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HIGHLIGHT

New spirometry recommendations from the Brazilian Thoracic Association – 2024 update

Bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) for multidrug- or rifampin-resistant tuberculosis: a systematic review

Hyperventilation worsens inflammatory lung injury in spontaneously breathing rats

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

1 dia inteiro
de controle de sintomas[3,4]

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

Recomenda-se duas doses (jatos) em cada narina uma vez ao dia[6]

Referências: *Corticosteroide tópico nasal - 1. Meltzer EO. Ann Allergy Asthma Immunol 2007; 98: 12-21. - 2. Patel P et al. ENT J. 2008; 87: 340-353. - 3. Meltzer EO et al. Ann Allergy Asthma Immunol 2007; 98: 175-181. - 4. Ratner PH et al. J Allergy Clin Immunol 2006; 118: 1142-1148. - 5. Chervinsky P et al. Ann Allergy Asthma Immunol 2007; 99: 69-76. - 6. Bula do Produto Omnaris, Data de acesso das informações: 2019.

OMNARIS® (ciclesonida) 1.1618.0265 INDICAÇÕES: Omnaris® é indicado para o tratamento de sintomas de rinite alérgica intermitente ou persistente, incluindo congestão nasal, coriza, prurido e espirros. CONTRAINDICAÇÕES: Omnaris® é contraindicado em pacientes com hipersensibilidade a qualquer dos seus componentes. Omnaris® não deve ser usado no caso de haver uma infecção nasal não-tratada. ADVERTÊNCIAS E PRECAUÇÕES: Raramente podem ocorrer reações imediatas de hipersensibilidade ou dermatite de contato após a administração de corticosteroides intranasais. Os pacientes com reação de hipersensibilidade conhecida a outros preparados de corticosteroides devem tomar cuidado quando usarem spray nasal de ciclesonida, pois pode ocorrer reação cruzada com outros corticosteroides. Pacientes em tratamento com medicamentos supressores do sistema imune são mais suscetíveis a infecções do que os indivíduos sadios. Varicela e sarampo, por exemplo, podem ter um curso mais grave ou até mesmo fatal em crianças ou adultos usuários de corticosteroides. Em crianças ou adultos que não tenham tido estas doenças ou não tenham sido adequadamente imunizadas, deve-se tomar cuidado particular para evitar sua exposição. Em caso de exposição a varicela ou a sarampo, o paciente deve procurar orientação médica adequada para tratamento profilático. Os corticosteroides intranasais devem ser administrados com cuidado principalmente a pacientes com infecções por tuberculose ativa ou inativa do trato respiratório, com infecções fúngicas ou bacterianas, locais ou sistêmicas, com infecções virais ou parasitárias sistêmicas ou com *Herpes simplex* ocular devido ao potencial de piora dessas infecções. Efeitos nasais locais: Ocorreram casos raros de perfuração do septo nasal em pacientes que administraram ciclesonida pela via intranasal. Por causa do efeito inibitório dos corticosteroides sobre a cicatrização de ferimentos, pacientes que tenham tido recentes úlceras no septo nasal ou sofrido cirurgia nasal ou trauma nasal não devem usar um corticosteroide nasal até que tenha ocorrido a cicatrização. Em estudos clínicos com Omnaris®, foi raro o desenvolvimento de infecções localizadas por *Candida albicans* no nariz e na faringe. Quando tal infecção surge, ela pode exigir tratamento com terapia local apropriada e descontinuação de Omnaris®. Portanto, pacientes em tratamento com Omnaris® por vários meses ou por um período mais longo devem ser examinados periodicamente quanto à evidência de infecção por *Candida* ou outros sinais de efeitos adversos sobre a mucosa nasal. Efeitos sistêmicos: Doses de Omnaris® maiores que as recomendadas devem ser evitadas. Quando usados em doses excessivas, efeitos corticoides sistêmicos podem ocorrer, como hipercorticismo e supressão adrenal, retardo de crescimento em crianças e adolescentes, diminuição na densidade mineral dos ossos, catarata e glaucoma. Se tais alterações ocorrerem, a dose de Omnaris® deve ser descontinuada devagar, consistente com os procedimentos aceitos para a descontinuação de terapia corticoide oral. Gravidez e lactação: A experiência com corticosteroides orais desde a sua introdução demonstra que, pelo fato de haver um aumento natural na produção de corticosteroides durante a gestação, a maioria das mulheres precisará de uma dose exógena de corticosteroide menor. Muitas nem precisarão de tratamento com corticosteroides durante a gestação. Categoria C de Risco na Gravidez – não existem estudos clínicos bem controlados em gestantes. Tal como acontece com outros corticosteroides, a ciclesonida deve ser administrada durante a gravidez somente se o benefício potencial para a mãe justificar o risco potencial para a mãe, o feto ou o bebê. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. Não se sabe se a ciclesonida é excretada no leite humano. Entretanto, outros corticosteroides são excretados no leite humano. Deve-se tomar cuidado se Omnaris® for administrado a lactantes. Omnaris® só deve ser administrado quando o benefício para a mãe que estiver amamentando for considerado maior que o risco potencial para a mãe e/ou criança. Efeitos não-teratogênicos: Pode ocorrer hipoadrenalismo em bebês nascidos de mães que tenham recebido corticosteroides durante a gestação. Pacientes pediátricos: Estudos clínicos controlados demonstraram que os corticosteroides intranasais podem causar redução na velocidade de crescimento de pacientes pediátricos. Os potenciais efeitos sobre o crescimento do tratamento prolongado devem ser ponderados com os benefícios clínicos obtidos e a disponibilidade de tratamentos seguros e efetivos alternativos aos corticosteroides. Pacientes idosos: Os estudos clínicos de Omnaris® não incluíram um número suficiente de indivíduos com 65 anos de idade ou mais para determinar se eles respondem de maneira diferente dos indivíduos mais jovens. Em geral, a seleção da dose para um paciente idoso deve ser cuidadosa, normalmente começando na extremidade inferior da faixa de dosagem, considerando a maior frequência de diminuição da função hepática, renal ou cardíaca e de doenças concomitantes ou aplicação de outras terapias. INTERAÇÕES MEDICAMENTOSAS: Em um estudo de interação medicamentosa, a coadministração de ciclesonida inalada por via oral e de cetoconazol oral, um potente inibidor do citocromo P450 3A4, aumentou a exposição (AUC) da des-ciclesonida em aproximadamente 3,6 vezes no equilíbrio dinâmico (*steady state*), enquanto os níveis de ciclesonida permaneceram inalterados. Portanto, cetoconazol deve ser administrado com cuidado com ciclesonida intranasal. Não se verificaram interações de Omnaris® com a alimentação. POSOLOGIA: Para crianças acima de seis anos de idade e adultos recomendam-se duas doses (jatos) em cada narina uma vez ao dia (50 mcg por jato; total 200 mcg por dia). Não se devem aplicar mais de duas doses (jatos) em cada narina diariamente. Omnaris® deve ser administrado exclusivamente pela via intranasal. A dose máxima diária recomendada é de 200 mcg por dia. A duração do tratamento dependerá da resposta ao uso da medicação e deve ser estabelecida pelo médico. REAÇÕES ADVERSAS: As reações adversas mais comuns que podem ocorrer durante o uso prolongado de Omnaris® são dor de cabeça, sangramento no nariz e infecções das vias aéreas superiores. Reações comuns (> 1/100 e < 1/10): Respiratórias – sangramento do nariz (8,4%), irritação da mucosa do nariz (4,3%); Sistema nervoso – dor de cabeça (1,6%). Reações incomuns (> 1/1.000 e < 1/100): Gastrintestinais – boca seca (0,2%), dispepsia (0,2%); Infecções – candidíase (0,2%), rinite (0,2%); Respiratórias – ressecamento nasal (0,4%), dor na garganta (0,4%), secreção nasal (0,3%,), irritação na garganta (0,2%); Outras – transtorno do paladar (0,2%), aumento do número de leucócitos (0,3%). Reações com frequência não conhecida (frequência não pode ser estimada a partir dos dados disponíveis): Perfuração do septo nasal. VENDA SOB PRESCRIÇÃO MÉDICA.

Contraindicações: Omnaris® é contraindicado em pacientes com hipersensibilidade a qualquer dos seus componentes. Omnaris® não deve ser usado no caso de haver uma infecção nasal não-tratada. **Interações medicamentosas:** Em um estudo de interação medicamentosa, a coadministração de ciclesonida inalada por via oral e de cetoconazol oral, um potente inibidor do citocromo P450 3A4, aumentou a exposição (AUC) da des-ciclesonida em aproximadamente 3,6 vezes no equilíbrio dinâmico (steady state), enquanto os níveis de ciclesonida permaneceram inalterados. Portanto, cetoconazol deve ser administrado com cuidado com ciclesonida intranasal.

COVIS PHARMA

Material exclusivo de uso do representante comercial
para promoção junto a profissionais de saúde habilitados
a prescrever e/ou dispensar medicamentos.
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Artificial intelligence in respiratory research: opportunities, pitfalls, and ethical considerations

Ricardo G Figueiredo[1,2,3], Juan Calderón[3,4,5]

The rapid advancement of technology in science is genuinely remarkable. The scientific community has been shocked by artificial intelligence's (AI) transformative potential in research, leveraging its generative capabilities through artificial neural networks, machine-learning algorithms, and large language models (LLMs), enabling them to analyze complex databases and mimic the human brain's data-processing functions.[1]

There is also great interest in AI being employed to elucidate underlying mechanisms of diseases and identify optimal treatments by detecting disease patterns and analyzing large databases.[2,3] Big Data in medical research represents a transformative shift in how researchers collect, analyze, and apply these data to improve patient outcomes, understand diseases better, and enhance healthcare delivery. This revolution is driven by the exponential growth of data from various sources, including electronic health records, genomic sequencing, and wearable health devices. Machine learning algorithms can integrate data in a multidimensional analysis, including genomics, metabolomics, social, environmental, and health records. Specifically in the respiratory field, AI could interpret pulmonary function tests as accurately as pulmonologists.[4] It can also assist in diagnosing small airway diseases by utilizing more advanced and complex methods such as oscillometry.[5] We are witnessing the beginning of a new era in respiratory care that empowers physicians, enhances diagnostic accuracy, and improves patient safety. Nevertheless, in daily medical practice, misclassification of diagnoses can have life-or-death consequences, making it essential to monitor the development and application of this technology closely. Quoting Prof. Judith Löffler-Ragg: "It is extremely important that we approach technological advancements, particularly AI, with both an open mind and a critical eye."

Ideally, AI would alleviate researchers from the burden of bureaucratic tasks, enhance human creativity, break down language barriers, and enable a shared control dynamic while humans retain responsibility and accountability. As generative AI continually improves through the increasing availability of data and user feedback, its impact on compliance with research methodology, data analysis, and the integrity of academic publishing becomes increasingly significant. However, biased data and models used to train AI systems can result in flaws being reflected in the final models or reports generated by AI, which may compromise the accuracy and reliability of the outcomes. This reflects the principle of "garbage in, garbage out," where flawed input inevitably leads to flawed results. Researchers should also be aware that LLMs, such as ChatGPT and Google Gemini, can hallucinate. This means that generative AI may produce highly convincing text with entirely incorrect concepts and even fabricate references that do not exist. This implies that any information produced by AI technologies must be carefully reviewed by a human and appropriately reported. There is growing concern that AI could contribute to a reproducibility crisis in science by fostering the proliferation of low-quality research.

An analysis of the Scopus database suggests that the proportion of research papers with titles or abstracts mentioning AI or machine-learning terms has increased to approximately 8%. The survey conducted by Van Noorden et al.,[6] involving over 1,600 researchers globally, revealed mixed feelings about the increasing role of AI in research. While most respondents recognized the potential benefits, such as faster data processing and the ability to approach previously infeasible research questions, significant concerns were raised. Major issues included the risk of AI systematic biases, making plagiarism easier, and introducing inaccuracies into research. The survey also highlighted that many researchers remain cautious about their broader adoption in scientific workflows.

Respiratory research funding is inadequate and inequitable, with a significant gap between the disease burden and research investment.[7] This disparity is especially pronounced among researchers from developing countries and non-native English speakers, who face additional obstacles in global research participation and recognition. Discrimination, exclusion, and stereotyping extend beyond data collection are embedded in societal inequalities, influencing how data is processed and classified.[8] Grammarly and ChatGPT offer valuable support to these researchers by helping them improve their writing style, clarity, and coherence of the manuscript. Generative AI tools can assist non-native speakers to engage more effectively with the global scientific community. Scite is an AI tool that employs LLMs to search academic literature using natural, plain language. It verifies the accuracy of references used to support ideas in a manuscript and alerts users to errata or retractions. This tool can be especially helpful for early-career researchers during the literature review process,

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5. Respiralab Research Group, Guayaquil, Ecuador.

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helping them refine their research before conceiving a final PICO (Patients of interest, Intervention to be studied, Comparison of intervention, and Outcome of interest) question.

Unfortunately, not everything that glitters is gold. While most editors and researchers acknowledge the increasing use of AI in scientific publishing, numerous reports of potential misuses in science have raised significant red flags. A case study involving the publishing process of an entirely AI-generated manuscript brings several concerns.[9] ChatGPT 3.5 can convincingly produce fabricated references that do not exist, raising concerns about the reliability and integrity of AI-generated academic content. The manuscript above was accepted by six of twelve submissions and provisionally accepted in another journal. Although editorial offices can screen incoming manuscripts for AI-generated content using GPTZero or Originality.AI, these tools currently cannot differentiate between the legitimate use of AI for grammar and writing enhancement and fully AI-generated text. This limitation poses challenges in accurately assessing the extent of AI involvement in manuscript preparation.

Several ethical issues have been raised regarding the use of AI in manuscript preparation, leading to swift policy adjustments in academic publishing. In recent years, the International Committee of Medical Journal Editors (ICMJE) developed recommendations that permit AI use but explicitly prohibit AI from being listed as an author, as it cannot take responsibility for the accuracy, integrity, or originality of the research.[10] Additionally, AI involvement must be disclosed, and authors are also responsible for ensuring the absence of plagiarism, including in AI-generated text and images, and must adequately attribute all quoted material with proper citations.

Plagiarism is a critical concern in scientific publishing. As hybrid human–AI writing becomes more common, the distinction between human and AI contributions may become increasingly difficult. Ideally, AI would augment human creativity, remove language barriers, and assist in various tasks while humans maintain control over the final output.[11] Although researchers can delegate aspects of writing to AI tools, they remain fully accountable for the content's accuracy, integrity, work originality, and adherence to ethical standards. The growing significance of AI in medicine has motivated the JAMA Network to introduce a dedicated section titled JAMA+ AI, which emphasizes the impact of AI on healthcare.[12]

While AI can be utilized throughout various stages of research—from formulating research questions to preparing manuscripts—,it should primarily be employed to enhance processes in research workflow, pattern recognition and trend analysis ("how"). However, the irreplaceable human capacities for creativity and critical thinking are essential for tackling more complex scientific questions and addressing uncertainties ("why"). These abilities are even more crucial in an era of advanced AI. We are now at a pivotal moment where it is essential to clearly define the areas of research and society in which AI can be safely integrated and determine the most effective strategies for its implementation. A comprehensive understanding of AI's potential risks and challenges is crucial to ensuring its responsible use in research.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

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While preparing this work, the authors used Grammarly to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the publication's content.

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Rasmussen's aneurysm

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

A 39-year-old man presented with a three-month history of cough and hemoptysis, as well as anorexia and weight loss (12 kg). A CT scan of the chest showed nodules and a thick-walled cavity in the right lung, as well as a large cavitary lesion on the left, containing a round mass surrounded by a halo of air (the air crescent sign). The mass showed intense enhancement after administration of iodinated contrast (Figure 1). The final diagnosis was active tuberculosis with a Rasmussen aneurysm (RA) on the left.

In patients with tuberculosis, hemoptysis is frequently caused by erosion of a bronchial artery or a pulmonary artery branch. Common causes of hemoptysis include bronchiectasis, aspergilloma, reactivation of tuberculosis, lung scar carcinoma, broncholithiasis, and RA. Contrast-enhanced chest CT and bronchoscopy are the methods of choice for the evaluation of pulmonary hemorrhage.[1,2]

The finding of a nodule or mass in a lung cavity has important diagnostic and therapeutic implications. Although aspergilloma is the most common cause of an intracavitary nodule, the differential diagnosis should include neoplasms (particularly bronchial carcinoma), (recovery phase of) angioinvasive aspergillosis, RA, and clots. The air crescent sign is commonly seen in patients with intracavitary nodules of any etiology. The air crescent sign is a crescent– or half-moon–shaped collection of air in the periphery of an intracavitary nodule or mass, separating the nodule or mass from the cavity wall.[1,3,4]

A change in the position of the nodule in the cavity when patient position is changed, especially during CT examinations in the supine and prone positions, can be useful in the differential diagnosis. It is extremely important to determine whether the nodule is free or attached to the cavity wall because, unlike a fungus ball or a clot, RA and cavitary lung cancer present as masses that are fixed to the cavity wall; that is, they do not move when patient position is changed. Intense contrast enhancement of the nodule is seen on CT scans of patients with RA and is useful in differentiating between aspergilloma and RA.[1,3,4]

In conclusion, RA should be included in the differential diagnosis of hemoptysis in tuberculosis patients presenting with the air crescent sign. Contrast-enhanced CT plays an important role in the evaluation of such patients.

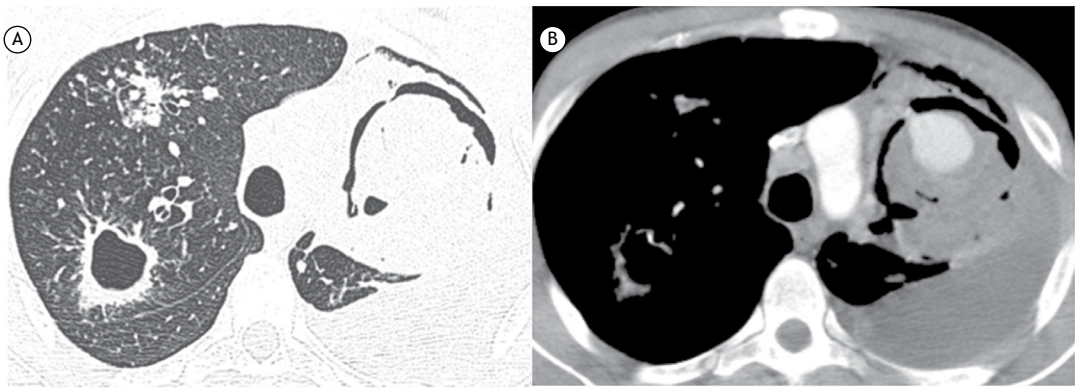

Figure 1. In A, CT scan of the chest with lung window settings at the level of the upper lobes, showing nodules and a thick-walled cavity in the right upper lobe. On the left, note a large cavitary lesion and an intracavitary mass, with air interposed between the mass and the cavity wall (the air crescent sign). In B, CT scan of the chest with mediastinal window settings after administration of intravenous contrast, showing intense enhancement of the intracavitary mass, consistent with a diagnosis of aneurysm formation (Rasmussen's aneurysm).

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The Global Burden of Disease project: an online tool to compare disease impact across geographical regions over time

Rogelio Perez-Padilla[1,2], Cecilia Maria Patino[1,3], Juliana Carvalho Ferreira[1,4]

PRACTICAL SCENARIO

Investigators from the *Instituto Nacional de Enfermedades Respiratorias* (INER, National Institutes of Respiratory Diseases) in Mexico aimed to analyze the burden of respiratory diseases in the adult Mexican population over a 30-year period. They needed trustworthy information about the incidence and mortality of several diseases over a large period and opted to use data from The Global Burden of Diseases (GBD) initiative. They found that respiratory diseases are responsible for approximately 30% of deaths among adults in Mexico, and that mortality due to chronic respiratory diseases has been rising since 1990 across both genders.[1]

THE GBD INITIATIVE

The GBD initiative, launched in 1991 by the World Bank and the World Health Organization, is a comprehensive framework that generates standardized health information worldwide.[2] It is used to identify health disparities and priorities, inform evidence-based public health decisions, and measure their impact. Managed by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington in the United States, the GBD's leading articles have been published in Lancet.[3]

The GBD's data allows comparisons across different regions, countries, populations, genders, and age groups from 1990 to 2021. Before the GBD, no consistent global reporting of the prevalence and mortality of diseases existed, thus several countries, especially low- and middle-income countries, lacked accurate health statistics.

The GBD project has been instrumental in promoting innovation in reporting disease impact. It introduced the concept of disability-adjusted life years (DALYs), a comprehensive measure of health that combines years of life lost by premature death (YLL) and years of life lived with disability (YLD). This approach, which considers both quantity (mortality) and quality (morbidity) of life, has significantly expanded our understanding of disease burden.

Chart 1. Main characteristics of Global Burden of Disease initiative of interest for respiratory diseases.

Scope of GBD
• Data on 371 diseases and injuries, 288 causes of death, and 88 risk factors; such data can be stratified by age and sex across 204 countries and territories from 1990 to 2021
• Vital statistics (births and deaths), household surveys (from health surveys, hospital discharge data, disease registers, annual health reports (countries and WHO)
Main GBD estimates
• Deaths (and causes, all-cause mortality), years of life lost (YLL), prevalence, incidence, population, and causes of injuries and impairment. Estimates by number, crude rate and age-adjusted rates, percentage, probability of death across countries, world regions (WHO, World Bank income levels), and over time (1990-2021)
• Life expectancy (LE), life tables (LTs), healthy life expectancy (HALE), years lived with disability (YLD), disability-adjusted life year (DALYs)
Sources and methodology for the generation of estimates
• Input from expert groups, World Health Organization, World Bank, UNICEF, and expert collaborators from a large variety of countries
• Bayesian statistical models adjusted for underreporting and poor data quality
Data retrieval tools
• The Global Health Data Exchange (GHDx) yields tables by cause, risk factor, sex, age, and year (1990-2021), as well as graphs and downloadable results. (https://vizhub.healthdata.org/gbd-results/
• The GBD 2021 Socio-Demographic Index 1950-2021 provides a composite indicator of development status strongly correlated with health outcomes. (https://ghdx.healthdata.org/record/global-burden-disease-study-2021-gbd-2021-socio-demographic-index-sdi-1950%E2%80%932021)
• The GBD 2021 Causes of Death and Nonfatal Causes Mapped to ICD Codes provides tables that contain ICD codes, for both ICD-9 and ICD-10, mapped to GBD 2021 causes of death and nonfatal causes.
• https://ghdx.healthdata.org/record/ihme-data/gbd-2021-cause-icd-code-mappings

GBD: Global Burden of Disease; and ICD: International Classification of Diseases.

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The GDB is easily accessible to clinicians, clinical researchers, epidemiologists, public health professionals, politicians, and the general public. It can be consulted online and includes tables, graphs, and open-access downloadable data. However, the GBD does not provide estimates for all diseases or risk factors, only for the most relevant ones, although the number has been increasing. Chart 1 shows the main characteristics of the GBD.

The GBD project covers a range of respiratory diseases and their risk factors.[1] These include chronic respiratory diseases, such as COPD, interstitial lung diseases, sarcoidosis, pneumoconiosis, and asthma. It includes respiratory infections, such as COVID-19, such as lower and upper respiratory infections, and tuberculosis, and respiratory neoplasms, such as lung and head-and-neck cancers. Commonly reported risk factors for respiratory diseases include air pollution (outdoor particulate matter and ozone, household air pollution, occupational exposures), active and passive tobacco smoking, and infections.

The GBD has been regularly updated since 1990, and most data are available at the Global Health Data Exchange website without cost (GHDx, https://ghdx.healthdata.org). It is a clinician-friendly source of information, including tables, graphs, and illustrations on the status of disease burden, which are key for presentations and introductions to thesis or manuscripts.

KEY MESSAGES

- The GBD is an open-access reliable database used to describe and compare estimates of respiratory health indicators across countries and regions over time.
- It is helpful for clinicians, epidemiologists, and public health officers.
- Empiric validation of the estimates should be sought, especially for areas lacking sufficient health information.

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The role of the pulmonary function laboratory in the management of gastrointestinal and liver diseases

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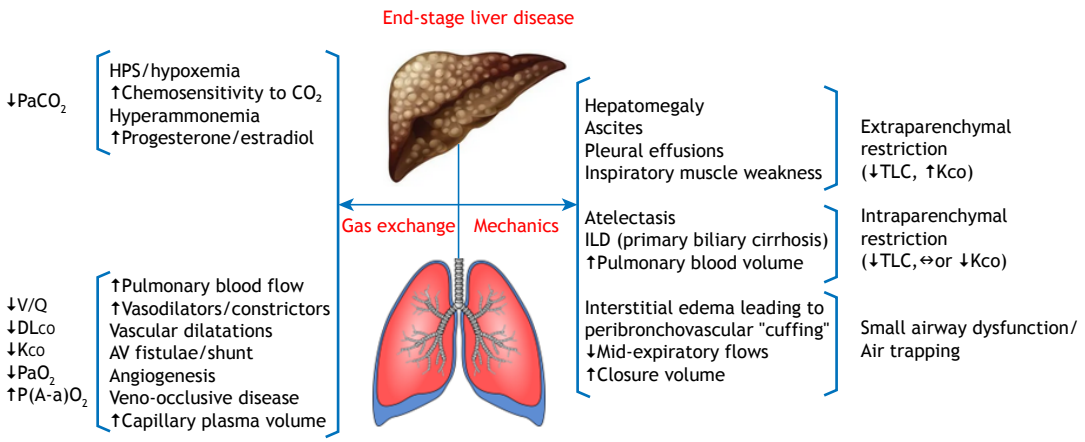
BACKGROUND

The respiratory and gastrointestinal (GI) systems share several embryogenic, anatomical, and physiological features. Pulmonary function tests (PFTs) are beneficial in detecting respiratory consequences of advanced liver disease and inflammatory bowel diseases (IBDs, mainly Crohn's disease and ulcerative colitis), which have potential implications for management.[1]

OVERVIEW

A 58-year-old man with cirrhosis secondary to long-term alcohol abuse (patient A) was referred for PFTs because of worsening dyspnea despite apparently stable end-stage liver disease. Mild intraparenchymal restriction was associated with severe impairment in DL_{CO} (adjusted for hemoglobin) and carbon monoxide transfer coefficient. A markedly enlarged alveolar-arterial oxygen gradient (44 mmHg) coexisted with moderate to severe hypoxemia (PaO_2 = 51 mmHg) and hypocapnia, plus mixed respiratory and metabolic alkalosis. Dyspnea and hypoxemia worsened from supine to seated position (i.e., the patient presented with platypnea-orthodeoxia syndrome). Testing with 100% inhaled oxygen revealed a shunt fraction of approximately 20%; extensive intrapulmonary vascular dilatations were confirmed with contrast-enhanced echocardiography and computed tomography (CT). A 49-year-old woman with Crohn's disease (patient B) reported three episodes of acute-on-chronic dyspnea and productive cough, together with worsening GI symptoms, over a one-year period. Sequential testing showed recurrent relapses of mild-to-moderate mixed obstructive and restrictive defects with air trapping seen on PFTs (high RV and high RV/TLC ratio) and on inspiratory-expiratory chest CT.

Hypoxemia in liver disease is strongly related to abnormal function of the pulmonary (micro)vasculature, secondary to either the production of or failure to clear a broad range of inflammatory, vasoactive, or proliferative/angiogenic mediators (Figure 1).[2] Hepatopulmonary syndrome, as was seen in patient A, is a gas exchange disorder characterized by severe arterial hypoxemia,



HPS severity	$P(A\text{-}a)O_2$ (mmHg)	PaO_2 (mmHg)
Mild	≥15	≥80
Moderate		60-79
Severe		50-59
Very severe		<50 and/or <350 @ 100% O_2 (Type 2 HPS)

Figure 1. A simplified overview of the main respiratory consequences of end-stage liver disease and their impact on common pulmonary function test results. The table depicts the gas exchange criteria used in grading the severity of hepatopulmonary syndrome. V/Q: (alveolar) ventilation/perfusion ratio; K_{CO}: carbon monoxide transfer coefficient; $P(A\text{-}a)O_2$: alveolar-arterial oxygen gradient; AV: arteriovenous; ILD: interstitial lung disease; ↓: decreased; ↑: increased; and ↔: preserved.

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occurring in up to a quarter of patients with cirrhosis or portal hypertension. The syndrome is caused by intrapulmonary vascular dilatation and can be subdivided into two types: type 1, causing diffusion-perfusion defect; and type 2, causing anatomic shunt. When the vasoconstrictive/proliferative consequences dominate, a smaller fraction (2-8%) of patients with cirrhosis develop portopulmonary hypertension. Characteristically, hypoxemia is less severe unless advanced pulmonary hypertension leads to the right-to-left shunt through a patent foramen ovale.[3] Because of the multiple mechanisms related to a low DL_{CO} (Figure 1), the expected pattern of extraparenchymal restriction (i.e., low TLC and supra-maximal carbon monoxide transfer coefficient) may not emerge in some patients despite voluminous ascites.

The spectrum of lung involvement in IBDs is broad, ranging from subclinical abnormal involvement to interstitial lung disease, airway disease (panbronchiolitis, bronchiolitis obliterans organizing pneumonia, and bronchiectasis), as was seen in patient B, inflammatory tracheal stenosis, vasculitis, pleural disease, and enteric-pulmonary fistulas, among other conditions. As such, the PFT abnormalities are heterogeneous, reported in 17-55% of patients.[4] Lung abnormalities can be present years following the onset of the disease, commonly occurring during active disease and even post-colectomy. The underlying pathogenesis may be associated with the fact that the colonic and respiratory epithelial cells share a common embryonic origin and similar mucosal immunity.

CLINICAL MESSAGE

Respiratory function should be assessed in all candidates for liver transplantation, given that primary disorders affecting the pulmonary circulation (hepatopulmonary syndrome and portopulmonary hypertension) are associated with poorer functional status, worst survival while on the waiting list, and unfavorable outcomes after the procedure.[5] Abnormal PFT findings may signal acute deterioration of IBDs even in the absence of overt respiratory symptoms: concomitant improvement in GI symptoms and lung function is not uncommon, illustrating the complexities involved in the lung-gut axis.[1]

AUTHOR CONTRIBUTIONS

All authors equally contributed to this manuscript.

CONFLICTS OF INTEREST

None declared.

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A new era of cystic fibrosis therapy with CFTR modulators

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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.[1] Its presentation in the epithelial cells of the body involves multiple systems, including the respiratory, digestive and reproductive systems. Individuals with this condition exhibit abnormal transport of chloride and bicarbonate in the secretory epithelia, resulting in thick and viscous secretions in the aforementioned systems.[2] However, the progressive lung disease remains the leading cause of both morbidity and mortality in CF. We are currently experiencing an exciting and significant change in the scenario of CF treatment, which can be attributed to the introduction of CFTR modulators in the treatment of the condition. These modulators are a class of molecules that work by improving the intracellular processing and function of the defective CFTR protein.[2] By improving the expression and function of the CFTR protein, these molecules act on the basic defect of the disease, a scenario never seen with several previous therapies.[1] It is worth noting that not all individuals with CF can use these therapies, as their actions are specific for some type of defects of CFTR expression/function, and therefore the indications rely on specific variants of the CFTR gene. As they represent completely new therapeutic approaches, the effects on the course of the disease have yet to be fully determined; however, due to the significant improvement of symptoms and lung function in individuals using modulators, it is likely that the life expectancy of CF patients will be considerably increased.[2]

A NEW ERA OF CF THERAPY WITH MODULATORS

The CFTR modulators are divided into two main groups: correctors and potentiators. The correctors act mainly in the endoplasmic reticulum, where they improve the structure and transport of the defective CFTR protein to the cell surface, ensuring that more CFTR protein reaches the appropriate site where it should work. An example is elexacaftor, indicated as a combination with another corrector (tezacaftor) for individuals with the *F508del* variant, the most common CF variant worldwide. The potentiators enhance the activity of CFTR proteins located on the cell surface by prolonging the open state of the channel, thereby allowing chloride to flow through the cell membrane more effectively. An example is ivacaftor, which increases the duration of CFTR channel opening to improve its functionality.[1,2]

The first CFTR modulator approved by the US Food and Drug Administration (FDA) in January of 2012 and by the Brazilian *Agência Nacional de Vigilância Sanitária* (ANVISA, National Health Surveillance Agency) in March of 2015 was Kalydeco® (ivacaftor). This modulator is indicated for CF individuals with gating variants and was initially tested in individuals with the *G551D* variant, the most common gating variant in the USA.[1,2] This medication has shown significant improvements in lung function, nutritional status, and respiratory symptoms reported by individuals with eligible variants. In the Brazilian CF population, the most common CFTR gating variant is *S549R*, which has been shown to be responsive to ivacaftor as well.[3] While *F508del* variants do have a gating defect when expressed in the cell membrane, the use of ivacaftor alone was not effective to rescue its function, and there was a need to improve processing and trafficking of *F508del* mutants. Therefore, to treat individuals with *F508del* variants, there was a need for combinations of correctors and potentiators, aiming to tackle both the expression and function of the CFTR protein.[1-3]

Following initial attempts of using combined modulators with low to moderate clinical effects, such as Orkambi® (lumacaftor and ivacaftor) and Symdeko® (tezacaftor and ivacaftor), a significant step was given when researchers identified the need for a combination of two correctors to improve *F508del* variants expression.[3] This finding resulted in Trikafta®, a medication combining two correctors (elexacaftor and tezacaftor), and one potentiator (ivacaftor). The effects of this combination can be noticed in diverse epithelial cells lining tubular organs affected by CF, including the lungs, gastrointestinal tract, and pancreas.[1,3] The results of clinical trials of Trikafta® for individuals with CF with at least one copy of the *F508del* variant were striking on several outcomes, such as lung function, rate of pulmonary exacerbations, sweat chloride concentrations, quality of life, nutrition, and glycemic status.[2,3] More data is emerging on real world experiences with this medication, as well as expansion of age groups and eligible *CFTR* variants.[3] Trikafta® was approved by the FDA in the United States in October of 2019, while it was authorized by ANVISA in Brazil in 2022.[4,5] Fortunately, in June of 2023, Trikafta® was incorporated into the Brazilian Public Health Care System, making it available to CF individuals who have at least one copy of the *F508del* variant and are 6 years of age or older.[4]

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Chart 1. Mechanism of action and *CFTR* variants approved by the US Food and Drug Administrations and the Brazilian National Health Surveillance Agency.

Modulators	Action Mechanism	FDA approved mutations	ANVISA approved mutations
Kalydeco® (Ivacaftor)	Potentiator, which allows the protein to remain open longer, facilitating greater ion passage.	Patients aged 1 month and older, who have one of the following CFTR mutations: 711+3A→G; 2789+5G→A; 3272-26A→G: 3849+10kbC→T; A120T; A234D; A349V; A455E; A1067T; D110E; D110H; D192G; D579G; D924N; D1152H; D1270N; E56K; E193K; E822K; E831X; F311del, F311L; F508C; F508C, S1251N†: F1052V; F1074L; G178E; G178R; G194R: G314E; G551D; G551S; G576A; G970D; G1069R; G1244E; G1249R; G1349D; H939R; H1375P: 1148T; 1175V; 1807M; 11027T; 11139V; K1060T; L206W; L320V; L967S; L997F; L1480P; M152V; M9521; M952T; P67L; Q237E; Q237H; Q359R; Q1291R; R74W: R75Q; R117C; R117G; R117H; R117L; R117P; R170H; R347H; R347L; R352Q; R553Q: R668C; R792G; R933G; R1070Q; R1070W; R1162L; R1283M; S549N; S549R; S589N; S737F: 5945L; 5977F; S1159F; S1159P; S1251N; S1255P; T3381; T10531; V232D; V5621; V754M: V1293G; W1282R; Y1014C; Y10320.	Patients aged 6 years and older, weighing 25 kg or more, who have one of the following gating (class III) CFTR mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. Also for patients aged 18 years and older who have an R117H mutation.
Trikafta® (Elexacaftor + Tezacaftor + Ivacaftor)	Correctors (Tezacaftor and Elexacaftor), which help more CFTR proteins reach the membrane, and a potentiator (Ivacaftor)	Patients aged 2 years and older, who have one of the following CFTR mutations: 3141del9; 546insCTA; A46D; A120T; A234D; A349V; A455E; A554E; A1006E; A1067T; D110E: D110H; D192G; D443Y; D443Y, G576A, R668C†; D579G; D614G; D836Y; D924N; D979V; D1152H; D1270N; E56K; E60K; E92K; E116K, E193K; E403D; E474K; E588V; E822K; F191V; F311del; F311L; F508C; F508C, S1251N† F508del; F575Y; F1016S; F1052V; F1074L; F1099L; G27R; G85E; G126D; G178E; G178R; G194R; G194V; G314E; G463V; G480C; G551D; G551S; G576A; G576A, R668C+; G622D; G628R; G970D; G1061R; G1069R; G1244E; G1249R; G1349D; H139R; H199Y; H939R; H1054D; H1085P: H1085R; H1375P: 1148T: 1175V; 1336K: 1502T: 1601F: 1618T: 1807M; 1980K; 11027T: 11139V; 11269N: 11366N; K1060T; L15P; L165S; L206W; L320V; L346P; L4535; L967S; L997F; L1077P; L1324P; L1335P; L1480P; M152V; M285R; M9521; M952T; M1101K; P5L; P67L; P205S; P574H; Q98R; Q237E; Q237H; Q359R; Q1291R; R31L; R74Q; R74W; R74W, D1270N; R74W, V201M; R74W, V201M, D1270N; R75Q; R117C; R117G; R117H; R117L; R117P; R170H; R258G; R334L; R334Q; R347H; R347L; R347P; R352Q; R352W; R553Q; R668C; R751L; R792G; R933G; R1066H; R1070Q; R1070W: R1162L; R1283M; R1283S; S13F; S341P: S364P; S492F; S549N; S549R; S589N; S737F; S912L; S945L; S977F; S1159F; S1159P; S1251N; S1255P; T3381; T1036N; T10531; V201M; V232D; V456A; V456F; V5621; V754M; V1153E; V1240G; V1293G; W361R; W1098C; W1282R; Y109N; Y161D; Y161S; Y563N; Y1014C; Y1032C.	Patients aged 6 years and older who have at least one F508del mutation in the CFTR gene.

CONCLUSION

The management of CF has been changing drastically over the last few years, especially after the introduction of CFTR modulators. Currently, 188,336 people have the disease in 96 countries, but only 27% of them gained access to this type of treatment. These data indicate that although there is an increasing availability of CFTR modulators, a significant disparity in access to these therapies is noticed, mainly in countries with limited financial resources.[6] The main barrier to a wider access remains the cost of these therapies. This sad situation needs a global collaboration toward new solutions to improve access, mainly in such countries. We hope that a true expansion of access to these transforming therapies will actually occur in the next few years, impacting the quality of life and life expectancy of individuals from different cultures and places of the world.

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LGBB, LMP, and MFGMF contributed to searching and writing. LVRFSF and LAP contributed to writing, reviewing, and editing. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

LGBB, LMP, and MFGMF declare no conflict of interest. LVRFSF and LAP disclose that they have received honoraria from Vertex Pharmaceuticals Incorporated due to previous sponsored lectures.

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ORIGINAL ARTICLE

Hyperventilation worsens inflammatory lung injury in spontaneously breathing rats

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ABSTRACT

Objectives: Here, we investigated the effects of hyperventilation on acute lung injury (ALI) in spontaneously breathing rats. **Methods:** Wistar rats were randomized to receive either intraperitoneal lipopolysaccharides (LPS) or saline, and intravenous infusion of NH_4Cl (to induce metabolic acidosis and hyperventilation) or saline. Four groups were established: control-control (C-C), control-hyperventilation (C-HV), LPS-control (LPS-C), and LPS-hyperventilation (LPS-HV). Venous blood gases were collected before and after NH_4Cl infusion and analyzed to confirm the presence of metabolic acidosis and hyperventilation. After euthanasia, lung injury was assessed using the ALI score, morphometric quantification of perivascular edema, neutrophil counts in the bronchoalveolar lavage, and mRNA expression of biological markers in the lung tissue. **Results:** Hyperventilation induced inflammatory lung injury in previously healthy lungs and exacerbated injuries previously induced by LPS (ALI score: C-C=0.14 [IQR 0.12; 0.14]; C-HV=0.36 [IQR 0.31; 0.37]; LPS-C=0.51 [IQR 0.50; 0.54]; LPS-HV=0.58 [IQR 0.56; 0.62]; p<0.01). Perivascular edema, neutrophil counts in bronchoalveolar lavage, and amphiregulin mRNA expression were higher in the LPS-HV group compared to the control group. **Conclusions:** Hyperventilation increased inflammatory injury in rats with ALI during spontaneous ventilation. These results suggest that the impact of vigorous spontaneous breathing efforts on worsening inflammatory lung injury warrants further investigation.

Keywords: acute lung injury, acute respiratory distress syndrome, spontaneous breathing, hyperventilation, lung injury.

INTRODUCTION

Mechanical ventilation (MV) is an essential treatment for many patients with severe forms of acute lung injury (ALI).[1] However, lung inflation during controlled positive pressure ventilation is heterogeneous, with greater expansion in the ventral regions compared to the dorsal regions. This ventilatory pattern worsens ventilation-perfusion (V/Q) matching and, consequently, impairs pulmonary gas exchange efficiency.[2] Moreover, MV can cause uneven distribution of distending pressure, thus increasing the risk of ventilator-induced lung injury (VILI).[3]

Allowing spontaneous effort during MV can minimize the heterogeneous distribution of distending pressure, increase lung aeration, and improve V/Q matching and oxygenation.[4] Additional potential benefits include enhanced hemodynamic performance, prevention of diaphragmatic atrophy, improved patient comfort, and a reduced need for aggressive sedation and/or paralysis.[5]

Conversely, recent evidence suggests that spontaneous efforts may contribute to lung injury, especially in severely injured lungs or when these efforts are vigorous. These efforts reduce pleural pressure (Ppl), increasing transpulmonary pressure and tidal volume (V_T), both of which are associated with lung injury.[6,7] In severely injured lungs with heterogeneous aeration, spontaneous efforts can also heighten local lung stress, leading to lung injury even with low V_T.[8] Additionally, a negative Ppl increases transmural vascular pressure (the difference between intravascular and extravascular pressure), promoting fluid leakage into the pulmonary interstitium and alveolar space.[9] This effort-related lung injury is termed patient self-inflicted lung injury (P-SILI).[10]

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During the COVID-19 pandemic, the concept of P-SILI was extended to patients not receiving mechanical ventilatory support. Some authors have postulated that strong spontaneous inspiratory efforts may exacerbate lung injury and edema by increasing tissue stress and pulmonary transvascular pressure. They advocated for early intubation and effective sedation, with or without paralysis, to break this cycle.[11] However, the extent to which inspiratory efforts are capable of aggravating lung injury, and whether the potential benefits of early intubation outweigh the risks associated with invasive MV, remains unclear. Due to the lack of robust evidence, some authors have questioned early intubation, favoring noninvasive strategies for patients with acute hypoxemic respiratory failure, suggesting that the liberal use of intubation and MV may increase mortality in these patients.[12]

In the present study, we used an established model of ALI induced by lipopolysaccharides (LPS) to investigate whether hyperventilation caused by metabolic acidosis exacerbates lung injury in rats during spontaneous ventilation.

METHODS

Adult male Wistar rats, weighing 280–360 g, were obtained from the Reproduction Biology Center of the Federal University of Juiz de Fora vivarium, in Minas Gerais, Brazil. This choice was made due to their favorable biological and physiological similarity to humans.[13] The number of animals used followed the reduction principle, with an anticipated range of 6–8 animals per experimental group, consistent with previous studies conducted by our research team.[14,15] The study was approved by the Animal Research Ethics Committee of the Federal University of Juiz de Fora (Protocol No.: 017/2022).

Experimental protocol

Initially, the rats were randomly assigned to two main groups: the LPS group and the control group. In the LPS group, the animals received 5 mg/kg LPS (serotype 055:B5; Sigma-Aldrich, Israel) intraperitoneally, dissolved in 0.5 mL of 0.9% saline solution. Meanwhile, the animals from the control group received an equivalent volume of 0.9% saline solution intraperitoneally.

After 24 hours, the rats were anesthetized with an intraperitoneal bolus of xylazine (8 mg/kg), midazolam (5 mg/kg), and ketamine (80 mg/kg). A polyethylene catheter was inserted into the left jugular vein for infusion of the solutions and to obtain blood samples for venous blood gas analysis (ABL90 FLEX; Radiometer, Copenhagen, Denmark).

The rats in the LPS and control groups were subsequently randomized into two subgroups, hyperventilation and control, resulting in four groups: control-control (C-C), control-hyperventilation (C-HV), LPS-control (LPS-C), and LPS-hyperventilation (LPS-HV) (Figure 1). The animals assigned to the hyperventilation groups (C-HV and LPS-HV) received intravenous infusions of 1.0 mL/kg of ammonium chloride (5 M-NH_4Cl; Pharmacology Laboratory, School of Pharmacy, Federal University of Juiz de Fora, Brazil) dissolved in 0.9% saline solution, totaling 3.5 mL over 180 minutes. The animals in the control groups (C-C and LPS-C) received venous infusions of the same volume of 0.9% saline solution over 180 minutes. In order to assess the success of inducing metabolic acidosis (HCO_3^- ≤ 15 mEq/L) and hyperventilation (reduction in $PvCO_2$ ≥ 25% compared to baseline), a venous blood sample was collected for gas analysis immediately after the infusion ended.

After infusion with NH_4Cl or saline, a tracheostomy was performed, and the trachea was cannulated with a 14-gauge tube. The rats were mechanically ventilated (Inspira ASV, Harvard Apparatus, USA) for one minute under the following parameters: volume-controlled mode, V_T of 6 mL/kg, respiratory rate of 80 breaths/min, inspiratory to expiratory ratio of 1:2, F_IO_2 of 21%, and PEEP of 5 cmH_2O.

Subsequently, a laparotomy was performed, and the animals were euthanized by exsanguination through sections of the abdominal aorta. The trachea was clamped at end-inspiration, and the lungs were removed for further analysis.

Lung histology

Following lung removal, the right caudal lobes were fixed in 10% buffered formaldehyde. After being embedded in paraffin, 4 µm-thick slices were cut and stained with hematoxylin–eosin. Morphological tests were performed using a light microscope (Zeiss, Hallbergmoos, Germany) by a pathologist who was blinded to the experimental details. ALI was assessed using the American Thoracic Society-recommended ALI score.[13] Briefly, 20 random fields filled with pulmonary alveoli were evaluated at 400× magnification and scored individually. Values of 0, 1, or 2 were used to represent injury severity based on the following findings: neutrophils in the alveolar space, neutrophils in the interstitial space, hyaline membranes, proteinaceous debris filling the airspaces, and alveolar septal thickening. To calculate the ALI scores, the sum of the five variables was weighted according to the relevance assigned to each one. The resulting score ranged from 0 (normal) to 1 (most severe injury).

Perivascular edema was quantified through morphometric analysis using the point-counting technique, as previously described.[16,17] At 400× magnification, we analyzed 10 randomly selected fields per lung, focusing on the transversely sectioned intraparenchymatous arteries and veins. The number of points falling within areas of perivascular edema (PE) and those within areas of vessels (V) were computed. The perivascular edema index was calculated as the PE/V ratio. The final perivascular index was the mean of the 10 analyzed fields. All measurements were performed using a blinded method.[16,17]

Clara cell secretory protein-16 (CC16), intercellular adhesion molecule 1 (ICAM-1), and amphiregulin expression

The right cranial lobes were crushed and transferred to microcentrifuge flex tubes containing TRIzol® reagent for total RNA extraction using a standard procedure. cDNA synthesis was carried out using a two-step cDNA synthesis kit (Promega, USA). One microgram of RNA was reverse-transcribed into cDNA via GoScript™ reverse transcriptase (Promega, USA), following the manufacturer's instructions, resulting in a total reaction volume of 20 µL. Real-time quantitative polynucleotide chain reaction (RT-qPCR) was performed with 5 µL of SYBR Green concentrate in a final volume of 10 µL containing 50 ng of cDNA. To determine the initial relative quantity of cDNA, samples were amplified with ICAM-1, CC16, and amphiregulin primers. The reactions were run on an Applied Biosystems 7500 RT-qPCR machine (Applied Biosystems, USA). An internal standard was established to normalize the relative gene expression level, and this standard was run with each experiment. Melt curve analyses were conducted for all genes, and the specificity and integrity of the PCR products were confirmed by the presence of a single peak. Relative expression was calculated based on the differences in cycle time of the internal standard (GAPDH) compared to that of the target mRNA. Duplicate CT values were analyzed in Microsoft Excel (Microsoft) using the comparative CT method (Applied Biosystems, USA).[14]

Bronchoalveolar lavage (BAL)

BAL collection was performed in the left lung by instillation and slow aspiration of 4 mL of phosphate-buffered saline solution containing ethylenediamine tetraacetic acid (10 nM). This procedure was repeated three times. Total leucocyte counts were measured in a Neubauer chamber under light microscopy after the samples were diluted in Turk solution. The cell pellet was resuspended in phosphate-buffered saline and stained with May-Grunwald-Giemsa for differential cell counts, which were performed on 300 cells.

Statistical analysis

Data were expressed as medians and interquartile ranges. The normality of the data was analyzed using the Shapiro-Wilk test. One-way ANOVA was used to compare normally distributed data among groups. To identify differences between the means in the post hoc analysis, Tukey's pairwise multiple comparison test was applied when a significant *F* ratio was obtained for a factor or for interactions between factors. For non-normally distributed data, the Kruskal-Wallis test was used, followed by the Mann-Whitney U test. Adjustments for multiple comparisons were made using Bonferroni's correction. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. The statistical analyses were performed using SPSS software, version 17.0.

RESULTS

A total of 32 rats were used to form the four groups. During the experimental period, six rats died: two from the C-C group, one from the C-HV group, one from the LPS-C group, and two from the LPS-HV group. In addition, one rat from the C-HV group was excluded because hyperventilation was not achieved by the end of the experiment (Figure 1).

Hyperventilation induction

NH_4Cl infusion induced metabolic acidosis, as evidenced by significantly lower levels of HCO_3^- in the C-HV and LPS-HV groups at the end of the experiment compared to baseline values ($p < 0.05$ for both comparisons). This metabolic acidosis resulted in hyperventilation in these groups, as indicated by the reduction in $PvCO_2$ levels after NH_4Cl infusion compared to baseline values ($p < 0.05$ for both comparisons) (Table 1).

