 18.9
High: >3x ULN	22 / 59.5
No information	8 / 21.6
Anti-CCP, n / %	
Low: <3x ULN	2 / 5.4
High: >3x ULN	27 / 73.0
No information	8 / 21.6
DAS-28 CRP	3.46 (1.33)
CDAI	13.20 (11.96)
HAQ	1.17 (0.96)
CRP	10.4 (8.59)
Charlson Comorbidity index	2.54 (1.57)
MEAS, n / %	2 / 5.4
Current medications, n / %	
Corticosteroids	20 / 54.1
Anti-TNF	3 / 8.1
Rituximab	3 / 8.1
Tocilizumab	1 / 3.7
iJAK	4 / 10.8
Synthetic DMARDs, n / %	
MTX	22 / 59.5
HQC	1 / 2.7
LFN	18 / 48.6
SSZ	0 / 0.0
AZA	1 / 2.7

ULN: upper limit of normal; Anti-CCP: anti-cyclic citrullinated peptide antibody; DAS-28 CRP: Disease Activity Score-28 with C-Reactive Protein; CDAI: Clinical Disease Activity Index for Rheumatoid Arthritis; HAQ: Health Assessment Questionnaire; CRP: C-Reactive Protein; MEAS: extra-articular manifestations; Anti-TNF: tumor necrosis factor antagonist; iJAK inhibitor: Janus kinase inhibitor; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; HCQ: hydroxychloroquine; LFN: leflunomide; SSZ: sulfasalazine; AZA: azathioprine. *Data expressed as mean (standard deviation), absolute/relative frequency, and median (minimum and maximum values).

p=0.044) and showed a trend toward differentiating early interstitial changes from normal scans in this population (p=0.043). However, KL-6 levels did not distinguish ILD from other abnormalities (p=0.593), and the ROC curve did not reach statistical significance (p=0.61). Regarding spirometry, absolute DLCO values (r_pb=0.46; p=0.006), FVC (r_pb=0.43; p=0.008), and FEV_1 (r_pb=0.42; p=0.010) were also associated with RA-ILD findings on HRCT.

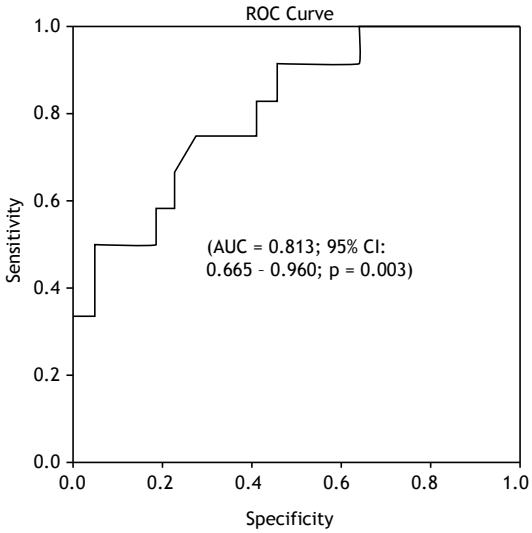

Figure 1. ROC curve from distance of 6MWT (cutoff = 462.55 m).

The findings related to the 6MWT in this study were promising. While the prognostic value of the 6MWT in ILD is well established,[6] its potential role as a screening tool for preclinical ILD remains largely unexplored. In an exploratory analysis of patients with RA-ILD (n=54), Boudal et al. (2024) reported a mean 6MWTD of 267.7 m; however, their cohort included patients with respiratory symptoms (30.2% with dyspnea and 55.6% with cough).[7]

Regarding KL-6, elevated serum levels have been associated with the presence and severity of RA-ILD,[8] although evidence supporting its utility in detecting preclinical disease is still limited. Similarly, previous studies have linked reduced FVC and DLCO values with increased disease severity in RA-ILD,[9] as well as with the presence of interstitial lung abnormalities in otherwise healthy individuals.[10] Given that RA-ILD symptoms often emerge late in the course of the disease,[1] early, non-invasive screening tools such as the 6MWT or KL-6 measurement could help identify patients who may benefit from further evaluation with HRCT.