Lung histology

Compared to the animals in the C-C group, the ALI scores of the rats in the LPS-C and LPS-HV groups were significantly higher ($p < 0.05$ for both comparisons). Analysis of each component of the score revealed that, compared to the C-C group, the LPS-C and LPS-HV groups exhibited greater neutrophil infiltration in both the alveolar and interstitial spaces, as well as increased amounts of alveolar proteinaceous debris ($p < 0.05$ for all comparisons). Among the rats that received LPS, the ALI score was greater in the LPS-HV group ($p < 0.05$). This difference was attributed to the greater alveolar and interstitial neutrophil infiltration observed in the LPS-HV group compared to the LPS-C group ($p < 0.05$ for both comparisons). In comparison with the C-C group, the C-HV group presented a higher ALI score ($p < 0.05$), with greater alveolar and interstitial neutrophil infiltration ($p < 0.05$ for both comparisons) (Table 2, Figure 2). Morphometric analysis revealed greater perivascular edema in the LPS-HV group compared to the C-C group ($p < 0.05$) (Figure 2). Representative histological images of the sagittal section of the right lower lobe, stained with hematoxylin-eosin, are shown in Figure 3.

Bronchoalveolar lavage

Intraperitoneal LPS injection followed by hyperventilation increased BAL cellularity, as evidenced by the higher number of neutrophils in the LPS-HV group compared to the C-C and C-HV groups ($p < 0.05$ for both comparisons) (Figure 4).

ICAM-1, CC16, and amphiregulin mRNA expression

The relative mRNA levels of biological markers associated with inflammation (ICAM-1), pulmonary stretch (amphiregulin), and epithelial cell damage (CC-16) are presented in Figure 4. The relative mRNA expression of amphiregulin was significantly greater

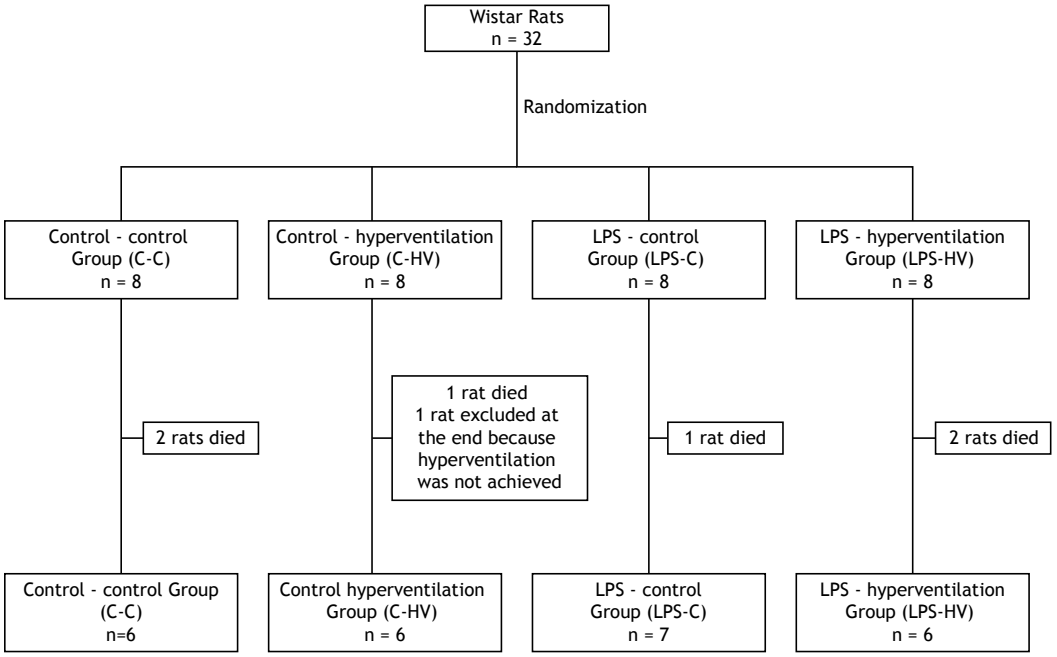

Figure 1. Animals included in the analyses.

Table 1. Venous blood gas parameters at baseline and at the end of the experiment.

	Group C-C (N = 6)	Group C-HV (N = 6)	Group LPS-C (N = 7)	Group LPS-HV (N = 6)
$PvCO_2$ (mmHg)				
Baseline	46 (41-47)	43 (42-48)	30 (28-30)*&	35 (32-38)
Final	57 (40-58)	29 (28-30)*#	30 (27-33)*	26 (26-30)*#
$DPvCO_2$	+12 (-7 +19)	-14 (-19 -14)	+2 (-3 +3)	-8 (-9 -7)
pH				
Baseline	7.35 (7.33-7.38)	7.38 (7.37-7.38)	7.42 (7.37-7.42)	7.32 (7.32-7.33)†
Final	7.28 (7.19-7.33)	7.33 (7.32-7.33)	7.38 (7.36-7.38)	7.22 (7.16-7.25)†
HCO_3^- (mEq/L)				
Baseline	23 (23-24)	25 (25-28)	18 (16-20)&	19 (14-19)&
Final	21 (18-22)	15 (14-15)*#	17 (15-18)	14 (11-14)*†#

C-C: control-control group; C-HV: control-hyperventilation group; LPS-C: lipopolysaccharide-control group; LPS-HV: lipopolysaccharide-hyperventilation group. HCO_3^-: bicarbonate; $PvCO_2$: venous carbon dioxide partial pressure; D: difference between final and baseline values. Data expressed as median and interquartile range (25% and 75%). * $p < 0.05$ when compared to C-C; & $p < 0.05$ when compared to C-HV; † $p < 0.05$ when compared to LPS-C; # final compared to baseline. Comparisons by Tukey's pairwise multiple comparison test, with Bonferroni correction.

in the LPS-HV group compared to the other groups ($p < 0.05$ for all comparisons) (Figure 4).

DISCUSSION

In our study, intraperitoneal injection of LPS led to inflammatory ALI, as evidenced by increased ALI scores, with greater alveolar and interstitial neutrophil infiltration in these animals than in the controls. The addition of hyperventilation induced by NH_4Cl infusion further exacerbated lung injury, as indicated by increased ALI scores, increased perivascular edema, a higher number of neutrophils in the BAL, and elevated mRNA expression of amphiregulin.

Intraperitoneal injection of LPS is an established experimental model of ALI characterized by histological changes (interstitial thickening, alveolar and interstitial neutrophil infiltration, and the presence of proteinaceous debris in the alveolar spaces), altered lung mechanics (increased elastance of the respiratory system), and effects on the alveolar-capillary barrier (increased lung wet/dry weight ratio and elevated albumin concentration in the BAL).[14] Typically, LPS-induced ALI results in mild impairments in gas exchange, including hypoxemia levels that can be managed without MV.[18] This characteristic played a decisive role in our selection of the injury model, aligning with our aim to investigate the role of P-SILI during spontaneous, unassisted breathing.

To induce hyperventilation, we applied a metabolic acidosis model through intravenous infusion of NH_4Cl. This compound is converted into H^+ and urea in the

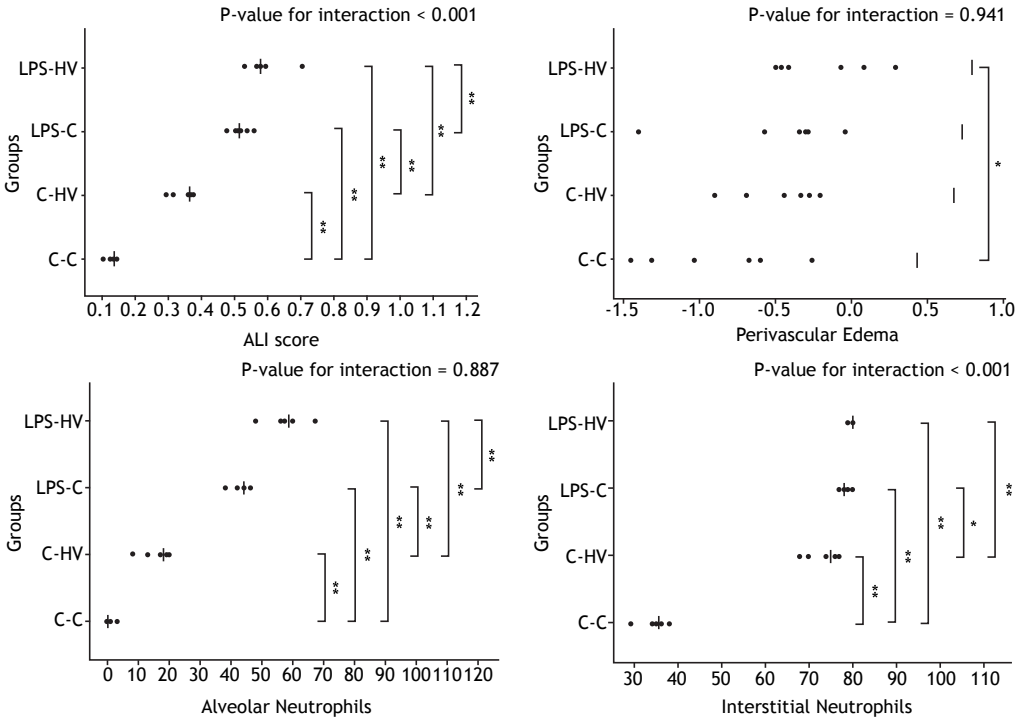

Figure 2. Acute lung injury score, perivascular edema, alveolar neutrophil counts, and interstitial neutrophil counts. ALI: acute lung injury; C–C: control–control group; C–HV: control–hyperventilation group; LPS–C: lipopolysaccharide–control group; LPS–HV: lipopolysaccharide–hyperventilation group. Each symbol represents an individual animal, and the black lines represent the median values of each group. * $p < 0.05$ - Comparisons by Tukey's pairwise multiple comparison test, with Bonferroni correction.

Table 2. Acute lung injury score and its components.

	Groups			
	C-C (N = 6)	C-HV (N = 6)	LPS-C (N = 7)	LPS-HV (N = 6)
Overall score	0.14 (0.12-0.14)	0.36 (0.31-0.37)*	0.51 (0.50-0.54)*Δ	0.58 (0.56-0.62)*Δ†
Alveolar neutrophils	0.0 (0.0-1.0)	18.0 (11.8-19.3)*	44.0 (42.0-46.0)*Δ	58.5 (54.0-61.8)*Δ†
Interstitial neutrophils	35.0 (32.8-38.0)	75.0 (69.0-76.3)*	78.0 (77.0-79.0)*Δ	80.0 (79.0-80.0)*Δ
Proteinaceous debris	2.0 (0.0-4.5)	5.5 (2.8-7.0)	10.0 (8.0-30.0)*	7.5 (3.5-19.0)
Septal thickening	0.0 (0.0-0.5)	4.0 (0.0-5.5)	2.0 (0.0-2.0)	0.5 (0.0-6.3)

C-C: control-control group; C-HV: control-hyperventilation group; LPS-C: lipopolysaccharide-control group; LPS-HV: lipopolysaccharide-hyperventilation group. Data expressed as median and interquartile range (25% and 75%). * $p < 0.05$ when compared to C-C; Δ $p < 0.05$ when compared to C-HV; † $p < 0.05$ when compared to LPS-C. Comparisons by Tukey's pairwise multiple comparison test, with Bonferroni correction.

liver, thus reducing renal HCO_3^- reabsorption. As described by Iwabushi et al. (2003), this model induces metabolic acidosis and compensatory hyperventilation during the infusion period.[19] Confirming the model's efficacy, the rats that received NH_4Cl exhibited lower levels of $PvCO_2$ at the end of the experiments compared to baseline values.

We demonstrated that hyperventilation intensified the degree of inflammatory lung injury induced by intraperitoneal LPS injection, as indicated by increased neutrophil infiltration in alveolar spaces observed in the histological analysis and higher neutrophil counts in the BAL. Our findings also revealed elevated expression of amphiregulin, a member of the epidermal growth factor family, which is upregulated in conditions of lung epithelial cell damage, as seen in VILI.[20] Previous experimental studies have shown that vigorous inspiratory efforts during mechanically-assisted breathing can cause or worsen lung injury. Yoshida et al. (2012) demonstrated in an experimental model of ALI induced by repeated lung lavage that vigorous spontaneous efforts can lead to lung injury, even when the plateau pressure is limited to < 30 cmH_2O.[6] Such efforts increase transpulmonary pressure, the total alveolar stretching pressure, resulting in a greater tidal volume. Both elevated transpulmonary pressure

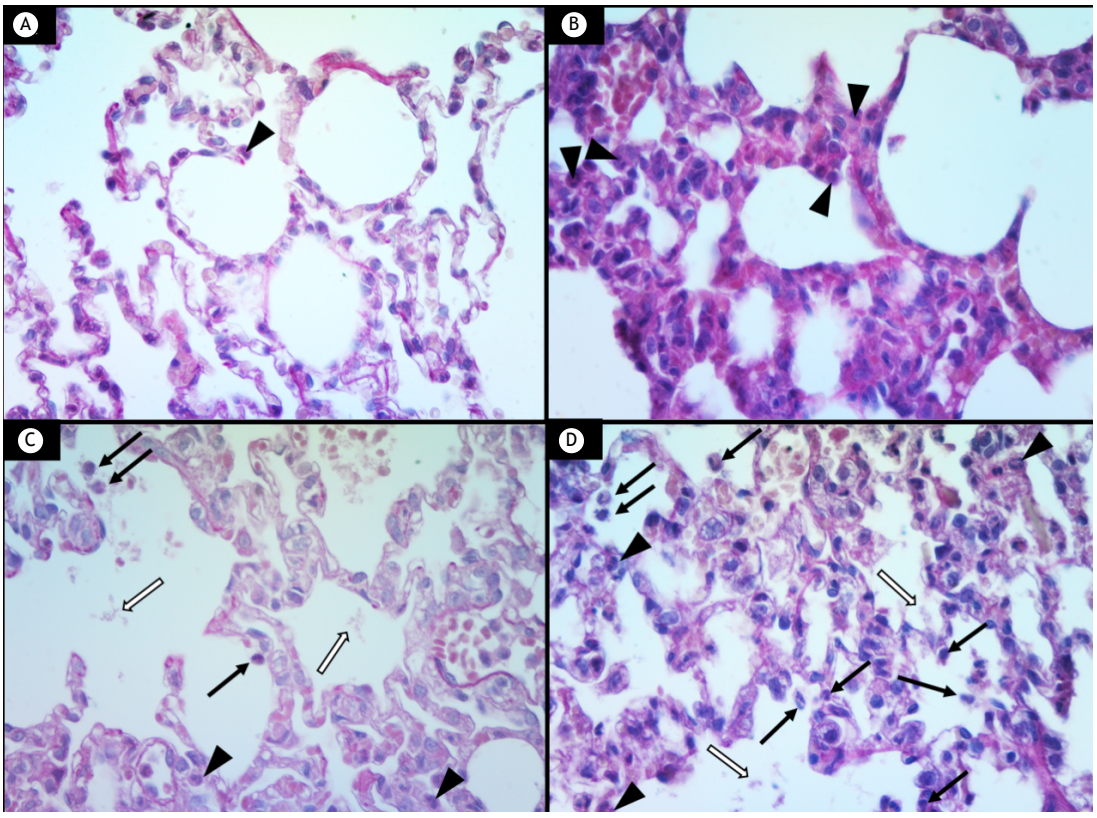

Figure 3. Representative images of histological analysis of the lower right lobe sagittal section stained with hematoxylin–eosin (H&E, 400×). (A) Control–control group; (B) Control–hyperventilation group; (C) LPS–control group; (D) LPS–hyperventilation group. Alveolar neutrophils (black arrows); interstitial neutrophils (arrowheads); proteinaceous debris (open arrows). Note that the LPS-hyperventilation group showed higher accumulation of neutrophils in the alveoli when compared to the other groups.

and tidal volume are associated with VILI and may be further exacerbated by high respiratory frequency.[6] Additionally, in heterogeneous lungs, such as in acute respiratory distress syndrome, spontaneous efforts affect the lung regions differently, with greater pleural pressure fluctuations in dependent regions compared to non-dependent ones. This phenomenon, known as *pendelluft*, leads to increased local transpulmonary pressure and tidal inflation in dependent regions, potentially raising the risk of VILI.[7]

Spontaneous efforts also elevate transmural vascular pressure by generating more negative pleural pressure, thereby contributing to pulmonary edema.[21] Supporting this theory, we demonstrated that rats with inflammatory ALI, where hyperventilation was induced by NH_4Cl, exhibited a higher perivascular edema index compared to the C-C group.

In contrast with previous studies, our model evaluated the impact of spontaneous efforts on ALI in extubated animals, an area where knowledge remains limited. Positive pressure ventilation can alter the effects of spontaneous efforts on the lungs in multiple ways. For instance, the application of positive end-expiratory pressure reduces *pendelluft* and promotes neuromechanical uncoupling of the diaphragm, both of which mitigate injury.[22] Furthermore, positive pressure ventilation also influences the transvascular pressure dynamics, adding further complexity to its effects. However, we are not the first to investigate the impact of spontaneous breathing in extubated subjects. Mascheroni et al. (1988) reported that severe hyperventilation during spontaneous breathing led to pulmonary dysfunction in an experimental ovine model with initially healthy lungs.[23] We built on their findings by examining the impact of hyperventilation on both healthy lungs and lungs previously injured by LPS injection through a factorial design. This approach allowed for a more accurate representation of clinical scenarios in which lung injury from spontaneous efforts may occur, and it helped clarify whether the harmful effects of spontaneous efforts vary based on the underlying lung condition. Our findings indicate that allowing vigorous spontaneous efforts can induce inflammatory injury in previously healthy lungs and exacerbate preexisting inflammatory lung injury.

Our results cannot be directly extrapolated to clinical practice. However, these findings align with data from experimental studies in large animals (all conducted during MV) and with the physiological basis for lung injury caused by spontaneous efforts. Nonetheless, the extent of this injury and its clinical

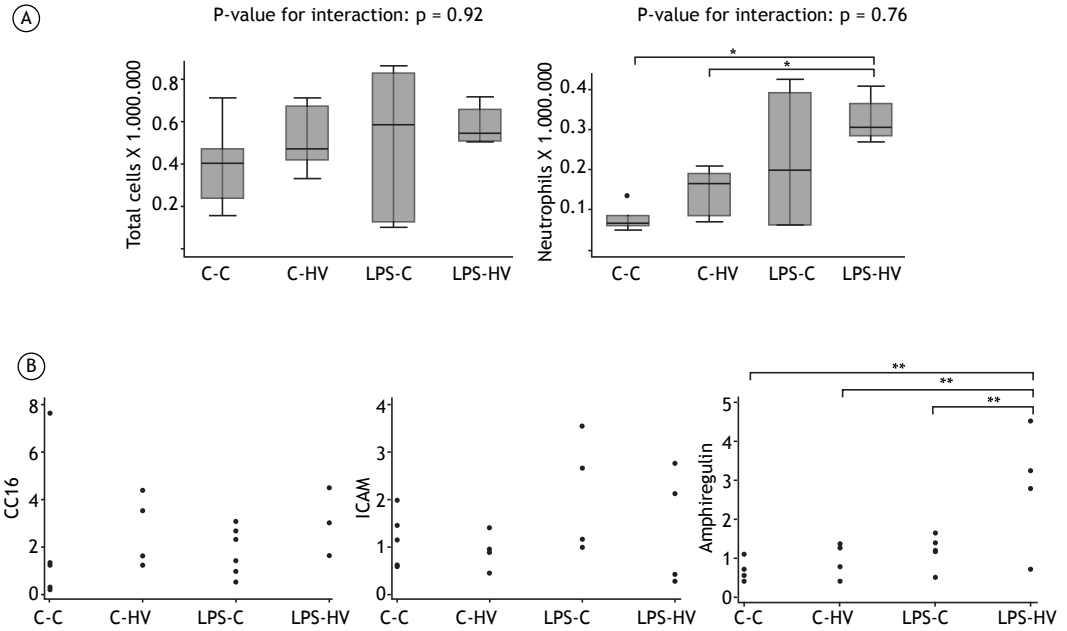

Figure 4. (A) Cell count in the bronchoalveolar lavage (BAL); (B) Relative mRNA levels of Clara cell secretory protein-16 (CC16), intercellular adhesion molecule 1 (ICAM-1), and amphiregulin in lung tissue. GAPDH was used as an internal standard for normalization. C–C: control–control group; C–HV: control–hyperventilation group; LPS–C: lipopolysaccharide–control group; LPS–HV: lipopolysaccharide–hyperventilation group. * p < 0.05 – Comparisons by Tukey's pairwise multiple comparison test, with Bonferroni's correction. ** p < 0.05 – Comparisons by the Mann-Whitney U test, with Bonferroni correction.

significance in ALI patients remain uncertain. During the COVID-19 pandemic, some authors suggested using noninvasive support (e.g., high-flow nasal oxygen, CPAP, or Bi-PAP) to limit excessive inspiratory efforts in mild cases of acute respiratory failure.[24] The same authors recommended early intubation, followed by effective sedation, for more severe cases or for patients whose respiratory patterns did not improve with noninvasive support.[11] The rationale behind these recommendations was the risk of progressive lung function decline (a VILI vortex) driven by patients' inspiratory efforts.[11,24] Other investigators did not adopt these recommendations, as no clinical study has yet demonstrated that vigorous inspiratory efforts cause clinically significant lung injury.[12] Moreover, if inspiratory effort-related lung injury exists in this context, clinicians must weigh its risks against those associated with invasive MV to make informed decisions.

The main limitation of our study was the inability to definitively exclude a potential direct effect of NH_4Cl or metabolic acidosis on lung injury. However, existing experimental evidence suggests that both NH_4Cl and metabolic acidosis may, in fact, confer a protective effect against VILI by mitigating pulmonary inflammation and reducing pulmonary edema formation, a major manifestation of VILI.[25-27] It is well established that the hypoventilation associated with hypercapnic acidosis is not only well tolerated by individuals with acute lung injury but can also exert protective effects against tissue damage.[28] Recent experimental studies indicate that metabolic acidosis may also offer protection against acute lung injury. In an *ex vivo* model of acute lung injury induced by ischemia-reperfusion, Laffey et al. (2000) reported that metabolic acidosis, achieved via hydrochloric acid administration, led to reduced lung injury, as evidenced by decreased pulmonary capillary permeability and a lower wet/dry weight ratio.[25] Additionally, in a VILI model using an isolated ventilated-perfused rabbit lung, the authors showed that metabolic acidosis was as effective as hypercapnic respiratory acidosis in preventing pulmonary edema formation, suggesting that acidosis itself exerts a protective effect against experimental VILI.[26] Similar protective effects have been reported for NH4Cl-induced metabolic acidosis by Hudalla et al. (2019), who demonstrated that it attenuated lung inflammation in an experimental model of pulmonary hypertension induced by Sugen 5416 and hypoxia. This resulted in reduced lung mRNA levels of proinflammatory mediators (such as tumor necrosis factor, interleukin-6, and C-C motif chemokine ligand 2), as well as decreased plasma interleukin-6 levels.[27] Considering these findings, along with evidence linking lung injury to excessive inspiratory efforts that overstretch the lung parenchyma, our experimental model of patient self-inflicted lung injury (P-SILI) appears plausible.

Other limitations of this study included the following: 1) The intraperitoneal LPS injection-induced ALI model resulted in metabolic acidosis. Consequently, even before NH_4Cl infusion, the two groups that received

LPS already exhibited acidosis and hyperventilation. Although NH_4Cl infusion intensified acidosis and hyperventilation in the LPS-HV group, this effect was less pronounced than in the LPS-C group. This smaller difference between the two groups may have limited the detection of hyperventilation-induced injury in LPS-injured lungs. 2) Our model used small animals (Wistar rats), in which regional differences in pleural pressure may not be as significant as in larger animals and humans. Since these regional differences in pleural pressure may play an important role in lung injury from inspiratory efforts, our model might have underestimated the negative impact of hyperventilation in previously injured lungs. 3) The mRNA expression of biological markers was not measured in all animals, resulting in a smaller sample size and reduced statistical power to identify group differences.

In conclusion, our findings demonstrate that hyperventilation exacerbates inflammatory injury in rats with ALI during spontaneous ventilation. These results indicate the need for further investigation into the role of vigorous spontaneous efforts in worsening inflammatory lung injury.

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AUTHOR CONTRIBUTIONS

The authors contributed to the paper as follows: study conception and design: J.D.N.F., M.M.R., E.L.V.C., J.R., L.M.F.L., B.V.P.; data acquisition: J.D.N.F., L.M.C.F., F.J.M.S., F.P., A.S.F., L.M.F.L., B.V.P.; data analysis and interpretation: J.D.N.F., M.M.R., E.L.V.C., L.M.C.F., J.R., F.J.M.S., F.P., A.S.F., L.M.F.L., B.V.P.; literature search: J.D.N.F., M.M.R.; drafting the article: J.D.N.F., M.M.R., L.M.F.L., B.V.P.; article revision, providing intellectual content of critical importance: E.L.V.C., L.M.C.F., J.R., F.J.M.S., F.P., A.S.F.; approval of the final version of the manuscript: J.D.N.F., M.M.R., E.L.V.C., L.M.C.F., J.R., F.J.M.S., F.P., A.S.F., L.M.F.L., B.V.P.

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ORIGINAL ARTICLE

Prevalence of allergic rhinitis, atopic dermatitis, and wheezing at 15 and 22 years of age: the 1993 Pelotas (Brazil) Birth Cohort Study

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ABSTRACT

Objectives: To estimate the prevalence of allergic rhinitis (AR), atopic dermatitis (AD), and wheezing, and to describe their patterns of co-occurrence according to different characteristics in adolescence and early adulthood. **Methods:** Cross-sectional analyses from the 15-year and 22-year follow-ups of the 1993 Pelotas (Brazil) Birth Cohort. The outcomes were assessed based on self-reported data, and the patterns of co-occurrence were determined using cluster analysis. The sample was described using absolute and relative frequencies according to the independent variables. Venn diagrams were generated to visualize the co-occurrence of AR, AD, and wheezing. **Results:** Data on AR, AD, and wheezing were available for 4,286 participants at 15 years and 3,789 at 22 years. At 15 years, AR was reported by 20.9% of participants, AD by 25.2%, and wheezing by 33.4%. Meanwhile, at 22 years, AR was reported by 24.6%, AD by 14.2%, and wheezing by 30.7%. Notably, the overlap between AR and wheezing was greater than that of the other conditions (6.9% at 15 years and 8.3% at 22 years). Participants with lower maternal education and lower income were more likely to report having "no health condition". At 15 years, White individuals most frequently reported "three conditions" (4.1%; p<0.001), whereas at 22 years, they primarily reported "two conditions" (15.6%; p<0.001). The co-occurrence of all three health conditions was found to be greater than expected, with an observed rate 2.1 times higher (95% CI 1.4 – 3.0) at 22 years. **Conclusions:** This study highlights the social gradient in the diagnosis and reporting of co-occurrence of AR, AD, and wheezing.

Keywords: asthma, wheezing, allergic rhinitis, atopic dermatitis, epidemiology.

INTRODUCTION

Allergic asthma is more common in childhood.[1,2] This phenotype is associated with a history of allergic rhinitis (AR), atopic dermatitis (AD), or both,[1,2] and its symptoms are typically triggered by allergens, such as pollen and dust mites.[2]

When considered separately, the prevalence of asthma, AR, and AD varies widely within and across countries.[3–5] In 2019, over 260 million people were diagnosed with asthma.[3] Population-based studies have reported prevalence estimates for AR ranging from 1.0% to 63.0% in adolescents and adults globally,[4,6] while the prevalence of AD has been shown to range from 3.4% to 33.7%.[4,5,7]

Temporal changes in the prevalence of these health conditions in childhood are described by the concept of the "atopic march".[8,9] This widely accepted hypothesis outlines a cascade of symptoms that typically begins with AD, which progresses to asthma and then AR, with AD often resolving as age increases.[10] However, some researchers argue that the natural history of these conditions may vary, exhibiting different developmental symptom profiles over time.[11,12]

The co-occurrence of asthma, AR, and AD has been observed to be more common than expected.[13,14] In the 1993 Pelotas (Brazil) Birth Cohort Study, participants with persistent symptoms of asthma, such as wheezing, had significantly higher odds of being diagnosed with an allergy (OR 6.18; 95% CI: 3.59 – 10.61) compared to those with never/infrequent wheezing.[15] However, despite the increasing prevalence of these conditions among adolescents and young adults in lower- and upper-middle-income countries,[1,16,17] few population-based studies have described the co-occurrence of all three conditions.

Pedersen et al. (2020) reported that the prevalence of having two atopic conditions peaked at 10.0% at 2 years of age and was approximately 3.4% among adults in a rural area of India.[16] In Brazil, the prevalence of these health conditions has also mostly been studied separately,[18–20] especially among adolescents and young adults.[15,21,22]

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The co-occurrence of asthma, AD, and AR reduces quality of life, rest, and academic performance among adolescents.[23–25] Further investigation is essential to better understand these combinations and to develop more effective health interventions that mitigate their effects.[23,24] This is particularly important during the transition from adolescence to adulthood due to its impact on long-term health outcomes and well-being.[26,27] Therefore, the objectives of the present study were: 1) to estimate the prevalence of allergic rhinitis, atopic dermatitis, and wheezing (as a proxy for asthma), both individually and jointly; and 2) to describe the frequency of their patterns of co-occurrence according to sociodemographic, behavioral, and health characteristics in adolescence and early adulthood, based on cross-sectional analyses from the 1993 Pelotas (Brazil) Birth Cohort.

METHODS

Study participants

The 1993 Pelotas (Brazil) Birth Cohort is a longitudinal, prospective, and population-based study that included all live births that occurred in hospitals in the city of Pelotas (RS), Brazil, in 1993. Among the 5,265 newborns, 5,249 (99.7%) were enrolled in this cohort study. From birth to the 22-year follow-up, subsamples have provided information on the participants' health. The present study used data collected in the 15-year and 22-year follow-ups, with response rates of 85.7% and 76.3%, respectively. The methodology, rationale, and updates of the cohort study have been described elsewhere.[28]

Outcomes

Three health conditions were assessed at ages 15 and 22 based on self-reported data:

1. Allergic rhinitis: "Have you ever been diagnosed with allergic rhinitis?"
2. Atopic dermatitis: "Have you ever been diagnosed with eczema?"
3. Wheezing: "Have you ever had wheezing or a whistling sound in your chest any time in the past?"

Covariates

The independent variables were measured at baseline (perinatal) and at the 15-year and 22-year follow-ups. At baseline: sex (male, female); skin color (White, Black, or Mixed); maternal age (≤ 19 years, 20–29 years, 30–39 years, ≥ 40 years); maternal education (0–4 years, 5–8 years, 9–11 years, ≥ 12 years); monthly income in multiples of minimum wage, equivalent to approximately US$ 240.00 (≤ 1, 1.1–3, 3.1–6, 6.1–10, ≥ 10); family history of allergy (no, yes); family history of asthma (no, yes); maternal smoking during pregnancy (no, yes); and birth weight (< 2500 g, ≥ 2500 g). At the 15-year and 22-year follow-ups: smoking status (never, former, or current) and weight status (normal weight, overweight, obese).

Statistical analysis

This cross-sectional study evaluated both follow-ups independently, and only individuals with complete data for all three health conditions (AR, AD, and wheezing) were included.

The co-occurrence of AR, AD, and wheezing was determined by cluster analysis. The observed-to-expected (O/E) ratio for each combination was calculated.[29,30] The expected prevalence for each of the eight possible combinations was determined by multiplying the observed prevalence of each health condition by the inverse of the observed proportion of missing conditions, assuming the independence of each condition. A cluster was considered statistically significant if the O/E ratio was greater than 1 and its respective 95% confidence interval (95% CI) did not include the unit (1).[29,31] The analyses and their respective 95% CIs were stratified by sex and conducted using Microsoft Excel, version 16.85 (Microsoft Corporation, Redmond, WA, USA).

The sample was described using absolute and relative frequencies based on the independent variables. Pearson's chi-square test or the chi-squared test for linear trends was applied, depending on the nature of the variables. A significance level of 5% was set for all tests. In order to visualize the simultaneous occurrence of AD, AR, and wheezing, Venn diagrams were generated, with each circle representing one of the three health conditions. These analyses were conducted using Stata software, version 18.0 (StataCorp LP, College Station, TX, USA).

Ethical aspects

Ethical approval for all follow-up visits was obtained from the Ethics and Research Committee of the Faculty of Medicine at the Federal University of Pelotas (UFPel). Informed consent was secured from all cohort members or from their guardians when the participants were under 18 years of age.

RESULTS

Data for all three health conditions were available for 4,286 participants at the 15-year follow-up and for 3,789 participants at the 22-year follow-up. Compared to those not included in the analysis, individuals with complete data were more likely to be female and less likely to have low maternal education (0–4 years) and low birth weight at both follow-ups (Supplementary Table S1).

The characteristics of the participants at each time point are shown in Table 1. At both follow-ups, most participants were female (51.1% and 53.2%), White (66.5% and 65.8%), and had mothers who had studied less than nine years (75.1% and 73.5%). At 15 years of age, 14.5% reported a family history of allergy, while 14.6% reported a family history of asthma. At 22 years of age, both were 19.5%. Similar proportions of participants had mothers who

Table 1. Characteristics of the participants who completed the questionnaires at the 15- and 22-year follow-ups: the 1993 Pelotas Birth Cohort, Brazil.

	At the 15-year follow-up (n = 4,286)		At the 22-year follow-up (n = 3,789)	
	N	(%)	N	(%)
Sex				
Female	2,192	(51.1)	2,015	(53.2)
Male	2,094	(48.9)	1,774	(46.8)
Skin color				
Black/Mixed	1,383	(33.5)	1,171	(34.2)
White	2,744	(66.5)	2,251	(65.8)
Maternal age (years)				
≤ 19	736	(17.2)	658	(17.4)
20 - 29	2,270	(53.0)	2,016	(53.2)
30 - 39	1,187	(27.7)	1,031	(27.2)
≥ 40	92	(2.2)	84	(2.2)
Maternal education (years)				
0 - 4	1,167	(27.3)	1,007	(26.6)
5 - 8	2,047	(47.8)	1,774	(46.9)
9 - 11	736	(17.2)	698	(18.4)
≥12	329	(7.7)	305	(8.1)
Income (minimum wage)				
≤ 1	769	(18.3)	660	(17.7)
1.1 - 3	1,777	(42.2)	1,542	(41.5)
3.1 - 6	1,017	(24.2)	924	(24.8)
6.1 - 10	333	(7.9)	312	(8.4)
>10	310	(7.4)	281	(7.6)
Family history of allergy				
No	3,665	(85.5)	3,236	(85.4)
Yes	621	(14.5)	553	(14.6)
Family history of asthma				
No	3,450	(80.5)	3,049	(80.5)
Yes	836	(19.5)	740	(19.5)
Maternal smoking during pregnancy				
No	2,865	(66.9)	2,552	(67.3)
Yes	1,421	(33.2)	1,237	(32.7)
Birth weight (grams)				
< 2500	388	(9.1)	341	(9.0)
≥ 2500	3,891	(90.9)	3,443	(91.0)
Smoking status				
Never smoked	3,441	(82.2)	2,758	(72.9)
Former or current smoker	744	(17.8)	1,028	(27.2)
Weight status				
Normal-weight	3,085	(75.9)	2,015	(56.9)
Overweight	648	(15.9)	953	(26.9)
Obese	332	(8.2)	572	(16.2)
Allergic Rhinitis				
No	3,391	(79.1)	2,858	(75.4)
Yes	895	(20.9)	931	(24.6)
Atopic dermatitis				
No	3,206	(74.8)	3,250	(85.8)
Yes	1,080	(25.2)	539	(14.2)
Wheezing				
No	2,855	(66.6)	2,626	(69.3)
Yes	1,431	(33.4)	1,163	(30.7)

smoked during pregnancy (33.2% and 32.7%) at both follow-ups.

The prevalence of AD, AR, and wheezing, as well as their co-occurrence, are shown in Figure 1. Wheezing was the most reported condition at both follow-ups, with 33.4% (95% CI 32.0 – 34.8) of individuals reporting it at 15 years and 30.7% (95% CI 29.2 – 32.2) at 22 years of age. AR was the least reported health condition at 15 years, while AD held this title at age 22. This pattern persisted when considering sex differences. Regarding the co-occurrence of these three conditions, 43.2% (95% CI 41.7 – 44.7) reported no health condition at 15 years, while almost half the participants (49.3%, 95% CI 47.7 – 50.9) did so at 22 years of age. Approximately one in every six females reported two health conditions at both follow-ups. In contrast, among males, the prevalence suggested a decrease over time (15.0%; 95% IC 13.5 – 16.6 at 15 years vs. 11.8%; 95% CI 10.4 – 13.4 at 22 years).

The intersection between AR, AD, and wheezing is presented in Figure 2. The overlap between AR and wheezing was greater than that of the other conditions, with 6.9% at the 15-year follow-up and 8.3% at the 22-year follow-up. The co-occurrence of all three conditions appeared to decline over time, from 3.5% at 15 years to 2.2% at 22 years.

The co-occurrence of AR, AD, and wheezing, according to demographic, socioeconomic, behavioral, and health characteristics at both follow-ups, is shown in Table 2. At 15 years, White individuals most frequently reported "three conditions" (4.1%; p<0.001), while at 22 years, they mostly reported "two conditions" (15.6%; p<0.001). At 22 years, males predominantly reported "no health condition" (53.6%; p<0.001), whereas females exhibited a higher frequency of "two conditions" (16.4%; p<0.001) and "three conditions" (2.8%; p=0.018).

"No health condition" was reported more frequently by individuals with lower maternal education and lower family income at both follow-ups. Approximately one in five individuals with higher maternal education reported having "two conditions" at both follow-ups. At the 22-year follow-up, "one condition" was predominantly reported by individuals whose mothers smoked during

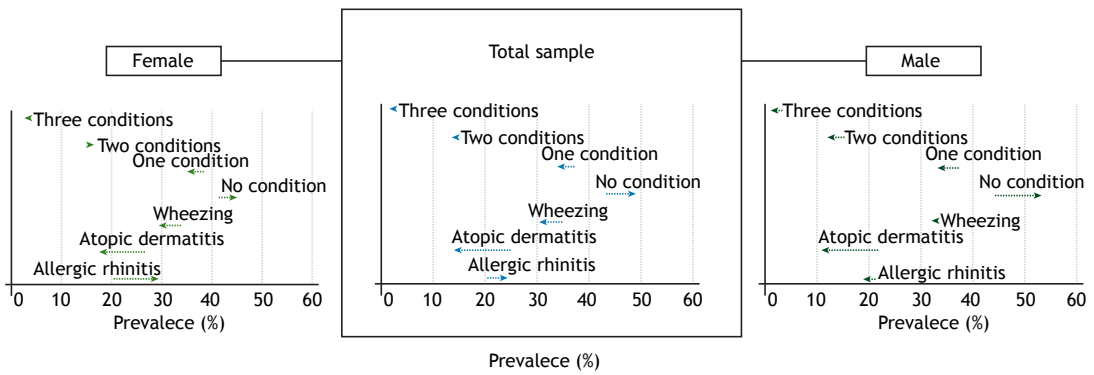

Figure 1. Prevalence (%) of allergic rhinitis, atopic dermatitis, wheezing, and their co-occurrence over follow-up periods in the 1993 Pelotas Birth Cohort, Brazil.

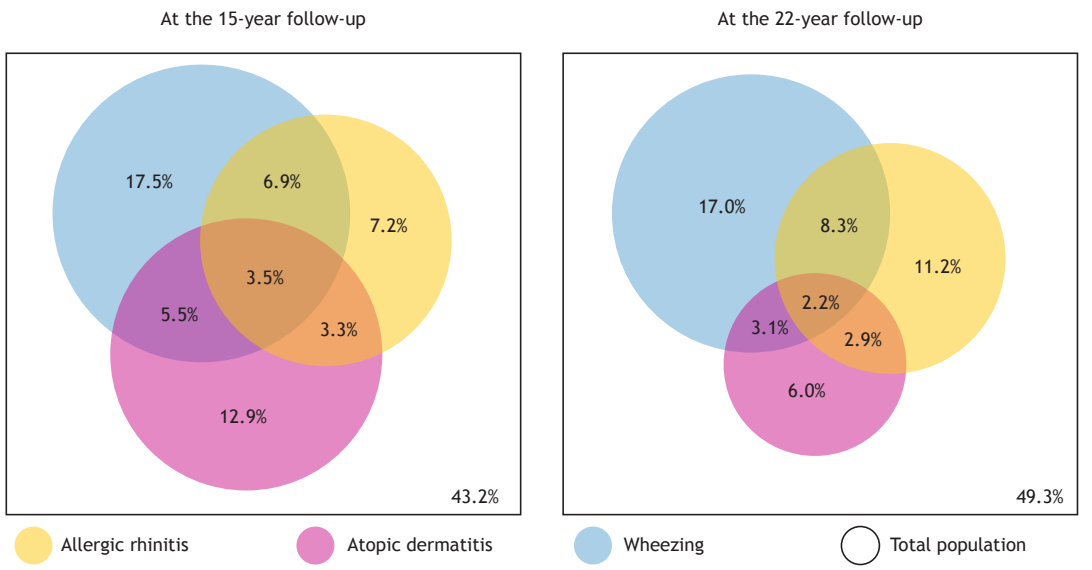

Figure 2. Venn diagram showing the proportions of allergic rhinitis, atopic dermatitis, and wheezing in the 1993 Pelotas Birth Cohort, Brazil.

pregnancy (36.8%; p=0.020), while "two conditions" (11.6%; p<0.001) and "three conditions" (2.7%; p=0.012) were reported less frequently. More than half of the participants who never smoked reported having "no health condition" at 22 years, compared to those who were former or current smokers (51.2% vs. 44.1%; p<0.001) (Table 2).

The eight potential combinations of AR, AD, and wheezing, along with their respective O/E ratios for the total sample and sex-stratified groups, are shown in Table 3. The frequency of different clusters with one health condition was observed to be lower than expected by chance at both follow-ups. In contrast, the frequency of clusters with two conditions, specifically the combination of AR and wheezing, was found to be higher than expected. This was statistically significant for both males (O/E = 1.4; 95% CI 1.2 – 1.6) and females (O/E = 1.3; 95% CI 1.1 – 1.5) at 15 years, as well as for the total sample at 22 years (O/E = 1.3; 95% CI 1.1 – 1.5). The co-occurrence of all three health conditions was observed to be greater than expected, being nearly double (95% CI 1.2 – 3.4) at 15 years and 2.1 times greater (95% CI 1.4 – 3.0) at 22 years (Table 3).

DISCUSSION

In this study, wheezing was the most commonly reported health condition at both follow-ups (17.5% at 15 years and 17.0% at 22 years). The co-occurrence of wheezing, AR, and AD appears to have declined over time, from 3.5% at 15 years to 2.2% at 22 years. However, the frequency of this cluster was twice and more than twice as high as expected by chance at the 15-year and 22-year follow-ups, respectively.

A recent systematic review of population-based studies of individuals aged 5–69 years[32] concluded that the global prevalence of current wheezing was 11.5% (95% CI 9.1 – 14.3). Conversely, the prevalence found in this study was more similar to that reported for ever wheezing (17.9%; 95% CI 14.2 – 22.3). Incorrect diagnoses and poor symptom control increase the risk of asthma exacerbations, which can manifest as wheezing and dyspnea. Consequently, due to limited access and/or availability of medication in lower- and upper-middle-income countries, asthma exacerbations may be more common in these regions.[1,32]

The global prevalence of AR in adults ranges from 1.0% to 63.0%, depending on geographic location.[6] In a city in the state of Rio Grande do Sul, Brazil, a ten percentage point decrease in AR prevalence was reported between 2011 and 2018 (63.3% vs. 50.5%).[20] In this study, the prevalence of AR at both follow-ups was lower than those reported in other studies, with AR being the least reported health condition at 15 years (20.9%), increasing to 24.6% at 22 years. This may be attributed to the prevalence being estimated exclusively based on self-reported medical diagnoses, which can be less accurate in lower- and upper-middle-income countries. In such settings, challenges such as limited access to healthcare, underdiagnosis, and variations in diagnostic criteria often affect the accuracy of these estimates.[33]

Globally, 11.0% of adolescents have experienced AD at some point in their lives.[4] Among adults, the prevalence of AD varies widely, ranging from 3.4% in Israel to 33.7% in Thailand.[5] In Brazil, the overall prevalence is around 9.2%, with the highest estimate found in the Southeast region and lower prevalence among individuals aged 18–24 years.[5] In the present study, the frequency of AD was higher when compared to the national average but decreased substantially from 25.2% at age 15 to 14.2% at age 22. Since this health condition is often confused with other skin disorders,[4,5,7] misdiagnosis or incorrect diagnosis can lead to inflated prevalence rates, which may help explain the decreased prevalence observed at age 22.[33]

The high prevalence of allergic asthma is thought to be attributed to shared genetic predispositions and common environmental exposures.[14,16,17] In this study, however, wheezing was most frequently reported as an isolated condition rather than co-occurring with other atopic diseases. This may be due to the fact that asthma can be non-allergic, cough-variant, adult-onset, associated with persistent airflow limitation, exercise-induced, or linked to obesity.[1,34] Additionally, since wheezing was analyzed as a proxy for asthma rather than through self-reported medical diagnosis, like AR and AD, there is a possibility of misdiagnosis or incorrect diagnosis.

Only 3.5% of the participants at age 15 and 2.2% at age 22 reported the co-occurrence of AR, AD, and wheezing. Similar results were observed by Pedersen et al. (2020) in a rural population in India.[16] Although both studies differ in their geographic and socioeconomic contexts, their findings indicate that, despite the likely absence of official medical diagnoses, the co-occurrence of these health conditions was more frequent than expected. Thus, both studies suggest that integrated approaches to identifying and managing these three health conditions could be beneficial across various global settings.[16]

Despite the low prevalence of co-occurrence compared to isolated conditions, it was observed more frequently than expected at both follow-ups, with the highest O/E ratio relative to other clusters. This suggests that evaluations should focus on multiple conditions, as this approach can improve patient care and support more effective public health interventions.[10,16] Recognizing the individual characteristics of each patient and considering all aspects of their health – rather than focusing solely on individual systems – enables the identification of potential interactions between comorbidities.[12] This holistic perspective not only facilitates improved individual health outcomes but also promotes the efficient allocation of healthcare resources, ultimately leading to a more effective response to the complex interplay of health conditions.[10,12]

The presence of one atopic condition significantly increases the likelihood of another.[12,16,17] In this study,

Table 2. Co-occurrence of allergic rhinitis, atopic dermatitis, and wheezing at the 15- and 22-year follow-ups: the 1993 Pelotas Birth Cohort, Brazil.

	At the 15-year follow-up (%)				At the 22-year follow-up (%)			
	No condition (n = 1,851)	One condition (n = 1,613)	Two conditions (n = 673)	Three conditions (n = 149)	No condition (n = 1,867)	One condition (n = 1,296)	Two conditions (n = 541)	Three conditions (n = 85)
Sex								
Male	44.8	36.6	15.0	3.7	53.6	33.0	11.8	1.6
Female	41.7	38.6	16.4	3.3	45.5	35.3	16.4	2.8
p-value	0.044	0.164	0.214	0.483	p<0.001	0.135	p<0.001	0.018
Skin color								
Black/Mixed	43.8	39.8	14.2	2.2	54.3	32.4	11.7	1.6
White	42.9	36.6	16.4	4.1	46.9	35.0	15.6	2.5
p-value	0.587	0.049	0.072	p<0.001	p<0.001	0.128	p<0.001	0.101
Maternal age (years)								
≤ 19	40.2	40.5	16.6	2.9	53.3	32.7	12.5	1.5
20 - 29	43.8	37.1	15.5	3.6	48.6	34.4	14.3	2.7
30 - 39	43.2	37.0	16.2	3.6	48.3	34.2	15.5	1.9
≥ 40	50.0	38.0	8.7	3.3	45.2	41.7	11.9	1.2
p-value	0.189	0.420	0.247	0.786	0.130	0.425	0.326	0.244
Maternal education (years)								
0 - 4	47.7	36.6	12.3	3.4	54.2	34.1	10.2	1.5
5 - 8	43.0	39.1	15.2	2.6	52.4	32.9	12.6	2.1
9 - 11	38.8	36.6	20.0	4.6	37.8	37.8	21.5	2.9
≥12	38.3	34.7	21.3	5.8	41.6	33.4	21.0	3.9
p-value	p<0.001	0.250	p<0.001	p<0.001	p<0.001	0.142	p<0.001	0.044
Income (minimum wage)								
≤ 1	45.8	40.1	12.0	2.2	55.3	33.9	10.0	0.8
1.1 - 3	44.6	36.8	15.8	2.9	50.6	34.1	13.2	2.1
3.1 - 6	39.1	40.4	16.9	3.5	47.4	33.8	15.9	2.9
6.1 - 10	43.5	32.4	18.9	5.1	43.3	36.9	17.0	2.9
> 10	40.0	34.2	17.7	8.1	40.9	32.4	22.8	3.9
p-value	0.021	0.024	0.012	p<0.001	p<0.001	0.830	p<0.001	0.014
Family history of asthma								
No	43.9	36.8	15.9	3.4	49.4	33.7	14.5	2.4
Yes	40.3	41.0	14.7	4.0	48.7	36.4	13.2	1.8
p-value	0.061	0.024	0.381	0.407	0.704	0.170	0.37	0.319
Maternal smoking during pregnancy								
No	43.3	36.7	16.4	3.6	48.8	33.0	15.6	2.7
Yes	43.0	39.6	14.3	3.2	50.3	36.8	11.6	1.4
p-value	0.860	0.068	0.073	0.436	0.387	0.020	p<0.001	0.012
Birth weight (grams)								
< 2500	42.3	41.8	13.4	2.6	48.4	35.8	14.1	1.8
≥ 2500	43.3	37.2	16.0	3.6	49.4	34.0	14.3	2.3
p-value	0.701	0.077	0.187	0.308	0.735	0.519	0.903	0.525
Smoking status								
Never smoked	43.7	37.1	15.9	3.2	51.2	32.5	14.0	2.3
Former or current smoker	40.7	39.9	14.8	4.6	44.1	38.8	15.0	2.1
p-value	0.136	0.156	0.438	0.069	p<0.001	p<0.001	0.441	0.790
Weight status								
Normal-weight	44.6	37.3	15	3.1	50.4	33.2	14.0	2.4
Overweight	38.7	38.9	18.2	4.2	50.6	34.0	13.6	1.8
Obese	36.1	41.0	18.7	4.2	46.0	36.7	14.5	2.8
p-value	p<0.01	0.351	0.045	0.224	0.144	0.294	0.894	0.401

Table 3. Prevalence and co-occurrence of allergic rhinitis, atopic dermatitis, and wheezing at the 15- and 22-year follow-ups: the 1993 Pelotas Birth Cohort, Brazil.