This study assessed the association between screening test results and the diagnosis of preclinical RA-ILD, as identified on HRCT. These findings should be interpreted with caution due to the small sample size, which may limit the robustness and generalizability of the conclusions. Validation in larger cohorts is necessary to confirm these results and to further investigate their potential role in refining RA-ILD screening strategies. Nonetheless, in this cohort of asymptomatic RA patients with high autoantibody titers, a 6MWD of less than 462.55 meters was significantly associated with the presence of interstitial abnormalities on HRCT. Elevated serum KL-6 levels also demonstrated an association, reinforcing the potential value of these biomarkers in RA-ILD risk assessment.

AUTHOR CONTRIBUTIONS

Study conceptualization: ALBA, MFBRG, EVM; data curation: ALBA, MDML, MFBRG, EVM; formal analysis: ALBA, MFBRG, EVM; funding acquisition: ALBA, MFBRG, EVM; investigation: ALBA, MDML, MFBRG, EVM; methodology: ALBA, MFBRG, EVM; project administration: EVM; writing: ALBA, MFBRG, EVM.

ACKNOWLEDGMENTS

We thank the Brazilian Society of Rheumatology, as well as the Rheumatology and Pneumology teams at the Clinics Hospital of the Federal University of Minas Gerais (UFMG), for their support in this project.

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Indoor air pollution from firewood combustion in Indigenous *malocas* in the Brazilian Amazon: exposure to fine particulate matter and associated health risks

Adriana Gioda[1]

Firewood remains a primary source of domestic energy for millions of people worldwide, especially those in low- and middle-income countries. In Brazil, this reality is particularly acute among Indigenous, *quilombola*, and riverine populations living in remote areas with limited access to electricity or liquefied petroleum gas.[1] Although the use of biomass fuel is deeply rooted in cultural traditions, it also presents a serious and often overlooked public health concern: chronic exposure to indoor air pollution, especially fine particulate matter, i.e., particles that are equal to or less than 2.5 μm in diameter ($PM_{2.5}$).

In Brazil, there are approximately 1.7 million Indigenous people, most of whom face vulnerabilities such as poverty, limited health care access, and energy insecurity. This letter presents findings from a pilot study conducted in traditional Indigenous dwellings (*malocas*) across various ethnic communities in the Legal Amazon. The study sought to quantify $PM_{2.5}$ concentrations from firewood combustion and assess associated noncarcinogenic health risks. Nine villages were visited, each including 1-20 *malocas*. Approximately 80% were sampled during medical outreach, with sampling durations ranging from 20 min to 1 h. The fire was not lit in some huts, which were therefore compared with those in which it was. Additionally, outdoor measurements were taken in order to identify the sources of $PM_{2.5}$. Because of family challenges and the lack of electricity, the sampling time could not be extended. A daily exposure of 8 h was assumed on the basis of observations that Indigenous individuals, especially women and children, spend an average of 8 h near indoor fire pits. Each *maloca* typically housed five to seven occupants from extended families. Although the primary objective of the pilot study was to characterize exposure levels, preliminary discussions were initiated with community members and leaders regarding potential mitigation strategies, such as improving ventilation and modifying the design of fire pits. An air quality monitor with a $PM_{2.5}$ sensor of 0-999 μg • m^{-3} (TEMTOP M-2000, Elitech, Brazil) was used in order to measure $PM_{2.5}$ levels, as reported elsewhere.[1]

The results show that $PM_{2.5}$ concentrations varied significantly between the indoor environment and the outdoor environment. The mean indoor $PM_{2.5}$ concentration during the burning of firewood was 203 ± 261 μg/m^3 (range, 20-999 μg/m^3), whereas outdoor levels averaged only 9.5 ± 5.5 μg/m^3 (range, 0.7-23 μg/m^3). Indoor concentrations exceeded the WHO daily recommendation of 15 μg/m^3 by more than tenfold, whereas outdoor levels remained within the recommended limit. Indoor-to-outdoor ratios > 1 confirmed that indoor combustion was the primary source of $PM_{2.5}$. Significant differences ($p < 0.05$) were observed between the following scenarios: fire on vs. fire off; fire on vs. liquefied petroleum gas; and indoor vs. outdoor environments. These findings highlight the critical role of combustion type and ventilation in shaping exposure.