At the 15-year follow-up															
				Total sample				Female				Male			
No. of cond.	AR	AD	W	O (%)	E (%)	O/E	95% CI	O (%)	E (%)	O/E	95% CI	O (%)	E (%)	O/E	95% CI
0	0	0	0	43.2	39.4	1.1	0.9 - 1.2	41.7	38.4	1.1	1.0 - 1.1	44.8	40.5	1.1	1.1 - 1.2
1	1	0	0	7.2	10.4	0.7	0.5 - 0.9	7.2	9.9	0.7	0.6 - 0.8	7.2	11.0	0.7	0.6 - 0.7
1	0	1	0	12.9	13.3	1.0	0.8 - 1.2	13.7	14.1	1.0	0.9 - 1.1	12.1	12.4	1.0	0.9 - 1.1
1	0	0	1	17.5	19.8	0.9	0.8 - 1.1	17.8	19.8	0.9	0.8 - 1.0	17.3	19.8	0.9	0.8 - 0.9
2	1	1	0	3.3	3.5	0.9	0.6 - 1.5	3.4	3.6	0.9	0.8 - 1.2	3.2	3.4	0.9	0.8 - 1.2
2	0	1	1	5.5	6.7	0.8	0.6 - 1.1	6.4	7.3	0.9	0.8 - 1.0	4.5	6.1	0.7	0.6 - 0.9
2	1	0	1	6.9	5.2	1.3	0.9 - 1.8	6.5	5.1	1.3	1.1 - 1.5	7.3	5.4	1.4	1.2 - 1.6
3	1	1	1	3.5	1.8	2.0	1.1 - 3.4	3.3	1.9	1.8	1.3 - 2.3	3.7	1.7	2.2	1.7 - 2.9
At the 22-year follow-up															
				Total sample				Female				Male			
No. of cond.	AR	AD	W	O (%)	E (%)	O/E	95% CI	O (%)	E (%)	O/E	95% CI	O (%)	E (%)	O/E	95% CI
0	0	0	0	49.3	44.8	1.1	1.1 - 1.2	45.5	41.0	1.1	1.1 - 1.2	53.6	49.3	1.1	1.0 - 1.1
1	1	0	0	11.2	14.6	0.8	0.7 - 0.9	13.8	17.2	0.8	0.7 - 0.9	8.2	11.5	0.7	0.6 - 0.8
1	0	1	0	6.0	7.4	0.8	0.7 - 1.0	7.2	8.7	0.8	0.7 - 1.0	4.6	5.8	0.8	0.7 - 1-0
1	0	0	1	17.1	19.9	0.9	0.8 - 0.9	14.3	17.1	0.8	0.8 - 0.9	20.1	23.3	0.9	0.8 - 0.9
2	1	1	0	2.9	2.4	1.2	0.9 - 1.6	4.1	3.7	1.1	0.9 - 1.4	1.5	1.4	1.1	0.8 - 1.6
2	0	1	1	3.1	3.3	0.9	0.7 - 1.2	3.4	3.6	0.9	0.7 - 1.2	2.8	2.8	1.0	0.8 - 1.3
2	1	0	1	8.3	6.5	1.3	1.1 - 1.5	8.9	7.2	1.2	1.1 - 1.5	7.6	5.4	1.4	1.2 - 1.7
3	1	1	1	2.2	1.1	2.1	1.4 - 3.0	2.8	1.5	1.8	1.3 - 2.5	1.6	0.6	2.5	1.6 - 4.1

No. of cond.: number of conditions; AD: atopic dermatitis; AR: allergic rhinitis; W: wheezing; O: observed value; E: expected value; O/E: observed/expected value; 95% CI: 95% confidence interval.

▲ Voltar ao sumário

the co-occurrence of AR and wheezing was found to be more frequent than other combinations and appeared to increase over time. A cross-sectional study showed a strong association between asthma and AR (OR 8.39; 95% CI 6.48 – 10.86).[16] Other studies suggest that up to 50% of AR cases may present with asthma symptoms, while nasal symptoms are observed in up to 85% of people with asthma.[20,35] Furthermore, having AD is also associated with asthma (OR 5.56; 95% CI 4.26 – 7.26).[16]

Our findings also indicate that the number of conditions reported by participants is strongly associated with sociodemographic factors. Specifically, males were more likely to report having no health conditions compared to females, a trend that was more pronounced at the 22-year follow-up. While AR, AD, and asthma often have higher prevalence rates in males during childhood, this trend can reverse in adulthood.[1,20] In addition, females generally exhibit greater health-seeking behaviors and are more likely to seek medical care for symptoms or health concerns.[36]

Participants from lower socioeconomic backgrounds (e.g., lower maternal education and family income) and Black/Mixed individuals were more likely to report having "no health conditions". Brazil, known for its significant socioeconomic and ethnic disparities since colonial times, is one of the most unequal countries in the world.[37] This may explain why White individuals and those in better socioeconomic circumstances often have better access to healthcare and more accurate diagnoses, resulting in the reporting of more health conditions in this study. This highlights an important social gradient in this context.[33,37,38] Furthermore, it emphasizes the need for health policies that address these inequalities and promote equitable access to healthcare services for all population groups.[33]

This study had some limitations. First, as a cross-sectional study, it cannot establish a clear temporal association between exposures and outcomes. Second, differences between respondents and non-respondents at both follow-ups may affect the results, particularly due to the social gradient.[33] Males, as well as participants with low maternal education (0–4 years) and low birth weight, may be underrepresented in the study sample. This nonresponse bias could lead to an underestimation of the co-occurrence of AR, AD, and wheezing in these groups, as their lower use of healthcare services may result in fewer diagnoses being recorded. Third, the variables were measured through self-reporting, which can introduce social desirability and recall biases.[39]

Additionally, observing wheezing alone may not fully capture asthma cases, potentially leading to an underestimation of prevalence. However, according to Sistek et al. (2001), wheezing is the most sensitive single symptom (75.0%) for diagnosing asthma and is considered a proxy for the disease.[40] On the other hand, there were notable strengths to this study. It utilized data from a cohort of live births, which is representative of the urban area of Pelotas, and achieved high response rates, allowing for the extrapolation of results to similar settings/middle-income countries. Moreover, the training of interviewers to assess reliability ensured the quality of the collected information.

This study highlights the social gradient in the diagnosis and reporting of the co-occurrence of AR, AD, and wheezing. These findings are important for formulating more effective health policies regarding the diagnosis and treatment of these conditions, as well as for allocating targeted resources to the groups most in need of intervention. Additionally, since atopy increases the risk of allergic asthma, individuals with AR and/or AD should be monitored for respiratory symptoms. Further research is needed to address these disparities and improve the early detection and management of AR, AD, and wheezing.

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AUTHOR CONTRIBUTIONS

The authors contributed to the paper as follows: methodology: G.A.M., P.W., P.D.O., F.C.W.; investigation: A.M.B.M., H.G., F.C.W.; formal analysis: G.A.M., F.C.W.; resources: A.M.B.M., H.G., F.C.W.; funding acquisition: A.M.B.M., H.G., F.C.W.; writing – original draft: G.A.M.; writing – review & editing: A.F.S.A., V.L.P., P.W., P.D.O., F.C.W.; supervision: A.F.S.A., V.L.P., P.W., P.D.O., F.C.W.

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Silica-exposed patients with silicosis show shorter telomeres than do unexposed individuals: a pilot study in a population in southeastern Brazil

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ABSTRACT

Objective: Silicosis is a pneumoconiosis characterized by fibrosis of the lung parenchyma caused by the inhalation of silica particles. Silica dust inhalation is associated with inflammation and induction of oxidative stress in the lungs. This oxidative stress affects telomeres, which are short tandem DNA repeats that cap the end of linear chromosomes. We aimed to determine whether telomere length (TL) correlates with silicosis or severity of silicosis in silica-exposed workers in Brazil. **Methods:** We included 200 men in southeastern Brazil: 100 with silicosis and 100 who had not been exposed to silica. We extracted DNA from buccal cells and assessed TL by multiplex quantitative polymerase chain reaction. **Results:** The median TL was significantly shorter in the patients with silicosis than in the unexposed controls ($p < 0.0001$), although it did not differ between the patients with simple silicosis and those with complicated silicosis ($p = 0.961$). We also found that, in patients with silicosis, TL was influenced by smoking ($p = 0.034$) and by a history of personal protective equipment use in the workplace ($p = 0.002$). **Conclusions:** Silica exposure appears to have an impact on TL, which was found to be shorter in patients with silicosis than in unexposed controls. Further studies are needed in order to confirm the impact that oxidative stress caused by silica inhalation has on telomeres.

Keywords: Silicosis; Oxidative stress; Inflammation; Telomere.

INTRODUCTION

Silicosis is an irreversible, incurable nodular pulmonary fibrosis caused by the inhalation and deposition of dust containing crystalline silica. It is the most prevalent pneumoconiosis in Brazil and elsewhere.[1] Exposure to silica occurs in various industrial occupations, mainly in activities related to civil construction and mining but also in the cosmetics and steel industries.[2] Despite all efforts to prevent and eradicate the disease, millions of workers around the world are still affected by silicosis. In the assessment made by the Global Burden of Disease Study, in 2017, it was estimated that 10,400 lives are lost to silicosis every year.[3] In Brazil, approximately 3 million workers were exposed to silica in the formal labor market in 2018, corresponding to more than 1% of the Brazilian population, and there is a trend toward increased hiring in this sector because of the growing civil construction and mineral extraction markets.[1]

On the basis of the radiological manifestations, chronic silicosis is subdivided into simple and complicated forms.[4] The simple form is characterized by the presence of well-defined nodules measuring 1-10 mm (typically 3-6 mm), diffusely distributed in the upper lung zones, that agglomerate and calcify in some cases. The complicated form is characterized by the presence of large pulmonary opacities as a result of the fusion of nodules > 10 mm. These conglomerates can increase in size, destroying the lung architecture, thus generating translucent areas corresponding to pulmonary emphysema.[5] In the complicated form, the disease continues to progress even after the exposure to silica has ceased.[6]

Silica dust inhalation is associated with inflammation and induction of oxidative stress.[7-9] In the lungs, activated alveolar macrophages generate reactive oxygen species (ROS).[8] The ROS can activate nuclear factor-kappa B and the production of inflammatory mediators, as well as mediating chronic tissue damage and fibrosis.[8,9] In addition, oxidative stress due to excessive production of ROS leads to modification of lipids, proteins, and nucleic acids, causing cell dysfunction and damage.[10]

Telomeres are short tandem DNA repeats that cap the end of linear chromosomes by forming protective

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loops through the binding of members of the shelterin complex of proteins.[11,12] Telomeres must contain a minimum of repeats to function effectively. In somatic cells, because of incomplete DNA replication of 5′ ends, telomere sequences are gradually reduced with every cell division. When telomeres reach a critical length, unprotected chromosome ends are recognized as double-stranded breaks by cellular DNA repair machinery, triggering cellular senescence.[11,13] Telomere repeats can also be lost via oxidative damage.[13,14] The telomeric DNA is less repaired than elsewhere in the chromosomes, and oxidative damage thus accelerates telomere shortening.[14]

Inflammatory diseases related to oxidative stress are also associated with acceleration of telomere shortening.[15] Several lung diseases have been studied to evaluate the impact on TL, including interstitial lung diseases,[16,17] idiopathic pulmonary fibrosis,[10,18,19] COPD,[17,20] and COVID-19.[21] To our knowledge, there has been only one previous study evaluating TL in the contexts of silicosis and asbestosis.[22]

Previous studies have reported that that there is a strong correlation between buccal and blood telomeres, in terms of their relative length, as determined by quantitative polymerase chain reaction (qPCR).[23,24] Therefore, the aim of this study was to analyze buccal TL in a sample composed of healthy individuals and silica-exposed workers with silicosis, in order to evaluate the impact of silicosis on buccal TL.

METHODS

Subjects

This was a cross-sectional pilot study involving a sample of 200 male individuals in southeastern Brazil: 100 were patients with a history of exposure to silica and diagnosed with silicosis (silicosis group); and 100 were individuals from the general population, with no history of silica exposure, who were recruited from hospital staff and university administrative personnel (control group). All of the patients were treated at the Outpatient Clinic for Occupational Lung Diseases of Antônio Pedro University Hospital, operated by Fluminense Federal University, in the city of Niterói, Brazil; at the Pulmonology Outpatient Clinic of Pedro Ernesto University Hospital, operated by Rio de Janeiro State University in the city of Rio de Janeiro, Brazil; or at the Sérgio Arouca National School of Public Health, operated by the Oswaldo Cruz Foundation, also in the city of Rio de Janeiro.

The project was approved by the local research ethics committees: the Human Research Ethics Committee of the Fluminense Federal University School of Medicine (Reference no. 40086114.7.0000.5243); the Research Ethics Committee of Pedro Ernesto University Hospital (Reference no. 40086114.7.3001.5259); and the Research Ethics Committee of the Sérgio Arouca National School of Public Health (Reference no. 40086114.7.3002.5240). All participating subjects gave written informed consent. Only individuals ≥ 18 years of age were included in this study. A questionnaire was employed in order to collect sociodemographic and clinical data, including age (in years); skin color; occupational activity; total number of years of silica exposure; total number of hours worked per week; total number of hours of silica exposure; years elapsed since cessation of the exposure; smoking history; and use of personal protective equipment (PPE) in the workplace. The time elapsed since cessation of the exposure was defined as the difference (in years) between the time of silicosis diagnosis and the time of sample collection and classification of the disease as simple or complicated. For the patients with silicosis, smoking history (in pack-years) was also evaluated.

The diagnosis of silicosis was based on the occupational history of exposure to silica and radiographic findings consistent with the disease, according to the International Classification of Radiographs of Pneumoconiosis established by the International Labor Organization.[25] Simple silicosis was characterized by a radiological pattern of opacities < 1.0 cm in diameter, whereas complicated silicosis was characterized by opacities ≥ 1.0 cm in diameter.[25,26] Disease severity was assessed by using a profusion scale to classify the number of characteristic opacities on chest X-rays, divided into four categories (from 0 to 3) and twelve common subcategories. All of the patients were relieved from work after the diagnosis of silicosis was confirmed.

All pulmonary function tests were performed with a spirometer (MS-PFT; Jaeger, Würzburg, Germany), in accordance with standards established by the American Thoracic Society/European Respiratory Society and the Brazilian Thoracic Association. The lung function parameters evaluated were FEV_1 (% of predicted), FVC (% of predicted), and the FEV_1/FVC ratio.

Laboratory procedures

Genomic DNA was extracted from buccal cells by using standard procedures.[27] The TL was measured by monochrome multiplex real-time qPCR, as described by Cawthon et al.[28] The mean TL was determined by comparing the telomere DNA and that of a single-copy reference gene (albumin, *ALB*), amplified simultaneously, resulting in the telomere/single-copy gene (T/S) ratio. Each sample was assayed in triplicate; the final individual T/S ratio (relative TL) was the average of the three values. Each reaction included 10 µL 2× SYBR Green Supermix (Bio-Rad Laboratórios do Brasil, São Paulo, Brazil), 1.8 µL of 10 µM each of both telomere primers (Telg, 5′ ACACTAAGGTTTGGGTTTGGGTTTGGGTTTGGGTTAGTGT 3′ and Telc, 5′ TGTTAGGTATCCCTATCCCTATCCCTATC CCTATCCCTAACA 3′), 1.8 µL of 10 µM each of both albumin primers (Albu, 5′ CGGCGGCGGGCGGCGCG-GGCTGGGCGGAAATGCTGCACAGAATCCTTG 3′ and Albd, 5′ GCCCGGCCCGCCGCGCCCGTCCCGCCGGAAAAG-CATGGTCGCCTGTT 3′), 1.4 µL of molecular-filter water and 5 µL of genomic DNA (4 ng/µL), to yield a 20-µL reaction. The CFX96 real-time PCR system

(Bio-Rad Laboratórios do Brasil) was used, with the following reaction conditions: 95°C for 3 min, two cycles at 94°C for 15 s, and 49°C for 15 s, followed by 32 cycles at 94°C for 15 s, 62°C for 10 s, and 74°C 15 s (signal acquisition), 84°C for 10 s, and 88°C for 15s (signal acquisition). The threshold cycle (Ct) values for telomere amplification were provided by the 74°C reads, and Ct values for *ALB* amplification were provided by the 88°C reads.

A target-specific no-template control was used in all plates, and positive controls (DNA from HeLa cells) were allocated to random wells on random plates to assure plate-to-plate concordance. As a reference for standard curve calculation, DNA from HeLa cells (Sigma-Aldrich) was serially diluted (10 ng/μL, 2 ng/μL, 0.4 ng/μL, 0.08 ng/μL, and 0.016 ng/μL). The CFX manager software, version 3.1 (Bio-Rad Laboratórios do Brasil) was used in order to generate standard curves, as well as Ct values for telomere and reference gene (*ALB*) signals. To ensure high reproducibility of samples, only assays with real-time PCR efficiencies of 95-105% and intra-assay coefficients of variation of less than 1% were included in the analysis.

Statistical analysis

Continuous variables were analyzed using the two-tailed Student's t-test or Mann-Whitney U test (for two-group comparisons) and are expressed as mean and standard deviation or as median and interquartile range. Because the data were not normally distributed, as ascertained with the Kolmogorov-Smirnov test, the relative TL (T/S ratio) was compared between phenotypes (healthy vs. silicosis and simple vs. complicated silicosis) by using the Mann-Whitney test. Levene's test was used in order to test the equality of variances in the groups. Spearman's correlation coefficients were calculated to determine the relationships between continuous variables and TL. Multiple regression analysis was also performed and was adjusted for any significant variables.

Statistical analyses were performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corp., Armonk, NY, USA), and graphs were plotted with GraphPad Prism 5 software, version 5.0 (GraphPad Software Inc., La Jolla, CA, USA). Values of $p < 0.05$ were considered significant.

RESULTS

Demographic characteristics of the sample are shown in Table 1. No significant difference in age was observed between the silicosis and control groups ($p = 0.555$). In our sample, the proportion of self-reported black and brown individuals was significantly higher in the silicosis group than in the control group ($p < 0.0001$). We also observed that the proportion of patients who reported using PPE was significantly higher among those with simple silicosis than among those with complicated silicosis ($p = 0.04$).

Unexpectedly, TL did not correlate with age in the sample as a whole ($\rho = 0.027$, $p = 0.793$). Also in the sample as a whole, the median TL was shorter among the individuals with a history of smoking than among those with no smoking history—0.94 (0.72-1.34) vs. 1.15 (0.92-1.43)—and the difference was significant ($p = 0.034$). No significant differences were observed among the self-reported skin colors white, brown, and black in terms of the median TL—1.28 (0.92-1.38), 1.32 (0.93-1.73), and 1.14 (0.92-1.38), respectively ($p = 0.174$).

As depicted in Figure 1, the median TL was 1.08 (0.83-1.39) in the silicosis group and 1.45 (1.18-1.85)

Table 1. Sociodemographic characteristics, clinical characteristics, and lung function parameters among men with and without silicosis (N = 200).

Variable	Silicosis group				Control group	p
	Form		p	Total		
	Simple (n = 42)	Complicated (n = 58)		(n = 100)	(n = 100)	
Age (years)[a]	51.24 ± 5.62	52.21 ± 5.42	0.387	51.80 ± 5.50	51.16 ± 9.32	0.555
Self-reported skin color[b]						
White	18 (43)	22 (38)		40 (40)	69 (69)	< 0.0001
Brown	17 (40)	20 (34)	0.439	37 (37)	26 (26)	
Black	7 (17)	16 (28)		23 (23)	5 (5)	
Smoking history[b]	20 (48)	30 (52)	0.685	50 (50)	31 (31)	0.006
Use of PPE[b]	20 (61)	13 (31)	0.040	33 (48)	-	-
Years of silica exposure[a]	22.5 ± 8.94	20.21 ± 8.50	0.196	21.17 ± 8.72	-	-
Total number of hours worked per week[c]	45.00 (40.00-50.00)	50.00 (40.00-50.00)	0.767	45.00 (40.00-50.00)	-	-
Years elapsed since exposure cessation[c]	9.00 (2.50-17.00)	14.00 (9.00-20.00)	0.06	11.50 (5.00-20.00)	-	-
FVC (% of predicted)[a]	83.00 ± 19.99	77.13 ± 20.86	0.180	79.88 ± 19.79	-	-
FEV_1 (% of predicted)[a]	75.55 ± 21.46	61.97 ± 22.20	0.003	67.67 ± 22.80	-	-
FEV_1/FVC ratio[c]	75.00 (65.00-81.85)	67.07 (56.00-74.78)	0.002	70.39 (57.50-77.50)	-	-

PPE: personal protective equipment. [a]Expressed as mean ± SD. [b]Expressed as n (%). [c]Expressed as median (IQR).

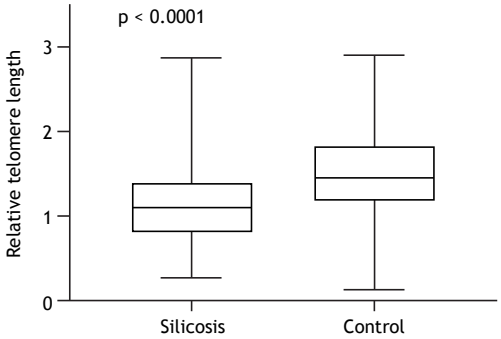

Figure 1. Comparison of telomere length between patients with silicosis (n = 100) and healthy controls (n = 100). Relative telomere length is presented as the telomere/single-copy gene ratio.

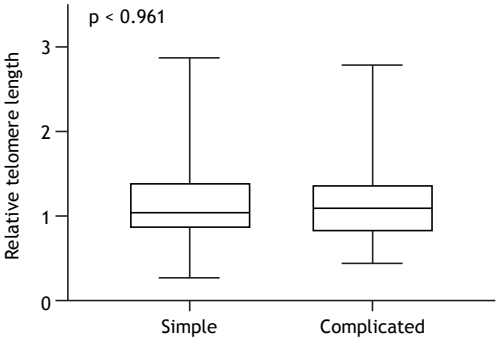

Figure 2. Comparison of telomere length between patients with simple silicosis (n = 42) and patients with complicated silicosis (n = 58). Relative telomere length is presented as the telomere/single-copy gene ratio.

in the control group, a difference that was significant ($p < 0.0001$). Given the size of the study sample, Levene's test did not show differences in the variance of TL between the two groups ($p = 0.222$). Because we observed a significant difference between the silicosis and control groups in terms of the self-reported skin color (Table 1), we also stratified TL by skin color. We observed a statistically significant difference between the silicosis group and the control group in terms of the median TL among the individuals who described their skin color as white—1.08 (0.82-1.42) and 1.38 (1.18-1.72), respectively ($p = 0.007$)—as well as among the individuals who described their skin color as brown—1.07 (0.76-1.43) and 1.58 (1.31-2.32), respectively ($p < 0.0001$)—although not among the individuals who described their skin color as black—1.09 (0.92-1.33) and 1.40 (1.11-1.88), respectively ($p = 0.053$), which might be result of the fact that there were few such individuals in the control group (n = 5). Smoking history also differed between the two groups, and the multiple regression analysis controlling for these variables confirmed the significance of TL ($p < 0.0001$), smoking history ($p = 0.0004$), self-reported white skin color ($p < 0.0001$), and self-reported brown skin color ($p < 0.0001$), although, as in the individual analysis, not self-reported black skin color ($p = 0.057$).

As illustrated in Figure 2, the median TL was similar between the patients with simple silicosis and those with complicated silicosis—1.05 (0.85-1.41) and 1.10 (0.80-1.37), respectively ($p = 0.961$). Levene's test did not show differences in variance of TL between simple and complicated silicosis ($p = 0.344$).

In the silicosis group, Spearman's correlation coefficient did not show TL to correlate with age ($\rho = 0.071$, $p = 0.484$), duration of exposure to silica ($\rho = 0.024$, $p = 0.813$), years elapsed since the cessation of exposure ($\rho = -0.006$, $p = 0.956$), smoking history ($\rho = 0.237$, $p = 0.098$), FEV_1 ($\rho = 0.042$, $p = 0.678$), FVC ($\rho = 0.052$, $p = 0.605$), or the FEV_1/FVC ratio ($\rho = -0.033$, $p = 0.741$). The same was observed for those variables in the comparison between simple and complicated silicosis ($p > 0.05$).

A history of PPE use in the workplace showed an influence on TL in the silicosis group. The median TL was longer among the patients who had used PPE on the job than among those who had not—1.23 (0.95-1.39) and 1.11 (0.79-1.43), respectively ($p = 0.002$).

DISCUSSION

Telomeres confer stability on the chromosome and preserve genomic stability. When telomeres reach a critical minimum length, cells cannot divide and the cell enters cell-cycle arrest or undergoes apoptosis[12] In the present study, we compared the TL in buccal cells from men with silicosis and those in buccal cells from men who had not been exposed to silica, as well as comparing TL between men with simple silicosis and those with complicated silicosis. We also evaluated the heterogeneity of TL related to epidemiologic factors such as age, duration of exposure to silica, time elapsed since the cessation of exposure, smoking history, and PPE use in the workplace.

We found TL to be significantly shorter in patients with silicosis than in unexposed individuals. Exposure to environmental agents such as silica dust results in an imbalance between oxidants and antioxidants, which leads to oxidative stress.[29] The increase in ROS production is related to increased production of inflammatory mediators, oxidative DNA damage, and lung cell death.[7,9] One hypothesis is that the increase in cell division to compensate for cell death or senescence, triggered by oxidative stress, accelerates telomere shortening.[13] In addition, the nucleotide base guanine is more sensitive to oxidative stress and more likely to be oxidized when in sequence, forming G-quadruplexes.[30] Telomeres present a high guanine content (TTAGGG), making them more prone to DNA double-strand breaks caused by oxidative stress.[13]

The relationships among oxidative stress, inflammation, and TL have been addressed for several pulmonary conditions. Shortening of leukocyte

telomeres has been identified as a potential biomarker associated with increased mortality in different clinical phenotypes of pulmonary fibrosis.[16] A recent study suggested that leukocyte telomere shortening increases the risk of COPD and interstitial lung disease,[17] and a meta-analysis including four studies also indicated an association between short telomeres and COPD.[20] In patients with idiopathic pulmonary fibrosis, short telomeres have been observed in leukocytes,[10,18] alveolar cells,[18] and lung tissue samples from patients with lower overall survival.[19] Case-control studies in lung cancer have produced conflicting results, demonstrating, variously, that the risk of lung cancer is higher when telomeres are shorter[31-33] and when they are longer.[34-37] Recent studies have also shown a correlation between telomere shortening and COVID-19 severity, although a recent meta-analysis did not find any evidence of such an association.[21]

Occupational exposure to coal dust and products of combustion was evaluated in a previous study conducted in southern Brazil.[38] The authors found that exposure to coal dust was associated with telomere shortening and an increase in global DNA methylation, suggesting that these variables are good candidate biomarkers for occupational exposure to coal and its derivatives.

Patients with silicosis have higher levels of oxidative stress, which might have an impact on the composition of their telomeres. To our knowledge, there has been only one study evaluating leucocyte TL and *TERT/TERC* variants in the contexts of silicosis and asbestosis.[22] As we observed in our study, silicosis and asbestosis were both found to be associated with shorter telomeres, suggesting that occupational exposure to dust predominantly contributes to telomere shortening. Those authors observed no differences in TL between the patients with silicosis and those with asbestosis. Among the patients with silicosis, 8.3% had *TERT* variants and no *TERC* variants were detected. The authors also observed no significant differences in TL between the carriers and noncarriers of *TERT* variants. In addition, telomerase variants and short telomeres were not found to be associated with the severity of both pneumoconioses, as was observed in the present study for silicosis severity.

Telomeres in blood leukocytes and buccal cavity epithelial cells are known to shorten with exposure to tobacco smoke.[39] Cigarette smoke contains chemicals that cause heavy oxidative stress in cells by producing free radicals.[40] In our sample, smoking was also correlated with TL, although when we considered these two variables in a case-control analysis by multivariate regression, the association between silicosis and shorter TL was maintained. Therefore, silica exposure has an impact on TL in addition to that of smoking.

In the present study, neither the duration of exposure to silica nor the time elapsed since the cessation of that exposure was found to correlate significantly with TL. This seems to indicate that even with a short exposure time, silica crystals have toxic effects on telomeres. However, we observed that the use of PPE protected patients against telomere shortening. These data underscore the urgent need to raise awareness among workers and to implement policies that encourage more effective use of PPE in the workplace.

Our study has some limitations. Because it was a pilot study, our sample size was too small to detect differences in silicosis severity and TL. The toxicity of silica particles might differ depending on particle size, surface charge, and concentration, as well as on exposure time, and we did not have access to this information for our sample. In addition, we did not evaluate exposed individuals without silicosis. A prospective study involving patients with silicosis and healthy silica-exposed individuals might provide even more consistent information about the effect of silica exposure on TL.

The search for biomarkers that can predict the course of a disease in order to inform decisions regarding its management is a valuable pursuit. Unfortunately, there is as yet little understanding of the impact that genetic biomarkers have on silicosis or silicosis severity, and no such biomarkers have been validated. The data generated in this study contribute to a better understanding of the effects that exposure to silica on telomere shortening in patients with silicosis, a disease that has not been widely studied in Brazil.

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AUTHOR CONTRIBUTIONS

FBK, ASFN, and MCSC conceived the study. FBK, LCC, and MCSC designed the study. ASFN, LCC, KCRS, HAC, PCR, WC, and MCSC performed sample collection. FBK, LCC, and MCSC oversaw data collection. FBK performed the data analysis. FBK and MCSC drafted the manuscript. FBK, ASFN, LCC, KCRS, HAC, PCR, WC, and MCSC made revisions to the manuscript. All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension: short- and long-term results from a cohort in Brazil

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ABSTRACT

Objective: A significant number of patients with chronic thromboembolic pulmonary hypertension (CTEPH) are not eligible for pulmonary endarterectomy and may be treated with balloon pulmonary angioplasty (BPA). Although BPA programs have recently been developed in Brazil, no results have yet been published. The objective of this study was to assess the clinical and hemodynamic progression of the first patients treated with BPA at our center. **Methods:** This was an observational study of 23 patients with CTEPH enrolled in the BPA program of a specialized center in Brazil between 2015 and 2020. **Results:** After a mean of 5.6 ± 1.3 sessions and 11 ± 2.8 treated segments/patient (at a mean of 6.7 ± 2.9 months post-BPA), there was a 26% decrease in mean pulmonary artery pressure (51 ± 11 vs. 38 ± 11 mmHg; $p < 0.0001$), a 43% decrease in pulmonary vascular resistance (10 ± 3.7 vs. 5.7 ± 3.3 WU; $p < 0.0001$), and a 22.5% increase in the cardiac index (2.38 ± 0.6 vs. 2.95 ± 0.6 L/min/m^2; $p < 0.0001$). There was an increase in the six-minute walk distance and an improvement in functional class. Acute lung injury with clinical manifestations was observed after 7% of the BPA sessions. None of the patients required intubation. During a mean outpatient follow-up period of 38 ± 22 months, two patients were referred for additional BPA sessions due to clinical worsening and new hospitalizations. Two deaths were recorded (due to CTEPH progression and gastrointestinal bleeding, respectively). **Conclusions:** Among this first group of patients treated with BPA in Brazil, there was significant short- and long-term clinical improvement, together with a low frequency of complications.

Keywords: Hypertension, pulmonary; Pulmonary embolism; Angioplasty, balloon.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) develops from the restriction of flow in pulmonary arterial branches by organized thrombi (remnants of previous pulmonary embolisms), leading to progressive increases in pulmonary vascular resistance (PVR) and pulmonary arterial pressure, as well as microvascular remodeling and right ventricular dysfunction.[1,2] Patients typically present with dyspnea and reduced exercise capacity and may progress to right heart failure and death.[1,2] The five-year survival rate is estimated to be 10% for patients who have a mean pulmonary artery pressure (mPAP) exceeding 50 mmHg and do not receive therapeutic interventions.[3]

Pulmonary endarterectomy (PEA), a potentially curative surgery, is the preferred therapy for eligible cases of CTEPH.[2,4-6] However, approximately one-third of patients with CTEPH who are evaluated at expert centers are deemed to have inoperable disease due to severe comorbidities or involvement of distal arterial branches that are inaccessible to the surgeon or disproportionate to the increase in PVR.[7] In these cases or when pulmonary hypertension (PH) persists post-PEA, pharmacological therapy has a limited effect on hemodynamic parameters, with no evidence of an impact on mortality.[4,6,8-11]

Balloon pulmonary angioplasty (BPA), an endovascular treatment, has the potential to significantly improve hemodynamics and functional capacity, representing an alternative for patients with inoperable CTEPH.[4,6,7,11-23] Since the initial publications over two decades ago, the BPA technique has undergone numerous refinements, enhancing its safety and contributing to a global increase in the number of centers offering this treatment.[11,14-31] Currently, BPA is mentioned in specific guidelines as an

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alternative for selected cases of inoperable CTEPH.[4,6] In Brazil, no results of the use of this therapeutic approach have yet been published. In this study, we describe and analyze the short- and long-term outcomes of the first patients who underwent BPA in our group.

METHODS

In this observational study, symptomatic patients with CTEPH, deemed candidates for BPA and followed on an outpatient basis at the University Hospital Professor Edgard Santos (HUPES) between February of 2015 and August of 2020, were sequentially selected for inclusion. The diagnosis of CTEPH was established using imaging methods (scintigraphy or computed tomography pulmonary angiography), together with invasive pulmonary angiography and right heart catheterization (RHC) showing an mPAP > 25 mmHg with a pulmonary artery occlusion pressure ≤ 15 mmHg and a PVR > 3 WU, after 3 months of effective anticoagulation (the definition prevailing at that time).[32]

All patients were assessed by our multidisciplinary team consisting of pulmonologists, interventional cardiologists, and thoracic surgeons. Contraindications to PEA were determined on the basis of anatomical and technical criteria, such as predominantly distal disease involvement, or on the basis of high surgical risk attributed to the presence of comorbidities or previous surgery. Patients with potentially operable CTEPH who did not have access to PEA due to difficulties related to the public health care system, or who refused to undergo surgery for personal reasons, were also assessed for BPA eligibility. The technical feasibility of performing BPA was determined by the interventional cardiologists on the team.

We included patients who completed treatment with BPA, underwent follow-up RHC 3-12 months thereafter, and were followed as outpatients at the HUPES for more than 12 months after the last angioplasty session. Patients who did not complete the treatment were excluded, as were those who were followed as outpatients at another facility.

Data were collected during outpatient medical consultations, as well as by reviewing medical records and procedure reports. Data collection was retrospective for the first seven patients and prospective for the remainder. This study was approved by the Research Ethics Committee of the HUPES, and all participating patients gave written informed consent.

BPA procedure

Each BPA was performed in multiple sessions, in a staged manner, with intervals of more than one month between sessions. When possible, the first two BPA sessions were scheduled within 7 days of each other. The therapeutic target was the maximal reduction in mPAP until further pulmonary branch angioplasties were no longer possible, because of technical aspects or patient risk, or until there were no further complaints of dyspnea.

The procedure was conducted via femoral or internal jugular vein puncture under local anesthesia and mild sedation, with access to the pulmonary circulation via RHC. Unfractionated heparin at a dose of 5,000 IU was administered intravenously at the start of the procedure. A long (65-90 cm) 7-Fr sheath—Flexor Raabe (Cook Medical, Bloomington, IN, USA) or Destination (Terumo, Tokyo, Japan)—was inserted up to the pulmonary artery, after which a 6-Fr guiding catheter (Launcher Multipurpose or Launcher Judkins Right; Medtronic, Minneapolis, MN, USA) was inserted into the sheath. After the guiding catheter had been positioned in the target vessels, angioplasty was performed by advancing a 0.014" guide wire and inflating semi-compliant balloons in arterial segments with obstructive lesions and restricted flow, without the need for stent implantation. The duration of each session was generally limited to a fluoroscopy time of 60 min or a contrast volume of 300 mL, whichever came first.

To reduce the risk of acute pulmonary injury and vascular complications, balloons with a diameter of 2.0 mm or less than 50% of the reference vessel diameter were used in the initial sessions. In subsequent sessions, balloons close to the diameter of the treated vessels were used. All patients were observed in the intensive care unit for 24-48 h after each angioplasty session. Laboratory monitoring of renal function was conducted during hospitalization and after discharge.

In the initial patients treated, oral anticoagulation with coumarins was suspended 3-4 days before each BPA session. From 2019 onward, that suspension was requested only when the international normalized ratio (INR) was greater than 3.0. Direct oral anticoagulants were suspended the day before each session. In the absence of pulmonary or puncture site bleeding, oral anticoagulation was reintroduced within the first 12-24 h after each session. In cases of coumarin use, subcutaneous enoxaparin was used until an INR of 2.0 was achieved. All patients were discharged only after adjustment of oral anticoagulation.

BPA outcomes

Hemodynamic, biochemical, and six-minute walk test (6MWT) data were obtained at baseline and at 3-12 months after the last BPA session. This follow-up interval was chosen to allow sufficient time for hemodynamic and clinical stabilization after the last BPA session, as well as to enable patients to undergo RHC and comprehensive clinical evaluations within the first year post-BPA. Medium- and long-term clinical follow-up data were obtained up to the last recorded medical contact. The patients were categorized by New York Heart Association functional class (NYHA-FC). Before and 3 months after treatment, quality of life

was measured with the Minnesota Living with Heart Failure (MLHF) questionnaire.[33]

Procedural data, such as the number of BPA sessions, number of pulmonary segments addressed, and number of obstructive lesions treated, were obtained. Intravascular obstructive lesions were described according to an angiographic classification proposed in a previous study.[30] Complications occurring during the procedures, such as vascular perforation, dissection, or both, and during in-hospital evolution, such as acute pulmonary injury and contrast-induced nephropathy, were identified.

Statistical analysis

A descriptive analysis of the data was conducted. The main variables studied to evaluate the potential effectiveness of the treatment were short-term mPAP and PVR, and, from a functional standpoint, short- and long-term NYHA-FC. Acute lung injury with clinical manifestations was the main variable used in order to assess the safety of the treatment.

Continuous numerical variables are expressed as mean and standard deviation or as median and interquartile range, depending on their distribution. Categorical variables are expressed as absolute values and percentages. Comparative analyses between baseline and post-last session hemodynamic, clinical, and laboratory data were performed by using t-tests for paired samples with normal distribution, the Wilcoxon test for paired samples with non-normal distribution, or McNemar's test for categorical variables. Values of $p < 0.05$ were considered statistically significant. Data analysis was performed with GraphPad Prism, version 10.2.2 for macOS (GraphPad Software, San Diego, CA, USA), www.graphpad.com.

RESULTS

Between February of 2015 and August of 2020, 23 of 32 patients selected for BPA were included in the analysis (Figure 1; Table 1). The reasons for BPA indication were technically inoperable distal disease in 15 patients (65%), high-risk comorbidities for PEA in 2 (9%), lack of access to PEA in 5 (22%), and refusal to undergo surgery in 1 (4%).

The majority of the patients were female. In the sample as a whole, the mean age was 50 ± 13.8 years and the median symptom duration prior to the first BPA session was 36 months (IQR, 24-54 months). All patients exhibited exertional dyspnea and NYHA-FC III or IV, despite pharmacological treatment. Nearly all of the patients were under continuous treatment with a pulmonary vasodilator at stable doses, with a median treatment duration of 6 months (IQR, 3-8 months). Five of the 6 patients with potentially operable CTEPH were treated with pulmonary vasodilators only after the decision to undergo BPA had been made. Only 5 patients were taking riociguat (a soluble guanylate cyclase stimulator) before BPA.

The conclusion of BPA treatment was based on the absence of any remaining vessels technically suitable or anatomically relevant for intervention in 14 cases (61%), patient choice following perceived sufficient

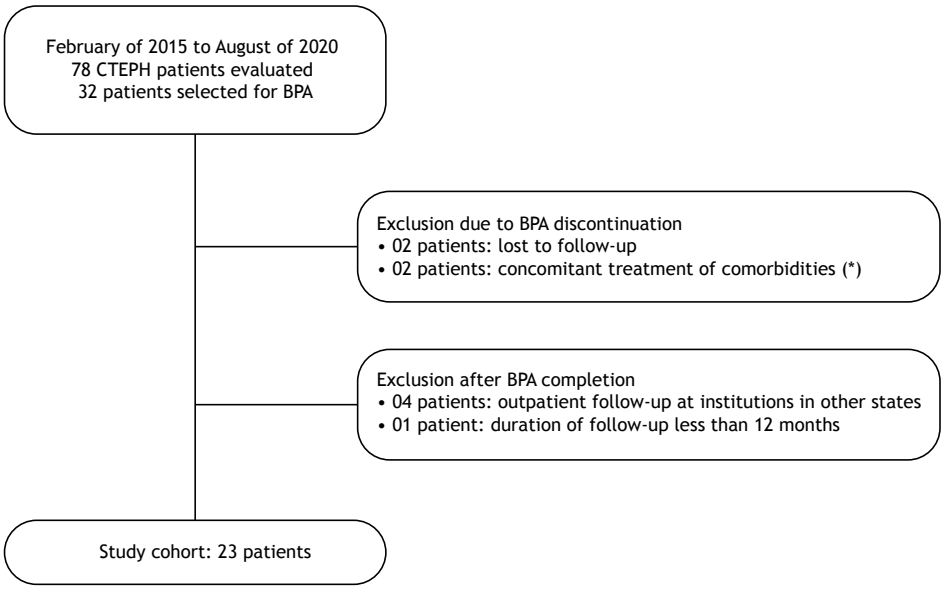

Figure 1. Flow chart of the patient selection process. *One patient had congenital isolated stenoses in the right arterial interlobar pulmonary branch, concurrent with CTEPH lesions in the segmental vessels of the left lung. After significant hemodynamic and clinical improvements following stent implantation in the right interlobar branch, this patient was excluded from the study cohort to prevent confusion in interpreting the effects of BPA. The other patient had a significant psychiatric disorder that complicated the performance of BPA sessions and the interpretation of clinical outcomes. After three BPA sessions, we decided to prioritize treatment of the psychiatric condition. BPA: balloon pulmonary angioplasty; and CTEPH, chronic thromboembolic pulmonary hypertension.

Table 1. Baseline characteristics of the study cohort.

Baseline characteristic	(N = 23)
Age (years), mean ± SD	50 ± 14
Female sex, n (%)	20 (87)
BMI (kg/m^2), mean ± SD	27.3 ± 4.5
Previous VTE, n (%)	12 (52)
Thrombophilia, n (%)	4 (17)
Hypertension, n (%)	12 (52)
Previous PEA, n (%)	1 (4)
Symptom duration (months), median (IQR)	36 (24-54)
Time from diagnosis to BPA, median (IQR)	14 (9-28)
NYHA-FC II/III/IV, n/n/n	0/11/12
Patients on oxygen therapy, n (%)	7 (30)
Medications in use, n (%)	
Riociguat	5 (22)
Sildenafil	15 (65)
Bosentan	8 (35)
No vasodilator	1 (4)
Furosemide	18 (78)
mPAP (mmHg), mean ± SD	51 ± 10.7
PVR (WU), mean ± SD	10 ± 3.7
RAP (mmHg), mean ± SD	13 ± 5.3
CI (L/min/m^2), mean ± SD	2.4 ± 0.6
SvO_2 (%), mean ± SD	57.7 ± 9
Hemoglobin (g/dL), mean ± SD	14 ± 1.9
Creatinine (mg/dL), mean ± SD	0.9 ± 0.19
Urea (mg/dL), mean ± SD	33 ± 7.8

BPA: balloon pulmonary angioplasty; VTE: venous thromboembolism; PEA: pulmonary endarterectomy; NYHA-FC: New York Heart Association functional class; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; CI: cardiac index; and SvO_2: mixed venous oxygen saturation.

Table 2. Procedural data and complications.

Variable	Value
Treatment duration (months), mean ± SD	12.5 ± 6.8
BPA sessions, n	128
Number of BPA sessions/patient, mean ± SD	5.6 ± 1.3
Fluoroscopy time (min/session), mean ± SD	60 ± 17.3
Contrast medium volume (mL/session), mean ± SD	295 ± 65
Treated lung segments, n	253
Treated lung segments (n/patient), mean ± SD	11 ± 2.7
Untreated lung segments (n/patient), mean ± SD	3 ± 1.8
Treated obstructive lesions, n	422
Lesion type, n (% of all lesions)	
A	48 (11.4)
B	252 (59.7)
C	85 (20.0)
D	28 (6.6)
E	9 (2.1)
Procedure-related complications, n (% of all sessions)	
Acute lung injury	9 (7)
Hemoptysis	9 (7)
Mechanical ventilation	0
NPPV	4 (3.1)
Arterial perforation	6 (4.7)
Arterial dissection	20 (15.6)
Acute kidney injury	2 (1.6)

BPA, balloon pulmonary angioplasty; and NPPV, Non-invasive positive pressure ventilation.

clinical improvement in 5 cases (21%), lack of clinical improvement in 2 cases (9%), and an unfavorable risk-benefit ratio in 2 cases (9%).

Patients underwent a mean of 5.6 ± 1.3 sessions of BPA over a mean time of 12.5 ± 7.0 months (Table 2). The mean of pulmonary segments addressed per patient was 11 ± 2.7. Follow-up RHC was performed for hemodynamic reevaluation at a mean of 6.7 ± 3.0 months after the last angioplasty session. Comparing the values obtained at the end of treatment with those obtained at baseline, we observed significant improvements in hemodynamic parameters, including a 26% reduction in mPAP (51 ± 11 mmHg vs. 38 ± 11 mmHg; $p < 0.0001$), a 43% decrease in PVR (10 ± 3.7 mmHg vs. 5.7 ± 3.4 mmHg; $p < 0.0001$), and a 22.5% increase in the cardiac index (2.38 ± 0.6 L/min/m^2 vs. 2.95 ± 0.6 L/min/m^2; $p < 0.0001$). In addition, an mPAP lower than 25 mmHg was achieved in 4 patients. Within the first 6 months after the last session, there was also a reduction in the median plasma level of B-type natriuretic peptide (256 pg/mL [IQR, 130-180 pg/mL] vs. 46 pg/mL [IQR, 19-130 pg/mL]; $p < 0.0001$), an increase in the mean 6-minute walk distance (273 ± 127 m vs. 370 ± 114 m; $p < 0.0001$), and symptom improvement with reductions in NYHA-FC and in home oxygen use (Table 3; Figure 2). The 6MWT was performed a median of 4 months (IQR, 3-7 months) after the last BPA session. The quality of life of the patients, as determined by the mean MLHF score, improved significantly following the angioplasties (64.5 ± 16 vs. 27.7 ± 15.5; $p < 0.0001$). In a patient who had received sildenafil monotherapy prior to BPA, the pulmonary vasodilator treatment was withdrawn. It was also possible to discontinue furosemide in 8 of the 18 patients who were using it before BPA ($p = 0.008$).

Obstructive lesions were located in the lower lobes in 55% of the interventions, in the upper lobes in 20%, in the middle lobe in 18%, and in the lingula in 8%. The majority (80%) of the obstructive lesions addressed were type B, corresponding to lesions appearing as "webs" or "slits" within vessels, or type C, corresponding to subocclusive vascular lesions (Table 2; Figure 3). Interventions in type D and E lesions were associated with vascular complications in 28% and 11%, respectively, whereas interventions in type A, B, and C lesions were associated with a lower rate of complications (2.0%, 4.4%, and 6.0%, respectively). Vascular dissections and perforations

Table 3. Effects of balloon pulmonary angioplasty on hemodynamic, laboratory and clinical parameters.

Parameter	Baseline	Final	Variation		P value
			Absolute	Relative	
sPAP (mmHg), mean ± SD	91 ± 17	69 ± 19.4	− 22	− 24%	< 0.0001
mPAP (mmHg), mean ± SD	51 ± 10.7	38 ± 11	− 13.2	− 25.9%	< 0.0001
PVR (WU), mean ± SD	10 ± 3.7	5.7 ± 3,4	− 4.3	− 43.0%	< 0.0001
CI (L/min/m^2), mean ± SD	2.38 ± 0.6	2.95 ± 0.6	+ 0.46	+ 22.5%	< 0.0001
RAP (mmHg), mean ± SD	13 ± 5.3	8.8 ± 4.9	− 4.2	− 32%	0.0012
HR (bpm), mean ± SD	85 ± 11.4	74 ± 12	− 10.7	− 12.6%	< 0.0001
SvO_2 (%), mean ± SD	57.7 ± 9	67.4 ± 6	+ 9.7	+ 16.8%	< 0.0001
SaO_2 (%), mean ± SD	92 ± 4.2	95.5 ± 3.2	+ 3.5	+ 3.8%	0.0002
BNP (pg/mL), median (IQR)	256 (130-380)	46 (19-130)	− 168	− 56.8%	< 0.0001
6MWD (m), mean ± SD	273 ± 127	370 ± 113.8	+ 97	+ 35.5%	< 0.0001
SpO_2 at peak exercise, mean ± SD	85.3 ± 8	89.6 ± 4.5	+ 4.3	+ 5.0%	0.0068
Hemoglobin (g/dL), mean ± SD	14 ± 1.9	13.3 ± 1.3	− 0.7	− 5%	0.09
Creatinine (mg/dL), mean ± SD	0.9 ± 0.19	0.9 ± 0.2	− 0.02	0%	0.5
Oxygen therapy, n	7	3	− 4	− 57%	0.13

sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; CI: cardiac index; SvO_2: mixed venous oxygen saturation; BNP: plasma B-type natriuretic peptide; and 6MWD: six-minute walk distance.

were observed in 15.6% and 4.7% of the 128 sessions, respectively, usually without immediate clinical repercussions. Only 2 vascular perforations (1.6%) resulted in hemoptysis during the procedure and were treated through prolonged proximal balloon inflation and reversal of anticoagulation, without the need for vascular embolization. Acute lung injury with clinical manifestations was observed after 9 (7%) of the 128 sessions. Clinical manifestations were characterized by dyspnea at rest, with or without hemoptysis, or a drop in SpO_2 accompanied by pulmonary crackles upon auscultation of the thoracic regions in which the segments subjected to interventions were located, within the first 48 h post-BPA. Noninvasive positive pressure ventilation (NPPV) was required in 4 interventions (3%), and nasal oxygen supplementation was required in the others, all patients showing gradual improvement 3-5 days after BPA. Acute kidney injury was detected following 2 (1.6%) of the BPA sessions, with spontaneous reversal of creatinine to baseline values within a few days of follow-up.