Other studies involving Indigenous communities reported high indoor concentrations of $PM_{2.5}$. Bunnell et al.[2] reported mean indoor $PM_{2.5}$ levels of 38 μg/m^3 among Navajo homes using coal-fired heating. In comparison, the Hopi tribe showed mean concentrations of 36.2 μg/m^3, which decreased to 14.6 μg/m^3 without heating.[3] Although these values are concerning, they remain substantially lower than those observed in the *malocas* in Brazil, where open fires are used daily for cooking and warmth. In Mexico, Hernández et al.[4] documented a mean indoor $PM_{2.5}$ concentration of 114 ± 140 μg/m^3 among the Tzotzil. In Bolivia, Quechua homes reached daily averages of 240 ± 210 μg/m^3.[5] The aforementioned studies suggest that $PM_{2.5}$ levels in homes relying on biomass can vary greatly on the basis of fuel type, duration of exposure, housing structure, and cooking practices.

To estimate noncarcinogenic risk, we applied the U.S. Environmental Protection Agency hazard quotient model.[6] The hazard quotient is calculated as the ratio of average daily dose to reference dose. For $PM_{2.5}$, the reference dose used was 5 μg/kg/day. Using a measured indoor concentration of 203 μg/m^3, we applied the following equation:

$$ADD = C \times IR \times EF \times ED/\mathrm{BW} \times \mathrm{AT}$$

where *ADD* is the average daily dose; *C* is the indoor concentration; *IR* is the inhalation rate (20 m^3/day); *EF* is the exposure frequency (8 h/day, i.e., 0.333 days/day); *ED* is the exposure duration (30 years); *BW* is the body weight (70 kg); and *AT* is the average time (30 × 365 = 10,950 days).

The resulting hazard quotient was 3.84, which was significantly above the threshold of 1, indicating a potential for chronic adverse effects such as respiratory and cardiovascular disease.

To our knowledge, the pilot study reported herein represents the first quantitative assessment of $PM_{2.5}$

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ISSN 1806-3756

exposure in Indigenous Brazilian *malocas*. Although the study acknowledges limitations related to sampling duration and other factors, it underscores the urgent need for further studies aimed at understanding the health risks associated with biomass combustion. In a previous study, we found high $PM_{2.5}$ levels attributed to open-fire wood burning, a finding suggesting that similar conditions are present in the *malocas*.[1] Indoor sources of $PM_{2.5}$ can contribute to respiratory diseases and deaths. Data from the Brazilian National Ministry of Health Special Department of Indigenous Health show that 21.6% of all deaths among Indigenous children under one year of age are attributed to respiratory illnesses, underscoring a preventable health crisis. Furthermore, 2024 data from the Brazilian *Núcleo Ciência Pela Infância* show that respiratory diseases are the leading cause of death among Indigenous children under four years of age, accounting for 18% of all deaths in this age group. In Guarani communities, overcrowded homes with open fires have been strongly linked to higher hospitalization rates for respiratory infections.[7]

To safeguard these communities, it is essential to strengthen Indigenous health systems; invest in household energy transitions; and conduct long-term exposure assessments.

AUTHOR CONTRIBUTIONS

AG: conceived, planned, and performed the experiments that led to this study; interpreted the data; wrote the manuscript; critically revised the manuscript for important intellectual content; and approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

FINANCIAL SUPPORT

None.