The mean duration of the clinical outpatient follow-up period was 38 ± 22 months, during which time most of patients maintained the same NYHA-FC. Clinical worsening with hospital admissions was observed in 4 patients with a median time to hospitalization of 39 months (IQR, 13.8-64.0 months). Two of those patients were referred for another series of BPA sessions after angiographic reevaluation, to treat arterial branches not addressed in the initial series. There were two deaths unrelated to the pulmonary angioplasties: one in a 26-year-old patient, from progressive PH, at 7 months after BPA (considered a nonresponder to the interventional treatment); and the other in a 53-year-old patient, from hemorrhagic shock secondary to gastrointestinal bleeding associated with oral anticoagulation with warfarin, 44 months after the last BPA session.

DISCUSSION

This observational study describes the short- and long-term effectiveness and safety of BPA as an alternative to PEA as a therapeutic approach for symptomatic patients with CTEPH, conducted by a PH referral medical group in Brazil. Ours represent the first published BPA results for Brazil.

In this study, pulmonary angioplasties were indicated after careful assessment by a specialized multidisciplinary team as part of the proposed treatment protocol for patients with CTEPH, reflecting the medical practice of the team during the study period. The hemodynamic criteria used in order to define PH were those in effect at the time of patient selection.[32] Thus, in accordance with the latest diagnostic criteria,[34] patients with CTEPH who had an mPAP of 20-25 mmHg were not included.

Follow-up RHCs performed after BPA demonstrated significant hemodynamic improvement, including reductions in pulmonary arterial and right chamber pressures, decreased PVR, and increased cardiac index associated with a reduction in resting heart rate, indicating increased ventricular systolic volume. The respective 26% and 43% decreases in mPAP and PVR (the primary hemodynamic variables investigated) were not as pronounced in our patient sample as in those evaluated in studies conducted in Japan, in which reductions ranging from approximately 40% to approximately 60% were reported.[14,15,17-22] The more modest hemodynamic impact observed in our study could be attributed to a few factors. The first is the learning curve effect on the interventional cardiologists who performed the angioplasties, given that these were the first patients treated by our group. In addition, the mean baseline mPAP in our sample was higher than that reported in most previous studies of BPA. Furthermore, the long duration of symptoms prior to BPA suggested that our patients

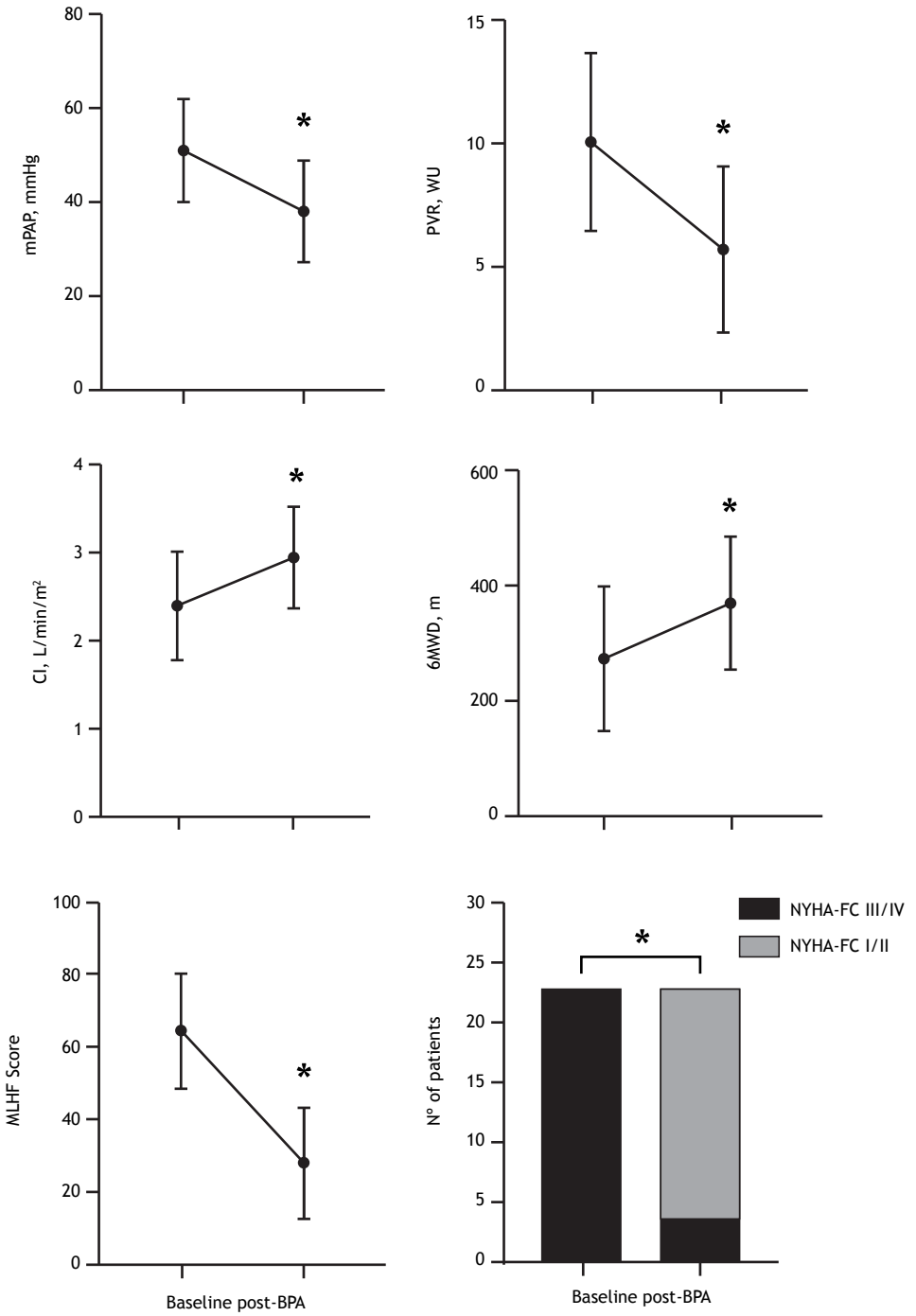

Figure 2. Effects of balloon pulmonary angioplasty (BPA) on clinical and hemodynamic parameters. BPA: balloon pulmonary angioplasty; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CI: cardiac index; 6MWD: 6-minute walk distance; NYHA-FC: New York Heart Association functional class; MLHF: Minnesota Living with Heart Failure (questionnaire). *p < 0.0001.

had advanced CTEPH and were therefore at a higher risk of advanced microvascular disease, which might diminish the response to endovascular treatment. Another potential factor is the selection criteria for BPA and PEA used by our group. At centers in Japan, the majority of patients with CTEPH are referred for BPA, whereas the inverse occurs at centers in Europe and North America.[7] Our criteria seem more aligned with European and North American standards, although we are partly constrained to refer patients for surgery due to limitations related to the public health care system in Brazil, leading to some patients with potentially operable disease undergoing BPA. When comparing the hemodynamic results obtained at our

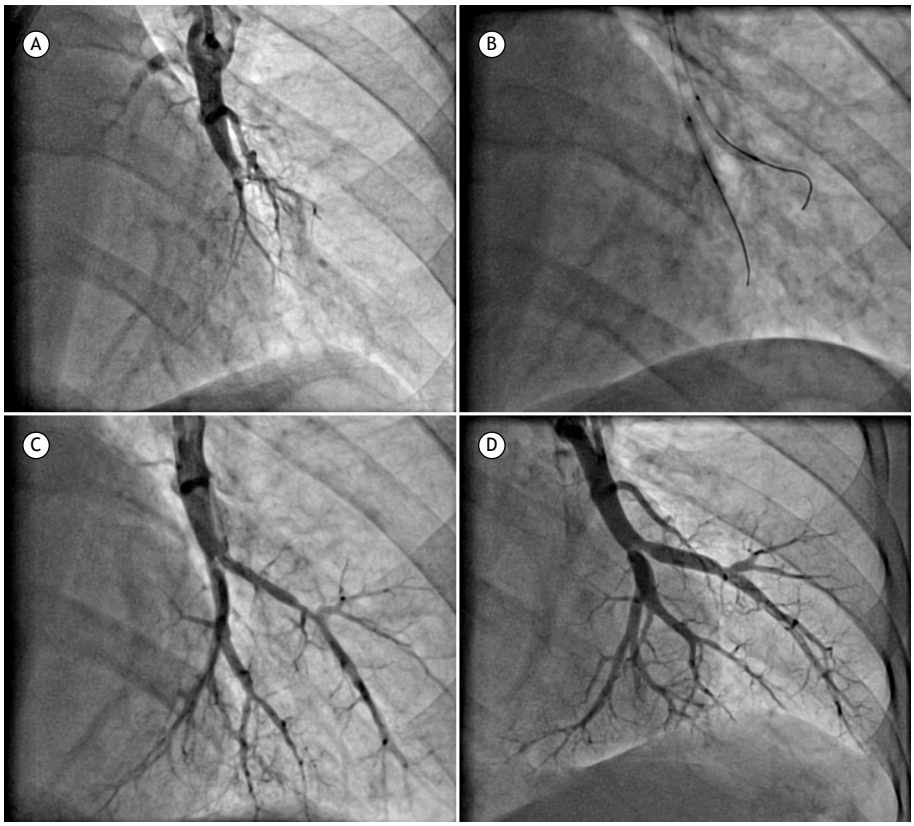

Figure 3. Balloon pulmonary angioplasty of arterial branches (A8 and A7) to anterior and medial segments of the left inferior lobe, depicted by selective pulmonary angiograms from A to D. A: Subocclucded branches (type C obstructive lesions) with distal narrowing and flow reduction. B: Balloon pulmonary angioplasty. C: Immediate result. D: Selective angiogram after 6 months, demonstrating vascular patency and positive remodeling.

center with those obtained at centers in Europe, we observed similar improvements in mPAP, PVR, and the cardiac index.[23-25] Moreover, we cannot disregard possible genetic differences among the populations of Japan, Europe, and Brazil that may influence disease characteristics and treatment responses.

The frequency of adverse events in our study was low compared with that reported in previous studies, likely due to our less aggressive interventional approach, which might also have influenced the extent of hemodynamic improvement observed. Vascular dissections and perforations were not associated with clinical manifestations in most cases. Among the 128 sessions performed, perforations that required immediate endovascular intervention occurred in only 2. Acute lung injury with clinical manifestations was observed after 9 (7%) of the sessions, affecting 6 (26%) of our patients, and NPPV was required in 4 events involving 3 of those patients. Mechanical ventilation was not required for any of the patients in our sample, and there were no in-hospital deaths.

Clinically, BPA led to significant improvement in NYHA-FC and in functional capacity assessed by the 6MWT. Discontinuation of diuretics and home oxygen was possible in a significant proportion of patients. The NYHA-FC remained unchanged in most patients throughout the extensive clinical follow-up period. New hospital admissions occurred in 3 patients due to worsening of symptoms related to CTEPH and in 1 patient due to worsening dyspnea associated with the progression of chronic mitral valve disease. Among the 3 patients with worsening CTEPH, 2 underwent a new series of BPA sessions after reevaluation by interventional cardiologists, because these were among the first patients treated by our group, in whom obstructive lesions that were more complex had not initially been addressed because of technical limitations of the learning curve. After the new series, those patients reported further symptom improvement.

An improvement in quality of life was evidenced by the decrease in MLHF scores at 3 months after BPA. We used the Portuguese-language version of the MLHF questionnaire to evaluate the patients in our study, considering the similarity of symptoms and impact on quality of life in patients with right cardiac effects associated with CTEPH, compared with patients with left heart failure, for whom the MLHF questionnaire was originally created and validated.[33] Therefore, its applicability in individuals with PH not associated with left heart disease, like those in the present study, has yet to be validated, and we should interpret

the results as hypothesis-generating. In addition to all of the previously mentioned limitations, the present study also has the limitations inherent to a single-center observational study, including the lack of a control group.

In conclusion, the present study describes significant hemodynamic and clinical improvement, together with a low frequency of complications, in the first patients with CTEPH undergoing BPA by a specialized group in Brazil. The study population, which presented signs of advanced PH, impaired quality of life, and a guarded prognosis, showed good long-term clinical progression after completion of the interventional treatment.

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AUTHOR CONTRIBUTIONS

FSFS, MGF, and IAM: design and planning of the study; interpretation of the findings; writing or revision of all preliminary drafts and of the final version of the manuscript; and approval of the final version of the manuscript. MFLS, CMCL, RA, PHAC, MSV, VOJ, and LEFR: writing or revision of all preliminary drafts and of the final version of the manuscript; and approval of the final version of the manuscript. All authors read and approved the final version of the manuscript.

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Outcomes of segmentectomy versus lobectomy in adults with non-cystic fibrosis bronchiectasis

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ABSTRACT

Objective: Surgical resection remains the gold standard treatment for bronchiectasis in patients who present with hemoptysis or suppuration, as well as in those who do not respond to clinical treatment. We sought to investigate the efficacy of sublobar resection (segmentectomy) and compare it with that of lobar resection (lobectomy) in patients with non-cystic fibrosis bronchiectasis. **Methods:** Patients undergoing lobectomy or segmentectomy between 2019 and 2023 were included in the study. We analyzed intraoperative complications and postoperative outcomes, including length of hospital stay, length of ICU stay, and disease recurrence. **Results:** There was no significant difference between the lobectomy and segmentectomy groups regarding the occurrence of intraoperative complications such as bleeding > 1000 ml, cardiogenic shock, and ventilatory instability ($p > 0.999$). However, the frequency of complications was significantly lower in the segmentectomy group than in the lobectomy group ($p = 0.016$). Hospital stays were longer in the lobectomy group than in the segmentectomy group (16 days vs. 5 days; $p = 0.027$), as were ICU stays (7 days vs. 1 day; $p = 0.006$). There was no significant difference between the lobectomy and segmentectomy groups regarding the recurrence rate ($p = 0.541$). **Conclusions:** Early identification of bronchiectasis patients who are candidates for surgical resection is essential because those who are identified as such early on are candidates for parenchyma-sparing resections, which are similar to lobar resections in terms of disease control and lead to shorter hospital stays and better postoperative outcomes.

Keywords: Bronchiectasis; Thoracic surgery; Disease-free survival.

INTRODUCTION

Infectious lung diseases are a heterogeneous group of diseases including community-acquired pneumonia and rare fungal infections.[1] In a small portion of cases, irreversible changes in the lung architecture can lead to chronic conditions. Common features include irreversible dilatation and distortion of the bronchial tree, the causes of which are many.[2] The incidence of bronchiectasis in adults ranges from 3.7 cases/100,000 population to 52 cases/100,000 population.[2]

Pulmonary tuberculosis is the main cause of postinfectious bronchiectasis. Pulmonary tuberculosis is a public health problem mainly in developing countries, despite public health policies aimed at mitigating it. Most patients with pulmonary tuberculosis develop pulmonary sequelae such as cavitation, which occurs in approximately 40%.[3,4]

Surgical resection for bronchiectasis consists of removing permanently damaged lung areas into which antibiotic penetration is poor, serving as a reservoir for bacteria and fungi and thus leading to recurrent infections.[5]

Anatomical lung resection (lobectomy) is the procedure of choice for the surgical management of bronchiectasis; however, sublobar resections have been used as parenchyma-sparing procedures in cancer patients.[6] Sublobar resections have been validated in multicenter randomized studies in the field of thoracic oncology, with survival rates and perioperative complications similar to those of lobar resections.[7] However, there is a lack of studies investigating the efficacy and safety of sublobar resections in comparison with lobar resections in patients with infectious lung diseases.

Although the two procedures are theoretically the same from a technical point of view, they can be very different in terms of how they are performed and the postoperative complications that can occur in cases of cancer or inflammatory disease, the rate of postoperative complications being high in patients with inflammatory or infectious diseases.[8]

Given the lack of studies examining sublobar resections in patients with bronchiectasis, the objective of the present study was to estimate the efficacy of sublobar resection by calculating disease-free survival and complication rates, as well as by analyzing postoperative outcomes

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such as duration of chest tube drainage, length of hospital stay, and length of ICU stay, in patients with non-cystic fibrosis (CF) bronchiectasis undergoing sublobar or lobar resection.

METHODS

This was a single-center retrospective study of prospective data from the Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN, USA) database maintained by the Thoracic Surgery Department of the University of São Paulo School of Medicine *Hospital das Clínicas* Heart Institute, located in the city of São Paulo, Brazil. All data are anonymous and were collected anonymously, thus ensuring the confidentiality of patient data.

Patients > 18 years of age with non-CF bronchiectasis undergoing sublobar resection between 2019 and 2023 for the surgical treatment of complications or as an adjunct to clinical treatment were compared with those undergoing lobar resection for symptom control. All of the patients included in the present study underwent chest CT, the reported findings being consistent with bronchiectasis. Data on the cause of bronchiectasis were collected from patient medical records, including symptoms (suppuration and hemoptysis), a history of pulmonary tuberculosis confirmed by diagnostic tests, and occupational exposure. Patients with CF bronchiectasis were excluded. Other exclusion criteria were as follows: patients with missing data on the type of resection performed and those without outpatient follow-up.

All data were entered into a Microsoft Excel spreadsheet for statistical analysis. Categorical variables were expressed as absolute numbers and percentages. Numerical variables with normal distribution were expressed as mean and standard deviation, whereas those with asymmetric distribution were expressed as median and interquartile range. The demographic data were compared by means of the chi-square test, the t-test, or the Mann-Whitney test, depending on the type of variable. Values of $p < 0.05$ were considered significant.

The study was approved by the University of São Paulo School of Medicine *Hospital das Clínicas* Research Ethics Committee (Protocol no. 6.750.919/CAAE 33365720.2.0000.0068) and was conducted in accordance with the Declaration of Helsinki.

RESULTS

Of a total of 65 patients undergoing surgical resection for bronchiectasis between 2019 and 2023, 27 were excluded because of missing data on the type of resection performed or lack of outpatient follow-up. Therefore, the study sample consisted of 38 patients in the 19- to 71-year age bracket (mean age, 47.77 ± 13.78 years). Most were female and White (61% and 76%, respectively). Table 1 shows the general characteristics of the study population. As can be seen in the table, there was a significant difference between the patients who underwent lobar resection (the lobectomy group) and those who underwent sublobar resection (the segmentectomy group) in terms of percent predicted FEV_1 ($p= 0.003$). Pulmonary tuberculosis sequelae were the main cause of bronchiectasis in both groups (47% in both groups), and hemoptysis followed by suppuration was the most common reason for surgery (in 21% of those in the lobectomy group and in 12% of those in the segmentectomy group).

Whether a given patient is a candidate for lobar or sublobar resection depends on the degree of lung parenchyma involvement. In the group of patients who underwent segmentectomy, 2 underwent wedge resection and 11 underwent anatomical resections, the most common being right upper lobe anterior segmentectomy (in 4 patients), followed by left upper lobe trisegmentectomy. In the group of patients who underwent lobectomy, right upper lobectomy was the most common procedure (performed in 15 patients), followed by left upper lobectomy (in 9).

As can be seen in Table 2, there was no significant difference between the lobectomy and segmentectomy groups regarding the rate of bleeding ($p = 0.385$) or the occurrence of intraoperative complications such as bleeding > 1000 ml, cardiogenic shock, and ventilatory instability ($p > 0.999$).

As can be seen in Table 3, there was a significant association between the type of treatment and surgical complications ($p = 0.016$). The frequency of complications was significantly lower among those who underwent segmentectomy than among those who underwent lobectomy (15% vs. 56%; $p = 0.016$). Complications included prolonged air leak and clinical signs and symptoms such as fever, hypotension, postoperative pain, empyema, and hemothorax. Although there were no significant differences between the lobectomy and segmentectomy groups regarding the rate of bleeding or the occurrence of intraoperative complications, there was a marginal association between the type of treatment and the need for reoperation (Table 4).

The recurrence rate is an important factor to consider when analyzing parenchyma-sparing resections. As can be seen in Table 5, there was no significant difference between the lobectomy and segmentectomy groups regarding the recurrence rate ($p = 0.541$). As can be seen in Figure 1, the patients who underwent lobar resections had longer ICU and hospital stays.

DISCUSSION

Chronic lung infection, particularly pulmonary tuberculosis, is an important area of expertise for thoracic surgeons, especially those in developing countries. In patients with bronchiectasis and symptoms such as hemoptysis and suppuration, resection of the affected area is the gold standard treatment.[4] However, robust prospective and retrospective studies on this topic are currently scarce.

Table 1. General characteristics of the study sample, by type of surgical treatment. [a]

	Total sample	Type of surgical treatment		p
		Lobectomy	Segmentectomy	
	(N = 38)	(n = 25)	(n = 13)	
Age, years	47.77 ± 13.78	47.85 ± 14.06	47.62 ± 13.78	0.951
VEF_1, % predicted	73.32 ± 23.17	65.32 ± 23.71	88.69 ± 11.89	0.003
Operative time	292.89 ± 87.96	304.60 ± 91.90	270.38 ± 78.30	0.281
Sex				0.136
Female	23 (61%)	13 (52%)	10 (77%)	
Male	15 (39%)	12 (48%)	3 (23%)	
Race				0.793
Asian	1 (2.6%)	1 (4.0%)	0 (0%)	
White	29 (76%)	18 (72%)	11 (85%)	
Black	8 (21%)	6 (24%)	2 (15%)	
Etiology of bronchiectasis				0.185
Aspergillosis	7 (18%)	3 (12%)	4 (31%)	
Galvanization	1 (2.6%)	0 (0%)	1 (7.7%)	
Histiocytosis	1 (2.6%)	0 (0%)	1 (7.7%)	
Repeat infection	9 (24%)	7 (28%)	2 (15%)	
Tuberculosis	18 (47%)	13 (52%)	5 (38%)	
Tuberculosis/aspergillosis	2 (5.3%)	2 (8.0%)	0 (0%)	
Indication for surgery				0.857
Fungus ball	3 (7.9%)	1 (4.0%)	2 (15%)	
Hemoptysis + fungus ball	1 (2.6%)	1 (4.0%)	0 (0%)	
Hemoptysis + suppuration	1 (2.6%)	1 (4.0%)	0 (0%)	
Hemoptysis	21 (55%)	14 (56%)	7 (54%)	
Suppuration	12 (32%)	8 (32%)	4 (31%)	

[a]Data expressed as mean ± SD or n (%).

Table 2. Association between bleeding and the type of surgical treatment.

Surgical treatment	Total sample	Bleeding		p
		No	Yes	
	(N = 38)	(n = 31)	(n = 7)	
Lobectomy	25 (66%)	19 (61%)	6 (86%)	0.385
Segmentectomy	13 (34%)	12 (39%)	1 (14%)	

Table 3. Association between complications and the type of surgical treatment.

Surgical treatment	Total sample	Complications		p
		No	Yes	
	(N = 38)	(n = 22)	(n = 16)	
Lobectomy	25 (66%)	11 (44%)	14 (56%)	0.016
Segmentectomy	13 (34%)	11 (85%)	2 (15%)	

In the present single-center study, we investigated the efficacy of sublobar resection (segmentectomy) in comparison with that of lobar resection (lobectomy) in patients undergoing surgical treatment for non-CF bronchiectasis. We analyzed perioperative complications and disease-free survival, both of which are important when analyzing parenchyma-sparing resections.

In the group of patients undergoing lobar resection, pulmonary function tests were significantly lower. [8] In addition, operative time was longer in the lobectomy group than in the segmentectomy group, although the difference was not significant. This means that pulmonary involvement was more severe in the patients who underwent lobar resection, the procedure presenting greater technical difficulty.

Pulmonary tuberculosis was the leading cause of bronchiectasis (in nearly half of the patients in the present study), a finding that is consistent with the literature. [2] Hemoptysis and suppuration were the most common reasons for surgery, occurring in approximately 90% of the study population. Hemoptysis has been reported to account for approximately 40% of all surgical indications. [9] Approximately twice as many patients in the lobectomy group vs. the segmentectomy group had bleeding > 1,000 ml and complications during the surgical procedure, including bleeding, air fistula, hemodynamic instability, and ventilatory instability.

There was a marginal association between lobectomy and the need for reoperation, the main causes being empyema and hemothorax. However, there was a significant association between lobectomy and the occurrence of perioperative complications. In addition, the patients in the lobectomy group had

Table 4. Association between reoperation and the type of surgical treatment.

	Reoperation			
	Total sample (N = 38)	No (n = 31)	Yes (n = 7)	Value of p
Surgical treatment				0.072
Lobectomy	25 (66%)	18 (58%)	7 (100%)	
Segmentectomy	13 (34%)	13 (42%)	0 (0%)	

Table 5. Association between recurrence and the type of surgical treatment.

	Recurrence			
	Total sample (N = 35)	No (n = 32)	Yes (n = 3)	Value of p
Surgical treatment				0.541
Lobectomy	22 (63%)	21 (66%)	1 (33%)	
Segmentectomy	13 (37%)	11 (34%)	2 (67%)	

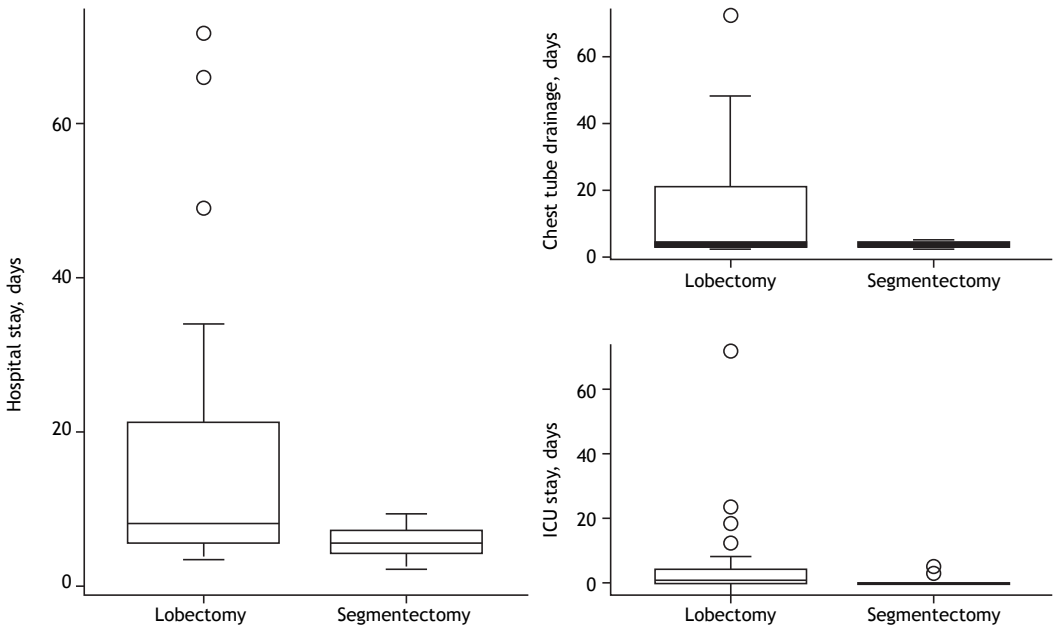

Figure 1. Length of hospital stay, ICU stay, and chest tube drainage in patients undergoing lobectomy or segmentectomy for the surgical treatment of non-cystic fibrosis bronchiectasis.

longer hospital stays, longer ICU stays, and longer chest tube drainage.

The results of the present study are similar to those of a study conducted by Yang et al., [3] who reported that sublobectomy and lobectomy were both effective in the surgical treatment of cavitary pulmonary tuberculosis. However, the sublobectomy group had fewer intraoperative blood losses, shorter stays, and fewer perioperative complications than did the lobectomy group ($p < 0.05$). [3]

With regard to the disease recurrence rate in the present study, there was no significant difference between the lobectomy and segmentectomy groups.

Patients undergoing lung resection tend to have pulmonary involvement that is more severe and, consequently, more severe clinical and functional deterioration, all of which are closely related to intraoperative and perioperative outcomes. Patients undergoing lobar resection tend to have more complications, including a higher bleeding rate.

Early identification of bronchiectasis patients who are candidates for surgical resection is essential because those who are identified as such early on are candidates for parenchyma-sparing resections, which are similar to lobar resections in terms of disease control and lead to shorter hospital stays and better postoperative outcomes.

AUTHOR CONTRIBUTIONS

JSMN: Writing and/or revision of all preliminary drafts and the final version of the manuscript. IAC: Design and planning of the study, as well as interpretation of findings. AWM: Revision of all preliminary drafts and the final version of the manuscript. RMT and PMPF: Providing critical review for significant intellectual content and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Durvalumab as consolidation therapy in patients who received chemoradiotherapy for unresectable stage III NSCLC: Real-world data from an expanded access program in Brazil (LACOG 0120)

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ABSTRACT

Objective: The PACIFIC trial established standard therapy for patients with unresectable stage III NSCLC who did not progress after platinum-based concurrent chemoradiation therapy. However, real-world data, particularly from Latin America, remain limited. The LACOG 0120 study aimed to evaluate the efficacy and safety of consolidation therapy with durvalumab in a real-world setting in Brazil. **Methods:** Patients with unresectable stage III NSCLC who received chemoradiotherapy followed by durvalumab consolidation therapy through an expanded access program were evaluated. The primary objective was to assess progression-free survival (PFS). Secondary endpoints included overall survival (OS), treatment compliance, and safety, with a focus on the incidence and severity of immune-mediated adverse events (NCT04948411). **Results:** Thirty-one patients from seven centers were evaluated. Median follow-up was 50.3 months (95% CI: 48.6–54.4). Median PFS was 9.9 months (95% CI: 7.3–52.4), with a 36 month-PFS of 34.5% (95% CI: 17.7–52.1). Median OS was 34.9 months (95% CI: 26.0–NR), and the 36 month-OS was 46.3% (95% CI: 25.7–64.6). Durvalumab was administered for a median of 17 cycles (10 to 24), with 45.2% of patients completing the planned therapy. The main reason for discontinuation was disease progression. Treatment-related adverse events of any grade occurred in 12 patients (38.7%), with grade 3 events reported in two (6.5%). Pneumonitis was observed in 4 patients (12.9%) – grade 3 in 1 patient. **Conclusions:** PFS was lower in this analysis compared to the PACIFIC trial; however, OS was similar, indicating comparable efficacy in a real-world setting among Brazilian patients with unresectable stage III NSCLC. No new safety concerns were identified.

Keywords: Non-Small-Cell Lung Cancer; Durvalumab; Consolidation Therapy; Real-World Data; Brazil.

INTRODUCTION

Non-small-cell lung cancer (NSCLC) continues to be a major global health concern. In 2020, it was the leading cause of cancer-related deaths worldwide, ranking first among men and second among women.[1] In Brazil, the National Cancer Institute (INCA) reported 16,009 deaths in men and 12,609 deaths in women in 2020,[2] along with an estimated 32,560 new cases in 2023. These figures, however, may be underestimated due to significant underdiagnosis and underreporting.[3] Despite this, both Brazil and the United States have observed a decline in the incidence of lung cancer, although a rise in the proportion of localized disease diagnoses was reported in the US.[3,4] Nevertheless, approximately one-third of patients continue to be diagnosed with locally advanced tumors.[1]

For decades, concomitant platinum-based chemotherapy and radiotherapy was the standard of care for patients with unresectable stage III NSCLC and good performance status.[5,6] Despite its curative intent, the median progression-free survival (PFS)

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was only 8 months, with a 5-year overall survival (OS) of only 15% to 30%. Recently, the phase III PACIFIC trial (NCT02125461) evaluated consolidation therapy with anti-programmed cell death ligand-1 (anti-PD-L1) in patients with unresectable stage III NSCLC who did not experience disease progression after chemoradiotherapy (CRT). The results showed that durvalumab significantly improved PFS, with a median of 16.9 months in the experimental group compared to 5.6 months in the placebo group.[7] Furthermore, the median OS was 47.5 months in the durvalumab group versus 29.1 months in the placebo arm.[7] As a result, consolidation therapy with durvalumab for 12 months has become the standard of care for patients with unresectable, locally advanced NSCLC.

In Brazil, the National Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária* [ANVISA]) approved this therapeutic modality for unresectable stage III NSCLC in July 2018. Despite the benefits demonstrated in the long-term follow-up of the PACIFIC trial,[7] at the time of designing this study, the treatment had not yet been approved in the public healthcare system. Recently, however, the National Commission for the Incorporation of Technologies into the Unified Health System (*Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde* [CONITEC]) approved durvalumab consolidation therapy, though it is not yet widely available. While most patients tolerate immunotherapy well, serious immune-mediated adverse events (imAEs), which may hinder its therapeutic benefits, have been reported. Although these events were generally well managed in clinical trials, further validation in a less selected population is warranted.[7,8]

The PACIFIC trial, conducted across 235 centers in six countries, demonstrated the benefits of immune checkpoint inhibitors (ICI) in 12-month consolidation therapy with durvalumab. Real-world data have validated these benefits; however, further validation is needed in Latin American populations.[9-13] The LACOG 0120 trial sought to evaluate durvalumab consolidation therapy following CRT in the Brazilian population, which, to the best of our knowledge, still lacks real-world data confirming the benefits of consolidation immunotherapy.

METHODS

The LACOG 0120 trial (NCT04948411) was a non-interventional, observational, retrospective cohort study based on the PACIFIC trial's Early Access Program (EAP) in Brazil. Eligibility criteria included patients with stage III NSCLC who were treated concurrently or sequentially with platinum-based chemoradiation therapy, received at least one dose of durvalumab in the EAP, and showed no evidence of disease progression. These patients were the first in Brazil to receive this therapy, both before and shortly after its approval by the national regulatory authority.

The characteristics and treatment patterns of patients with stage III NSCLC were retrospectively collected from their medical records, while disease status and survival data were gathered retrospectively or prospectively until all patients completed a minimum 3-year follow-up. All patients enrolled in the EAP underwent definitive CRT (concurrent or sequential) and subsequently received durvalumab until disease progression or intolerability, with no fixed maximum duration—diverging from the 12-month treatment duration specified in the PACIFIC trial. Furthermore, maintenance therapy could be continued despite disease progression if the investigator believed the patient was still benefiting from the intervention. Unlike the original PACIFIC trial, which required durvalumab therapy to begin within a maximum of 42 days,[8] Brazilian approval for this consolidation therapy imposed no such restriction. However, the LACOG 0120 investigators set a limit of 3 months for starting treatment to allow time for baseline disease assessment and recovery from adverse events related to definitive therapy, without delaying immunotherapy initiation to the point of losing the immunogenic boost from chemoradiotherapy. The participants' evaluations also included assessments of disease and medical history, physical examinations, biochemical and hematological assays, and documentation of concomitant medication use.

The primary objective was to describe the PFS of patients treated with durvalumab following definitive chemoradiotherapy for stage III, unresectable NSCLC in Brazil. PFS was defined as the time from the initiation of durvalumab treatment to disease progression or death from any given cause, whichever occurred first. It was measured using the Response Evaluation Criteria in Solid Tumors (RECIST) method, version 1.1.[14]

The secondary objective was to determine overall survival (OS), defined as the time from the start of durvalumab treatment to death from any cause. Safety was also a secondary objective and included the rates of temporary and permanent treatment discontinuation, the incidence and severity of adverse events, the duration of treatment interruptions due to adverse events, reasons for treatment discontinuation, and the concomitant use of corticosteroids, immunosuppressants, endocrine therapies, and antibiotics.

Demographic characteristics such as age, sex, and smoking status, as well as clinical aspects, including disease stage, performance status, NSCLC histology, response to CRT, immunohistochemistry, and molecular testing, were described and evaluated. Additionally, details regarding the strategy and duration of CRT, the number of cycles, the type of chemotherapy used, and RT specifics were also assessed.

To describe the baseline stage, the 8th edition of the Tumor Node Metastasis (TNM) classification from the International Association for the Study of Lung Cancer (IASLC) and the Union for International Cancer Control (UICC) was used.[15] In addition, treatment patterns at the time of disease progression were analyzed, including the duration and type of therapy. Finally, the exploratory objective was to assess the

impact of durvalumab consolidation therapy on clinical outcomes and the role of PD-L1 expression in the response to immunotherapy.

Safety was analyzed through physical examinations, the Eastern Cooperative Oncology Group performance status (ECOG PS),[16] hematological tests, and assessments of renal and thyroid function, liver injury, and metabolic markers. Tumor evaluations were guided by RECIST version 1.1. However, as these evaluations were not mandatory by the study protocol and were performed according to the local standard of care, data on objective responses, disease stability, progression, and death were collected when available from the medical records. The objective response rate (ORR) was defined as the proportion of patients achieving a partial or complete response, as assessed by RECIST version 1.1.

The investigators maintained accurate and complete data records by using electronic case report forms and ensuring the application of informed consent forms, approvals, and notifications where applicable. Data were collected from patient charts and recorded in REDCap, an electronic data capture system, which was supplemented by a series of programmed data-quality checks to automatically detect and prevent the entry of out-of-range or anomalous data.

The trial protocol was approved by an institutional review board and conducted in accordance with Brazilian regulations and Good Clinical Practice guidelines. It was also approved by the Institutional Ethics Committee.

Statistical Analyses

The patient sample in the present study was based on the number of patients enrolled in the durvalumab EAP study; no hypothesis testing or power analysis was conducted. Patients who received at least one dose of durvalumab were included in the intention-to-treat population.

Descriptive statistics were used to summarize demographic, clinical, and treatment characteristics, as well as to assess safety. The ORR was calculated with the corresponding 95% two-sided confidence interval (95% CI) using standard methods based on binomial distribution. Estimates of median PFS and OS, along with their respective 95% CIs, were determined using the Kaplan-Meier method.

In order to describe the treatment effect in detail, we evaluated the duration of treatment, the time from the end of CRT to durvalumab initiation, treatment interruptions due to adverse events, reasons for treatment discontinuation, and the need for concomitant use of corticosteroids, immunosuppressants, endocrine therapies, or antibiotics.

RESULTS

A total of 33 patients from seven clinical centers were evaluated, two of whom did not meet the eligibility criteria. Thirty-one patients who provided written informed consent and were treated in the Brazilian durvalumab EAP between September 2017 and June 2018 were included in this study. According to the 8th edition of the IASLC, the patients had stage IIIA to IIIC NSCLC, with adenocarcinoma being the most common histology (58.1%), followed by squamous cell carcinoma (32.3%). The median age at durvalumab initiation was 66.4 years (range 50.5 – 85.8). Baseline patient characteristics are shown in Table 1.

Most patients were male (67.7%), former or current smokers (80.6%), and had an ECOG performance status of 0, 1, or 2 before chemoradiotherapy (25.8%, 54.8%, and 3.2%, respectively) (Table 1). All patients had comorbidities, with hypertension being the most common (11.4%), followed by diabetes (7.1%) and hypothyroidism (4.3%).

In the initial staging, 51.6% of the patients underwent CNS imaging, primarily using MRI (87.5%). Although it was not a criterion for inclusion in the study, 83.9% of the patients were evaluated with PET-CT. Invasive mediastinal staging was performed in 29% of the patients.

Among the 18 patients with adenocarcinoma, the EGFR status was available for 10 (55.6%), with 2 patients (20%) presenting EGFR mutations. The ALK status was tested in 55.6% of the participants, and the ROS status was tested in 11.1%; all of them were ALK and ROS wild-type. Unfortunately, the low rate of molecular evaluations for oncogenic mutations reflects the limited number of tests performed in our clinical practice, indicating that this practice is not yet widespread. PD-L1 expression levels were reported in 35.5% of the patients; of these, 27.2% had a PD-L1 expression <1%, and 72.3% had expression ≥1%. The predominant immunohistochemical assay used was the 22C3 pharmDx antibody kit (Dako Inc., CA, USA), in 63.6% of cases.

Chemoradiotherapy Efficacy and Safety

Only seven patients (22.6%) received induction chemotherapy, with carboplatin combined with paclitaxel being the preferred regimen. Most patients received carboplatin-based chemoradiotherapy (80.6%). The associated agents included paclitaxel (64.5%), etoposide (19.4%), and pemetrexed (9.7%).

Overall, 20 out of the 31 patients received IMRT (64.5%), with a mean total delivered dose of 57.9 Gy. CRT interruption was not necessary for most patients (80.6%). Around 20% underwent sequential chemoradiotherapy. Adverse events (AEs) occurred in 45.2% of the patients during CRT, with the most common symptoms being dysphagia (12.9%) and nausea (12.9%). Only 1 patient (3.2%) developed pneumonitis. During definitive treatment, AEs of any grade were observed in 41.9% of the patients, with grade 3 AEs occurring in only 9.7%. Approximately 55% of these events were considered unrelated to treatment.

Table 1. Epidemiological and clinical features.

Characteristic	Statistics (N = 31)
Median age in years (range)	66.4 (50.5-85.8)
Sex - n (%)	
Male	21 (67.7)
Female	10 (32.3)
Skin color - n (%)	
White	24 (77.4)
Black	2 (6.5)
Mixed	1 (3.2)
Unknown	4 (12.9)
Smoking status - n (%)	
Never	4 (12.9)
Former	21 (67.7)
Current	4 (12.9)
Unknown	2 (6.5)
ECOG performance status prior to chemoradiotherapy - n (%)	
0	8 (25.8)
1	17 (54.8)
2	1 (3.2)
Unknown	5 (16.1)
Tumor histological type - n (%)	
Adenocarcinoma	18 (58.1)
Squamous cell carcinoma	10 (32.3)
Adenosquamous carcinoma or NOS	3 (9.7)
Stage / AJCC Stage 8th edition - n (%)	
IIIA	10 (32.3)
IIIB	15 (48.4)
IIIC	3 (9.7)
Unknown	3 (9.7)
Primary tumor - n (%)	
T1a	3 (9.7)
T1b	1 (3.2)
T1c	1 (3.2)
T2a	3 (9.7)
T2b	2 (6.5)
T3	6 (19.4)
T4	9 (29.0)
Unknown	6 (19.4)
Regional lymph nodes - n (%)	
N0	1 (3.2)
N1	3 (9.7)
N2	13 (41.9)
N3	8 (25.8)
Nx	1 (3.2)
Unknown	5 (16.1)

Most patients (83.9%) did not undergo new CNS imaging, and 64.5% did not have a new PET-CT before chemoradiotherapy. The evaluation following CRT showed that the best response was a partial response in most patients (71%). Stable disease was observed in 9.7% of the patients, with complete response in 3.2%. None of them experienced disease progression during definitive treatment. Only two patients received additional adjuvant chemotherapy after CRT (6.5%).

Durvalumab Efficacy

After a median follow-up period of 50.3 months (95% CI: 32.3 – 54.4), the median PFS from durvalumab initiation was 9.9 months (95% CI: 7.3 – 52.4) (Figure 1A). The PFS rates from the start of durvalumab at 12, 24, and 36 months were 46.7% (95% CI: 28.4 – 63.0), 39.5% (95% CI: 22.2 – 56.3), and 34.5% (95% CI: 17.7 – 52.1), respectively.

Data on survival at the third year of follow-up indicated that 51.6% of the patients had already died. Among these deaths, 75% were related to cancer progression. The median OS was 34.9 months (95% CI: 26.0 – NR) in the overall population (Figure 1B). The OS rates from the start of durvalumab at 12, 24, and 36 months were 89.3% (95% CI: 70.3 – 96.4), 72.6% (95% CI: 50.7 – 86.0), and 46.3% (95% CI: 25.7 – 64.6), respectively.

Patients with adenocarcinoma had a longer median OS than those with squamous cell carcinoma, although this difference was not statistically significant. The median PFS was 15.4 months (95% CI: 5.0 – 52.4) for adenocarcinoma, while it was not reached (95% CI: 2.3 – NR) for squamous cell carcinoma (Figure 2A). The median OS was 52.4 months (95% CI: 26.0 – NR) for adenocarcinoma and 34.9 months (95% CI: 10.2 – NR) for squamous cell carcinoma (Figure 2B). This study lacked the statistical power to detect differences in survival between the different histologies due to the small sample size. The patients were evaluated during consolidation therapy, with the best responses as follows: 9.7% showed a complete response, 19.4% showed a partial response, 19.4% had stable disease, and 19.4% had progressive disease. The best response could not be assessed in approximately 32% of the patients.

Durvalumab Compliance and Safety

The median duration of treatment with durvalumab was 9.7 months (IQR: 6.0 – 11.1), with a median of 17 cycles (10 to 24). The median time to start immunotherapy after chemoradiation was 1.86 months (IQR: 1.18 – 2.89). Temporary interruption was necessary in 16.1% of cases, with the main causes being toxicity and suspected active infection. Approximately half (45.2%) of the patients completed 12 months of planned durvalumab therapy. Among the 17 patients who were unable to complete definitive treatment, 15 (88.2%) had progressive disease, 1 (5.9%) lost follow-up, and 1 (5.9%) died from complications of a second primary tongue cancer.

During consolidation immunotherapy, 61.3% and 38.7% of the patients reported experiencing AEs and treatment-related AEs, respectively. The most common AEs related to durvalumab were pain and cough (16.1%), followed by pneumonitis and AST/ALT abnormalities (12.9%), hypothyroidism, dyslipidemia,

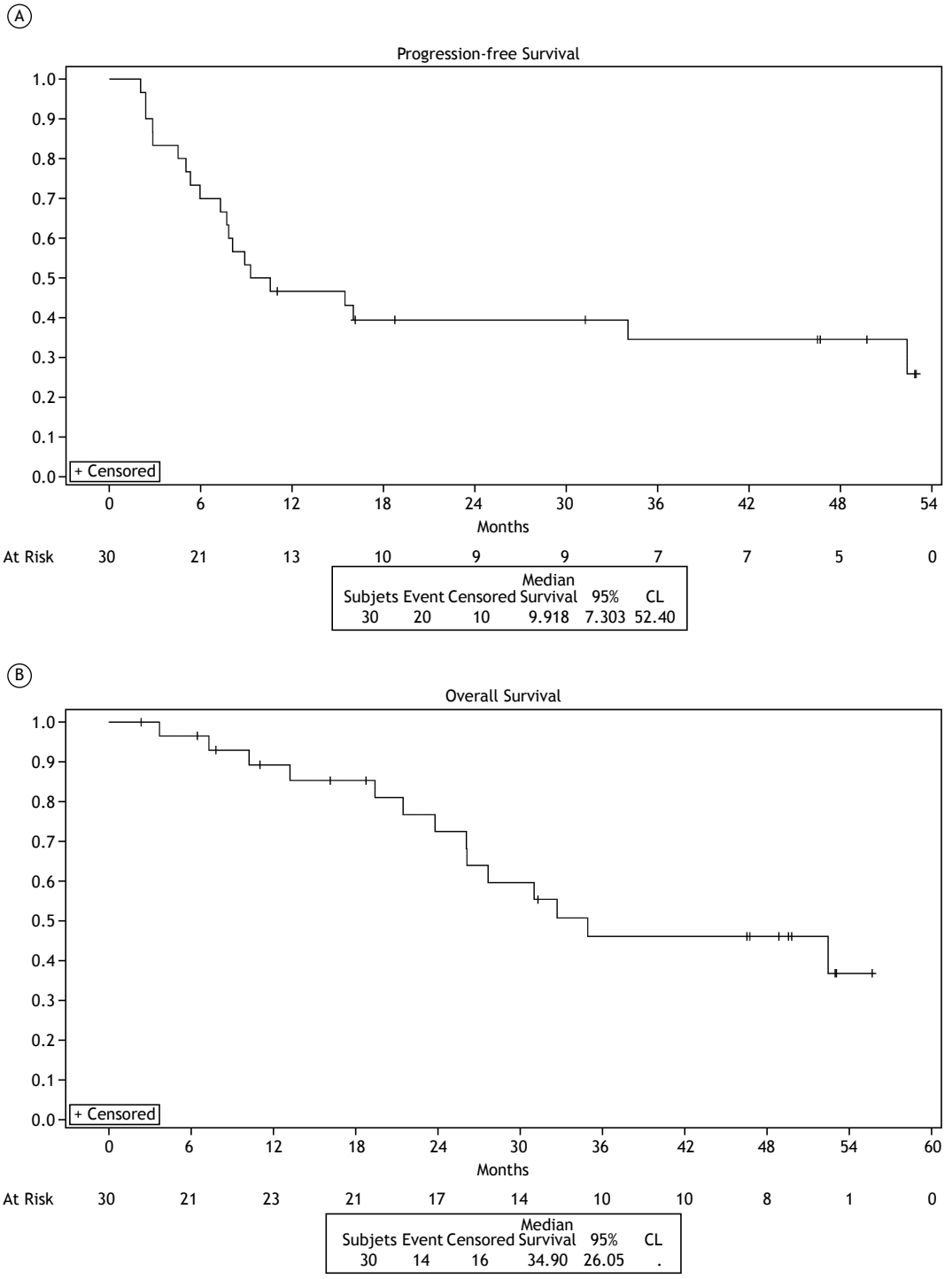

Figure 1. Progression-free survival (A) and overall survival (B) from the start date of durvalumab therapy. CL: confidence interval.

fatigue, pruritus, and localized urticaria (6.4%), and anemia, myalgia, pulmonary thrombosis, hypotension, nausea, decreased visual acuity, inappetence, upper airway obstruction, and vomiting (3.2%). Most AEs were grade 1 or 2 (97.3%), with only 1 (2.7%) being grade 3. Those related to immunotherapy are shown in Table 2.

Regarding the nine immune-mediated AEs observed during consolidation therapy, there were 4 reported cases of pneumonitis (12.9%), 3 of hypothyroidism (9.7%), and 1 of pruritus (Table 3). Systemic steroids were used in 5 patients, and no other immunosuppressive agent was required. The frequency of pneumonitis was similar to that reported in other

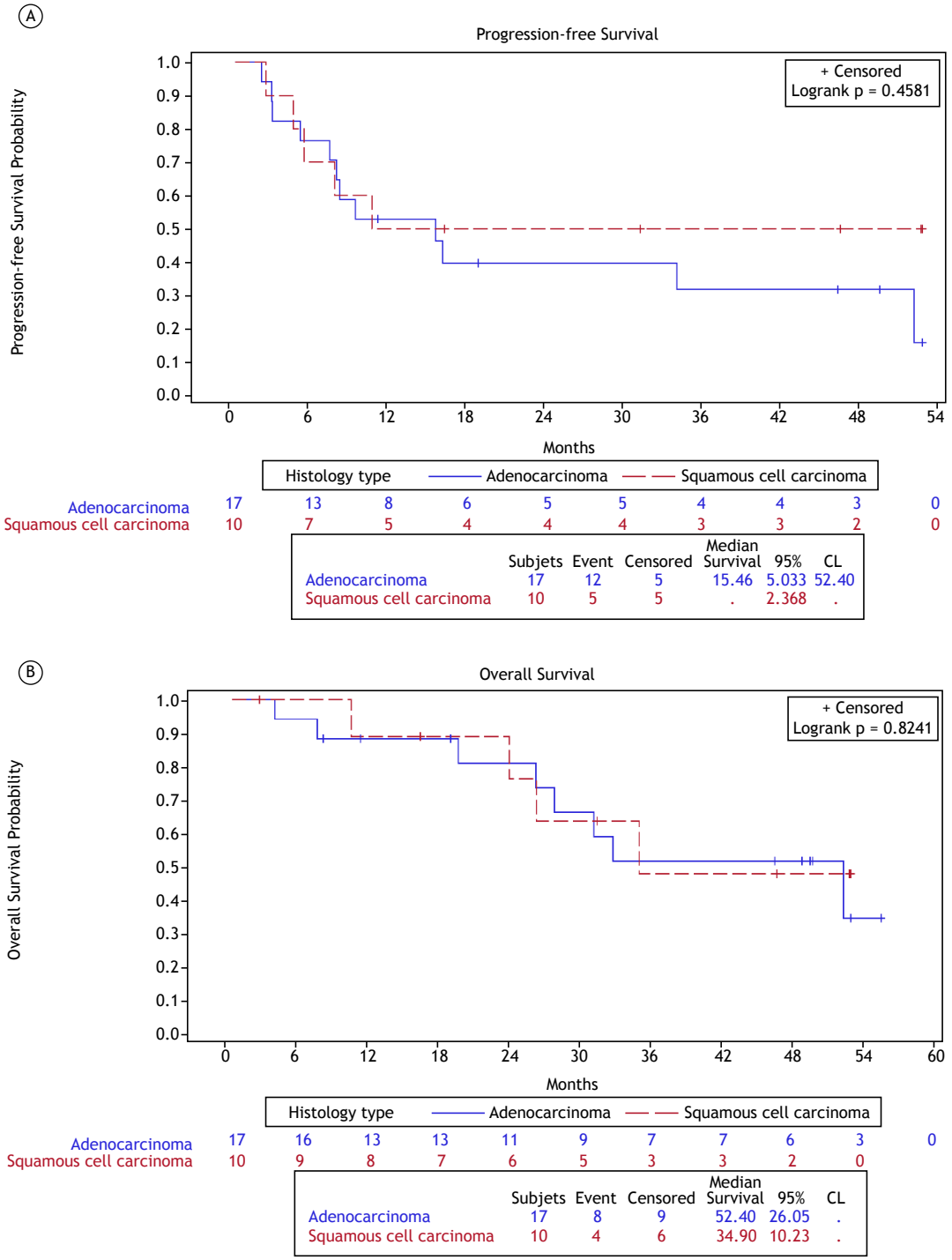

Figure 2. Progression-free survival (A) and overall survival (B) by histological subtype from the start date of durvalumab therapy. CL: confidence interval.

studies involving immune checkpoint inhibitors. One patient had grade 3 pneumonitis, and no cases of grade 4 or 5 were reported.

Among the patients whose disease progressed, the most affected sites were distant lymph nodes (27.8%), brain (11.1%), bone (11.1%), adrenal glands (11.1%), lungs (5.6%), mediastinum (5.6%), and pleura/pericardium (5.6%). The frequency of CNS implants during the study period was 12.9%. Among these patients, half experienced neurological symptoms related to their disease.

Approximately 70% of the 31 patients with disease progression underwent subsequent systemic therapy. Among these 12 patients, a total of 41.7% received

Table 2. Treatment-related adverse events during consolidation therapy.

Adverse event	Total n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Cough	5 (16.1)	4 (12.9)	1 (3.2)	0 (0.0)
Pain	5 (16.1)	5 (16.1)	0 (0.0)	0 (0.0)
Pneumonitis	4 (12.9)	1 (3.2)	2 (6.4)	1 (3.2)
AST/ALT abnormality	4 (12.9)	4 (12.9)	0 (0.0)	0 (0.0)
Hypothyroidism	2 (6.4)	1 (3.2)	1 (3.2)	0 (0.0)
Dyslipidemia	2 (6.4)	2 (6.4)	0 (0.0)	0 (0.0)
Fatigue	2 (6.4)	2 (6.4)	0 (0.0)	0 (0.0)
Pruritus	2 (6.4)	2 (6.4)	0 (0.0)	0 (0.0)
Localized urticaria	2 (6.4)	1 (3.2)	1 (3.2)	0 (0.0)
Anemia	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)
Myalgia	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)
Pulmonary thrombosis	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)
Hypotension	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)
Nausea	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)
Reduced visual acuity	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)
Inappetence	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)
Upper airway obstruction	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)
Vomiting	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)

The percentages presented in this Table were calculated using the total number of patients (N=31) as the denominator.

Table 3. Immune-mediated adverse events during consolidation therapy.

Adverse event	Total n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Pneumonitis	4 (12.9)	1 (3.2)	2 (6.4)	1 (3.2)
Hypothyroidism	3 (9.7)	1 (3.2)	2 (6.4)	0 (0.0)
Pruritus	1 (3.2)	1 (3.2)	0 (0.0)	0 (0.0)

The percentages presented in this Table were calculated using the total number of patients (N=31) as the denominator.

at least one line of treatment, 33.3% received two lines, 16.7% received three lines, and 8.3% received four lines. Chemotherapy was the primary choice of systemic treatment (74.9%), while 16.7% of patients received Osimertinib, and 8.3% received Crizotinib. Additionally, 16.1% of the patients received palliative radiotherapy.

DISCUSSION

To the best of our knowledge, LACOG 0120 is the first study to provide real-world data on Brazilian patients who received durvalumab through an EAP. Conducted across seven Brazilian centers, this study analyzed the treatment outcomes of patients treated with the PACIFIC regimen. The median PFS was 9.9 months, lower than the results reported in the European (PACIFIC-R)[10] and Korean (PACIFIC-KR)[13] studies, with median PFS values of 21.7 and 25.9 months, respectively. The median PFS observed herein was also lower than the 5-year analysis of the PACIFIC trial, at 9.9 months compared to 16.9 months.[7]

The mean age of the patients in our study was approximately 65 years, similar to findings reported in other studies.[10,13] Former and current smokers accounted for roughly 80% of the patients, comparable to Western and Korean data, where smokers represented approximately 90% and 80%, respectively.[10,13] Adenocarcinoma was the predominant histology, except in the Korean population, which reported 52.2% of cases as squamous cell carcinoma.[14] Among the patients in LACOG 0120, 58.1% had stage IIIB or IIIC disease, reflecting a cohort with more advanced disease compared to the PACIFIC-R study.[10] In contrast, a German study included patients with stage IV disease.[11] In the present study, initial evaluations showed a higher usage of PET-CT and MRI, suggesting a growing preference for advanced imaging modalities during the initial staging and assessment of these patients.

The European population had a 2-year OS rate of 71.2%,[10] while the Korean population reported 71%.[14] In the PACIFIC study population, the 2-year OS rate was 63.3%, lower than the rates observed in real-world data analyses, including the Brazilian cohort, which had a 2-year OS rate of 72.6%.[7,10-13]

In real-world studies, high expression of PD-L1 was associated with better survival rates, and patients with mutated EGFR showed less benefit from consolidation ICI after CRT.[9-13] Our study had similar rates of

EGFR mutations and PD-L1 expression. Despite these similarities, the trial lacked the statistical power to detect differences between subgroups due to the small number of patients.

In these populations, chemotherapy regimens were mostly based on platinum, with a predominance of carboplatin use in the Brazilian population, which differed from the European and Korean populations, where cisplatin was predominantly used. There were no major differences in response rates or toxicity related to these variables.[10-14] The number of patients who completed the durvalumab consolidation regimen was similar across the samples. The European population received a higher number of durvalumab doses compared to the Brazilian study (22 vs. 17.9 doses).[10] In spite of the higher dose density in the PACIFIC-R population and its higher PFS, the 2-year survival rates were very similar when compared to LACOG 0120.[10] Some important limitations worth mentioning in evaluating our results include the limited sample size and the low rate of molecular assessments to evaluate somatic driver mutations.

Adverse events occurred in 61.3% of the patients in our study, with most being grade 1 or 2. Regarding immunotherapy-related pneumonitis, 4 cases (12.9%) were reported, with only 1 case classified as grade 3 (3.2%). Our study did not reveal any new safety signals, and when compared to the PACIFIC trial, it showed a lower rate of adverse events, including pneumonitis, and a lower rate of durvalumab discontinuation.[7,8]

Our study reported no new safety signals regarding immune-related AEs, even in the context of low-middle-income countries with limited resources for diagnosing and managing such events. In addition, our patients were treated within the public health system, which faces challenges in patient awareness and access, particularly regarding treatment-related complications. Systemic steroids were used in 16% of the patients, and no need for any other immunosuppressive agent was noted.

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AUTHOR CONTRIBUTIONS

All authors contributed substantially to the project, as defined by the International Committee of Medical Journal Editors (ICMJE), participating in the study design, data interpretation, article writing, critical review of intellectual content, and/or final approval of the version to be published. All authors have read and agreed to the published version of the manuscript. Their specific contributions are as follows: study conceptualization – M.Z., A.C.Z.G.; data curation – R.G.J., G.G.; formal analysis – R.G.J.; funding acquisition – M.Z., A.C.Z.G.; investigation – M.Z., A.C.Z.G., V.G., A.K.S., E.M., C.M., W.F.B., W.N.W.J., M.P., Y.B., R.Y., C.E.B.S.; methodology – M.Z., A.C.Z.G.; project administration – M.Z., A.C.Z.G., G.G.; resources – M.Z., A.C.Z.G.; software – R.G.J., G.G.; supervision – R.G.J., G.G.; validation – M.Z., A.C.Z.G., G.G.; visualization – R.G.J.; writing - original draft – M.Z., A.C.Z.G., G.G., R.G.J., L.J.R., C.A.M.; writing - review & editing – M.Z., V.G., A.K.S., E.M., C.M., W.F.B., W.N.W.J., M.P., Y.B., R.Y., C.E.B.S., L.J.R., C.A.M., R.G.J., G.G., A.C.Z.G.

DECLARATION OF INTERESTS

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The remaining authors declare no conflicts of interest.

DATA SHARING STATEMENT

The study protocol and data, including trial-level data (analysis datasets), as well as other information (*e.g.*, clinical study reports or analysis plans), are available upon request from the investigators. These clinical trial data can be requested by any qualified researcher engaged in rigorous, independent scientific research and will be provided following the review and approval of a research proposal, statistical analysis plan, and execution of a data-sharing agreement. Data requests can be submitted to the corresponding author at any time after the acceptance of this manuscript for publication.

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ORIGINAL ARTICLE

Expert perspectives on tuberculosis screening procedures for migrants

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ABSTRACT

Objective: To evaluate the perspectives of tuberculosis experts from different countries regarding national screening procedures. **Methods:** This was a qualitative descriptive study. Data were collected by using electronic, anonymized surveys with experts in tuberculosis in seven different countries within two World Health Organization regions (Europe and Africa). Thematic analysis was employed. **Results:** The survey results indicate that there are varied perceptions of and experiences with national guidelines on screening for and treatment of tuberculosis (especially in the population tested), the appropriate timing of screening, types of tests, best practices, barriers, and limitations of the screening. The participants highlighted the importance of integrating health care services into the community to achieve people-centered health care. The study also sheds light on the importance of involving trained nurses and social workers in the screening process and of networks to ensure continuity of care. **Conclusions:** The overall perceptions of the respondents underscore the importance of standardized screening guidelines. The ongoing collaboration between public health services, the private sector, and the community is essential to reduce tuberculosis transmission, as well as to provide substantial public health and economic benefits.

Keywords: Europe; Communicable diseases; Transients and migrants; Public health; Tuberculosis.

INTRODUCTION

Tuberculosis continues to be the leading cause of death from a single infectious disease agent among adults worldwide.[1] In 2022, tuberculosis was responsible for 1.3 million deaths and accounted for a mean of 1.85% (range, 1.69-2.05%) of disability-adjusted life-years (DALYs) worldwide across all causes of disease, regardless of age and sex. In 2021, in the World Health Organization (WHO) European region, tuberculosis accounted for a mean of 0.16% (range, 0.15-0.17%) of the total deaths and a mean of 0.2% (range, 0.18-0.2%) of DALYs worldwide.[2] Controlling tuberculosis in the migrant community is highly complex because the extraordinary magnitude of migration patterns has created significant obstacles to the local control of infectious diseases.[3] Migration has increased worldwide, with a particularly marked impact in European countries, and is one of the most pressing public health challenges of our time.[4-6] Migrants account for 5.1% of the population of Europe, which now includes an estimated 23 million people from non-European Union countries.[7] In several European countries, migrants account for the majority of patients with tuberculosis. Evidence from the WHO and European Centre for Disease Prevention and Control (ECDC) supports screening all migrants for active tuberculosis with chest X-rays and screening immigrants from high tuberculosis-burden countries for latent tuberculosis infection (LTBI) by using tuberculin skin tests (TSTs) or interferon-gamma release assays (IGRAs).[8-11] Differences in screening protocols across Europe underscore the need for standardized practices. The aim of this study was to review screening guidelines, gathering insights on national protocols from tuberculosis experts in various countries, to develop recommendations for a Delphi consensus statement on harmonizing tuberculosis screening practices.

METHODS

This study used qualitative methods, including an online survey with open and closed questions, targeting experts from seven countries in the WHO regions of Europe and Africa. The experts, all of whom were individuals responsible for tuberculosis patient care or national guideline influence, included clinicians, public health professionals, researchers, and industry members. The survey aimed to capture expert opinions on a broad range of subjects, in order to achieve theoretical saturation. Distributed via Microsoft Forms, the survey was emailed to experts through the International Union Against Tuberculosis and Lung Disease (IUATLD), a global technical and scientific organization.

The survey questions covered participant demographics (sex, age, and level of education), geographic region, country of practice, sector of activity, years of experience

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in the area of tuberculosis, involvement with tuberculosis in migrants, direct patient contact, and the annual number of tuberculosis cases managed. Other questions elicited the perspective of the experts on the following topics: at what point screening for latent and active tuberculosis should occur; who is responsible for identifying the cases that should undergo tuberculosis screening; what tests should be recommended for screening for latent and active tuberculosis; what kind of support migrants with latent and active tuberculosis should receive in terms of treatment, continuity of care, and follow-up; the recommended practices for tuberculosis screening in migrant populations; and the barriers to, limitations of, and potential harms in screening for tuberculosis in the migrant population. The IUATLD secretariat invited members via email, and participants consented, with identifying data accessible only to the research team. The data were collected between March and May of 2024 and were exported to an Excel spreadsheet. Employing an inductive approach, we developed a thematic analysis framework to categorize themes, subthemes, and emerging categories from participant answers to the open-ended answers. The thematic analysis was manually conducted using a Word document according to the protocol devised by Braun and Clarke.[12] The lead investigator conducted the initial coding and discussed it with the rest of the team, subsequently making adjustments. To guarantee trustworthiness, we followed the thematic analysis phases proposed by Nowell et al.[13]:

1. "Becoming familiar with the data"—thoroughly reading and re-reading all statements, taking notes on possible themes, and organizing the data in a table format using a word processor
2. "Creating initial codes"—utilizing a codebook specially developed for this study
3. "Identifying themes"—ensuring, in an inductive (bottom-up) manner, that the themes were closely tied to the native language of the participant (This data-driven approach involved coding the data without forcing it into a pre-existing coding framework.)
4. "Reviewing themes"—one researcher conducting the initial coding and another reviewing and refining the codes related to the identified themes, until a consensus is achieved
5. "Defining and naming themes"—designating the themes in the most self-explanatory way possible
6. "Writing the report"—reviewing and validating the themes for additional member checking and production of the final codes and themes. The selected quotes were translated hermeneutically to enhance clarity without changing their meaning.

The study was approved by the Ethics Committee of the University of Porto Institute of Public Health, in the city of Porto, Portugal (Reference no. CE24260). All stages of the study were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Study documents were securely stored and encrypted with password protection.

RESULTS

The study participants (respondents) comprised eleven experts, most (72.7%) of whom were men, with a mean age of 55.9 ± 9.4 years and a mean number of years of experience in the area of tuberculosis of 27.5 ± 9.7. Nearly all (90.9%) had experience with migrant populations. Among those directly treating patients (n = 5), the mean annual number of tuberculosis cases managed was 160 ± 116. Over half (54.5%) of the eleven respondents had tuberculosis screening experience. The respondents were working in a total of seven countries: the United Kingdom (n = 4); Netherlands (n = 2); Germany (n = 1); Finland (n = 1); Switzerland (n = 1); Italy (n = 1); and New Zealand (n = 1). The overall characteristics of the experts are shown in Table 1.

The majority (63.6%) of the experts agreed that immigrants should be screened for tuberculosis upon entry into the host country, whereas 27.2% were of the opinion that screening should occur before entry and 27.2% were of the opinion that it should occur after entry. According to 54.5% of the experts, in their countries, public health services are

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

Variable	(N = 11)
Sex	
Male	8 (72.7)
Female	3 (27.3)
Age (years), mean ± SD	55.9 ± 9.4
Highest academic degree	
Doctorate	7 (63.6)
Bachelor's	2 (18.2)
High school diploma or equivalent	1 (9.1)
Other	1 (9.1)
Years of experience in tuberculosis, mean ± SD	27.5 ± 9.7
Annual number of cases managed,[b] mean ± SD	160 ± 116
Country of practice	
United Kingdom	4 (36.3)
Netherlands	2 (18.2)
Finland	1 (9.1)
Germany	1 (9.1)
Switzerland	1 (9.1)
Italy	1 (9.1)
New Zealand	1 (9.1)
World Health Organization region	
Europe	9 (81.8)
Africa	2 (18.2)
Primary area of activity	
Academia	5 (45.4)
Public sector	4 (36.3)
Civil society	1 (9.1)
Other	1 (9.1)

[a]Values expressed as n (%), except where otherwise indicated. [b]Only seven (63.6%) of the respondents had direct contact with tuberculosis patients in their daily practice.

primarily responsible for identifying cases that should undergo tuberculosis screening. Three respondents (27.2%) reported that screening occurs at migration centers, and two (18.3%) reported that it occurs at primary care facilities. According to the experts, the main tests recommended for screening (for active tuberculosis and for LTBI) were as follows (proportion of respondents): X-ray (90.9%); IGRA (64.0%); symptom questionnaire (36.0%); QuantiFERON-TB Gold In-Tube assay (18.2%); TST (18.0%); and molecular testing (9.1%). The perceptions of the experts regarding screening are presented in Table 2.

The analysis of the open-ended questions identified three main themes: 1) perceptions of the support that migrants should receive; 2) perceptions about recommended practices; and 3) perceptions about barriers to, limitations of, and potential harms of screening. Respondent ages are reported as their ages at the time of their participation in the study. Table 3 displays the themes, subthemes, and categories derived from the thematic analysis. Below, we give an account of participant descriptions of the emerging themes.

Perceptions of the support that migrants should receive

Concerning the perception of the experts regarding the support and specifically the treatment that migrants with latent or active disease should receive, almost half (45.4%) of the participants pointed out the need for access to free tuberculosis health care services and free treatment for active tuberculosis and LTBI.

> *"Tuberculosis treatment (and preventive therapy) should be completely free of charge for the person (which is not the case in Germany)."*
>
> *– Male, 57 years*

The involvement of the community was mentioned several times throughout the participant responses and was considered the key element in coordinating with the health services.

Table 2. Perceptions of experts (N = 11) regarding screening migrants for tuberculosis.

Variable	n (%)
Timing	
Upon entry	7 (63.6)
Pre-entry	3 (27.2)
Post-entry	3 (27.2)
Authority responsible	
Public health	6 (54.5)
Migration services	3 (27.2)
Primary care	2 (18.3)
Tests	
X-ray	10 (90.9)
Interferon-gamma release assay	7 (64.0)
Symptoms questionnaire	4 (36.0)
QuantiFERON-TB Gold In-Tube assay	2 (18.2)
Molecular testing	1 (9.1)

> *"Migrants require an invitation to acquire a new approach to accessing health care and make optimal use of community service in the new country. Screening activities lend themselves to engagement in health care processes and developing partnership behaviors in health care. Therefore, in this setting, I would recommend providing a 'community' for the treatment to be administered/monitored—a local pharmacy, clinic, and dedicated general practitioner—focusing on offering more than drug therapy, making this a place of engagement in re-orientating health-related behaviors and literacy."*
>
> *– Male, 54 years*

Social support was also identified as fundamental during the continuity of care. The respondents consistently highlighted the importance of offering screening as part of a health care package, rather than as a stand-alone procedure, offering social support, including accommodation and food in close support tailored to the needs of the individual.

> *"[. . .] stable accommodation, benefits, and food for the duration of tuberculosis treatment . . ."*
>
> *– Male, 57 years*

The participants also pointed out that person-centered care, health education, and literacy are essential for continuity of care. Another important element considered important by the participants for the screening of tuberculosis in migrants was the use of video-observed therapy or directly observed therapy. Participants consistently emphasized the need for physicians, nurses, and social workers to play an active role during the screening procedures.

> *"[. . .] video-observed therapy or directly observed therapy, social support if needed . . ."*
>
> *– Female, 57 years*

Regarding follow-up, the participants also highlighted the need for continuous care. According to the experts, the exact follow-up time depends on clinical conditions. In contrast, some experts suggested that the follow-up should occur during the period of treatment completion; one of the participants suggested a follow-up period of 12 months after completion of treatment for drug-resistant tuberculosis and 2 years in the case of preventive treatment refusal.

> *"Free treatment and follow-up to completion of treatment (12 months after completion of treatment for drug-resistant tuberculosis); if preventive treatment declined, follow-up for 2 years . . ."*
>
> *– Male, 67 years*

From the evaluation of the participant's perspectives, there is a consensus that the screening of tuberculosis should exclude active tuberculosis, especially from high endemic countries of tuberculosis.

> *"All migrants from tuberculosis-endemic countries should be screened as per local or ECDC recommendations."*
>
> *– Male, 45 years*

Table 3. Themes, subthemes, and categories derived from a thematic analysis of the survey responses.

Theme	Sub-theme	Category	Definition	Sample expert quotations
Perceptions about support that migrants with latent tuberculosis and active tuberculosis should receive	Treatment	Procedure	This theme aims to describe participant understanding of the support that migrants should receive during the screening procedure, in which the national system of the host country is involved, and the coordination of that system with other services.	"Tuberculosis treatment (and preventive therapy) should be completely free of charge for the person (which is not the case in Germany)." - male, 57 years
	Continuity of care	Support	This theme aims to describe participant understanding of the continuity of care that migrants should receive during the screening procedure, in which the national system of the host country is involved, and the coordination of that system with other services.	"Offer tuberculosis screening as part of a health care package, rather than a stand-alone process, with screening and support for other conditions." - male, 57 years
	Follow-up	Prevention	This theme aims to describe participant understanding of the follow-up that migrants should undergo during the screening procedure, in which the national system of the host country is involved, and the coordination of that system with other services.	"Free treatment and follow-up to completion of treatment (12 months after completion of treatment for drug-resistant tuberculosis); If preventive treatment declined, follow-up for 2 years . . ." - male 67 years
Perceptions about recommended screening practices	Perceptions about the usefulness of protocols	Procedures	This theme aims to describe participant knowledge about national and international screening protocols.	"Current practices are not based on the recent literature in all countries. The practices inside countries might also vary. It would be very useful to have common renewed guidelines for European low incidence countries or probably also other European Union countries would be beneficial. The same recommendations are not suitable for every country in the world." - female, 57 years
	Insights about the protocol used	Procedures	This theme aims to describe participant priorities regarding and comprehension of their local screening protocols.	"Detecting active tuberculosis among people coming from highly endemic countries [. . .] But for the elimination of tuberculosis, all migrants need to be screened for tuberculosis infection afterwards as well." - male, 48 years
Perceptions about barriers to screening	Potential harms	Stigma and discrimination	This theme aims to describe participant understanding of the potential harms of screening.	"Stigma, concerns that they may be deported once they access care . . ." - male, 45 years
	Barriers	Accessibility	This theme aims to describe participant knowledge about the main barriers of screening	"[. . .] direct and indirect costs of access to care." - male, 45 years
		Accessibility		"Poor documentation and mapping of migrant population". - male, 38 years
		Accessibility		"[. . .] no understanding of the local language and practices; direct and indirect costs of access to care; lack of trust in health care providers." - male, 45 years
		Health literacy		"Migrants from tuberculosis-endemic nations frequently lack an understanding of latent tuberculosis infection conceptually, and it is time-consuming to incorporate this educational element into the process". - female, 54 years
		Policy		"In Germany, there is as yet no comprehensive strategy to combat tuberculosis; quite low tuberculosis competence generally at public health care facilities, clinics, hospitals, and general practitioner offices [. . .] and money, the problem seems too small for most politicians." - male, 57 years

The participants perceive that screening for infection is also crucial to eliminating tuberculosis.

> *"Detecting active tuberculosis among people coming from highly endemic countries [. . .] But for the elimination of tuberculosis, all migrants need to be screened for tuberculosis infection afterwards as well."*
>
> *– Male, 48 years*

Some respondents emphasized that screening protocols should take into consideration the characteristics of the target population and the duration of their stay in the host country.

> *"It depends on the type of migrant and the reason to migrate: symptom screening among refugees under humanitarian emergency; chest X-ray and other examinations . . ."*
>
> *– Male, 69 years*

For instance, for short stays by individuals from tuberculosis-endemic countries, including students, temporary workers, and visitors, the screening should cover active tuberculosis using X-ray and sputum smear microscopy. Screening for active tuberculosis should be performed for all individuals who will have an extended stay (≥ 6 months). In addition, the use of an IGRA for detecting LTBI should be considered for individuals under 55 years of age.

> *"I would add that transient populations (students, temporary workers, and visitors) from endemic nations require screening of at least active pulmonary tuberculosis by chest X-ray and sputum algorithm for any abnormalities. Entrants planning a longer stay (≥ 6 months) should be screened for active tuberculosis, and individuals under 55 years of age require screening for LTBI by X-ray of the chest, IGRA, and QuantiFERON."*
>
> *– Female, 54 years*

Entry screening practices for migrants vary by country and often include multiple stages and methods. The approaches range from mandatory screenings for active tuberculosis upon arrival to follow-up screenings for LTBI, especially for individuals from high-incidence regions or those staying for longer periods. This comprehensive approach aims to identify and manage tuberculosis infections early, thereby preventing the spread of the disease.

> *"In my country, the entry screening for migrants who are coming from highly endemic countries and plan to stay in the Netherlands for > 3 months are mandatorily screened for tuberculosis. Other persons are screened with an X-ray at entry and follow-up screening for 2 years (not mandatory). We plan to replace these follow-up screenings with a tuberculosis infection screening shortly after entry (the first X-ray)."*
>
> *– Female, 59 years*
>
> *"Adult migrants from high- and middle-incidence countries in collective housing settings or mass accommodation should undergo X-ray screening before moving in; adult working migrants from high-incidence countries in vulnerable professional settings (e.g. hospitals, nursing homes, and kindergartens) should also undergo X-ray screening, as well as being offered LTBI screening and preventive therapy, if necessary. All adult migrants from high-incidence countries (> 100/150 cases/100,000 population?) or with a history of contact with tuberculosis should be offered LTBI screening and preventive therapy at immigration or soon thereafter. All children from middle- or high-incidence countries or who are close contacts of adults with a history of tuberculosis should undergo LTBI screening and receive preventive therapy if needed."*
>
> *– Male, 58 years*

One respondent considered the detection of infection too expensive to be performed *en masse*. Screening for active tuberculosis can be performed by using the symptoms questionnaire known as the MM-CHECK, which is available in 33 languages.[14] Another respondent made the observation that the guidelines for migrant screening varied across European countries and were not based on the most recent literature. That respondent proposed the establishment of uniform guidelines for use throughout Europe.

> *"Current practices are not based on the recent literature in all countries. The practices inside countries might also vary. Having common renewed guidelines for low-incidence European countries or probably other European Union countries would be beneficial. The same recommendations are not suitable for every country in the world."*
>
> *– Female, 57 years*

Most participants pointed out that stigma is one of the most critical barriers to screening. Some respondents also identified discrimination and the fear of deportation as barriers.

> *"Stigma, concerns that they may be deported once they access care . . ."*
>
> *– Male, 45 years*
>
> *"Stigma is a huge factor. The screening process appears to imply 'contagiousness' or considering the migrant 'lesser' or possessing "otherness" which is not aided by the physical premises of the screening activities frequently being poorly resourced, crowded, and often difficult to access."*
>
> *– Female, 54 years*

The participants also noted that migrants are a particular population with different needs. They are highly mobile, sometimes without documentation, and hard to reach, which limits their identification and can have a negative impact on screening coverage.

> *"Poor documentation and mapping of the migrant population . . ."*
>
> *– Male, 38 years*

Other potential barriers to screening identified by the respondents included misconceptions and lack of health literacy regarding active tuberculosis and infection.

> *"Migrants from tuberculosis-endemic nations frequently lack understanding of LTBI conceptually, and it is time-consuming to incorporate this educational element into the process."*
>
> *– Female, 54 years*

Language and cultural barriers were reported to restrict access to health care. The experts also pointed out that the direct and indirect costs associated with migrants are significant barriers to tuberculosis screening. In addition, the costs associated with the screening in the health care provider perspective , as well as low numbers of and a lack of training of health care professionals, were identified as potential barriers to or limitations of tuberculosis screening. Two respondents mentioned the lack of an appropriate test for the diagnosis of infection, which increases the risk of overtreatment and of a higher number needed to treat, with the same risk of adverse effects from the medication.

> *"Since the screening and diagnostic tests for LTBI are the same test, not including expert or good clinical assessment could risk overtreatment."*
>
> *– Female, 54 years*

Policy barriers were also identified by one participant who considered that tuberculosis in migrants is not a priority of the politicians in his country.

> *"In Germany, there is as yet no comprehensive strategy to combat tuberculosis; quite low tuberculosis competence generally at public health care facilities, clinics, hospitals, and general practitioner offices [. . .] and money, the problem seems too small for most politicians."*
>
> *– Male, 57 years*

Table 4 illustrates the public health implications of the data derived from our thematic analysis.

DISCUSSION

This study sought insights from tuberculosis experts on screening practices, revealing consensus on the lack of standardized guidelines and the benefits of harmonization. Experts agreed on the need for screening throughout the migrant journey, not just at the destination, and emphasized cross-country networks for continuity of care. Integrating community health services and involving social workers and trained nurses was highlighted as key to delivering people-centered care. Some low-incidence European countries now follow WHO and ECDC guidelines, screening high-risk migrants with chest X-rays for active tuberculosis and with TST or IGRA for LTBI. Although screening benefits public health by detecting cases of tuberculosis early, challenges remain in defining target populations, cost-effectiveness, and optimal test timing, as well as in addressing cultural and training barriers.[14-18] As a result, screening procedures and best practices for detecting active tuberculosis and LTBI vary significantly across European countries. An essential strength of this qualitative study lies in its pioneering approach to current recommendations and perspectives of experts in tuberculosis from different countries regarding screening for LTBI and active tuberculosis. To our knowledge, this is the first study to provide a comprehensive overview of perspectives and recommendations on screening for tuberculosis. Including the perspectives of eleven experts who report on national recommendations, best practices, barriers to, and facilitators of screening enhances the utility of our findings. This qualitative study, involving experts in multiple countries, expands current evidence on tuberculosis screening. Respondents agreed that screening should occur throughout the migration process, not only at the destination, and that national networks are essential for continuity of care. They also unanimously emphasized the importance of providing free tuberculosis treatment for LTBI and active tuberculosis, together with access to primary care and health assessments to improve screening effectiveness. This study has limitations, including overrepresentation of the United Kingdom, a lack of representation of all WHO European Region countries and of low- and middle-income countries, a small sample size, and limited insights from migrants themselves, which restricts generalization and depth. Despite these limitations, the study offers unique strengths: it is, to our knowledge, the first to include a diverse range of tuberculosis experts across roles and countries; it used anonymized interviews for systematic data collection; and it provides a detailed dataset by including participant demographics and various aspects of tuberculosis screening. Considering all the limitations, barriers, and challenges highlighted by the participants, we proposed general and urgent strategies to increase the effectiveness of tuberculosis screening. Effective tuberculosis screening for migrants is facilitated by a network of primary care, public health, and hospitals, with community and social services integration playing key roles. Free access to screening, trained general practitioners, nursing staff, and social workers are priorities. Health literacy and promotion are essential, as are improving communication and considering the legal status and length of stay of migrants. Accurate testing and adapting to the diverse needs of migrants, together with clear, standardized guidelines, improve screening. Addressing resource constraints and ensuring long-term follow-up for LTBI are vital for better outcomes and harmonized procedures.

This study provides new insights into tuberculosis screening and treatment across different countries, particularly within the WHO European Region, and offers valuable guidance for developing harmonized guidelines for tuberculosis screening among migrants.

Table 4. Public health implications derived from the thematic analysis.

Aspect	Key findings	Public health approach suggestion
Support for migrants	Nearly half of the participants (45.4%) emphasized the need for free access to tuberculosis health care services and treatment, for active and latent tuberculosis.	Implement policies for free access to tuberculosis health care services and treatment for all migrants, for active and latent tuberculosis.
Community involvement	The involvement of the community is crucial in supporting migrants with tuberculosis. It enhances engagement in health care processes and helps develop health-related behaviors and literacy.	Develop community-based health programs to engage migrants, leveraging local resources like pharmacies, clinics, and community centers.
Social support	Social support, including accommodation and food, is fundamental during the continuity of care. Tuberculosis screening should be part of a comprehensive health care package that includes social support tailored to the needs of the individual.	Integrate social support services, such as housing and food assistance, into tuberculosis care programs for migrants.
Person-centered care	Essential elements for continuity of care include person-centered approaches, health education, and literacy.	Focus on person-centered care models that include comprehensive health education and literacy programs tailored to the needs of migrants.
Use of technology	The use of VOT or DOT is important for ensuring adherence to treatment and follow-up.	Utilize VOT or DOT to monitor and support treatment adherence among migrants with tuberculosis, ensuring continuous and effective care.
Continuous follow-up	Continued care is necessary, with follow-up duration dependent on clinical conditions. Some experts suggest follow-up during the treatment period, while others recommend up to 12 months post-treatment for drug-resistant tuberculosis or 2 years in the case of preventive treatment refusal.	Establish follow-up protocols based on clinical conditions, including extended follow-up periods for drug-resistant tuberculosis and cases of preventive treatment refusal.
Screening practices	There is a consensus that tuberculosis screening should exclude active tuberculosis, especially in migrants from highly endemic countries. The screening should be adapted to the migrant characteristics and duration of stay. Short-term visitors from endemic areas should be screened for active tuberculosis using X-ray and sputum tests, whereas long-term entrants should also be screened for LTBI using an IGRA and QuantiFERON-TB Gold In-Tube assay.	Implement adaptive screening protocols based on the migrant's stay duration and origin, utilizing X-ray, sputum tests, and IGRA for comprehensive tuberculosis detection.
Variability in practices	Screening practices vary by country, often including mandatory screening for active tuberculosis upon arrival and follow-up screenings for LTBI for long-term visitors. Some participants called for uniform guidelines across Europe to standardize practices.	Develop and adopt standardized tuberculosis screening guidelines across European countries to ensure consistent and effective screening practices.
Barriers and limitations	Stigma, discrimination, fear of deportation, and lack of understanding of tuberculosis were identified as major barriers. Other barriers include language and cultural differences, lack of documentation, high mobility of migrants, and costs associated with screening and treatment.	Implement culturally sensitive and accessible tuberculosis screening programs that address stigma, discrimination, and fear, providing support for undocumented and mobile populations.
Resource constraints	Participants highlighted the lack of training among health care professionals and inadequate resources for screening activities. There is also a concern about the lack of appropriate tests for LTBI diagnosis, leading to potential overtreatment and adverse effects.	Increase training for health care professionals in tuberculosis care and invest in resources for screening activities. Develop better diagnostic tools for LTBI to avoid overtreatment and manage adverse effects.
Policy and political will	Policy barriers exist, with some participants noting that tuberculosis in migrants is not prioritized by politicians in their countries. A comprehensive strategy and greater tuberculosis competence in public health services are needed.	Advocate for comprehensive national and international tuberculosis strategies that prioritize migrant health, supported by political commitment and sufficient funding.

VOT: video-observed therapy; DOT: directly observed therapy; IGRA: interferon-gamma release assay; and LTBI: latent tuberculosis infection.

▲ Voltar ao sumário

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AUTHOR CONTRIBUTIONS

MP, AA, and RD designed the study. MP collected the data. MP analyzed and interpreted the data and statistics. MP, DNM, AA, and RD interpreted the results and wrote the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Perceptions and experiences of directly observed treatment in tuberculosis: insights from a mixed-methods cross-sectional study

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ABSTRACT

Objective: The demanding nature and psychosocial burdens of directly observed treatment (DOT) have opened a path to alternative strategies such as video-observed therapy (VOT), which offers comparable treatment outcomes and patient satisfaction while potentially saving time and reducing costs. The objective of this study was to evaluate the perceptions and experiences of patients and health care professionals regarding DOT and other treatment strategies implemented in Portugal. **Methods:** Patients with a confirmed diagnosis of tuberculosis, treated at the Vila Nova de Gaia Outpatient Tuberculosis Centre in the last two years, were asked to complete a brief questionnaire, as were health care professionals working in the northern region of Portugal. Differences were analysed with chi-square tests, complemented by thematic analysis. **Results:** A total of 62 individuals completed the questionnaire: 29 health care professionals and 33 patients. There were significant differences between the two groups in their views regarding the impact of DOT on treatment outcomes, with health care professionals perceiving a higher degree of negative effects and patients expressing greater satisfaction. Long travel distances, transportation issues and high costs were some of the challenges mentioned by the patients. Significant differences were also found regarding the role DOT plays in ensuring treatment adherence, with patients emphasising personal responsibility and its importance in preventing loss to follow-up and strengthening relationships with health care professionals. Dose dispensing was favoured for its convenience in specific situations, and VOT was generally preferred to reduce constant travelling. Both parties raised some concerns. **Conclusions:** Existing discrepancies suggest a misalignment between patient experiences and health care provider perceptions, underscoring the need for enhanced communication and a more nuanced understanding of patient perspectives when designing and implementing different tuberculosis treatment adherence strategies.

Keywords: Treatment adherence and compliance; Directly observed therapy; Patient satisfaction; Tuberculosis.

INTRODUCTION

Tuberculosis continues to be a major global health issue, being the second leading cause of death from an infectious agent after COVID-19.[1] Although the global incidence of tuberculosis is declining, it remains high in several countries, including Portugal, which, for 2022, reported one of the highest rates in the European Union and European Economic Area, at 14.6 cases per 100,000 population.[2]

Tuberculosis treatment involves multiple drugs taken over several months, depending on the type and extent of the disease, making it demanding because of its duration, drug load and possible adverse effects.[3,4] Directly observed therapy (DOT), recommended by many organisations,[5] ensures that patients take medication under supervision, helping to complete the treatment, detect adverse events early and encourage adherence.[6-8] However, evidence on the effectiveness of DOT is mixed, some studies showing that it can hinder adherence,[6] as well as requiring substantial clinical, human and financial resources (75% of tuberculosis treatment costs are linked to DOT).[6,8,9] It also imposes a psychosocial burden on patients, who face daily trips to health care facilities, affecting their privacy, work life and transportation expenses, as well as increasing the stigma associated with tuberculosis, even after it has been cured.[10,11] Alternatives to DOT are gaining traction. Although self-administered therapy (SAT) is not widely accepted, video-observed therapy (VOT) is emerging as a viable option because of advances in video technology,[12] allowing remote monitoring of medication intake and adverse events.[13] Studies show VOT achieves similar

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treatment outcomes and improves patient satisfaction while saving time and reducing costs, leading the US Centers for Disease Control to recommend it as an alternative to in-person DOT.[13] The aim of the present study was to evaluate the perspectives of patients and of health care professionals (HCPs) on DOT and other solutions for taking medication, such as VOT or SAT with dispensing doses.

METHODS

This was a cross-sectional study conducted in the northern region of Portugal. Our study population was composed of two subgroups of adults (individuals ≥ 18 years of age): HCPs currently working with tuberculosis in this region and patients with a confirmed diagnosis of tuberculosis who were treated at the Vila Nova de Gaia Outpatient Tuberculosis Centre in the last two years. Individuals who could not understand or complete the questionnaire were excluded.

Two different mechanisms were used for participant recruitment. The HCPs were contacted through the mailing lists of specialized services, and the questionnaire was forwarded for data collection. Patients were recruited during routine clinical appointments and were invited to provide their responses to the same questionnaire.

The questionnaire included open and closed questions to capture participant opinions and experiences based on common hindrances reported in the literature and by senior HCPs. It comprised 17 questions: some on the impact that DOT has on quality of life and some regarding views on VOT and SAT. The same questionnaire was used for both groups, with minor adjustments to personal pronouns. Google Forms was used for dissemination. Ethical approval was obtained from the Northern Regional Health Administration Ethics Committee (Reference no. CCS/2023/694), and informed consent was obtained from all participants.

Frequencies for each variable were tested using chi-square tests for independence to assess differences in perceptions between HCPs and patients. When more than 20% of the cells had expected frequencies below 5, Fisher's exact test was conducted for 2 × 2 contingency tables,[14] whereas the Fisher-Freeman-Halton test was applied for larger contingency tables.[15] Statistical computations were performed with IBM SPSS Statistics software package, version 27.0 (IBM Corporation, Armonk, NY, USA). Two-tailed significance is assumed for $p < 0.05$. Qualitative data were analysed through thematic analysis.[16] After familiarisation with the material, initial codes were developed and collated into potential themes. Once themes were identified, they were reviewed and refined to accurately reflect the data collected before the analysis proceeded.

RESULTS

From September 2023 to January 2024, sixty-two valid questionnaires were completed. Twenty-nine were completed by HCPs, and thirty-three were completed by patients. Table 1 summarises the sociodemographic statistics for both subgroups.

Perceived impacts of in-person DOT

As shown in Table 2, statistical variation was found between HCPs and patients in terms of their perceptions of the negative impacts of DOT on treatment satisfaction ($p < 0.001$), maintenance ($p < 0.001$) and completion ($p < 0.01$). Smaller proportions of the patients reported perceived negative impacts as it relates to treatment satisfaction, maintenance and completion (66.7%, 78.8% and 78.8%, respectively), whereas the HCPs demonstrated a tendency toward greater recognition of the negative impacts, as evidenced by the higher proportions of responses in the other categories. Some variation was also registered when assessing the positive effects of DOT on the same variables, i.e., treatment maintenance ($p < 0.05$), completion ($p < 0.05$) and satisfaction ($p < 0.01$), particularly in the last category, the patients reporting a higher degree of satisfaction than did the HCPs (76.7% vs. 41.3%).

Participants mentioned several reasons that or circumstances in which a patient would take the

Table 1. Participant sociodemographic characteristics, by subgroup.

Characteristic	Patients (n = 33) n (%)	HCPs (n = 29) n (%)
Gender		
Female	8 (24.2)	23 (79.3)
Male	25 (75.8)	6 (20.7)
Age group (years)		
25-34	6 (18.2)	6 (20.7)
35-44	4 (12.1)	8 (27.6)
45-54	11 (33.3)	10 (34.5)
55-64	4 (12.1)	4 (13.8)
65-74	5 (15.2)	1 (3.4)
≥ 75	3 (9.1)	0 (0)
Professional category	n/a.	
Physician		15 (51.7)
Nurse		14 (48.3)

HCPs: health care professionals.

Table 2. Participant perceptions of the impact of directly observed therapy, by subgroup.

Variable	Patients (n = 33) n (%)	HCPs (n = 29) n (%)	p*
Perceived usability of DOT			
Ensuring treatment adherence			0.047
Never	4 (12.1)	0 (0)	
Rarely	3 (9.1)	1 (3.4)	
Sometimes	0 (0)	0 (0)	
Often	4 (12.1)	10 (34.5)	
Always	22 (66.6)	18 (62.1)	
Early detection of adverse events			0.674
Never	4 (12.1)	1 (3.4)	
Rarely	1 (3.0)	2 (6.9)	
Sometimes	2 (6.1)	1 (3.4)	
Often	8 (24.2)	10 (34.5)	
Always	18 (54.6)	15 (51.7)	
Negative impact of DOT			
Daily life			0.426
Never	13 (39.4)	13 (44.8)	
Rarely	2 (6.1)	5 (17.2)	
Sometimes	8 (24.2)	6 (20.7)	
Often	5 (15.2)	4 (13.8)	
Always	5 (15.2)	1 (3.4)	
Family and social context			< 0.001
Never	19 (57.6)	3 (10.3)	
Rarely	2 (6.1)	4 (13.8)	
Sometimes	1 (3.0)	12 (41.4)	
Often	3 (9.1)	8 (27.6)	
Always	8 (24.2)	2 (6.9)	
Work/study context			0.025
Never	6 (18.2)	4 (13.8)	
Rarely	1 (3.0)	3 (10.3)	
Sometimes	2 (6.1)	9 (31.0)	
Often	0 (0)	9 (31.0)	
Always	4 (12.1)	4 (13.8)	
Does not work/study	19 (57.6)	-	
No response	1 (3.0)	-	
Activities of daily living			< 0.001
Never	16 (48.5)	3 (10.3)	
Rarely	4 (12.1)	5 (17.2)	
Sometimes	1 (3.0)	8 (27.6)	
Often	3 (9.1)	8 (27.6)	
Always	9 (27.3)	5 (17.2)	
Overall treatment results			0.068
Never	26 (78.8)	18 (62.1)	
Rarely	1 (3.0)	6 (20.7)	
Sometimes	4 (12.1)	4 (13.8)	
Often	0 (0)	1 (3.4)	
Always	2 (6.1)	0 (0)	
Treatment maintenance			< 0.001
Never	26 (78.8)	11 (37.9)	
Rarely	1 (3.0)	12 (41.4)	
Sometimes	4 (12.1)	5 (17.2)	
Often	0 (0)	1 (3.4)	
Always	2 (6.1)	0 (0)	
Treatment completion			0.002
Never	26 (78.8)	13 (44.8)	
Rarely	1 (3.0)	10 (34.5)	
Sometimes	4 (12.1)	5 (17.2)	
Often	0 (0)	1 (3.4)	
Always	2 (6.1)	0 (0)	
Treatment satisfaction			< 0.001
Never	22 (66.7)	5 (17.2)	
Rarely	2 (6.1)	8 (27.6)	
Sometimes	5 (15.2)	10 (34.5)	
Often	0 (0)	6 (20.7)	
Always	4 (12.1)	0 (0)	

Continue...▶

Table 2. Participant perceptions of the impact of directly observed therapy, by subgroup. (Continued...)

Variable	Patients (n = 33) n (%)	HCPs (n = 29) n (%)	p*
Positive impact of DOT			
Daily life			0.520
Never	7 (21.2)	2 (6.9)	
Rarely	3 (9.1)	3 (10.3)	
Sometimes	7 (21.2)	7 (24.1)	
Often	6 (18.2)	9 (31)	
Always	10 (30.3)	8 (27.6)	
Family and social context			0.007
Never	13 (39.4)	3 (10.3)	
Rarely	5 (15.2)	9 (31.0)	
Sometimes	4 (12.1)	8 (27.6)	
Often	1 (3.0)	5 (17.2)	
Always	10 (30.3)	4 (13.8)	
Work/study context			0.010
Never	8 (25.0)	5 (17.2)	
Rarely	0 (0)	12 (41.4)	
Sometimes	2 (6.3	5 (17.2)	
Often	1 (3.0)	3 (10.3)	
Always	3 (9.1)	4 (13.8)	
Does not work/study	18 (54.5)	-	
No response	1 (3.0)	-	
Activities of daily living			0.008
Never	14 (42.4)	3 (10.3)	
Rarely	4 (12.1)	13 (44.8)	
Sometimes	4 (12.1)	5 (17.2)	
Often	4 (12.1)	5 (17.2)	
Always	7 (21.2)	3 (10.3)	
Overall treatment results			0.022
Never	7 (21.2)	0 (0)	
Rarely	0 (0)	1 (3.4)	
Sometimes	1 (3.0)	2 (6.9)	
Often	5 (15.2)	9 (31.0)	
Always	19 (57.6)	17 (58.6)	
No response	1 (3.0)	-	
Treatment maintenance			0.033
Never	6 (18.2)	0 (0)	
Rarely	0 (0)	1 (3.4)	
Sometimes	2 (6.1)	3 (10.3)	
Often	5 (15.2)	10 (34.5)	
Always	20 (57.6)	15 (51.7)	
No response	1 (3.0)	-	
Treatment completion			0.010
Never	6 (18.2)	0 (0)	
Rarely	0 (0)	1 (3.4)	
Sometimes	1 (3.0)	3 (10.3)	
Often	4 (12.1)	10 (34.5)	
Always	22 (66.7)	15 (51.7)	
No response	1 (3.1)	-	
Treatment satisfaction			0.004
Never	6 (18.2)	1 (3.4)	
Rarely	1 (3.0)	5 (17.2)	
Sometimes	3 (9.1)	11 (37.9)	
Often	5 (15.2)	5 (17.2)	
Always	17 (51.5)	7 (24.1)	
No response	1 (3.0)	-	

HCPs: health care professionals; and DOT: directly observed therapy. *Fisher-Freeman-Halton test.

medication without the direct observation of an HCP, namely the closure of health care services "*on weekends and public holidays*", "*scheduled appointments at other institutions*" or "*being in hospital for cancer treatment (chemotherapy/radiotherapy) or other lengthy treatments*". Problems such as logistics and travel to the health care centre were also mentioned, with "*logistical constraints*", "*long distance from the outpatient tuberculosis centre*" and "*poor access to public transportation*" being the most common. Some

participants also referred to professional reasons for not using DOT, such as "*extended holiday periods*", "*starting work before the health care centres open*" and "*absence for work reasons*", most of them agreeing upon a defined period or context. Some HCPs also mentioned a "*lack of motivation*" on the part of some patients, possibly due to a "*lack of communication*" between the two parties.