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Accidental chest penetration of a glass foreign body

Simone Duarte Damato[1], Alessandro Severo Alves de Melo[1], Edson Marchiori[2]

A 20-year-old previously healthy man reported falling from his own height onto a mirror and suffering a cut in the left infrascapular region. He sought emergency care, where the cut was sutured. He continued to have pain in the area and returned the following day, when a chest X-ray showed a foreign body on the left (Figure 1A). The patient was referred to the hospital, where further imaging showed a high-density linear foreign body in the left hemithorax, in addition to a pneumothorax (Figure 1B-E). He underwent pleural drainage and surgery, during which a glass foreign body (mirror fragment) measuring approximately 30 cm was removed (Figure 1E). The patient progressed well and was discharged four days later in excellent condition.

Intrathoracic foreign bodies include iatrogenic foreign bodies, objects that have migrated through the airways, and traumatic intrathoracic foreign bodies. Glass exhibits high density on chest radiography and CT. CT is the best imaging method for the evaluation of such trauma. Even minor impalement injuries may cause serious complications, including organ damage and life-threatening bleeding. Accurate visual, manual, and instrumental wound exploration is always necessary. Surgical removal of the foreign body is the first-choice treatment.[1,2]

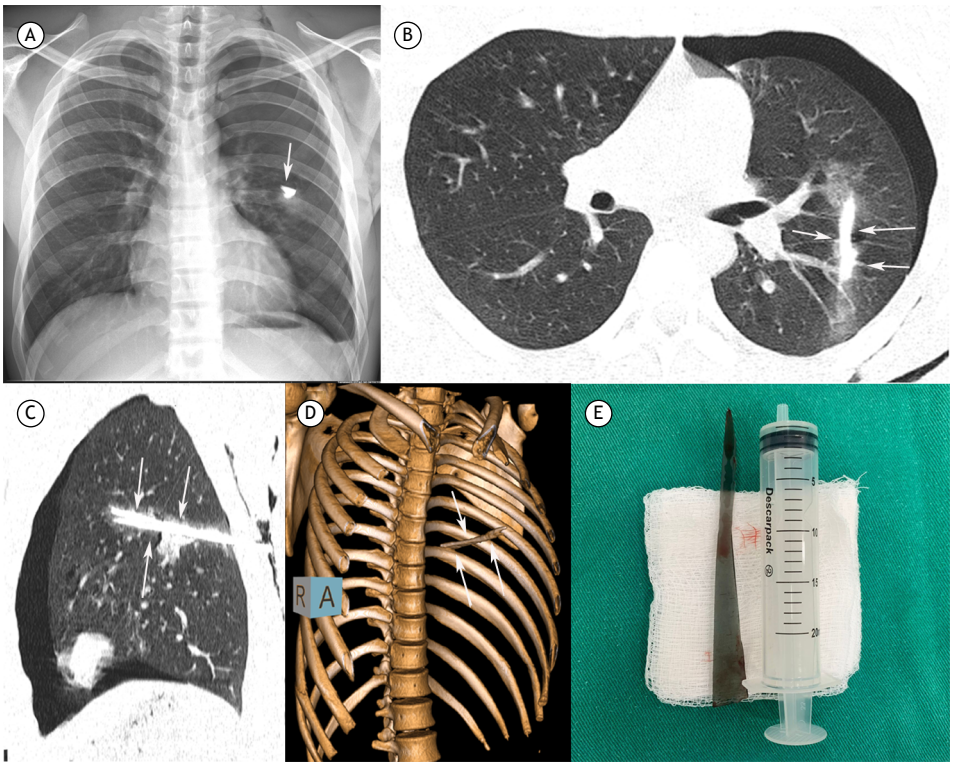

Figure 1. Chest radiograph (A) showing a dense foreign body in the left hemithorax (arrow). Axial (B) and sagittal (C) chest CT images and 3D reconstruction (D) demonstrating a dense linear foreign body in the left lung and ground-glass opacities (hemorrhage) in the periphery. Note also the pneumothorax on the left. (E) The mirror fragment removed from the patient, measuring about 30 cm.