A discrepancy was also noted within subgroups, with participants acknowledging positive and negative impacts for the same variables. Despite the existing differences in the positive impact on activities of daily living ($p < 0.01$), work/study context ($p < 0.05$) and family/social context ($p < 0.01$); some statistical variation was also found when participants considered the negative impact in the same fields, i.e., activities of daily living ($p < 0.001$), work/study context ($p < 0.05$) and family/social context ($p < 0.001$). Work-related constraints, namely "*I have to be present at work, and coming here causes difficulties*" and other socio-economic factors, such as transportation issues due to "*long distances to the centre*" or "*transport network issues*" and the fact that treatment-related "*expenses are challenging*", were some of the challenges faced by patients during DOT.

The proportion of participants who perceived DOT to have a negative impact in the social and family context was greater among the HCPs than among the patients (75.9% vs. 36.3%). When the focus was on the impact of DOT on activities of daily living, the patients mentioned a negative influence in a greater proportion than did the HCPs (39.4% vs. 13.3%). In contrast, more HCPs than patients viewed DOT as having a positive impact on activities of daily living (82.7% vs. 69.7%).

There was general agreement between HCPs and patients regarding the relationship between DOT usability and ensuring the early detection of adverse events during treatment. However, there was some disagreement regarding the effectiveness of DOT as a mechanism for ensuring adherence ($p < 0.05$), as fewer patients than HCPs registered a favourable perspective (21.2% vs. 3.4%), because patients understand that although DOT is assumed to provide a direct "*improvement of treatment adherence*", "*It doesn't make sense to make the nurse responsible for something that I should manage myself*", given the "*work overload of health care professionals*".

A few patients stated that without regular follow-up, "*people will end up giving up on treatment, especially as it's a long process.*" DOT "*provides confidence to health care professionals and to the patients themselves*". Most of the HCPs seem to perceive DOT as a positive strategy that provides "*a gain in health*", "*complete treatment adherence and monitoring of side effects*", "*better treatment adherence*" and "*better patient supervision, ensuring that the treatment strategy is followed correctly*".

Dose dispensing in SAT

Regarding the appropriateness of dispensing doses, patients and HCPs agreed that it can be appropriate (78.8% and 58.7%, respectively), for "*those who are responsible*", as they would still take their medication in the same way. It would be an excellent way to avoid "*mobilising so many human resources*" and "*travelling*", making it "*more convenient to take home*". If there is "*a family member responsible for support [. . .] dispensing doses is more useful* [than is DOT]". In regard to how SAT might work, some disagreements are noted ($p<0.05$), as most (54.9%) of the patients tend to think that dose dispensing could occur more than 4 times per week, whereas 35.8% of the HCPs think that it should occur 1-3 times per week, as this should not be considered routine but should only be used for "*justifiable reasons*", such as "*weekends and public holidays*" and when "*it is impossible to go to the health centre*". However, some HCPs stated that it can be appropriate "*to the extent that there is a balance between rigour and also reasonableness/flexibility*" due to "*dispensing doses being one of the facilitating measures for treatment adherence, based on a relationship of trust*."

No statistical variation was found between patients and HCPs when they were asked if they considered SAT to be more advantageous than DOT in any aspect (see Table 3). General agreement was attained as patients and HCPs, respectively, considered SAT to be more beneficial in terms of the family and social context (69.6% and 72.4%), work/study context (72.7% and 65.5%) and activities of daily living (71.4% and 62.1%), whereas they considered it less advantageous in terms of treatment outcomes, specifically maintenance (71.4% and 69.0%) and completion (60.0% and 79.3%).

Perceived suitability of VOT

More patients than HCPs (78.8% vs. 58.7%) perceived VOT to be more appropriate than DOT as an strategy for improving adherence to tuberculosis treatment ($p < 0.01$), as it "*could be useful to avoid travelling*" and "*much more comfortable*". In addition, there was a notable difference between the two subgroups in terms of the perception regarding the periodicity of VOT ($p < 0.05$), 55.6% of the patients favouring continuous monitoring through VOT over DOT, whereas HCPs suggested a more flexible or varied approach (Table 3). When considering the impact of VOT in major domains of life, patients and HCPs had similar perceptions of the benefits of VOT in the family and social context (69.2% and 86.2%, respectively) and in the work/study context (60.0% and 86.2%, respectively). However, more HCPs than patients (89.7% vs. 61.5%) felt that VOT is more advantageous than DOT in terms of the impact on activities of daily living ($p < 0.05$), especially for "*tech-savvy users who find it difficult (due to distance or daily routines) to travel to a health centre for DOT*" and with higher "*health literacy*", patients and HCPs both stating that VOT is "*much more comfortable*", precludes "*travelling to the outpatient centre*" and "*does not overburden the national health care system*". Regarding treatment outcomes, neither groups appeared to have a defined

Table 3. Participant perceptions of the impacts of self-administered therapy and video-observed therapy, by subgroup.

Variable	Patients (n = 33) n (%)	HCPs (n = 29) n (%)	p
To what degree is...?			
Dose dispensing/SAT			0.107*
Inadequate	5 (15.2)	5 (17.2)	
Slightly adequate	2 (6)	7 (24.1)	
Moderately adequate	5 (15.2)	4 (13.8)	
Very adequate	5 (15.2)	7 (24.1)	
Extremely Adequate	16 (48.4)	6 (20.8)	
VOT			0.010*
Inadequate	9 (27.3)	2 (7.0)	
Slightly adequate	2 (6.1)	4 (13.8)	
Moderately adequate	4 (12.1)	9 (31.0)	
Very adequate	4 (12.1)	9 (31.0)	
Extremely Adequate	14 (42.4)	5 (17.2)	
At what frequency should...occur?			
Dose dispensing/SAT			0.014*
Never	3 (9.1)	0 (0)	
1-3 times per week	11 (33.3)	17 (58.6)	
4-6 times per week	6 (18.2)	6 (20.7)	
Always	11 (33.3)	2 (6.9)	
No response	2 (6.1)	4 (13.8)	
VOT			0.036*
Never	4 (12.1)	0 (0)	
1-3 times per week	7 (21.2)	6 (20.7)	
4-6 times per week	1 (3.0)	6 (20.7)	
Always	15 (45.4)	9 (31.0)	
No response	6 (18.2)	8 (27.6)	
In these contexts, is dose dispensing...than DOT?			
Family and social context			1.000
Less advantageous	7 (21.2)	8 (27.6)	
More advantageous	16 (48.5)	21 (72.4)	
No response	10 (30.3)	-	
Work/study context			1.000†
Less advantageous	3 (9.1)	10 (34.5)	
More advantageous	8 (24.2)	19 (65.5)	
No response	22 (66.7)	-	
Activities of daily living			0.557
Less advantageous	6 (18.2)	11 (37.9)	
More advantageous	15 (45.4)	18 (62.1)	
No response	12 (36.4)	-	
Overall treatment results			0.093†
Less advantageous	10 (30.3)	24 (82.8)	
More advantageous	7 (21.2)	5 (17.2)	
No response	16 (48.5)	-	
Treatment maintenance			0.746
Less advantageous	10 (30.3)	20 (69.0)	
More advantageous	4 (12.1)	9 (31.0)	
No response	19 (57.6)	-	
Treatment completion			0.156†
Less advantageous	9 (27.3)	23 (79.3)	
More advantageous	6 (18.2)	6 (20.7)	
No response	18 (54.5)	-	
Treatment satisfaction			0.546
Less advantageous	9 (27.3)	11 (37.9)	
More advantageous	9 (27.3)	18 (62.1)	
No response	15 (45.4)	-	
In these contexts, is VOT...than DOT?			
Family and social context			0.192
Less advantageous	8 (24.2)	4 (13.8)	
More advantageous	18 (54.5)	25 (86.2)	
No response	7 (21.2)	-	

Continue...▶

Table 3. Participant perceptions of the impacts of self-administered therapy and video-observed therapy, by subgroup. Continued...)

Variable	Patients (n = 33) n (%)	HCPs (n = 29) n (%)	p
Work/study context			0.067
Less advantageous	6 (18.2)	4 (13.8)	
More advantageous	9 (27.3)	25 (86.2)	
No response	18 (54.5)		
Activities of daily living			0.024
Less advantageous	10 (30.3)	3 (10.3)	
More advantageous	16 (48.5)	26 (89.7)	
No response	7 (21.2)	-	
Overall treatment results			0.763
Less advantageous	9 (27.3)	17 (58.6)	
More advantageous	9 (27.3)	12 (41.4)	
No response	15 (45.4)	-	
Treatment maintenance			0.771
Less advantageous	9 (27.3)	13 (44.9)	
More advantageous	9 (27.3)	16 (55.2)	
No response	15 (45.4)	-	
Treatment completion			1.000
Less advantageous	9 (27.3)	14 (48.3)	
More advantageous	9 (27.3)	15 (51.7)	
No response	15 (45.4)	-	
Treatment satisfaction			0.104
Less advantageous	8 (24.2)	5 (17.2)	
More advantageous	12 (36.4)	24 (82.8)	
No response	13 (39.4)	-	

HCPs: health care professionals; SAT: self-administered therapy; VOT: video-observed therapy; and DOT: directly observed therapy. *Fisher-Freeman-Halton test. †Fisher's exact test.

notion of the impact of VOT, except in the area of treatment satisfaction, in which both perceived VOT to be more advantageous than DOT (Table 3).

Even though the advantages of VOT over DOT seem to be clear, patients and HCPs both raised some issues: "*not everyone has a mobile phone*"; "*health care centres lack an information technology platform suitable for VOT*"; "*raises privacy issues*"; "*hinders the therapeutic relationship*" and adherence due to "*forgetfulness*"; may not allow "*adverse effects* [to be] *detected at an early stage*"; and "*tech-challenged users*" may be dependent on "*someone using the equipment*" with them.

DISCUSSION

The findings of this study provide valuable insights into the perceptions and experiences of HCPs and patients regarding different treatment adherence strategies, namely DOT, SAT and VOT. We were able to understand the perceived impact of DOT, underscoring the complexity of tuberculosis treatment adherence and highlighting the shared and divergent views of HCPs and patients across various domains, including treatment satisfaction, activities of daily living and the social context.

The HCPs and patients agreed on the relevance of DOT for the early detection of adverse events. However, the two groups were not in agreement regarding whether DOT is an adequate means of ensuring adherence to tuberculosis treatment, converging with literature that shows the rigidity of DOT to be unsupportive of treatment adherence.[6,11,17] It is likely that HCPs perceive DOT as an effective strategy because it aligns with their clinical objectives of a rigid pattern of compliance to prevent treatment failure and the spread of drug-resistant tuberculosis strains.[18] However, patients likely view adherence differently, considering that factors such as autonomy, convenience and their ability to manage treatment play a more significant role.[19]

Most of the study participants perceived VOT as acceptable and beneficial, although there were some disagreements regarding the frequency with which it should occur. The failure to monitor adverse events and difficulty establishing a close relationship with the HCP were major patient concerns. Although VOT offers several advantages, including convenience and potential cost savings, it also presents technological barriers and privacy concerns that must be addressed before it can effectively be implemented.[20] Perceived barriers include limited technology skills, inadequate cellular connectivity, lack of reliable internet access, limited availability of electricity, smartphone cost and internet use fees.[21]

The physician-patient relationship, an integral part of DOT, is also a relevant dimension that supports treatment adherence. Health care providers can help patients find a less negative meaning in their tuberculosis treatment, providing support rather than

mere surveillance and control.[17] This approach may be more effective than rigidly applying DOT without considering individual factors and determinants.[17,19,22] The barriers to observed therapy in tuberculosis treatment are multifaceted, encompassing socio-cultural, economic, technological and logistical challenges that demand a multi-agency approach with patient-centred care options.[20,21,23]

People-centred tuberculosis care involves integrating patient needs and values into treatment, providing psychosocial and socio-economic support, involving patients in treatment decisions and ensuring flexible, decentralised care models.[24-28] It emphasises the importance of considering the social circumstances, needs and values of patients throughout their treatment journey. This approach aims to improve adherence, reduce loss to follow-up and enhance overall treatment outcomes by involving patients in their care decisions and providing holistic support.[24,25,28]

To achieve people-centred care in tuberculosis treatment, it is essential to integrate holistic support, involve patients in decision-making, provide continuous training for health care providers, implement supportive policies and address stigma and discrimination. These measures collectively enhance patient engagement, adherence and treatment outcomes, ultimately contributing to the global effort to end tuberculosis.[24-28]

Our study has some limitations. The cross-sectional design limits causal inferences, although future longitudinal studies could provide deeper insights into adherence strategies over time. Although our sample reflects experiences in northern Portugal, it was relatively small, which limits the generalisability of the results. In addition, there could have been a selection bias, as more engaged participants could lead to a positive bias. Using qualitative and quantitative methods allowed us to enhance the comprehension of the quantitative findings through thematic analysis. Furthermore, our study contributes to the currently limited body of research on subjective patient experiences in Portugal during tuberculosis treatment and DOT. The inclusion of HCPs added the comparison potentiality, offering critical insights into the intricacies of the physician-patient relationship and the current burdens associated with DOT.

In conclusion, there is an apparent misalignment between patient and HCP perspectives, highlighting a critical need for improved communication and a more person-centred approach to tuberculosis treatment. The challenges of adherence, the potential of VOT and the psychosocial burden of DOT extend beyond Portugal and have broader implications for global tuberculosis management. These findings offer valuable insights that can inform more flexible, patient-centred strategies in other countries facing similar challenges.

AUTHOR CONTRIBUTIONS

DA: data collection and analysis, and drafting of the manuscript. JPR: data curation and analysis, and drafting of the manuscript. PB: data curation and analysis. MV: data analysis tool provision, data analysis, and drafting of the manuscript. RD: study conception and design, data curation and analysis, and drafting of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Asthma-related deaths in Brazil: data from an ecological study

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ABSTRACT

Objective: The aim of this study was to present epidemiological data on hospitalizations and deaths related to asthma in Brazil over the past 11 years. **Methods:** An ecological study was conducted on asthma-related hospitalizations and mortality in Brazil from 2013 to 2023, using data extracted from the Department of Informatics of the Brazilian Unified Health System and the Mortality Information System. **Results:** Asthma-related deaths showed an increasing trend during the analyzed period. A surge in deaths was observed in 2022 compared to 2014 (difference between means = 56.08 ± 19.7; 95% CI = 15.2–96.9). The mean number of deaths was higher among females, with their rate remaining stable, while the rate for males increased. Individuals aged >60 years accounted for approximately 65% of all asthma-related deaths from 2013 to 2023, with a strong direct correlation observed between age and the number of deaths, regardless of sex. During the same period, the total number of asthma-related hospitalizations in Brazil showed a declining trend, decreasing from 134,322 in 2013 to 87,707 in 2023. **Conclusion:** Over the past 11 years, asthma-related deaths have increased in Brazil, with the majority occurring among females. Older individuals accounted for most asthma-related deaths, and a positive correlation was observed between age and the number of deaths.

Keywords: asthma, mortality, hospitalization, epidemiology.

INTRODUCTION

Asthma affects approximately 339 million individuals worldwide.[1] In Brazil, the prevalence of asthma symptoms is estimated at 23% among adolescents and adults.[2] As with other chronic non-communicable diseases, most asthma patients should be managed in primary care, typically requiring low doses of inhaled corticosteroids for disease control.[3] Despite the universal and free availability of inhaled corticosteroids for the treatment of asthma in Brazil, the number of hospitalizations and deaths remains high.[4] In 2013 alone, 2,047 individuals died of asthma in the country, equating to five asthma-related deaths per day.[5] These deaths are preventable, highlighting the need for improved management of this condition. Reliable and valid data are critical for objective health situation analysis, decision-making, and health action planning. Measuring the health status of a population is a fundamental public health activity, relying on the systematic recording of mortality and survival data.[6] In this context, the aim of our study was to present epidemiological data on asthma-related deaths and hospitalizations in Brazil over the past 11 years.

METHODS

This ecological study analyzed asthma-related mortality and hospitalizations in Brazil between 2013 and 2023. Data were extracted from the official databases of the Mortality Information System (SIM)[7] and the Department of Informatics of the Unified Health System (DATASUS).[8] Population and geographic indicators were obtained from the Brazilian Institute of Geography and Statistics (IBGE) censuses[9] of 2010 and 2022, as well as from available population projections for historical series. Data collection took place in June 2024.

Data on asthma-related deaths were extracted exclusively from SIM,[7] which records deaths that occurred in both public and supplementary healthcare systems, as well as those outside hospital settings. The selected parameters included: "reference years" (2013 to 2023), "place of record" (deaths by place of residence), "indicator" (International Classification of Diseases [ICD]-10 codes J45 [asthma] and J46 [status asthmaticus]), "age group" (<1, 1–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and >80 years), and sex (male or female). These parameters were used to generate tables with annual asthma-related death numbers on the Integrated Health Surveillance Platform of the Ministry of Health. The data for 2023 are preliminary.

Absolute numbers of hospitalizations, mean/total hospitalization costs, and mean length of stay per year were derived from the "Epidemiology and Morbidity" tables under the "Hospital Morbidity of SUS" section, "General by Place of Hospitalization," for the geographic scope

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"Brazil by Region and State – from 2008." These tables were generated by the Integrated Health Surveillance Platform of the Ministry of Health, using DATASUS[8] as the data source. The options selected included "year/month of service," "age group," "hospitalizations," "total cost," "mean hospitalization cost," "mean length of stay," and "asthma" in the morbidity list on the platform. It is important to note that DATASUS[8] data refer exclusively to patients hospitalized within SUS. The second half of the 2023 data, according to DATASUS, was subject to updates. Regarding hospitalization costs, the monetary value of each hospitalization is provided by DATASUS and is based on billed Hospital Admission Authorizations (HAAs) that contain the studied ICD codes. Hospitalization cost values in Brazilian real (R$) were converted to USD using the exchange rate of R$ 1.00 = USD 5.66, as of July 3, 2024.

The asthma mortality rate was calculated using the formula: (absolute number of asthma-related deaths × 100,000)/population per year.[10] Population estimates for each year were calculated based on an annual population growth rate of 0.52% for the periods 2013–2021 and 2023. The populations reported in the IBGE census[9] were used for 2010 and 2022. The same population growth rate was applied to both sexes.

Normality was assessed using the Shapiro-Wilk test. Analysis of variance (ANOVA) was performed to test for significant variations in total deaths and deaths according to sex, with the Bonferroni test used to identify where differences between means occurred. Non-parametric tests were used to analyze hospitalization costs. The Kruskal-Wallis test was applied to assess differences in total and mean hospitalization costs, as well as hospitalization rates over the study period, according to age group. Linear regression analysis was conducted to determine whether the total cost value (number or mean cost of hospitalizations) explained the hospitalization costs; the R^2 and the 95% confidence interval were used to determine the accuracy of the results. Spearman's correlation coefficient was calculated to analyze the relationship between age and mortality. All analyses were performed using Jamovi® version 2.2, Orange® version 3.37, and Stata® version 16.0 software, with the significance level set at 5%.

Ethical Aspects

Ethical review was not required for this study, as it involved a retrospective analysis of anonymized data in the public domain, aligning with CNS Resolution 466/12. Also, this study did not receive any funding.

RESULTS

Asthma Mortality

Between 2013 and 2023, asthma-related deaths showed an overall increase, as illustrated in Figures 1a and 1b. Notably, there was a rise in deaths in 2020, totaling 2,734, followed by a decline in 2021 (2,488 deaths), another increase in 2022 (2,802 deaths), and a slight decrease in 2023 (2,611 deaths). Despite these fluctuations, the number of deaths remained higher compared to 2013.

Female mortality was consistent throughout the analyzed period (2013–2023; p = 0.16). In contrast, significant variation was observed in male mortality, as determined by ANOVA with Bonferroni correction (Table 1). Considering both sexes, a notable increase in deaths was identified when comparing 2014 to 2022, with a difference between means (DM) of 56.08 ± 19.7 (95% confidence interval [CI] = 15.2–96.9; p = 0.02).

The increase in deaths among males between 2020 and 2023 explains the overall rise in asthma-related deaths. Despite this increase, the mean number of deaths among females was higher than that observed among males in all years (p < 0.005) (Figures 1a and 1b).

The overall asthma mortality rates per 100,000 inhabitants remained stable between 2013 and 2023. However, an upward trend was observed in male mortality rates over the same period (Table 2).

Considering the distribution of deaths by sex, the majority occurred in females (63%). However, among children and adolescents (≤19 years), mortality was higher in males than in females. Between the ages of 15 and 29 years, the number of deaths was nearly equal between sexes. From age 30 onward, deaths were more frequent among women.

In the age-stratified analysis, we observed a progressive increase in asthma-related mortality with age, with older age groups having the highest mortality rates (Figure 2). The highest proportion of deaths occurred in the >70 (31.65%) and >80 years (31.65%) age groups. Individuals aged over 60 accounted for approximately 65% of all asthma-related deaths during the study period. Mortality among children aged <1 year was relatively low compared to other age groups, representing only 0.60% of the total deaths. Although it represented a small proportion of the total deaths, the 20–39 years age group accounted for approximately 6–9%. Furthermore, a strong positive correlation was observed between age and the number of deaths, regardless of sex (Figure 2).

Asthma-related hospitalizations in SUS

Between 2013 and 2023, the total number of asthma-related hospitalizations in SUS in Brazil showed a declining trend, decreasing from 134,322 hospitalizations in 2013 to 87,707 in 2023 (Figure 3a). A significant decline in asthma-related hospitalizations was observed in 2020 compared to other years (p-value < 0.05), followed by an increase in subsequent years. By 2023, the numbers returned to the pattern seen during the pre-pandemic period. The mean length

Table 1. Significant differences in mean deaths considering annual and sex comparisons.

Statistically significant differences	DM ± SD	95% CI	p-value
Male 2013 x 2020	19.91 ± 7.45	4.46 - 35.4	0.02
Male 2014 x 2020	27.66 ± 6.34	14.5 - 40.8	0.0002
Male 2015 x 2020	24 ± 6.67	10.2 - 37.8	0.002
Male 2016 x 2020	23.33 ± 6.36	10.1 - 36.5	0.003
Male 2014 x 2021	19 ± 3.82	11.1 - 26.9	0.05
Male 2014 x 2022	25.66 ± 6.25	12.7 - 38.6	0.001
Male 2015 x 2022	22 ± 6.59	8.34 - 35.7	0.008
Male 2016 x 2022	21.33 ± 6.28	8.31 - 34.4	0.01
Male and Female 2014 x 2022	56.08 ± 19.7	15.2 - 96.9	0.02

DM= Difference between means; SD= Standard deviation; CI= Confidence interval. Results with statistically significant differences.

of hospitalization in SUS was 3 days throughout the study period.

According to DATASUS, the mean cost of asthma-related hospitalizations during the study period gradually increased, rising from USD 95.25 in 2013 to USD 126.65 in 2023 (Figure 3c).

The total cost of hospitalizations in SUS (Figure 3b) showed a strong positive correlation ($r = 0.95$; $p < 0.001$) with the number of hospitalizations. In the linear regression analysis, the number of hospitalizations explained 90% of the total cost ($R^2 = 0.9$; $p < 0.001$) (Figure 4).

Asthma-related hospitalizations by age group

Regarding asthma-related hospitalizations across the different age groups, the increase observed in 2021 and 2022 occurred mainly in individuals younger than 14 years of age. Notably, hospitalizations in the 5–9 years age group rose by 85% in 2022 compared to the previous year. In contrast, in the 20–29 and 30–39 years age groups, hospitalizations decreased slightly during the same period. Among individuals aged >60 years, there was a noticeable increase in hospitalizations in 2021 and 2022 compared to 2020, with the largest rise observed in the 70–79 years age group. This age group accounted for 32% of all hospitalizations in the last two evaluated years. The number of asthma-related hospitalizations remained stable in 2023 compared to 2022.

DISCUSSION

We observed variation in the absolute number of asthma-related deaths in Brazil over the past 11 years, with a notable upward trend. Comparing 2014 and 2022, the mean number of asthma-related deaths per year was 2,445, corresponding to approximately 6.76 deaths per day. A similar study[5] conducted between 2008 and 2013 reported 2,047 deaths in 2013, equating to approximately five deaths per day, along with a 10% reduction in total deaths during the analyzed period. In contrast, our study showed an increase in the number of deaths from 2019 to 2022, with the number in 2023 being similar to that in 2013. These findings do not support a trend of reduction in the absolute number of asthma-related deaths in Brazil over the past 11 years. Notably, the mentioned study[5] analyzed only data associated with ICD-10 J45. In contrast, our study also included ICD-10 J46 (status asthmaticus), which accounted for 6–14% of the total deaths over the past 11 years.

Recently, an article was published reporting mortality data in Brazil between 2008 and 2021, identifying 8,497 asthma-related deaths during that period and a decrease in the number of deaths over time.[11] However, that study relied solely on data from DATASUS,[8] which reflects deaths based on HAA forms coded as asthma within SUS. In contrast, the SIM system[7] (the source of our data) uses Death Certificates (DCs) as the source document, thereby providing official and more comprehensive asthma-related death data. DATASUS shows HAA data for asthma-related hospitalizations concluded with the outcome "discharge by death," making its mortality data incomplete. SIM, on the other hand, reports the cause of death as listed on the DC, regardless of the HAA coding, place of death (hospital or home), or whether it occurred in the public or supplemental healthcare system. Thus, the SIM system offers a more reliable representation of asthma-related mortality in Brazil.

Mortality rates in the country are a critical public health concern. Despite government efforts to provide free medications, a significant number of asthma-related deaths have been observed among the Brazilian population. This study did not aim to analyze the causes of increased mortality; therefore, we can only speculate on the contributing factors. Since 2009, Brazil has implemented a policy for free access to medications through the "Popular Pharmacy" program, which includes the provision of inhaled corticosteroids (beclomethasone) and short-acting bronchodilators (salbutamol).[12] Additionally, since 2002, the Ministry of Health has supplied free, high-cost medications—such as budesonide, the combination of budesonide-formoterol, and biologics like mepolizumab and omalizumab (for severe cases)—to support asthma treatment.[13]

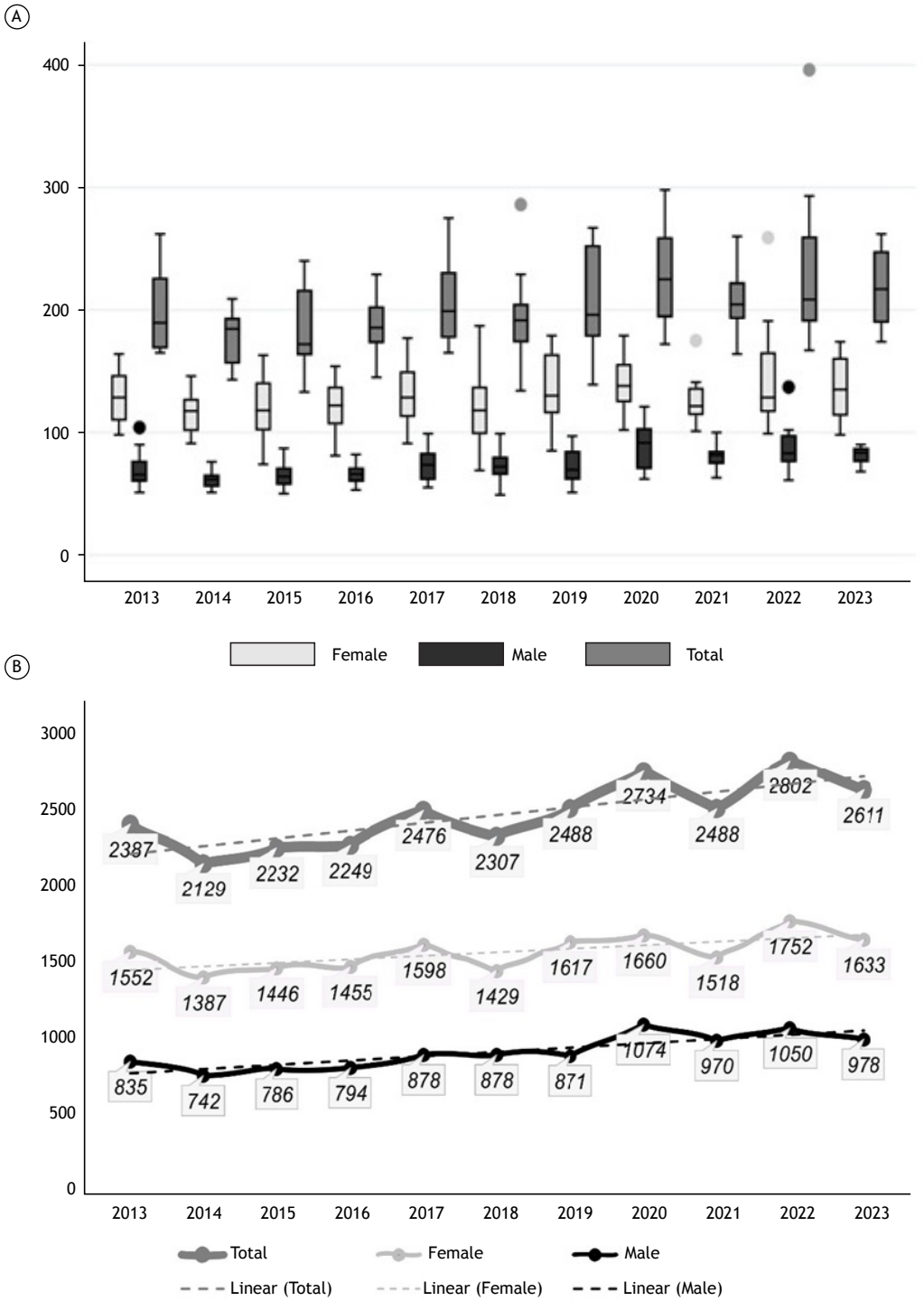

Figure 1. (a) Box Plot: Mortality trends considering the monthly median per year between 2013 and 2023, with variations by sex (male vs. female). Mean number of deaths among females were higher than those among males ($p < 0.005$). (b) Annual quantitative mortality trends by sex (male vs. female) between 2013 and 2023.

Inhaled corticosteroids are essential for the treatment of asthma[3] and for reducing asthma-related mortality.[14] However, asthma management involves several challenges, including low treatment adherence, difficulties with inhalation techniques, limited health education, and poor health literacy among the population. Moreover, asthma management has evolved considerably in recent decades, and implementing complex guidelines for primary and secondary care professionals remains challenging, requiring the availability of practical management guides[15] and the establishment of ongoing medical

Table 2. Annual mortality rates per 100,000 inhabitants in Brazil.

Year	Total	Male	Female
2013	1.23	0.88	1.56
2014	1.09	0.77	1.39
2015	1.14	0.81	1.44
2016	1.14	0.82	1.44
2017	1.25	0.90	1.58
2018	1.16	0.90	1.40
2019	1.24	0.88	1.58
2020	1.36	1.09	1.61
2021	1.23	0.98	1.47
2022	1.38	1.06	1.67
2023	1.19	0.98	1.55

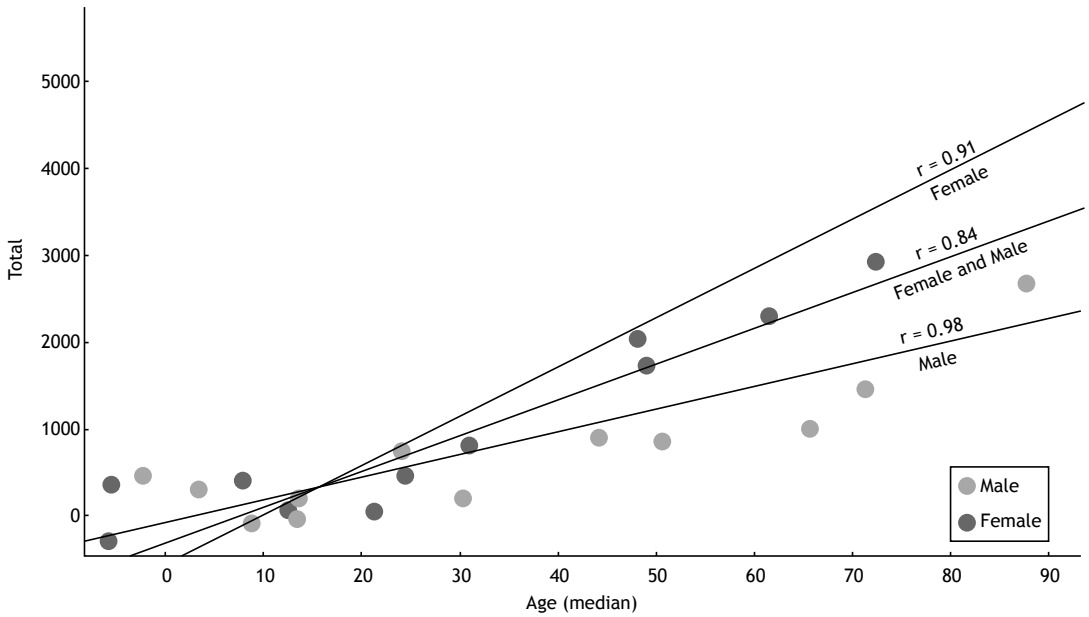

Figure 2. Spearman's correlation: relationship between median age and the number of deaths by sex (dark grey: female; light gray: male; black: both sexes).

education programs, particularly for primary care professionals, who are responsible for managing most patients with asthma.

In the present study, we observed that the highest number of deaths occurred between 2020 and 2022, coinciding with the coronavirus disease (COVID-19) pandemic.[16] A systematic review and meta-analysis[17] involving 131 studies and over 410,000 patients found no association between asthma and increased COVID-19 severity or worse outcomes in infected individuals. However, the use of systemic corticosteroids for asthma exacerbation treatment—whether recent (within the past 120 days) or frequent (two courses of 40 mg/day for at least 3 days per year)—was identified as an independent risk factor for increased severity of COVID-19 and higher mortality.[18]

We can speculate that the increase in asthma-related deaths during the pandemic period occurred among severely ill patients who frequently used systemic corticosteroids or among mildly ill patients who faced disruptions in routine medical care due to social isolation measures, lost access to asthma control medications, or discontinued regular use of systemic corticosteroids.

Most deaths occurred among females. Throughout the observation period, the mean number of deaths among females was higher than that among males. Until 2010, the asthma mortality rate per 100,000 inhabitants in Brazil, calculated based on data from DATASUS, was higher in females than in males (females: 0.241 vs. males: 0.193 per 100,000).[19] In 2022, according to SIM data, we observed a higher mortality rate compared to 12 years earlier (females: 1.67 vs. males: 1.06). However, the earlier data[19] were calculated exclusively using DATASUS, while our findings were based on SIM data, using the distinct methodological characteristics described previously.

The prevalence of asthma varies with age, being more pronounced in males during childhood and puberty, but more prevalent in females during adulthood.[20]

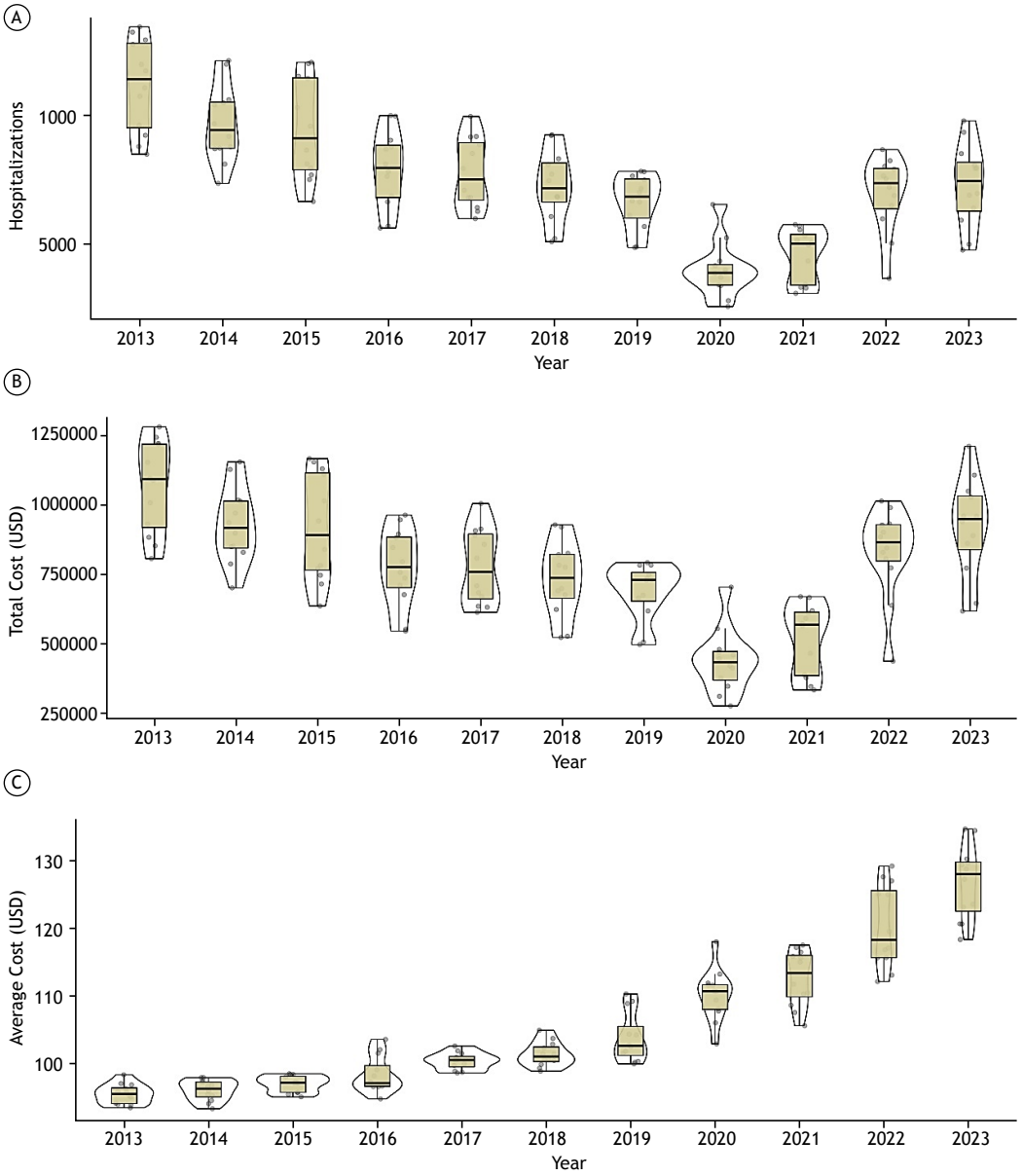

Figure 3. Box Plot graph, with means and medians, and violinplot to determine where the most accumulated data is. (a) Total number of hospitalizations due to asthma in SUS between 2013 and 2023; (b) Total cost of hospitalizations due to asthma in SUS between 2013 and 2023; (c) Mean hospitalization costs due to asthma in SUS between 2013 and 2023. Note the significant drop in asthma-related hospitalizations in 2020 ($p < 0.05$).

Factors such as sex hormones, genetic and epigenetic variations, social and environmental influences, and differences in therapeutic responses contribute to the observed disparities between sexes in terms of asthma incidence, prevalence, and severity. Severe asthma is more common in females than in males, and females tend to exhibit poorer asthma control and more frequent exacerbations compared to males.[21]

However, the increase in male mortality observed in recent years is noteworthy. This trend may be attributed to lower healthcare-seeking behaviors among males, as well as potential shortcomings in asthma management within the healthcare system.

Older individuals account for 66% of asthma-related deaths in Brazil, with a positive correlation between age and the number of deaths, regardless of sex. Compared to adult asthma patients, older patients experience more frequent and severe exacerbations, worse lung function, and a higher prevalence of comorbidities,[22] all of which may contribute to the elevated mortality in this age group. Older asthma patients are also more likely to be underdiagnosed and, as a result, inadequately treated.[23] Notably, a decade ago, older patients had higher rates of emergency department utilization, greater mortality, more hospitalizations,

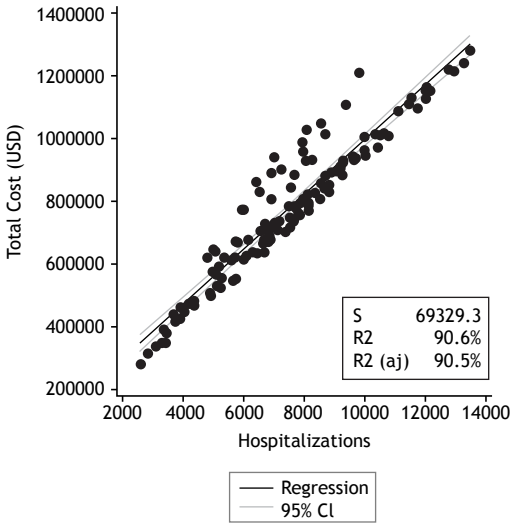

Figure 4. Linear regression. Association between the number of hospitalizations and the total cost. Monthly dispersion. $R^2 = 0.90$; $p < 0.001$.

and longer hospital stays compared to adult asthma patients.[24]

The number of asthma-related hospitalizations in Brazil through SUS[8] has decreased over the past 11 years, dropping from over 130,000 in 2013 to approximately 87,000 in 2023. During this period, the number of inpatient pulmonology beds for adults declined from 1,822 to 1,622,[8] while Brazil's population grew by nearly 7.5%.[9] This suggests that the reduction in hospitalizations may be attributed to a decrease in available resources rather than an improvement in asthma care.

Approximately 66% of the hospitalizations occurred in the pediatric age group (under 14 years). However, the number of pediatric beds also decreased by over 10,000 during this period, from 44,060 in January 2013 to 32,980 in January 2023.[8] This reduction in available beds may explain the decline in hospitalizations, rather than a true improvement in asthma-related outcomes.

In 2020, during the COVID-19 pandemic, a sharp decline in asthma-related hospitalizations was observed in Brazil. At that time, care patterns were restructured to prioritize the treatment of severe COVID-19 cases, leading to a greater allocation of hospital beds for these patients. Despite the reduction in the absolute number of asthma-related hospitalizations and the stability of the mean length of stay (3 days), the mean cost per asthma-related hospitalization increased progressively. However, the total cost of hospitalizations was not primarily driven by this rise in the mean cost but was instead influenced by the overall reduction in the number of hospitalizations.

In Brazil, approximately 75% of the population relies on SUS, while the remainder uses the Supplemental Healthcare System.[8] Consequently, the reduction in hospital bed availability significantly impacts a large portion of the population. An inverse relationship has been observed between the rise in asthma-related deaths and the decline in available hospital beds. According to SIM,[7] around 60% of asthma-related deaths from 2013 to 2023 occurred in hospitals (SUS and supplemental), 10% in other healthcare settings, and 27% at home. These findings suggest that with fewer hospital beds, patients with more severe conditions may be prioritized for admission. The high proportion of deaths occurring outside hospitals is particularly concerning, as it indicates gaps in asthma care, both in maintenance and acute treatment. This highlights the urgent need for public measures to train healthcare professionals in asthma management, especially in emergency units nationwide.

This study had some limitations. First, as an ecological study, it was not possible to establish direct relationships between individual-level variables. Instead, we analyzed the variables collectively and conducted a literature review to explore potential explanations. Another limitation was the reliance on secondary data sources, which raises the possibility of diagnostic errors, particularly in distinguishing asthma from chronic obstructive pulmonary disease (COPD)—a common challenge in older individuals.[23] It is important to note, however, that asthma is frequently underdiagnosed in this population. Therefore, if diagnostic errors occurred, mortality and hospitalization rates for individuals over 60 years of age are likely even higher.

Despite these limitations, our data provide valuable insights into asthma mortality rates in Brazil. We believe these findings can play a crucial role in informing the planning and implementation of public health policies for asthma management.

In conclusion, asthma-related deaths in Brazil have increased over the past 11 years, particularly between 2014 and 2022. The majority of deaths occurred in females. Older individuals also accounted for most asthma-related deaths, with a positive correlation observed between age and the number of deaths, regardless of sex. Meanwhile, the number of asthma-related hospitalizations in Brazil has decreased over the same period.

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AUTHOR CONTRIBUTIONS

All authors contributed substantially to the project, participating in the study design and planning, the interpretation of findings, writing and revision of all preliminary drafts and the final version, and the approval of the final version of the manuscript.

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New spirometry recommendations from the Brazilian Thoracic Association – 2024 update

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ABSTRACT

The latest pulmonary function guideline from the Brazilian Thoracic Association was published in 2002, since which there have been updates to international guidelines (mainly those from the European Respiratory Society and the American Thoracic Society), as well as new national and international publications on various aspects of the performance, interpretation, and clinical implications of spirometry. Despite those updates, a careful analysis of what applies to the reality in Brazil is essential, because there have been studies that evaluated individuals who are representative of our population and who could show responses different from those of individuals in other regions of the world. This document is the result of the work of a group of specialists in pulmonary function who evaluated relevant scientific articles that could be applicable to the population of Brazil. After the discussions, new spirometry guidelines were drawn up, covering various aspects such as its technical parameters and performance; its indications and contraindications; its interpretation; concepts of normality and their related variability; reference values; classification of functional severity; and response to an inhaled bronchodilator. Finally, the guidelines emphasize the need to always interpret spirometry results in the context of the clinical condition of the patient and of the pretest probability.

Descriptors: Respiratory function tests; Spirometry; Respiratory physiological phenomena.

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INTRODUCTION

After the 2002 publication of the Pulmonary Function Testing Guidelines of the Brazilian Thoracic Association (BTA), documents related to the technical aspects and interpretation were published by international societies—the European Respiratory Society (ERS) and the American Thoracic Society (ATS)—as were several articles on the topic by authors working in Brazil. In order to update the recommendations on pulmonary function, the BTA brought together a group of pulmonologists working in the area to evaluate the changes suggested by recent additions to the literature.

In this first document, it was decided that only spirometry would be addressed, leaving lung volumes, DL_{CO}, and bronchial challenge testing for subsequent documents.

In consecutive meetings, the main topics were selected and distributed among groups of participants with a coordinator to evaluate the scientific literature and propose the BTA recommendation. Subsequently, each recommendation was discussed in detail, topic by topic, by all of the coordinators until a final conclusion was drawn.

Several statements regarding lung function are not based on objective studies; hence the importance of discussing each topic among experts in the field to build a consensus on recommendations. Another highly relevant aspect is the need to always seek to associate clinical data with the results of functional tests in the context of interpretation, especially for tests with marginal results (i.e., near-normal or with minimal alterations).

The main aspects related to the performance and interpretation of spirometry are discussed below. A text with more information is available in the supplementary material.

TECHNICAL ASPECTS OF SPIROMETRY

Patient orientation

When scheduling the test

When scheduling a spirometry test, inform the patient of which activities should be avoided prior to the test, and for how long before the test inhaled medications should be suspended.[1-3] Suspending caffeine consumption before the test is no longer considered necessary (see the supplementary material).[4-6] Patients should also be advised that they do not need to fast before the test.

Upon arrival at the pulmonary function laboratory

When a patient arrives at the pulmonary function laboratory, they should be told that spirometry is a noninvasive, safe, painless test that takes 30 min on average. A sample phrase is "the test will measure the capacity of your lungs and determine whether the values are normal or abnormal".[2]

A respiratory questionnaire about symptoms, smoking, previous illnesses, medications, and previous surgical procedures should be completed to assist the medical team in interpreting the examination. Chart 1 represents a proposed model of such a questionnaire.[2,7,8]

At this stage, demographic and anthropometric data (age, sex at birth, height, weight, and race/ethnicity) are collected. The technical details are described in the supplementary material.

Instructions for performing the test

The patient should be instructed to wash their hands. The sitting position is recommended over the standing position to avoid the risk of falling due to a loss of balance or syncope.[9]

The first step is to explain and demonstrate how to properly place the tube on the tongue, proper lip closure, placement of the nose clip, and the neutral head position.

Dental prostheses do not need to be removed if they are firmly fitted. However, the level of patient confidence in performing the maneuvers with a dental prosthesis in place should be taken into consideration.[10,11] A poorly affixed or loose prosthesis could impair patient performance, and such prostheses should preferably be removed prior to the spirometry.

Indications and contraindications

Spirometry is indicated for diagnosis, monitoring, evaluating dysfunction/disability, research, and studies, among other purposes (Chart 2).[2,3,12]

Most contraindications for performing spirometry are relative and depend on the assessment of the risk of complications, as opposed to the need to perform the test (Chart 3). In the forced maneuver, changes in blood pressure, including the potential increase in myocardial oxygen demand, as well as the intrathoracic, intra-abdominal, intracranial, intraocular, sinus, and middle ear pressures, can have adverse effects in some patients.[2,8,13] Data in the literature indicate that patients with thoracic or abdominal aortic aneurysms can safely undergo spirometry if the aneurysm is stable, smaller than 6 cm, and not growing over time,[14] such an aneurysm therefore not being considered a contraindication. An acute infection and impaired cognition are conditions that may lead to unsatisfactory patient performance and consequently the recording of values that represent an underestimation.

Acceptability and repeatability

FVC maneuver

It is recommended that at least three FVC maneuvers be performed, and more than eight attempts generally do not improve the quality of the test. Forced expiration in spirometry consists of four phases: 1) rapid and complete inspiration up to TLC; 2) expiration with a

Chart 1. Respiratory questionnaire on symptoms, history and exposure.

Respiratory questionnaire		
Smoking		
-Smoker ( ) Ex-smoker ( ) Never smoker ( )		
-At what age did you start smoking regularly?		
-How many cigarettes did/do you smoke per day?		
-How long ago did you stop smoking?		
Respiratory symptoms		
-Do you wheeze?	Yes ( )	No ( )
-Do you usually have a cough?	Yes ( )	No ( )
-Do you regularly cough up phlegm?	Yes ( )	No ( )
-Do you have shortness of breath during any of the following activities?		
Intense exercise	Yes ( )	No ( )
Walking uphill	Yes ( )	No ( )
Walking on level ground	Yes ( )	No ( )
Light activities, such as taking a shower	Yes ( )	No ( )
Lung diseases		
-Do you or have you ever had any lung disease?	Yes ( )	No ( )
Which? ( ) Asthma ( ) Bronchitis ( ) Emphysema ( ) Fibrosis ( ) Tuberculosis ( ) Other:		
-Do you use any medication for your lungs?	Yes ( )	No ( )
Which?		
-Have you ever had any chest or lung surgery?	Yes ( )	No ( )
Which?	How long ago?	
-Have you ever been intubated?	Yes ( )	No ( )
Other diseases		
- Anemia? Yes ( ) No ( )		
- Do you or have you ever had any other illness? Yes ( ) No ( ) If yes, which?		
( )Heart ( )"High blood pressure" ( )Rheumatologic disease ( )Cancer ( )Neurological disease		
( )Other. Specify:		
-Do you or have you ever worked in an environment with dust, smoke, or chemicals (silica, asbestos, coal dust, wood stove smoke, etc.)? Yes ( ) No ( )		
- Specify the job:		

Adapted from Mottram et al.[7] and Pereira et al.[8]

rapid and "explosive" start; 3) continuous expiration until reaching the 1-s plateau or until the maximum expiration time; and 4) new inspiration with maximum flow up to TLC. The acceptability criteria are described in Chart 4.

Proper start criteria

- There should be an inspiratory pause of ≤ 2 s before the expiratory maneuver.
- In individuals > 6 years of age, the back-extrapolated volume (BEV) should be ≤ 100 mL or up to 5% of FVC, whichever is greater; in children aged 2-6 years, the BEV should be ≤ 80 mL or 12.5% of FVC, whichever is greater (Figure 1). In 2019, the ATS recommended a BEV of ≤ 100 mL.[2] However, a recent study demonstrated that there is little difference between a BEV of 100 mL and a BEV of 150 mL in terms of the impact on FVC and FEV_1 repeatability.[15] In this document, a BEV of 100 mL is considered ideal, although values up to 150 mL are considered acceptable.
- The time to reach a PEF, defined as the rise time between 10% and 90% of peak flow, should be ≤ 150 ms; the PEF will typically have a steep (pointed) slope but can have a flatter (rounded) slope in children, young women, and patients with neuromuscular disease. The latest ERS/ATS guidelines do not recommend repeating a PEF measure to assess the quality of the maneuver, although the study cited as a basis evaluated only elderly individuals in whom the phenomenon of effort dependence is less evident, with less influence of PEF on FEV_1.[16] Therefore, the recommendation of the 2002 BTA guideline to inspect and select efforts in the flow-volume curves will be maintained, discarding those with submaximal efforts, that is, PEF variability should be ≤ 10% of the highest value (Figure 2).

Chart 2. Indications for spirometry.

Diagnosis
• Functional assessment of respiratory symptoms and signs
• Abnormal findings on additional tests (imaging, blood gas analysis, or pulse oximetry)
• Measuring the physiological impact of a disease on the respiratory system
• Prognostic (severity) assessment
• Screening of individuals at risk for respiratory diseases
• Preoperative risk assessment
• Postoperative evaluation after thoracic surgery
• Diagnosis of bronchial hyperresponsiveness on bronchial challenge testing
Monitoring
• Evaluate the effectiveness of a treatment
• Assess the progression and exacerbation of respiratory diseases
• Measure the effects of occupational or environmental exposure
• Monitor the use of drugs with potential pulmonary toxicity
Assessment of dysfunction and disability
• Evaluating patients in a rehabilitation program
• Assess risks as part of an insurance assessment or for legal reasons
Other uses of spirometry
• Research, clinical trials, and epidemiological surveys
• Derivation of reference equations
• Assess health status before starting risky/strenuous physical activities

Adapted from Graham et al.[2]

Chart 3. Contraindications for spirometry.

Increased myocardial demand or changes in blood pressure
• Acute myocardial infarction within a week
• Symptomatic systemic hypotension or severe hypertension
• Significant atrial or ventricular arrhythmia
• Decompensated heart failure
• Uncontrolled pulmonary hypertension
• Acute cor pulmonale/clinically unstable pulmonary embolism
• History of syncope during forced expiration/coughing
Due to increased intracranial/intraocular pressure
• Brain aneurysm
• Brain surgery (within the first four postoperative weeks)
• Recent concussion with persistent symptoms
• Eye surgery (within the last week, or up to a month, depending on the type of surgery)
Increases in sinus and middle ear pressures
• Sinus or middle ear surgery, or infection within a week
Due to increased intrathoracic and intra-abdominal pressure
• Aortic aneurysm greater than 6 cm, or with signs of progression
• Presence of pneumothorax in less than two weeks
• Thoracic surgery (wait four weeks)
• Abdominal surgery (wait four weeks)
• Third trimester pregnancy
Risk of infection
• Respiratory infection, including tuberculosis, during the communicable period
• Hemoptysis, significant secretion, oral lesions, or oral bleeding
Impaired cognition precluding the testing
• Cognition disorders/impaired concentration
• Dementia syndrome

Adapted from Graham et al.[2] and Cooper et al.[14]

Proper end criteria

- Expiratory plateau at the end of the expiratory maneuver is defined as a volume change ≤ 25 mL in the last second of expiration, as recorded by the computer.
- For the evaluation of forced expiratory time in healthy adults, we recommend that the maneuver be stopped after a plateau has been reached, which normally occurs at around 6 s in most individuals. In children < 10 years of age, the minimum forced expiratory time is 3 s, with < 1 s being accepted in preschoolers (in this case, $FEV_{0.75}$ or $FEV_{0.5}$ is used in place of FEV_1). A maximum forced expiratory time of 15 s is sufficient, because longer times generally do not alter the interpretation. We recommend accepting

Chart 4. Acceptability criteria in spirometry.

Back-extrapolated volume ≤ 100 mL or up to 5% of FVC (whichever is greater)
Time to reach a PEF ≤ 150 ms
PEF variability ≤ 10% of the highest value obtained
No evidence of zero flow error
No coughing in the first second of expiration*
No glottal closure after the first second of expiration**
At least one of three of the following criteria at the end of the maneuver: 1. Expiratory plateau ≤ 25 mL in 1 s 2. Expiratory time ≥ 10 s 3. FVC is within the repeatability criterion in cases without a 1 s plateau†
No evidence of obstruction of the mouthpiece or spirometer
No signs of leakage

*Required for an acceptable FEV_1 maneuver; in these cases, some maneuvers should be used only for FVC even if there is coughing in the first second. **Required for acceptable FVC; in these cases, some maneuvers should be used only for FEV_1 even if there is glottic closure after the first second. †Occurs when the patient cannot exhale sufficiently to sustain a plateau (e.g., children or patients with interstitial lung disease with increased elastic recoil), as long as the FVC is greater than or within the repeatability tolerance range of the highest FVC observed in the other maneuvers.

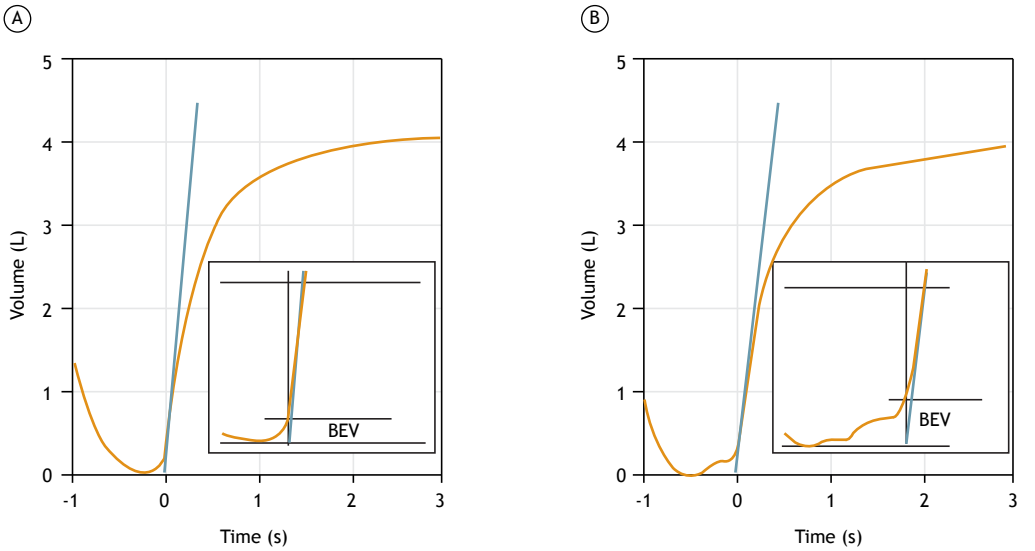

Figure 1. FVC and back-extrapolated volume (BEV) maneuver. The proper start of the test is with a sudden increase in flow, without hesitation. Time zero is found on the volume-time curve by a tangential line with a slope equal to the peak flow (blue line), defining the "real" time zero as the point where this line crosses the time axis. The BEV (calculated automatically in up-to-date equipment) is equal to the volume of gas expired before time zero. In this case, with an FVC of 4.0 L, the acceptable back-extrapolated limit is 200 mL (5% of FVC). The BEV was 136 mL (acceptable) for the curve A and 248 mL (unacceptable) for the curve B.

a forced expiratory time of 10 s as sufficient in individuals who do not achieve a plateau, given that some patients experience fatigue during longer forced maneuvers.

- The test (maneuver) should be discontinued even in the absence of a plateau if there is marked discomfort or syncope, if the subject is a child, or if there is marked restriction (for example, in some cases of muscular dystrophies), as long as the values obtained meet the repeatability criteria.
- Compare the FVC with the volume of maximum inspiration; that is, the forced inspiratory vital capacity (FIVC). It is recommended that the difference between the FIVC and FVC be < 100 mL or 5% of the FVC (whichever is greater) and that the expiratory and inspiratory curves "meet", indicating that the FVC maneuver started from an inspiration close to TLC (Figure 2). Occasionally, in cases of obstructive disorders, the FIVC can be greater than the FVC because of the phenomenon of dynamic compression of the airways during exertion.

Repeatability criteria between maneuvers

Repeatability is defined as the difference between the two highest measurements obtained in different maneuvers. The grading of quality in spirometry is related to acceptability and repeatability (Chart 5).

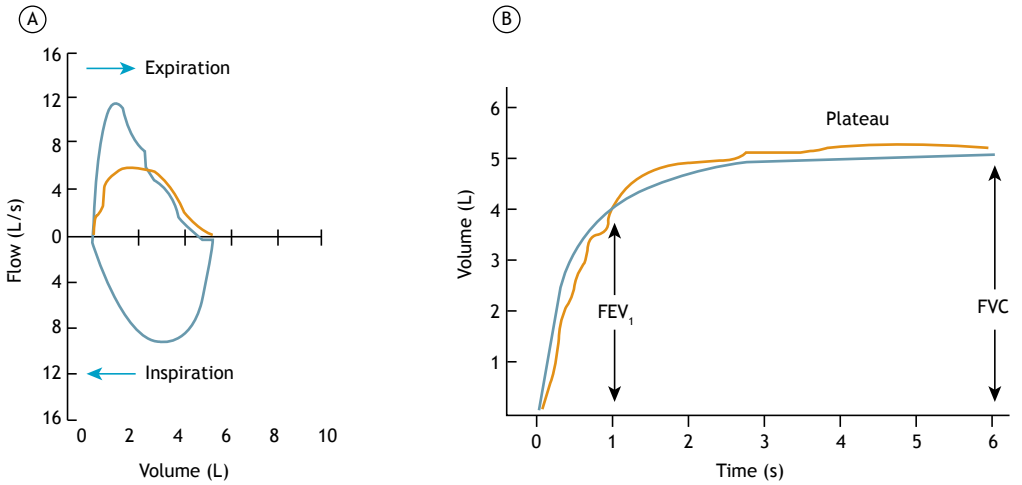

Figure 2. FVC maneuver: flow-volume curve (A) and volume-time curve (B). The usefulness of PEF can be seen in the flow-volume curves, with an adequate initial effort in the blue curve and a submaximal initial effort clearly demonstrated in the orange curve, which is not very evident in the volume-time curves. The detection of a constant flow close to or equal to zero at the end of the forced expiratory curve will be easily noticeable in the volume-time curve (expiratory plateau) and will be less evident in the flow-volume curve. Another desirable point is to obtain an adequate inspiratory curve with measurement of the forced inspiratory vital capacity. In this case, we observe an adequate maneuver with "meeting" of the expiratory and inspiratory curves in the blue flow-volume loop.

Chart 5. Grading of quality in spirometry.

Grade	Maneuvers	Repeatability > 6 years	
		FVC and FEV_1	PEF
A	≥ 3 acceptable	≤ 100 mL	≤ 10% of the highest value
B	≥ 2 acceptable	> 100 mL and ≤ 150 mL	≤ 10% of the highest value
C	≥ 2 acceptable	> 150 mL and < 200 mL	≤ 15% of the highest value
D	1 acceptable	N/A	N/A
Z	0 acceptable	N/A	N/A

N/A = not applicable.

Usable parameter definition (FEV_1 and FVC)

In some cases, maneuvers that do not meet the acceptability criteria can still provide FEV_1 and FVC values that are useful for interpretation. For example, early termination of a maneuver is not a reason to discard all data obtained, and FEV_1 may be a valid (usable) measurement, provided that there were no artifacts during the first second of the test.

Slow vital capacity maneuver

In addition to the forced step, the vital capacity maneuver can be performed by obtaining the parameters vital capacity, inspiratory capacity (IC), and RV, including the possibility of calculating the FEV_1/vital capacity (FEV_1/VC) ratio. In this case, it is preferable that the vital capacity maneuvers be performed before the FVC maneuvers, because some patients with severe airway obstruction have a momentarily high level of functional residual capacity (FRC) after maximum inspiratory effort and a consequent drop in IC as a result of dynamic lung hyperinflation.

In spirometry, the vital capacity is typically obtained during expiration. The vital capacity maneuver should be performed in a relaxed manner (except at the end of inspiration and expiration, which should be at maximum effort); starting from TLC to RV, with the end of the test defined by a variation in volume ≤ 25 mL for at least 1 s. The IC maneuver should also be performed in a relaxed manner, with at least three stable breaths in V_T, from FRC to TLC. Obtain at least three acceptable maneuvers (from up to eight maneuvers, if necessary) with stability of the baseline V_T in at least three breaths, with a difference of no more than 15% in relation to the highest value of V_T. If stability does not occur in eight respirations, proceed to the vital capacity maneuver.

The repeatability criteria for vital capacity and CI are ≤ 150 mL or 10% of the highest value (in individuals > 6 years of age). The highest vital capacity obtained should be selected. The mean of the CI values should be obtained from curves with stability at the baseline V_T (otherwise, the CI should not be valued).

CONSIDERATIONS ON THE INTERPRETATION OF SPIROMETRY

Reference values

Reference values for lung function are those obtained in individuals who have never smoked and without

current or previous cardiopulmonary or systemic diseases.[17] They should be obtained from the same population in which the tests will be applied, as they vary widely according to the country of origin. The equations selected for the various pulmonary function tests should be included in the pulmonary function reports.

Reference values are influenced by sex, height, and age. The use of separate equations for different races or the use of a multiracial equation is of great interest at present,[18] and more data are needed in order to make that choice for use in Brazil. Although body weight is a minor determinant of predicted values from forced spirometry, it is noteworthy that studies have excluded obese individuals. Reductions in lung volume can be found in obese individuals, the most common being reductions in RV and FRC.[19] Despite the minimal influence that body weight has on the predicted value, it is important to identify the weight or BMI of the patient in the report, because that can facilitate the interpretation of the results.

Lung volumes and maximal expiratory flows increase progressively during childhood and typically correlate well with height. Lung function reaches peak values at 18–20 years of age in women and a bit later, at around 25 years of age, in men because of an increase in inspiratory muscle strength in the latter.[20] Up to age 35, FVC and FEV_1 change little, declining progressively thereafter, with survival being longer in individuals with greater lung function.[21] Very elderly individuals who are able to perform spirometry have higher lung function values than do those who are not, and the use of derived values as a reference attenuates or abolishes the decrease in projected values; thus creating a selection bias. Therefore, it is correct to use extrapolated values to estimate predicted values in the very elderly.[22]

The expected range for lung function measurements is wide and, whenever possible, variations in lung function should be compared with values previously obtained from the same individual.

Reference equations

In the absence of values derived from the local population, it was previously recommended that foreign equations be adopted, which resulted in large biases depending on the study chosen.[23] A multicenter study conducted in Brazil was published in 2007.[23] The study involved 643 White adults, 20-85 years of age, who were evaluated with computerized flow spirometers, and the results were analyzed according to rigorous criteria.

In 2012, the Global Lung Function Initiative (GLI) proposed a set of equations for universal adoption.[24] A total of 74,187 nonsmoking individuals in 26 countries on five continents were included in equations derived by combining several studies. The quality of the curves was not assessed. In the GLI study, a new statistical model was proposed.[24]

A comparison of the GLI equation with data derived from the 2007 Brazilian sample showed that the lower limit of the predicted FEV_1/FVC ratio is significantly lower when the GLI equation is applied.[25] This results in it having lower sensitivity for diagnosing airflow obstruction, which can be attributed to the inclusion of several low-quality studies, widening the range of predicted values. Although the GLI committee insists on the universal adoption of these equations,[26] this underdiagnosis of obstruction underscores the importance of using the predicted values derived from our population.

Spirometry reference values for in Black adults in Brazil were published in 2018.[27] A comparison with predicted values derived for Whites showed lower values, especially in males, but with smaller differences than those suggested for individuals in the United States. We know that race alone might not be the only factor responsible for such a difference, because there could be socioeconomic and environmental factors that were not considered. Therefore, it is recommended that the equation specific to the Black race be reserved as an option for tests of Black individuals with borderline values, always being considered within the context of the clinical condition and the pretest probability of disease.

One large study on pediatric reference values in Brazil included children 3-12 years of age (Chart 6).[28] As was observed in adults, the adoption of GLI equations was found to reduce the sensitivity for the diagnosis of airflow obstruction, because the lower limits for the FEV_1/FVC ratio are also lower.

Lower limits

Various biological variables, such as FVC, when placed in order, will follow a distribution curve known as "normal" or Gaussian. The variation of the data around the mean is assessed by measures of dispersion, the most common of which is the standard deviation (SD). The mean ± 2 SD encompasses 95.4% of the sample values (47.7% on each side of the mean). The Z score (observed value – mean / SD) expresses how far, in multiples of SD, the individual is from the mean, and will be considered abnormal if less than 1.645 (Figure 3). Another way to estimate the lower limit is to determine it by the 5th percentile. When the distribution of values around the mean follows a normal curve, the 5th percentile and the Z score are very similar. In this situation, the choice of one of these two methods is irrelevant.

In statistics, if the dispersion around the regression curve is constant, the lower limit will be established by subtracting a fixed value from the predicted value. It follows that the lower limit cannot be established by a fixed percentage, such as 80% of the predicted FVC and FEV_1 in adults, which is an outdated simplification.[29] Ideally, the principles of clinical decision-making should be applied, requiring assessment of preclinical probability to determine

the presence or absence of disease in the face of values close to the threshold of abnormality.

If the dispersion around the regression decreases proportionally as the predicted value decreases, the residuals will better fit the normal distribution by logarithmic transformation of the variables. In this situation, the lower limit is a fixed percentage and is independent of the predicted value. Spirometric values in children and flows in adults fit this model better (Chart 6).[23,27,28]

A value situated at the lower limit of normal (LLN) means that 95% of the healthy reference population has a value above this value. Therefore, this does not mean that values slightly below the LLN indicate that the individual being tested is ill. For this, the pretest probability of disease must be considered. The respiratory questionnaire is intended to assess the pretest probability. A value close to the LLN can be considered abnormal in the presence of findings indicative of the condition under investigation. Obviously, values well below the LLN have a greater positive predictive value for disease.

Chart 6. National reference values according to sex and age group.

Age range	Male	Female
3-12 years	Jones et al.[28]	Jones et al.[28]
13-19 years		Mallozi MC[a]
13-24 years	Mallozi MC[a]	
> 20 years		Pereira et al.[23]
≥ 25 years	Pereira et al.[23]	

[a]Based on Mallozi MC. Valores de Referência para espirometria em crianças e adolescentes, calculados a partir de uma amostra da Cidade de São Paulo [thesis]. São Paulo: Escola Paulista de Medicina, Universidade Federal de São Paulo; 1995.

Interpretation of spirometry

Appropriate interpretation of spirometry requires measurements that meet the prerequisites for technical quality. Low-quality tests should be interpreted by expressing the appropriate level of uncertainty, and the possibility that the measured values could reflect technical rather than pathophysiological deficiencies should be considered.

FEV_1/FVC ratio

Obstructive ventilatory impairment is characterized by a disproportionate reduction in maximum airflow in relation to the largest volume of air that can be expired from the lungs after a maximal inspiration. The most important parameter in identifying airflow obstruction is the reduction in the FEV_1/FVC ratio below the 5th percentile of the predicted value (i.e., the LLN).

The definition of persistent airflow limitation as an FEV_1/FVC ratio < 0.70 after bronchodilator use was maintained in the GOLD guideline.[30] Although easy to remember, this criterion is controversial because it disregards the age-related physiological decline in the FEV_1/FVC ratio, leading to underdiagnosis and overdiagnosis of obstruction in young people and the elderly, respectively. Since 2005, the ATS/ERS consensus on spirometry interpretation has defined airflow limitation as an FEV_1/FVC ratio below the LLN.[26,31]

Several studies have compared the diagnosis of airflow limitation based on an FEV_1/FVC ratio < 0.70 with that based on an FEV_1/FVC ratio < LLN. In one large study, more than 11,000 patients, with a mean age of 63 years, were followed for 15 years. The definition

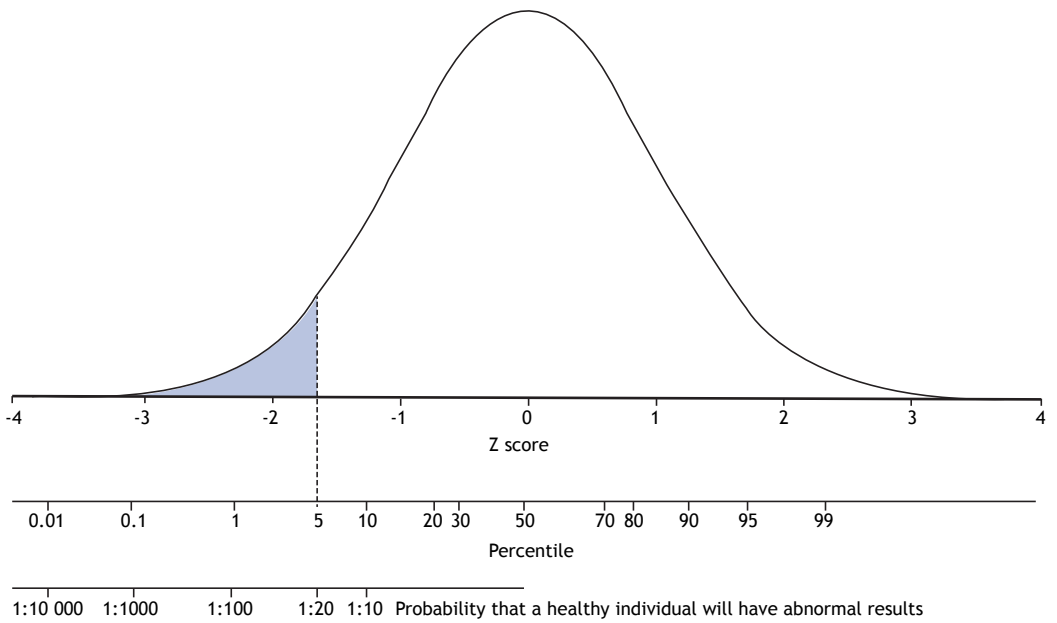

Figure 3. Derivation of the lower limit by the Z score and the 5th percentile of the residuals. This limit means that the result will be considered abnormal for one in every twenty healthy individuals.

of airflow obstruction based on an FEV_1/FVC ratio < 0.70 was more accurate than was that based on an FEV_1/FVC ratio < LLN in predicting respiratory-related hospitalization and death.[32] The equation used for the LLN was that of the GLI, which explains the inferiority in comparison to the fixed limit. With the GLI equation, as previously noted, the LLN is much lower than with other equations, such as the one suggested for Brazil,[25] which explains the lower sensitivity of the GLI equation to characterize the presence of airflow obstruction, and hence the apparent superiority of the fixed limit in the study cited above.

The GOLD guideline has also always characterized the presence of COPD by an FEV_1/FVC ratio < 0.70 after BD use. A recent study showed that individuals with pre-BD obstruction (defined as an FEV_1/FVC ratio < 0.70) but without post-BD obstruction had, after adjustment for other variables, a 6.2-times greater risk of developing COPD.[33] On the basis of these data, we suggest that the diagnosis of airflow obstruction be based on a pre-BD FEV_1/FVC ratio < LLN. It should be borne in mind that individuals with asthma can show this same type of response.

Another point of controversy concerns the interchangeable use of FVC or vital capacity as the denominator in the FEV_1 ratio. The FVC can underestimate vital capacity because of early closure of the small airways at low lung volumes in the forced maneuver. However, there is a risk of false-positive results for airflow obstruction, because the LLN of the FEV_1/VC ratio used in clinical practice comes from the same reference equations used in order to evaluate the FEV_1/FVC ratio, which might not be correct. Nevertheless, there is evidence that the use of the FEV_1/VC ratio increases the rate of individuals diagnosed with airflow obstruction presenting abnormalities consistent with airway dysfunction and a greater clinical probability of disease.[34-36] In individuals > 70 years of age, the FEV_1/VC ratio should be used with caution because it has been shown not to indicate a greater probability of disease or airway dysfunction.[35] In this age group, vital capacity and FVC values differ more widely in the reference population. Studies comparing the FEV_1/VC and FEV_1/FVC ratios in patients, using separate predicted values but derived from the same population sample, are needed to resolve this controversy.

Although airflow obstruction with reduced FVC most often corresponds to increased RV (air trapping), associated restriction characteristic of combined lung disease cannot be ruled out.[37] If it is not possible to measure TLC, a difference between FVC and FEV_1, in % of predicted (FVC% and FEV_1%, respectively), of ≥ 25 suggests, with a high degree of certainty,[38,39] airflow obstruction with air trapping (Figure 4). In a test with a reduced FEV_1/FVC ratio and reduced FVC%, with a difference between FVC% and FEV_1% < 25, measurement of TLC is recommended to better characterize the disorder (airflow obstruction with airtrapping or combined ventilatory disorder). In 3% of cases, TLC is reduced in the presence of preserved FVC in the context of obstruction.[39]

Forced expiratory flows

The first change associated with airflow obstruction indicative of COPD is believed to be a slowing of

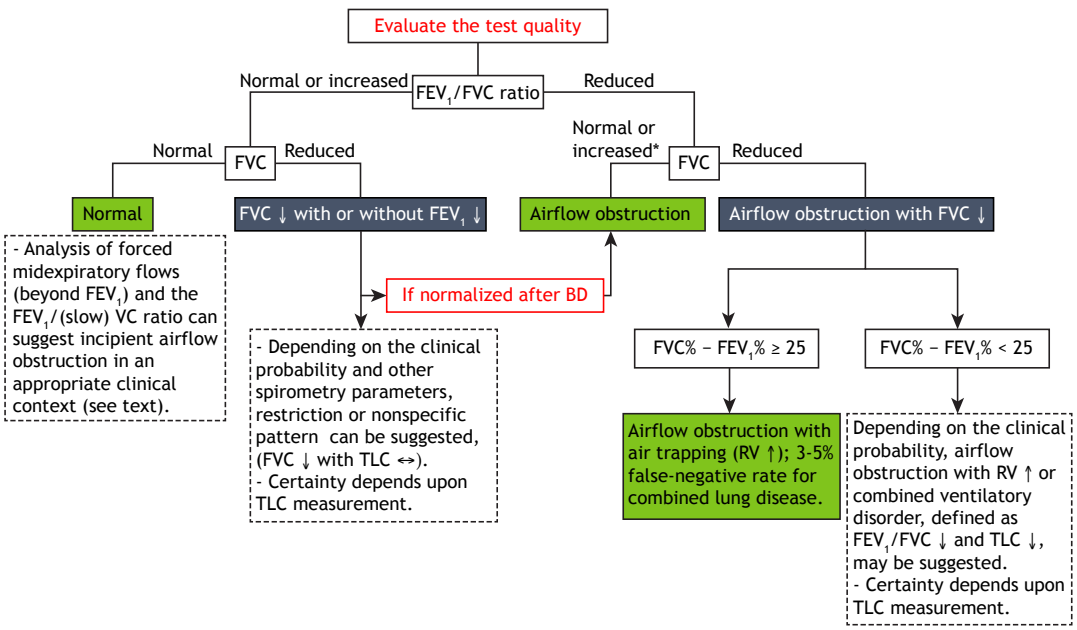

Figure 4. Spirometry interpretation algorithm. Increased (↑), normal (↔) or reduced (↓) values are relative to the statistical limits of normality: ↑ = above the upper limit of normal or > 95th percentile (Z score + 1.645) of the healthy population; ↓ = below the lower limit of normal or < 5th percentile (Z score − 1.645) of the healthy population. BD: bronchodilator; FVC%: FVC in percentage of the predicted value; FEV_1%: FEV_1 in percentage of the predicted value.

the mean expiratory and end-expiratory flows on forced spirometry. Although $FEF_{25-75\%}$ is one of the most widely studied parameters, it is considered to have high intra- and inter-individual variability and a wide normal range.[40] In many studies, that is due to inadequate derivation of predicted values, either by including tests without quality verification or by using inappropriate prediction equations, such as those derived from non-log-transformed data.[41]

Despite these limitations, a lower $FEF_{25-75\%}$ has been shown to be associated with more extensive emphysema, bronchial hyperresponsiveness, and lung hyperinflation, regardless of the FEV_1.[42] Other studies have shown that smokers with reduced $FEF_{25-75\%}$ and normal FEV_1/FVC are more likely to develop COPD thereafter.[43]

Still in the search for spirometry parameters that are more representative of more distal airways, the analysis of $FEF_{75\%}$, in one study,[44] added sensitivity to the FEV_1/FVC ratio for the detection of airflow limitation in symptomatic patients with suspected obstructive disease and preserved FVC.

It should be noted that flows can be considered reduced in isolation only in the presence of FVC within the predicted range. A reduction in lung volume results in proportionally lower flows. In the presence of reduced FVC, a reduction in the $FEF_{25-75\%}$/FVC ratio indicates airflow limitation. This parameter is particularly important for characterizing obstruction in children with an FEV_1/FVC ratio within the predicted range.

The ratio between FEV in 3 s and FVC[45] and the ratio between FEV in 3 s and FEV in 6 s have been suggested as alternative measures to assess the terminal portion of the spirometric curve,[46] but reference values are not available for the Brazilian population.

In brief, these additional parameters related to intermediate or more distal flows could be additional variables in patients with suspected obstructive disease.

Reduction in FEV_1 and in FVC with no reduction in the FEV_1/FVC ratio

A reduction in FEV_1 and in FVC with no reduction in the FEV_1/FVC ratio is a set of findings commonly described as suggestive of restrictive lung disease (RLD), which is, however, physiologically characterized by reduced TLC. The presence of restrictive disease (e.g., fibrosing interstitial lung disease) determined from a respiratory questionnaire, an increased FEV_1/FVC ratio (> 110% of the predicted value), with or without an $FEF_{25-75\%}$ > FVC in absolute values, and a convex expiratory flow-volume curve increase the likelihood of restriction.[47] Because vital capacity constitutes the majority of TLC, FVC < 50% of predicted is most commonly observed when TLC is reduced.[47]

In early obstruction, however, collapse of the small airways can reduce FVC and increase RV before the FEV_1/FVC ratio decreases, creating the possibility of a "pseudo-restrictive" pattern. The presence of significant variation in spirometric parameters after bronchodilator use confirms that. The clinical context, together with an analysis of the spirometry results, can help define which of these possibilities we are testing. If uncertainty remains, measurement of TLC is recommended (Figure 4).

A reduced FEV_1/FVC ratio with increased FVC or FEV_1 within the normal range can be due to dysanapsis (defined as a mismatch between the growth of the airways and that of the lung parenchyma), or more commonly, it can result from greater airway compression in younger men with expiratory muscles at a mechanical advantage due to larger lung volume ("variant of normal"). Whether this pattern represents airflow obstruction will depend on the clinical likelihood of obstructive disease and possibly on the results of additional functional testing.[48,49]

Severity classification

In assessing the severity of functional impairment, tests should ideally be able to assess its relationship with survival, quality of life, symptom intensity, and the probability of clinical worsening, hospitalization, or both.

However, because various diseases can manifest as the same respiratory disorder, the magnitude of functional limitation does not necessarily reflect the same prognosis among them. Factors other than lung function, such as anemia, sarcopenia, and heart disease, can influence the clinical outcomes of respiratory diseases. Traditionally, the consensuses on lung function from the main international societies have used studies that evaluated several functional parameters,[3,26] especially FEV_1 and FVC, to predict mortality in the most representative lung diseases, such as COPD for airflow obstruction and idiopathic pulmonary fibrosis (IPF) for RLD.

Classification: cutoff points

Obstruction: FEV_1 and the FEV_1/FVC ratio

Studies conducted in the 1970s and 1980s identified post-BD FEV_1% as the functional parameter that best correlates with survival in COPD, showing an association between progressive functional decline and mortality.[50-52] In various studies, FEV_1 < 50% of predicted values have been shown to correlate with worse survival. Among patients with an FEV_1 < 30% of predicted, the mean 5-year survival rate was found to be 25%. One study evaluated different cutoff values for severity classification in 611 individuals with COPD[53] and found that those proposed in the 1997 British Thoracic Society guidelines[54] and adopted by the BTA in 2002[3] had greater sensitivity and lower specificity for predicting 5-year mortality when compared with the 2023 GOLD and 1995 ATS scales (Table S1, supplementary material).[55]

More recently, a study involving 3,665 patients with COPD identified superiority of other cutoff points (≥ 70%, 56-69%, 36-55%, and ≤ 35% of predicted) to discern different levels of mortality in 5 years when compared with the GOLD cutoff points (≥ 80%, 50-79%, 30-49%, and ≤ 30% of predicted) and the proposed BODE cutoff points (≥ 65%, 50-64%, 36-49%, and ≤ 35% of predicted).[56] Finally, a new proposal for a classification system, using the Z score, was established because it correlated with the FEV_1% adopted by the ATS/ERS in 2005 and currently adopted in the 2022 international update.[26] However, some studies have questioned the validity of using the Z score, identifying inferiority when compared with the FEV_1%.[57,58] In view of the above and considering the various studies presented, this guideline considers that the cutoff points with the best applicability for classifying the severity of obstruction are those established by the BTA in 2002, which were therefore not modified.

In addition to FEV_1%, the FEV_1/FVC ratio has been used to classify the severity of OLD. Traver et al. demonstrated that it was inferior to FEV_1% for predicting mortality, given that FVC can be reduced in individuals with severe obstruction and air trapping, paradoxically increasing this ratio.[51] More recently, a new attempt was made to include the FEV_1/FVC ratio in the classification of airflow obstruction severity specifically in COPD,[59] suggesting that grading by the FEV_1/FVC ratio is similar to the GOLD classification of severity. Considering that the classification is for the assessment of the severity of airflow obstruction by lung function and not for the prognostic evaluation of patients with COPD alone, we opted to maintain only FEV_1% for the classification of the severity of obstruction in the present guideline.

Restriction: FVC

Although restriction is characterized by a reduction in TLC, few studies have evaluated the prognostic value of TLC in IPF, whereas the main clinical studies used FVC% as the primary outcome, this parameter being an independent prognostic factor, as well as being a reliable, reproducible measure that correlates well with clinical status in patients with IPF.[60]

With the aim of developing a simplified score capable of assessing the risk of mortality within 1 year, du Bois et al. evaluated data from 1,099 patients diagnosed with IPF.[61] An analysis of FVC% showed that, in comparison with patients with an FVC% > 80%, the risk of death was 5.9 times higher among those with an FVC% < 50% (95% CI: 2.6-6.4 times), 3.6 times higher among those with an FVC% of 51-65% (95% CI: 2.0-6.5 times), and 2.2 times higher among those with an FVC% of 66-79% (95% CI: 1.2-4.1 times).

The 2005 ATS/ERS guideline suggested that only the FEV_1% should be taken into account to classify the severity of all respiratory disorders (obstructive, restrictive, and mixed).[31] However, that proposal has been criticized because, in fibrosing lung diseases with restriction, the FEV_1% is better preserved by the greater elastic recoil than is the FVC, which results in an underestimation of the severity.[62] Therefore, the FVC% should be considered to classify the severity of restriction (all cutoff points mentioned are exemplified in Table S2 in the supplementary material). Chart 7 shows the proposed classification of RLD severity, and in the present guideline, we considered the best cutoff points to be those established in the aforementioned prognostic study of IPF conducted by Du Bois et al.[61]

Post-BD variation

Initial considerations

First, to assess post-BD variation, pre- and post-BD spirometry should meet all criteria for acceptance and reproducibility. Post-BD measurements cannot be interpreted if the pre-BD spirometry is not reproducible. In such cases, the post-BD test should not be performed. The pre- and post-BD efforts should be compared. A submaximal effort can result in higher FEV_1 values, with a false response to the bronchodilator.[63] Therefore, it is important to always check whether the PEF is acute pre- and post-BD and whether the highest post-BD value is ≥ 90% of the pre-BD value. Special attention should be paid to the pre- and post-BD forced expiratory time, since many patients are able to prolong expiration after bronchodilator use, with an increase in FVC. Therefore, to assess a significant variation in FVC after BD use, the post-BD forced expiratory time should not exceed 10% of that obtained in the pre-BD phase.[3]

Chart 7. Cutoff values for classifying the severity of Obstructive ventilatory impairment (on the basis of the post-bronchodilator FEV_1) and Restrictive ventilatory impairments (on the basis of the post-bronchodilator FVC), according to the recommendations of the current (2024) Brazilian Thoracic Association spirometry guidelines.

Severity	Obstruction	Restriction
	FEV_1%	FVC%*
Mild	≥ 60	> 65-LLN
Moderate	41-59	51-65
Severe	≤ 40	≤ 50

FEV_1%: FEV_1 in percentage of the predicted value; and FVC%: FVC in percentage of the predicted value. *Remember that the diagnosis of restrictive lung disease is based on the reduction of TLC. In the absence of this measurement, the report should be descriptive. Note: For individuals in whom spirometry was not able to define the presence of obstructive or restrictive lung disease, there is no recommendation regarding the classification of the severity of the disorder.

The assessment of BD response using FEV_1 and FVC is the most commonly used method in daily practice in pulmonary function laboratories. Flows derived from the flow-volume curve and the $FEF_{25\%-75\%}$ should not be considered in the assessment of BD reversibility.[26] Flows vary with airway caliber, which in turn depends on the lung volume at which they are measured. If lung volumes change after BD use (which is common), flows should be compared at the same lung volume (isovolume), which is not usually calculated.

The role of FVC variation is well established as an aggregator of FEV_1 variation. More severe obstruction results in greater improvement in FVC.[64,65] In patients with pulmonary emphysema, the post-BD variation in FVC is typically greater than is the post-BD variation in FEV_1.[66]

The use of a portable PEF meter to assess post-BD variation should be discouraged because FEF has lower sensitivity and specificity than do FEV_1 and FVC.[67]

Post-BD expressions and variations

The most common ways to express post-BD variation are absolute change, percentage increase in relation to the initial spirometric value, and percentage increase in relation to the predicted value (Chart 8).

A large study of 4,227 adults undergoing spirometry confirmed the advantages and disadvantages of the variations presented above.[68] Although the ATS/ERS guidelines published in 2005 considered the variation in relation to the initial value,[31] those published in 2022 consider it in relation to the predicted value.[26] The critique of this criterion is that it will be difficult for patients with low functional values to have a significant gain in relation to the expression in percentage of the predicted value. In the current guideline, we have maintained the recommendation to consider the variation in relation to the predicted value, which was already the expression adopted in the 2002 BTA guidelines,[3] although it is now not considered necessary to determine the gain in the absolute value (in mL).

Limits of post-BD variation in functional parameters

When we are confronted with the significance of a post-BD variation, we must ask ourselves to what aspect such significance refers. This point is critical given the heterogeneity across studies, which usually differentiate between significant variation that cannot be attributed to randomness and variation that is clinically significant. These aspects are analyzed in different cohorts, in analyses of symptomatic or at-risk individuals, or even in populations without such suspicion.

Regarding the value that best expresses a post-BD variation in percentage of predicted, a study that evaluated more than 10,000 healthy individuals in 14 different countries found the upper limits of variation to be 10% for FEV_1% and 9.2% for FVC%.[68] Based on these findings, the ATS/ERS recently adopted as a criterion a threshold of 10% of the predicted value to indicate a significant variation in FVC or FEV_1 in all spirometric tests, regardless of whether the results were categorized as normal or altered.[26]

A study conducted in Brazil evaluated the variation after administration of a placebo spray in 102 adult patients with airflow obstruction, with the aim of establishing the upper limits for changes in FEV_1, vital capacity, FVC, and IC resulting from random variation. Regarding the variation in relation to the predicted values, the maximum variations (upper limits of the 95% CIs) were found to be 6% and 7% for FVC and FEV_1, respectively.[69] In a large cohort study, a variation of > 8% in FEV_1% was found to be inversely associated with mortality in ill individuals and in a small proportion of healthy individuals.[70] Therefore, we recommend that a significant post-BD variation in FEV_1 or FVC be defined ≥ 10% of predicted for cases in which the pre-BD test result was categorized as normal and as an increase ≥ 7% of predicted for those in which it was categorized as abnormal.

The absence of significant variation after BD use does not imply that they should not be used in clinical practice, since other parameters not measured by spirometry can show reversibility. In addition, serial testing can show different values for the variation observed.

Post-BD variation in asthma and COPD

It is common to consider post-BD variation useful for making the distinction between asthma and COPD. One aspect of asthma is variability in lung function, bronchial hyperresponsiveness, and significant post-BD variation, the last being one of the criteria

Chart 8. Main expressions of variations after bronchodilator use. A hypothetical example was used for better clarification.

Example: FEV_1 = 500 mL; post-BD FEV_1 = 600 mL; FEV_1 = 2,500 mL		
Description	**Calculation**	**Advantages and disadvantages**
Absolute gain	(600 – 500) = 100 mL	Disadvantage: gain varies depending on sex, height, and age
Gain in % of baseline	(600 – 500) × 100 / 500 = 20%	Disadvantage: gain is inversely proportional to the degree of reduction in function at baseline
Gain in % of predicted value	[600 – 500] × 100 / 2500 = 4%	Advantage: minimizes the impact of differences in sex, age, height, and baseline function

BD: bronchodilator.

for the diagnosis of asthma established in the GINA and ERS guidelines.[71,72] However, in individuals with asthma, the spirometry results can be normal or show no significant post-BD variation, although neither condition excludes the diagnosis. Similarly, the idea that the absence of post-BD variation is necessary for the diagnosis of COPD is mistaken, since such variation is often present even in the absence of associated asthma. Therefore, the use of post-BD variation as the sole tool to differentiate between asthma and COPD is not recommended.[73-75] Patients with COPD who present a post-BD variation in FVC alone have more symptoms and worse lung function.[64]

Recommended bronchodilator and the interval between its administration and the post-BD testing

Given the availability and widespread use of albuterol, it is the recommended bronchodilator. It should be used at a dose of 400 μg, with a 15-min wait before performing the post-BD test.

FINAL CONSIDERATIONS

Spirometry is an essential diagnostic tool for any individual with or at risk of developing lung disease and is also a functional measurement to be used in individuals with higher-risk conditions, such as those who have undergone lung resection. For a correct diagnosis, it is essential that the spirometry findings be interpreted in conjunction with the clinical context and pretest probability for the individual. This concept becomes even more relevant for tests with borderline alterations. In this context, we suggest that the report not be limited to the functional diagnosis of obstruction or restriction and that expressions such as "correlate with clinical context or pretest probability" be used.

The choice of predicted values is important. Despite attempts by international initiatives to standardize the use of the GLI equation, we have seen significant differences in relation to other equations, mainly in that the GLI equation fails to characterize the presence of obstruction because it uses LLN values for the FEV_1/FVC ratio that are low in comparison with those predicted for the population of Brazil. It is of fundamental importance that new studies be conducted in order to update the reference values for adolescents, as well as for young women and men under 20 and 25 years of age, respectively.

Finally, the recommendation to characterize significant variation in bronchodilator response sought to adopt different limits for individuals with normal results on the initial spirometry tests than for those with functional abnormalities, because of the difference in the degree of response between those two populations.

AUTHOR CONTRIBUTIONS

All authors participated in the preparation and revision of the work, as well as approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) for multidrug- or rifampin-resistant tuberculosis: a systematic review

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ABSTRACT

Objective: To evaluate the available evidence comparing the use of the bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) regimen for 6 months with that of standard-of-care regimens for patients with multidrug-resistant or rifampin-resistant tuberculosis (MDR/RR-TB). **Methods:** This was a systematic review of clinical trials comparing the use of the BPaLM regimen with the standard of care in patients with MDR/RR-TB. The main outcome measure was an unfavorable endpoint (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, and recurrence), and secondary outcome measures included adverse events and serious adverse events. We searched the MEDLINE, EMBASE, Google Scholar, LILACS, and ClinicalTrials.gov databases, from their inception to January 31, 2024, with no limitation as to language or year of publication. The risk of bias was assessed by using the Cochrane risk-of-bias tool, and the quality of evidence was based on the Grading of Recommendations Assessment, Development and Evaluation approach. **Results:** A total of 3,668 studies were retrieved; only one (a randomized clinical trial) met the inclusion criteria and was included. In patients with MDR/RR-TB, treatment with the BPaLM regimen, when compared with the standard of care, reduced the risk of an unfavorable outcome (composite, number needed to treat [NNT] = 7); early treatment discontinuation (NNT = 8); adverse events and discontinuation (NNT = 12); and serious adverse events (NNT = 5). **Conclusions:** This systematic review of the use of BPaLM in patients with MDR/RR-TB, although it included only one study, showed that BPaLM is more effective than is the standard of care and has a better safety profile. That has major implications for guidelines on the treatment of MDR/RR-TB.

Keywords: Tuberculosis, multidrug-resistant; Antitubercular agents; Diarylquinolines; Linezolid; Moxifloxacin; Nitroimidazoles.

INTRODUCTION

The tuberculosis epidemic is a major global health problem, and drug-resistant tuberculosis contributes to its mortality worldwide. Globally, an estimated 410,000 people developed multidrug-resistant or rifampin-resistant tuberculosis (MDR/RR-TB) in 2022. However, only approximately two in five were diagnosed and started on treatment.[1] In addition, there is evidence suggesting that MDR-TB plays an important role in the development of post-tuberculosis lung disease, which is responsible for disability requiring rehabilitation.[2]

With longer treatment regimens, the treatment success rate in patients with MDR-TB is low (approximately 50%). A longer duration of treatment is associated with nonadherence and loss to follow-up. Therefore, the use of shorter treatment regimens that are efficacious and safe could significantly improve treatment success rates in MDR/RR-TB.[3]

The 2022 World Health Organization (WHO) consolidated guidelines from 2022 suggest the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg), and moxifloxacin (BPaLM) rather than the 9-month or longer (typically 18-month) regimens for MDR/RR-TB. In cases of documented resistance to fluoroquinolones, the same regimen but without moxifloxacin (the BPaL regimen) should be used.[4] Therefore, the objective of this systematic review was to evaluate the available evidence in favor of using the BPaLM regimen for 6 months, compared with other regimens, in patients with MDR/RR-TB.

METHODS

This systematic review adhered to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, and the study protocol conformed to the Grading of Recommendations

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Assessment, Development, and Evaluation (GRADE) framework.[5] Because we did not include individual patient data and all data used in the analysis had previously been published, no institutional review board approval was required. The intervention of interest was the use of the BPaLM regimen in patients with pulmonary MDR/RR-TB. The Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest framework was as follows: Patients—adults with pulmonary MDR/RR-TB; Intervention—BPaLM regimen; Comparison—with other regimens; and Outcomes—an unfavorable outcome (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, and recurrence), each of the outcomes in the composite measure, adverse events, and serious adverse events. Treatment failure was defined as need to discontinue or permanently replace at least two treatment drugs with a new regimen, because of adverse events or lack of conversion by the end of the intensive phase; because of bacteriological reversion (new positive culture) in the continuation phase after conversion to negative; or because of evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs. Loss to follow-up was defined as a patient whose treatment was interrupted for 2 or more consecutive months. We conducted a comprehensive search for randomized clinical trials and observational comparative studies, without imposing restrictions on the date of publication. The inclusion criteria encompassed studies available in full or with summaries and data in Portuguese, Spanish, English, or Italian. The protocol was registered on the international Prospective Register of Systematic Reviews platform (Protocol no. CRD42024527168). One author developed a search strategy that was revised and approved by the team, selected information sources, and systematically searched the following databases: MEDLINE, EMBASE, Google Scholar, LILACS, and ClinicalTrials.gov. The following search string was applied in the MEDLINE and EMBASE databases: (tuberculosis, multidrug-resistant OR drug-resistant tuberculosis OR MDR tuberculosis OR rifampicin-resistant tuberculosis) AND [(diarylquinolines OR bedaquiline) OR (fluoroquinolones OR moxifloxacin) OR (oxazolidinones OR linezolid) OR (nitroimidazoles OR pretomanid)]. For Google Scholar, LILACS and ClinicalTrials.gov, the search strategy was as follows: (tuberculosis) AND (bedaquiline AND moxifloxacin AND linezolid AND pretomanid).

Data extraction included information on authorship, publication year, patient characteristics, interventions, absolute numbers for each outcome, and follow-up duration. The extracted values underwent thorough comparison (Figure 1).