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ISSN 1806-3756

Red flags for thoracic endometriosis

Lorenzo Carriera[1,2], Roberto Lipsi[2], Angelo Coppola[3]

A 38-year-old Brazilian woman with a previous diagnosis of pelvic inflammatory disease presented to our hospital with a two-month history of dyspnea, chest pain, and dry cough. Chest CT revealed right-sided basal pleural effusion. The QuantiFERON-TB test result was positive. On the basis of those findings and the symptoms, we suspected a diagnosis of pleural tuberculosis. An explorative thoracentesis was performed. The aspirated pleural fluid was hemorrhagic. The cytological examination showed a predominance of histiocytes and leukocytes, and no malignant cells were detected. At that point, we decided to perform medical thoracoscopy to obtain biopsy specimens from the parietal pleura. The procedure revealed thickened pleura and small, wine-red lesions on the diaphragm and parietal pleura (Figure 1), findings suggestive of pleural endometriosis. Histopathological analysis confirmed the presence of epithelial glandular elements, and immunohistochemical staining was positive for CD10 and estrogen receptors. Thoracic endometriosis presents nonspecific symptoms, making the diagnosis challenging. In women of reproductive age presenting with chest pain and pleural effusion, endometriosis should be considered as a possible cause.[1] Hormone suppression therapy with gonadotropin-releasing hormone analogs can help alleviate symptoms as well as improving the overall quality of life and daily functioning.[2] Early recognition and multidisciplinary care are key to achieving better outcomes.[3]

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

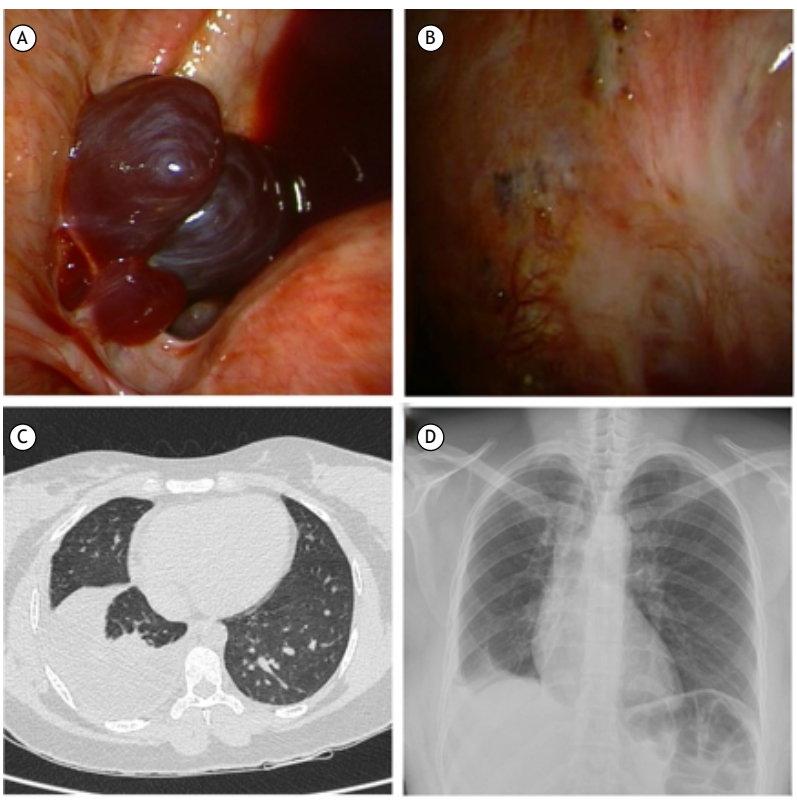

Figure 1. A) Wine-red nodules on the diaphragm visualized during medical thoracoscopy; B) Small punctiform wine-red lesions on the parietal pleura; C) Chest CT at admission, showing right-sided basal pleural effusion; D) Chest X-ray 1 month after the initiation of gonadotropin-releasing hormone therapy.

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

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