The risk of bias assessment utilized the modified Cochrane risk-of-bias tool.[6] The domains assessed were the randomization process (random sequence generation and allocation concealment), deviations from intended interventions (blinding), missing outcome data, bias in the measurement of the outcome, and selection of the reported results (intention-to-treat analysis, sample size estimation, and early interruption). Risk levels were categorized as low, high, or very high. A meta-analysis was conducted, and the quality of the evidence was assessed by the GRADE approach, the quality of evidence thus being categorized as high, moderate, low, or very low.[7]

The results related to the outcomes are expressed as continuous measures (means and differences of means) or categorical measures (absolute numbers and percentages, risk, or risk differences), with 95% confidence intervals. The analysis was performed with the software Review Manager, version 5.4 (RevMan 5; Cochrane Collaboration, Oxford, UK).[8]

RESULTS

A total of 3,668 studies were retrieved: 3,228 from MEDLINE; 107 from EMBASE; 333 from Google Scholar; 0 from ClinicalTrials.gov; and 0 from LILACS. After review of the title and abstracts, 3,478 manuscripts were excluded and 190 were selected for full text review. Of those 190 studies, one was included to support this evaluation.[9]. The only study included reported a two-stage, phase 2-3 randomized clinical trial with four intervention arms and one control arm. Therefore, it was not possible to perform a meta-analysis. However, since the study included had two distinct intervention arms with regimens that included BPaL, we used the statistical strategies typically used in meta-analyses to perform an indirect comparison between the results obtained with BPaL, with and without moxifloxacin, and the standard of care.

The study evaluated involved patients with RR-TB, detected before the start of the intervention. The intervention groups were as follows: arm 1—BPaL, consisting of bedaquiline at a dose of 400 mg daily for 2 weeks followed by 200 mg three times a week for 22 weeks, pretomanid at a dose of 200 mg daily for 24 weeks, and linezolid at a dose of 600 mg daily for 16 weeks followed by 300 mg daily for 8 weeks; and arm 2—BPaLM, with a regimen similar to the BPaL regimen, together with moxifloxacin at a dose of 400 mg daily for 24 weeks. The comparison considered in this analysis was any of the standard WHO-recommended regimens, which could vary according to the country/site, for 44-90 weeks, depending on the regimen used (Table 1).

The outcome measures used in our analysis were an unfavorable outcome (composite outcome including death, treatment failure, early treatment discontinuation, loss to follow-up, or recurrence), death, treatment failure, early treatment discontinuation, loss to follow-up, recurrence, and adverse events. A follow-up time of up to 72 weeks was considered (Table 2).

Risk of bias

In the study evaluated,[9] the risk of bias was very high because of a lack of blinding, losses ≥ 20%, the

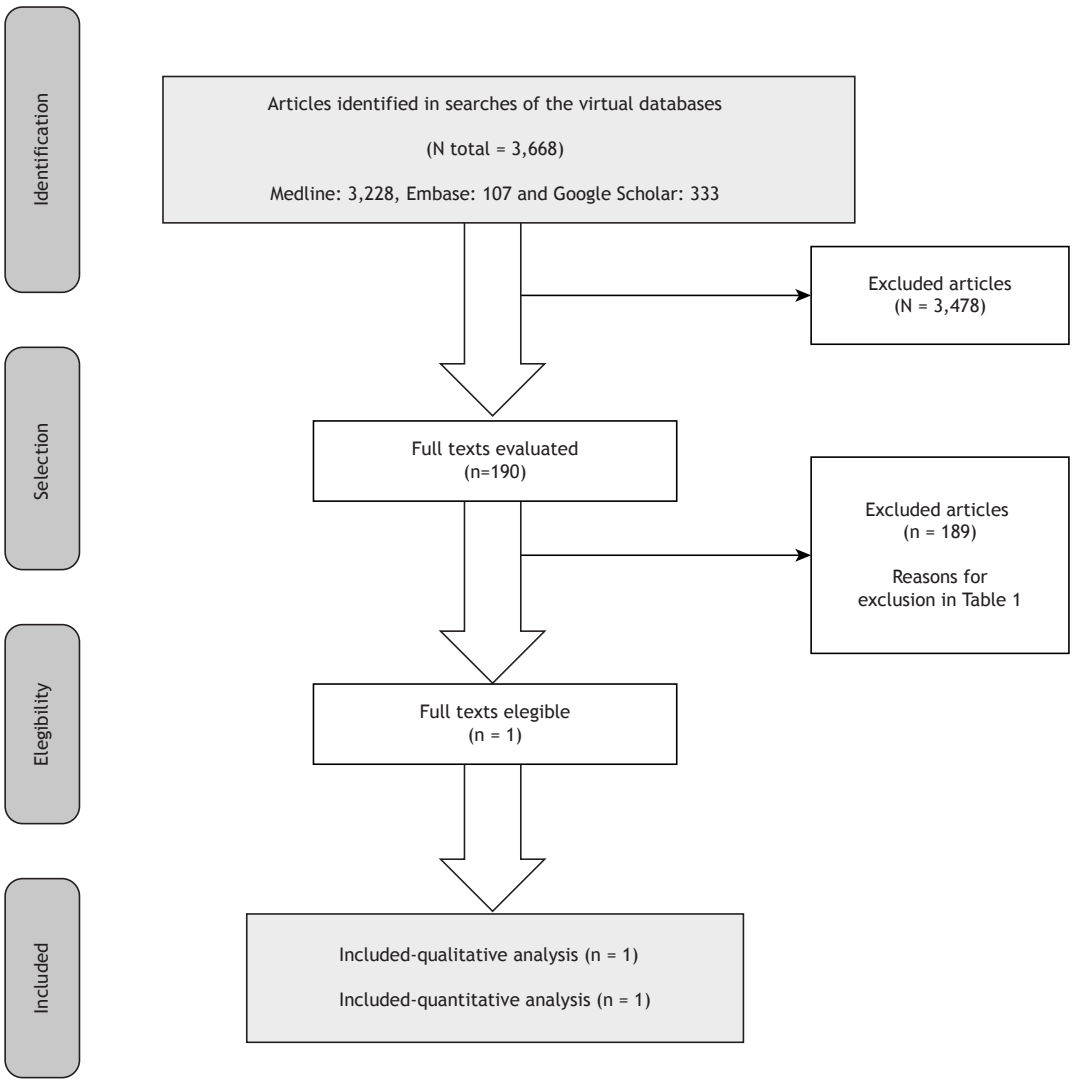

Figure 1. Flow chart of the evidence retrieval and selection process.

lack of an intention-to-treat analysis, the absence of sample size calculation, and early interruption (Table 3).

Results of the analysis by outcome

The risk of an unfavorable outcome was 14% lower (range, 6-23% lower) in the patients treated with the BPaLM regimen than in those receiving the standard of care. The same did not occur in the patients treated with the BPaL regimen (no difference in relation to the standard of care), as illustrated in Figure 2A. The quality of evidence for that risk was categorized as low (Table 4).

The risk of death in the patients treated with the BPaLM or BPaL regimen did not differ from that calculated for those receiving the standard of care (Figure 2B). The quality of evidence for that risk was categorized as low (Table 4).

The risk of recurrence in the patients treated with the BPaLM or BPaL regimen did not differ from that calculated for those receiving the standard of care (Figure 2C). The quality of evidence for that risk was categorized as very low (Table 4).

The risk of early discontinuation of treatment was 13% lower (range, 5-21% lower) in the patients treated with the BPaLM regimen than in those receiving the standard of care. The same did not occur in the group treated with the BPaL regimen (no difference in relation to the standard of care), as shown in Figure 3A. The quality of evidence for that risk was categorized as low (Table 4).

In comparison with the patients receiving the standard of care, the risk of adverse events leading to treatment discontinuation was 8% lower (range, 2-14% lower) in the patients treated with the BPaLM regimen and 7% lower (range, 1-13% lower) in those treated with the BPaL regimen (Figure 3B). The quality of evidence for that risk was categorized as low (Table 4).

Table 1. Description of the study included in the analysis.

FIRST AUTHOR	YEAR	DESIGN	PATIENTS	INTERVENTION	COMPARISON	OUTCOMES	TIME
Nyang'wa BT	2022	Phase II-III RCT	RR-TB (N = 123)	BPaL: bedaquiline at a dose of 400 mg daily for 2 weeks, followed by 200 mg three times per week for 22 weeks; pretomanid at a dose of 200 mg daily for 24 weeks; and linezolid at a dose of 600 mg daily for 16 weeks, followed by 300 mg daily for 8 weeks	BPaL + clofazimine at a daily dose of 100 mg (or 50 mg if the patient weighed < 30 kg) for 24 weeks or standard of care	Unfavorable outcome (a composite of death, treatment failure, treatment discontinuation, loss to follow-up, recurrence, and adverse events)	72 weeks
			RR-TB (N = 151)	BpaL + moxifloxacin at a dose of 400 mg daily for 24 weeks			

RCT: randomized clinical trial; RR-TB: rifampin-resistant tuberculosis; and BPaL: bedaquiline, pretomanid, and linezolid.

Table 2. Outcomes submitted for analysis.

STUDY	UNFAVORABLE OUTCOME (n/N)		DEATH (n/N)		EARLY DISCONTINUATION (n/N)		RECURRENCE (n/N)		ADVERSE EVENTS (DISCONTINUATION) (n/N)		SERIOUS ADVERSE EVENTS (n/N)		LOST TO FOLLOW-UP (n/N)	
	BPaL(M)	SOC	BPaL(M)	SOC	BPaL(M)	SOC	BPaL(M)	SOC	BPaL(M)	SOC	BPaL(M)	SOC	BPaL(M)	SOC
BPaL[9]	24/123	39/152	0/123	2/152	18/123	35/152	3/123	0/152	5/123	17/152	15/123	43/152	3/123	2/152
BPaLM[9]	17/151	39/152	0/151	2/152	15/151	35/152	0/151	0/152	5/151	17/152	14/151	43/152	2/151	2/152

BPaL: bedaquiline, pretomanid, linezolid; BPaLM: BPaL + moxifloxacin; and SOC: standard of care.

Table 3. Risk of bias in the study evaluated.[9]

RANDOMIZATION	BLINDED ALLOCATION	DOUBLE BLIND	BLINDED EVALUATOR	LOSSES	PROGNOSTIC CHARACTERISTICS	APPROPRIATE OUTCOMES	ITT ANALYSIS	SAMPLE ESTIMATION	EARLY INTERRUPTION	ADJUSTMENT FOR CONFOUNDERS
Low	Low	High	High	High	Low	Low	High	High	High	Low

ITT: intention-to-treat.

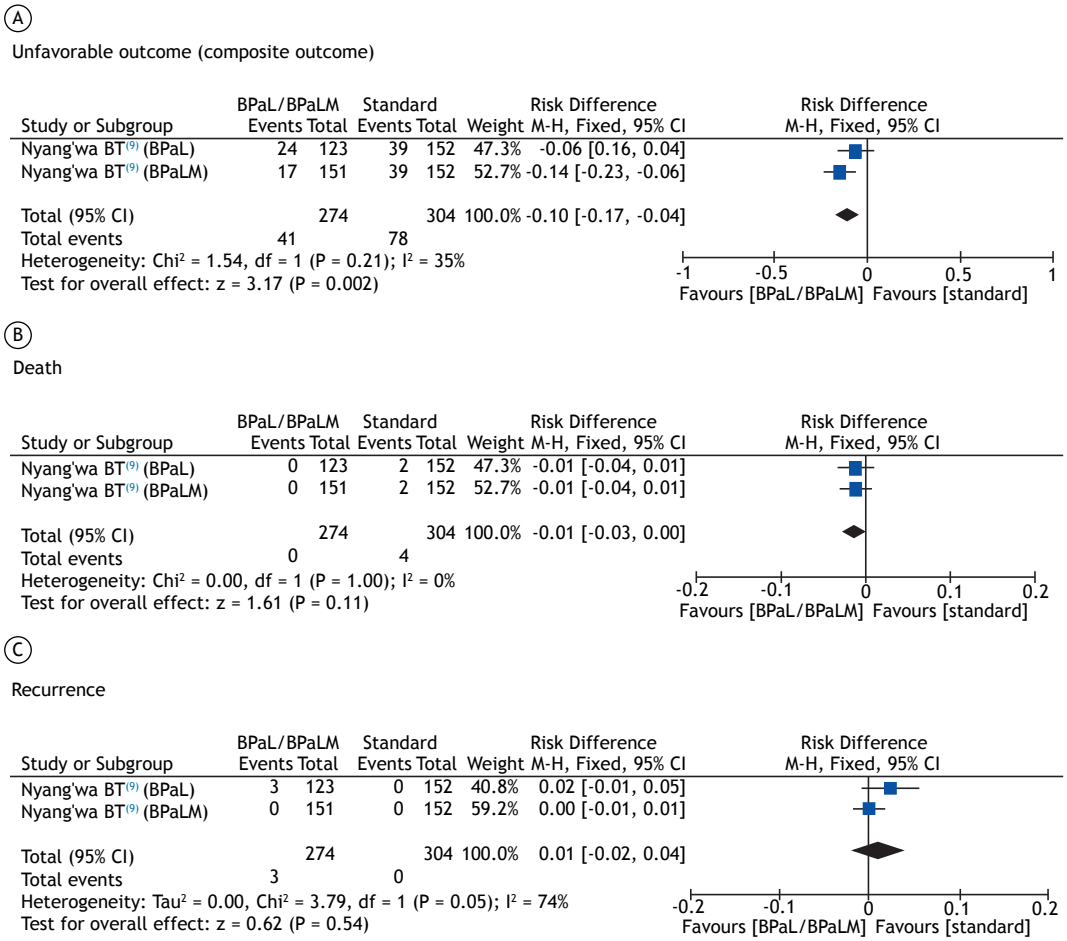

Figure 2. Analysis of the risk of (A) an unfavorable outcome (composite outcome), (B), death, and (C) recurrence, in patients treated with bedaquiline, pretomanid, and linezolid, with or without moxifloxacin (BPaL and BPaLM, respectively).

In comparison with the patients receiving the standard of care, the risk of serious adverse events was 19% lower (range, 10-28% lower) in the patients treated with the BPaLM regimen and 16% lower (range, 7-25% lower) in those treated with the BPaL regimen (Figure 3C). The quality of evidence for that risk was categorized as low (Table 4).

The risk of loss to follow-up in the patients treated with the BPaLM or BPaL regimen did not differ from that calculated for those receiving the standard of care (Figure 3D). The quality of evidence for that risk was also categorized as low (Table 4).

Synthesis of the evidence

In patients with RR-TB:

- Treatment with the shorter BPaLM regimen, when compared with the standard of care, reduces the risk of an unfavorable (composite) outcome (number needed to treat [NNT] = 7); early treatment discontinuation (NNT = 8); adverse events leading to discontinuation (NNT = 12); and serious adverse events (NNT = 5).
- Treatment with the BPaL regimen, when compared with the standard of care, reduces the risk of adverse events leading to discontinuation (NNT = 14); and serious adverse events (NNT: 7).

DISCUSSION

In this systematic review examining the efficacy and safety of the BPaLM regimen in patients with MDR/RR-TB, we found that treatment with BPaLM reduces the risk of an unfavorable outcome in comparison with the standard of care. In addition, the rates of early treatment discontinuation, adverse events leading to treatment discontinuation, and serious adverse events were lower in the BPaLM group than in the standard-of-care group. Adding moxifloxacin to the BPaL regimen in patients with MDR/RR-TB is recommended because it resulted in a lower risk of an unfavorable outcome and of early treatment discontinuation, as well as to a greater reduction in the risk of adverse events.

In the study evaluated in this systematic review,[9] 11% of the patients in the BPaLM group and 48% of those in the standard-of-care group evolved to at least one of the outcomes included in the composite primary outcome measure (unfavorable outcome).

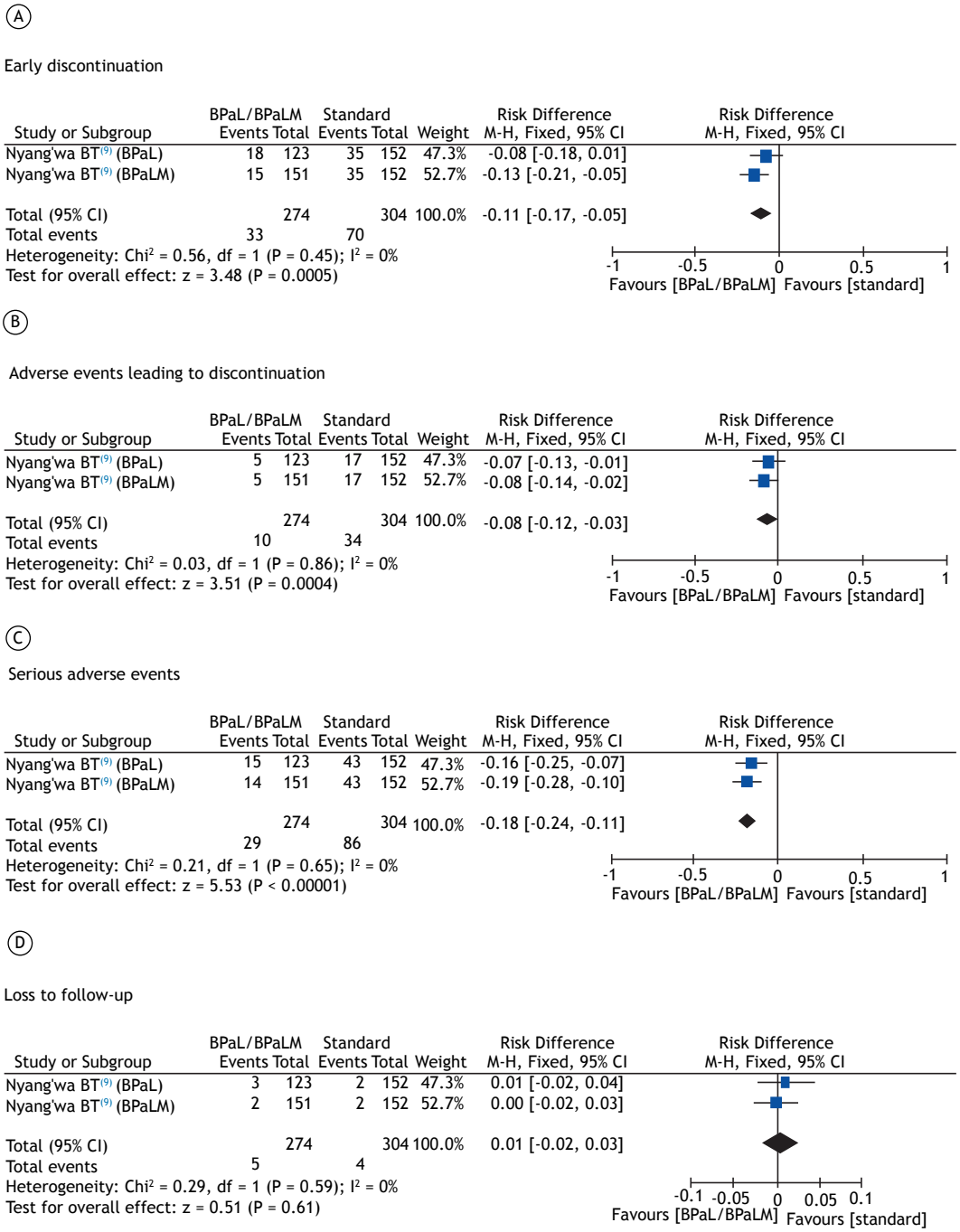

Figure 3. Analysis of the risk of (A) early discontinuation, (B), adverse events leading to discontinuation, (C) serious adverse events, and (D) loss to follow-up, in patients treated with bedaquiline, pretomanid, and linezolid, with or without moxifloxacin (BPaL and BPaLM, respectively).

The per-protocol analysis showed that at least one of those outcomes occurred in 4% of the patients in the BPaLM group and in 12% of those in the standard-care group. Although the fact that only one randomized trial has been published on the subject somewhat limits our certainty around this issue, it was a pragmatic trial, which increases generalizability, its result has already changed practice, and this regimen is now recommended by the WHO.[4] Reasons for the paucity of randomized clinical trials on the subject include the fact that for many decades no new drugs were approved to treat tuberculosis (bedaquiline was licensed in 2012) and a lack of funding for trials with expensive drug regimens in low- and middle-income countries, where MDR-TB is more common. Further evidence supporting its efficacy include the fact that the results are similar to those of two other studies,[10,11] involving shorter BPaL regimens in

Table 4. Quality of evidence regarding the use of bedaquiline, pretomanid, and linezolid, with or without moxifloxacin, in rifampin-resistant tuberculosis.

Certainty assessment							N of patients		Effect		Certainty	Importance
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BPaL or BPaLM n/N (%)	Standard of care n/N (%)	Relative (95% CI)	Absolute (95% CI)		
RISK OF AN UNFAVORABLE OUTCOME												
2	randomized trials	very serious[a]	not serious	not serious	not serious	none	41/274 (15.0)	78/304 (25.7)	RR 0.59 (0.42 to 0.83)	105 fewer per 1,000 (from 149 fewer to 44 fewer)	⊕⊕OO Low	Critical
RISK OF DEATH												
2	randomized trials	very serious[a]	not serious	not serious	not serious	none	0/274 (0.0)	4/304 (1.3)	RR 0.22 (0.03 to 1.89)	10 fewer per 1,000 (from 13 fewer to 12 higher)	⊕⊕OO Low	Critical
RISK OF EARLY DISCONTINUATION												
2	randomized trials	very serious[a]	not serious	not serious	not serious	none	33/274 (12.0)	70/304 (23.0)	RR 0.53 (0.36 to 0.77)	108 fewer per 1,000 (from 147 fewer to 53 fewer)	⊕⊕OO Low	Critical
RISK OF RECURRENCE												
2	randomized trials	very serious[a]	serious[b]	not serious	not serious	none	3/274 (1.1)	0/304 (0.0)	RR 8.64 (0.45 to 165.63)	0fewer per 1,000 (from 0 fewer to 0 fewer)	⊕OOO Very low	Major
RISK OF ADVERSE EVENTS (DISCONTINUATION)												
2	randomized trials	very serious[a]	not serious	not serious	not serious	none	10/274 (3.6)	34/304 (11.2)	RR 0.33 (0.17 to 0.65)	75 fewer per 1,000 (from 93 fewer to 39 fewer)	⊕⊕OO Low	Major
RISK OF SERIOUS ADVERSE EVENTS												
2	randomized trials	very serious[a]	not serious	not serious	not serious	none	29/274 (10.6)	86/304 (28.3)	RR 0.38 (0.26 to 0.55)	175 fewer per 1,000 (from 209 fewer to 127 fewer)	⊕⊕OO Low	Major
RISK OF LOSS TO FOLLOW-UP												
2	randomized trials	very serious[a]	not serious	not serious	not serious	none	5/274 (1.8)	4/304 (1.3)	RR 1.41 (0.39 to 5.14)	5 higher per 1,000 (from 8 fewer to 54 higher)	⊕⊕OO Low	Major

[a]No blinding, no intention-to-treat analysis, losses above 20%, no sample calculation, and interrupted early. [b]Heterogeneity ≥ 75%

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patients with extensively drug-resistant tuberculosis, that demonstrated a successful outcome in 84% and 93% of the patients, respectively. Conradie et al.[11] conducted a randomized trial of treatment for highly drug-resistant tuberculosis with bedaquiline and pretomanid, together with linezolid at two different doses, each with two different durations. All four treatment groups had favorable outcomes in the vast majority of patients (84-93%), the regimen with the best risk-benefit ratio being the one in which linezolid was used at a dose of 600 mg for 26 weeks.

Other shorter regimens have also been shown to be associated with successful outcomes in most patients. The STREAM trial[12] compared a short regimen (of 9-11 months) including moxifloxacin at a high-dose with a long, WHO-recommended regimen (of 20 months), for the treatment of patients with RR-TB. In the short regimen group, 78.8% of the patients had a favorable outcome, demonstrating that it was noninferior to the long regimen. In a retrospective cohort analysis on patients with RR-TB treated with a standardized all-oral short regimen (including bedaquiline and linezolid as the core drugs), treatment success was achieved in 75.2% of the patients.[13] The final analysis of the trial included in our review corroborates, with improved precision, the noninferiority of the BPaLM regimen when compared with the standard of care.[14] Recently, the regimen of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide showed promising results.[15]

Our study has some limitations. First, only one study met the inclusion criteria and was included for analysis. Therefore, a meta-analysis could not be performed. However, we evaluated each intervention arm that included BPaL, in comparison with the standard of care. More studies are needed in order to confirm these findings. Shorter regimens using newer antituberculosis drugs are relatively new, and there are several combinations of drugs that can be used. Therefore, this meta-analysis may need to be updated as more clinical trials of this treatment strategy are published. Second, the randomized trial evaluated was interrupted early for efficacy after recruitment of 75% of the planned sample, which could have resulted in an overestimation of the treatment effect.[16] Finally, the standard-of-care regimens varied across studies and could be updated as the WHO makes new treatment recommendations, although all regimens were in line with current WHO recommendations. Despite these limitations, the population included in the study was diverse, including HIV-coinfected patients and patients with fluoroquinolone-resistant tuberculosis, covering a broad spectrum of cases of RR-TB.

In conclusion, this systematic review of the use of BPaLM in patients with RR-TB found that treatment with this regimen is more effective and has a better safety profile in comparison with the standard of care. This finding has major implications for the development of new treatment guidelines that can contribute to better outcomes in tuberculosis treatment worldwide.

AUTHOR CONTRIBUTIONS

DRS and FCQM participated in the study design; search strategy; data analysis; drafting of the manuscript; writing and critical review of the manuscript; and project supervision.

FFF and JCF participated in the study design; search strategy; data analysis; writing and critical review of the manuscript; and project supervision.

MMPD and FDCJ participated in the study design; data analysis; and writing and critical review of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Multimodal treatment of chronic thromboembolic pulmonary hypertension: initial experience at a university hospital in southern Brazil

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TO THE EDITOR:

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease. The current classification of pulmonary hypertension divides it into five main groups based on the underlying cause, with CTEPH being the main cause in group 4.[1] Nonresolution of pulmonary arterial thrombi is the underlying pathophysiological mechanism. When associated with hyperflow vasculopathy in patent vessels, the disease progresses, culminating in right heart failure and death. The preferred treatment is pulmonary endarterectomy (PEA), which is indicated for patients with resectable lesions and acceptable surgical risk. For inoperable cases, drug treatment and balloon pulmonary angioplasty (BPA) are available. Here, we report two cases of patients treated with the currently recommended multimodal approach.

The first patient was a 59-year-old nonsmoker male who had been diagnosed with CTEPH three years before. Warfarin, furosemide, and a phosphodiesterase-5 inhibitor were prescribed. In March of 2023, the patient was evaluated by the pulmonary circulation team at the *Hospital de Clínicas de Porto Alegre*, located in the city of Porto Alegre, Brazil. His WHO functional class was IV, and he presented with clinical signs of right heart failure. A transthoracic echocardiogram showed a dilated right ventricle, as well as severe systolic dysfunction and elevated pulmonary artery systolic pressure (Table 1). Perfusion scintigraphy, CT angiography of the chest, and pulmonary arteriography showed complete occlusion of branches to the right middle and lower lobes (Figure 1), as well as bilateral stenotic, web-like lesions in branches to the other lung lobes. Right heart catheterization confirmed severe precapillary pulmonary hypertension (Table 1), with an estimated 1-year mortality > 20%.[1] During our multidisciplinary board meeting, the disease was considered surgically accessible, despite a very high surgical risk. The left lung lesions were treatable by PEA and BPA. A multimodal approach was proposed, including switching from tadalafil to riociguat; BPA on the left side; and PEA on the right. Between April and July of 2023, the patient underwent four BPA sessions aimed at reducing pulmonary vascular resistance and improving rehabilitation, thus reducing the surgical risk. Three to six branches were treated in each session (Figures 1). Selective segmental and subsegmental angiographies were performed with 6 Fr JR4, multipurpose, and JL3.5 guide catheters. The lesions in branches A1, A3, A5, A6, A7, A8, A9, and A10 were crossed with HI-TORQUE™ balance middleweight universal and Runthrough™ guidewires (Abbott Cardiovascular, Plymouth, MN, USA; and Terumo Corporation, Tokyo, Japan, respectively) and dilated with Euphora™ (Medtronic, Minneapolis, MN, USA) ballon catheters of 2.0 mm × 20 mm, 2.5 mm × 20 mm, 3.0 mm × 20 mm, 3.5 mm × 20 mm, and 4.0 mm × 20 mm for improvement in antegrade flow and venous return. There were no immediate complications. In September of 2023, PEA was performed under extracorporeal circulation (ECC), cooling down to 19°C. PEA was performed on the right side only, with circulatory arrests of 20 min and 12 min. The left side was not explored. Total ECC time was 240 min, and aortic cross-clamp time was 68 min. Anticoagulation with unfractionated heparin began 6 h after surgery. The patient was extubated on postoperative day (POD) 1. Pacemaker wires and drains were removed between PODs 2 and 4, and the patient was discharged from the ICU on POD 4. He was started on warfarin and was sent home on POD 10. Riociguat was discontinued. At two months after surgery, the patient was in WHO functional class I, showing better hemodynamics and exercise capacity (Table 1).

Our second patient was a 69-year-old nonsmoker male on sildenafil. The surgical risk was high, coronary angiography showing a 90% narrowing of the mid-segment right coronary artery and an 80% narrowing of the ostium of the posterior descending artery. Therefore, in March of 2023 multimodal treatment began by stenting the coronary vessels (Figure 1), with the patient being started on riociguat. Subsequently, branches A2, A4, A5, A7, A8, A9, and A10 on the left side were submitted to BPA. Finally, right-sided PEA was uneventfully performed in December of 2023, with a total ECC time of 290 min, an aortic cross-clamp time of 40 min, and a circulatory arrest of 10 min; again, the left side was not explored. Extubation and discharge from the ICU and the hospital occurred on PODs 1, 5, and 12, respectively. At three months after surgery, the patient was in WHO functional class I and otherwise asymptomatic.

CTEPH has encouraging survival rates when properly treated. Lifelong anticoagulation is of utmost

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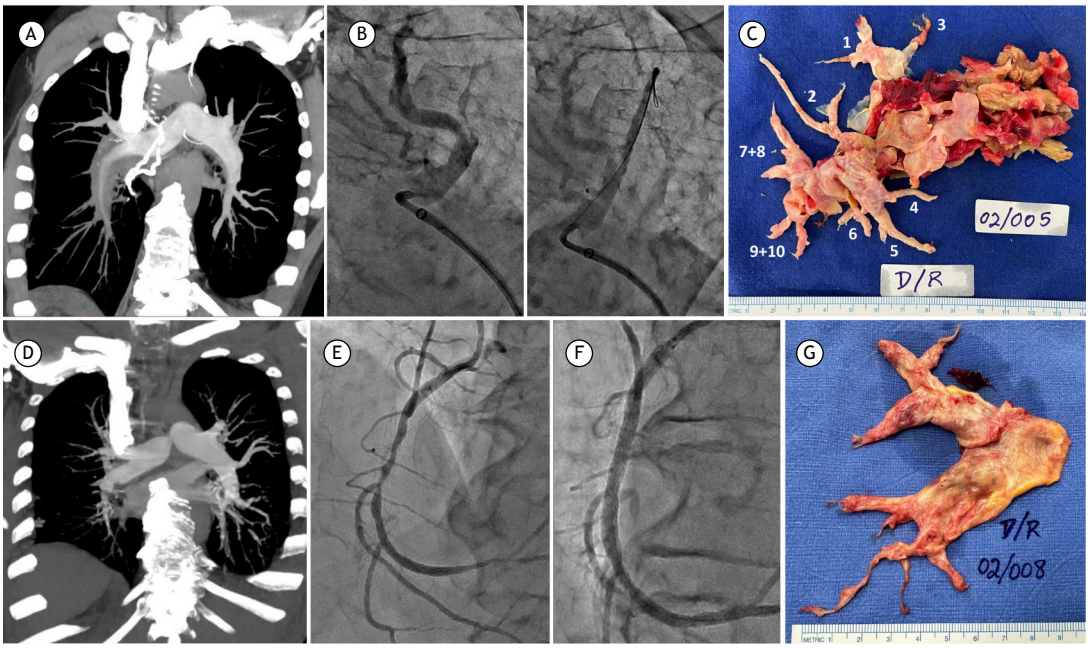

Figure 1. Multimodal treatment of two patients (patient 1, Figures 1A-D; patient 2, Figures 1E-H) with chronic thromboembolic pulmonary hypertension. In A, CT angiography of the chest showing the anatomical difference between the right and left sides. In B, stenotic lesion, left A3 branch. In C, balloon pulmonary angioplasty of the same branch with a 3 mm contrast-filled balloon and a guidewire. In D, surgical specimen, right side. The numbers indicate the corresponding arterial branches. In E, CT angiography of the chest showing central lesions on the right and peripheral lesions on the left. In F, right coronary artery showing multiple stenotic lesions. In G, right coronary artery showing clear flow improvement after stenting. In H, surgical specimen, right side.

Table 1. Clinical data before and after multimodal treatment of chronic pulmonary hypertension.

	Patient 1			Patient 2		
	Baseline on tadalafil	Post-riociguat + BPA	Post-surgery	Baseline on sildenafil	Post-riociguat + PCI + BPA	Post-surgery
WHO FC	IV	II	I	III	I	I
6MWD, m	211	350	475	200	353	378
BNP, pg/mL	526	221	54	408	210	35
TRV, m/s	4.2	3.6	2.3	4.3	4.2	2.7
PASP, mmHg	84	67	30	90	76	34
TAPSE, mm	14	15	18	15	12	8
RVFAC, %	15	25	33	24	18	30
mPAP, mmHg	47	38	22	51	45	21
CO, L/min	3.4	4.3	5.4	6.1	5.2	6.4
TPR, WUm^2	13.8	8.8	4.1	8.3	8.6	3.2
RAP, mmHg	8	10	6	8	9	5

BPA: balloon pulmonary angioplasty; PCI: percutaneous coronary intervention; FC: functional class; 6MWD: six-minute walk distance; BNP: brain natriuretic peptide. TRV: tricuspid regurgitation velocity; PASP: pulmonary artery systolic pressure, as estimated by echocardiography; TAPSE: tricuspid annular plane systolic excursion; RVFAC: right ventricular fractional area change; mPAP: mean pulmonary artery pressure; CO: cardiac output; TPR: total pulmonary resistance (mPAP/CO); and RAP: right atrial pressure.

importance.[2] Target-specific drugs for pulmonary hypertension are aimed at vasodilating and remodeling areas of preserved flow, reducing pulmonary vascular resistance, increasing cardiac output, and slowing the progression of vasculopathy. The soluble guanylate cyclase stimulator riociguat is the first-line drug.[3] However, mechanical treatments are the most effective and should be offered as the first choice.[4] PEA results in long-term survival rates > 80% and mortality rates of < 5% in specialized centers.[5] Nonetheless, only a few centers have the required technical expertise. BPA has gained momentum as an alternative treatment for inoperable disease and high surgical risk candidates. BPA targets small-caliber vessels but is not useful for central obstruction.

A nonrandomized comparative study conducted in Japan demonstrated the safety of bilateral sequential BPA and PEA for very high-risk patients.[6] In the

aforementioned study,[6] branches subjected to BPA were also surgically approached without interfering with the dissection plane. In a small case series, unilateral PEAs and contralateral BPA during the rewarming phase of surgery showed good results.[7] Sequential multimodal treatment has recently been described as an alternative to upfront PEA in high surgical risk patients with mixed lesions, i.e., surgically accessible on one side only.[8] Drug treatment is commonly the treatment of first choice because of its immediate availability and because of evidence of improved prognosis in high-risk PEA patients with the use of target-specific drugs.[9] The rationale is to approach mechanically (with BPA) the distal disease on the least affected side for improvement of symptoms, pulmonary vascular resistance, and cardiac output. Use of riociguat before BPA also reduces complications.[4] The combination of drugs and BPA may lower the surgical risk, allowing the most diseased side to be surgically approached, with shorter aortic cross-clamp/cardioplegia and circulatory arrest times.[8] At our center, the average circulatory arrest time is 38 min for bilateral cases, and in the cases reported here the most surgically challenging sides were not even explored. The surgical principles are the same for both approaches: adequate visualization of the dissection plane, circulatory arrest at 18-20°C, and complete clearance of all branches.[10]

Here, we observed the effect of combining optimized drug therapy and BPA. We believe that reduced pulmonary vascular resistance and increased cardiac output contributed to reducing the surgical risks. To the best of our knowledge, this is the first report of multimodal treatment of CTEPH in Brazil. This approach allows high-risk patients to undergo PEA safely.

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AUTHOR CONTRIBUTIONS

WL: conceptualization; data curation; project administration; writing—original draft; and writing—review and editing. RVW: validation; resources; and writing—review and editing. RPR: conceptualization; methodology; and writing—review and editing. IGB: data curation; methodology; and writing—review and editing. MBG: conceptualization; methodology; project administration; writing—original draft; and writing—review and editing.

CONFLICTS OF INTEREST

None declared.

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Primary pulmonary Hodgkin lymphoma presenting as cavitary lung lesions

Roberta Wartchow Machado[1], Felipe Welter Langer[1], Rodrigo dos Santos Ferrari[1,2,3]

A 27-year-old male smoker presented with a six-month history of chest discomfort and hemoptysis. His past medical history was otherwise unremarkable. Tuberculosis and immunodeficiency screenings were negative. An unenhanced chest CT scan revealed a 7-cm mass in the left upper lobe and prevascular lymphadenopathy (Figure 1A). Percutaneous and transbronchial biopsies were inconclusive. Follow-up imaging evidenced an increase in lesion size and central cavitation, as well as new bilateral peribronchial cavitary nodules (Figures 1B-1D). A left upper lobectomy was performed, and histopathological examination of the surgical specimen confirmed the diagnosis of nodular sclerosis Hodgkin lymphoma (Figures 1E and 1F).

Primary pulmonary Hodgkin lymphoma (PPHL) accounts for less than 1% of all lymphomas, nodular sclerosis being the most common type.[1,2] Symptoms are nonspecific and may include weight loss, fever, dry cough, and chest discomfort. On imaging, PPHL has a predilection for the upper lobes and may present as unilateral or bilateral parenchymal consolidations or nodules, which may cavitate in about 20% of cases.[1-3] Histological confirmation through incisional biopsy may be challenging because of background inflammation and necrosis, excisional biopsy being frequently required to establish a diagnosis.[3] Therefore, PPHL should be included in the differential diagnosis of otherwise unexplained parenchymal consolidations and cavitary nodules.

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

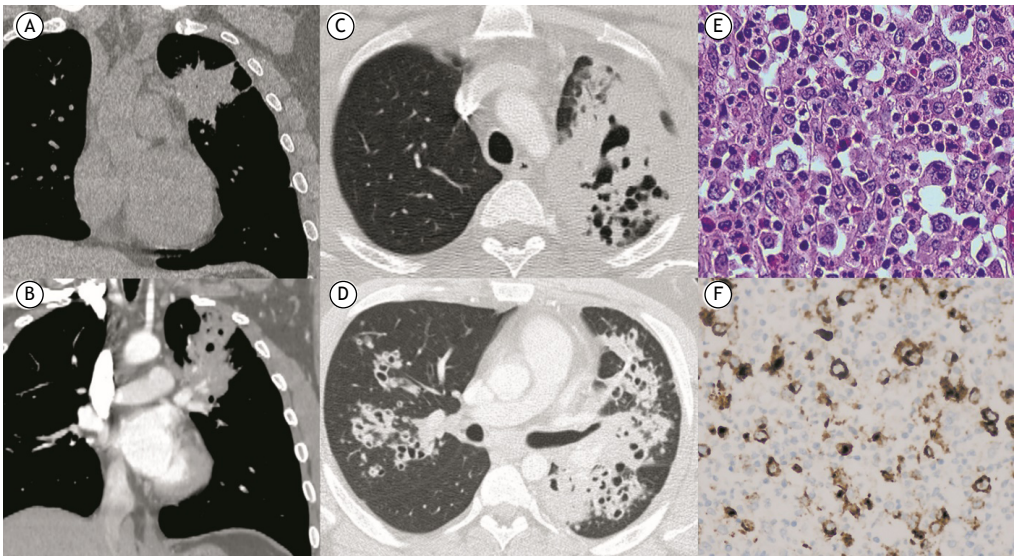

Figure 1. In A, unenhanced chest CT scan showing a mass of 7 cm in width in the left upper lobe. In B, contrast-enhanced chest CT scan performed 70 days after the initial scan, showing an increase in lesion size, as well as central cavitation. In C and D, follow-up contrast-enhanced chest CT scan performed six months after the initial scan, showing new bilateral cavitary peribronchial nodules. In E, histopathological analysis of the excised left upper lobe, showing Reed-Sternberg cells (H&E; magnification, ×20). In F, immunohistochemistry showing positivity for CD30.

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◄ Voltar ao sumário
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Middle lobe torsion following right upper lobectomy

Pedro Marx Nunes de Sousa[1], Felipe Welter Langer[2], Mariana Manica Tamiozzo[2]

A 69-year-old male patient was admitted for surgical excision of a right upper lobe adenocarcinoma measuring 8.1 cm × 7.2 cm × 5.5 cm. A right upper lobectomy with mediastinal lymphadenectomy was performed, and the adenocarcinoma was staged as pT4N0. On postoperative day 2, the patient presented with progressive dyspnea. An anteroposterior chest X-ray showed cranial displacement and atelectasis of the middle lobe (Figure 1A). A contrast-enhanced chest CT scan showed partial atelectasis of the middle lobe and obstruction of the middle lobe bronchus, as well as ground-glass opacities and smooth interlobular septal thickening (Figure 1B), with no enhancement in the middle lobe branches (Figure 1C). These findings were suggestive of middle lobe torsion. A middle lobectomy was performed, and histopathological examination confirmed the diagnosis of hemorrhagic infarction of the middle lobe (Figure 1D).

Middle lobe torsion is a rare occurrence in which the middle lobe is twisted on its bronchovascular pedicle, often following right upper lobectomy and leading to hemorrhagic infarction. Symptoms are often nonspecific, including dyspnea, fever, and chest pain in the early postoperative period. Although chest CT may not always show evidence of torsion, indirect signs such as atelectasis, bronchial narrowing, and abnormal vascular enhancement can aid in the diagnosis. Management typically involves emergency lobectomy.[1-3]

AUTHOR CONTRIBUTIONS

MMT was directly involved in reporting the CT scans depicted in this article. PMNS, FWL and MMT were equally involved in conceptualizing and supervising the study, as well as in drafting and editing the manuscript. Written consent for publication was obtained from the patient.

CONFLICTS OF INTEREST

None declared.

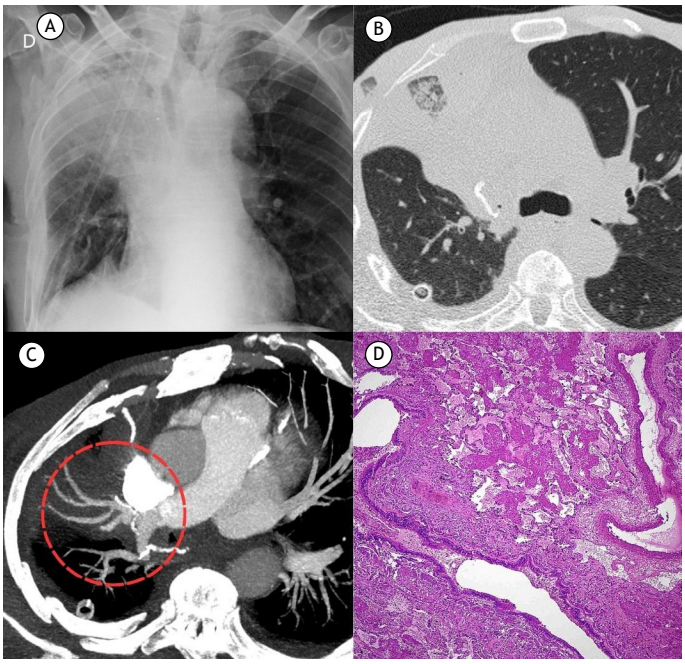

Figure 1. In A, anteroposterior chest X-ray showing atelectasis and cranial displacement of the middle lobe. In B and C, contrast-enhanced chest CT scans showing ground-glass opacities, interlobular septal thickening, and obstruction of the middle lobe bronchus, with no enhancement in the right middle lobe branches. In D, histopathological findings in the excised middle lobe, including areas of necrosis and activated pneumocytes, consistent with pulmonary parenchymal infarction.

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Left main bronchial rupture: bronchoscopy and chest CT

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A 72-year-old woman presented to our clinic with chronic cough. A chest CT scan showed an extrapleural lesion in the left upper lobe, suggestive of intercostal nerve schwannoma (Figure 1A). The patient was admitted for tumor resection by left video-assisted thoracoscopy. Intubation with a left-sided double-lumen endobronchial tube was required. The patient was admitted to the ICU and was successfully extubated. Twenty-four hours later she presented with subcutaneous emphysema in the neck, and a chest CT scan showed pneumomediastinum (Figure 1B). An emergency bronchoscopy was performed, showing a 3-cm rupture of the left main bronchus (Figures 1C and 1D). Given the clinical stability of the patient, muscle relaxants, oxygen therapy, and cough suppressants were prescribed, and a decision was made for conservative management with close monitoring. Four months later, a bronchoscopy was performed, showing scar tissue and resolution of the rupture (Figure 1E). Bronchial rupture after intubation with a double-lumen endobronchial tube has rarely been reported,[1] and mortality can be as high as 23%. Although bronchoscopy is the gold standard, chest CT can aid in locating the injury.[2] Mild symptoms and small ruptures can be managed with conservative treatment.[1]

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

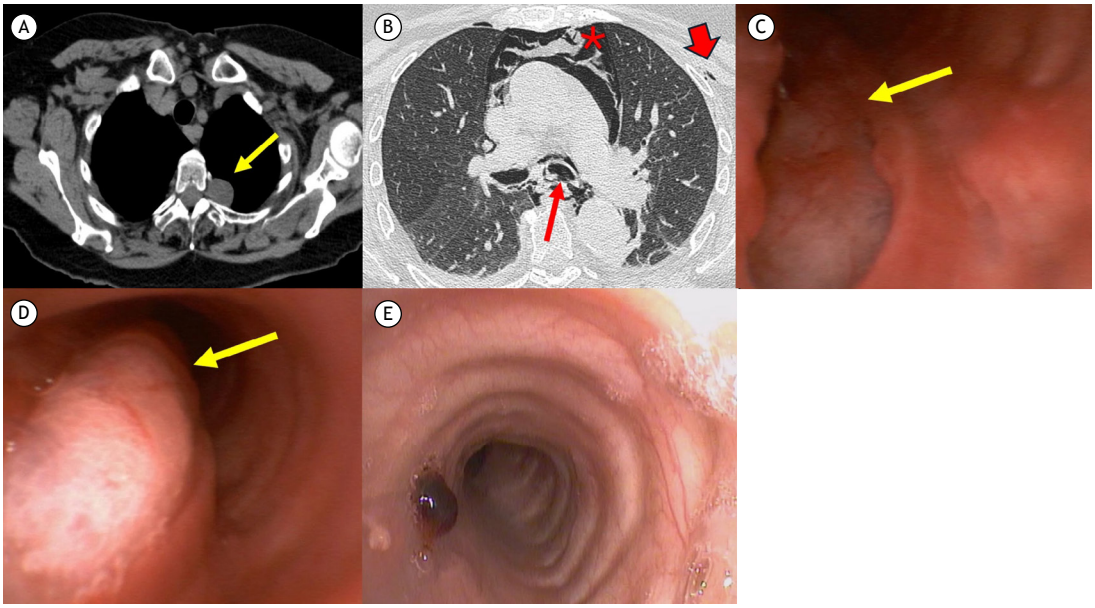

Figure 1. In A, axial unenhanced chest CT scan showing a left apical extrapleural lesion (arrow) arising from the intervertebral foramen, suggestive of a peripheral nerve sheath tumor (schwannoma). The diagnosis was confirmed after resection. In B, postoperative axial chest CT scan with lung window settings, showing a laceration of the posterior wall of the main bronchus (thin arrow). Note pneumomediastinum (asterisk) and mild subcutaneous emphysema (thick arrow). In C and D, bronchoscopic images showing the laceration during inhalation (arrow in C) and the lung protruding into the bronchial lumen during exhalation (arrow in D). In E, a bronchoscopy performed after four months of conservative treatment shows a small amount of granulation tissue on the posterior wall of the left main bronchus, with almost complete closure of the laceration.

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Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia in a male patient associated with pulmonary adenocarcinoma

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A 77-year-old hypertensive, diabetic, former-smoker male with a history of aortoiliac aneurysm repair presented with significant claudication and persistent productive cough, prompting evaluation. CT scans revealed multiple small pulmonary nodules (Figure 1A) and mosaic attenuation (Figure 1B), indicative of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), and a concerning 3.0-cm mass (Figure 1C) in the superior segment of the lower left pulmonary lobe, with slightly irregular margins, suggestive of carcinoma considering the patient's high-risk profile. ^{18}F-fluorodeoxyglucose PET-CT showed exclusive radiotracer uptake in the suspected lesion, with a maximum standardized uptake value of 6.0 (Figure 1D). Lobectomy was performed, and the mass was confirmed as a mucinous adenocarcinoma (programmed death-ligand 1 = 0%), with no mutational drivers, accompanied by multiple foci of neuroendocrine hyperplasia. The radiologist's expertise was crucial for distinguishing the imaging patterns of these lesions, highlighting the importance of radiological assessment in guiding clinical decisions.

Correctly differentiating DIPNECH nodules from malignancies is crucial to prevent misdiagnosis,[1] ensuring appropriate staging and management. This particular case stands out given the established female predominance in the epidemiology of DIPNECH within existing literature.[2] This underscores the necessity for radiologists to be vigilant for DIPNECH when evaluating male patients, despite the atypical gender presentation, when imaging phenotypes favor this condition, as in this case.

AUTHOR CONTRIBUTIONS

MdSBCP and AKM: image selection and preparation. AKM and FMC: gathering of clinical information. MdSBCP, AKM, and FMC: writing of the manuscript. AKM and FMC: reviewing of the final version of the manuscript. All authors approved that final version.

CONFLICTS OF INTEREST

None declared.

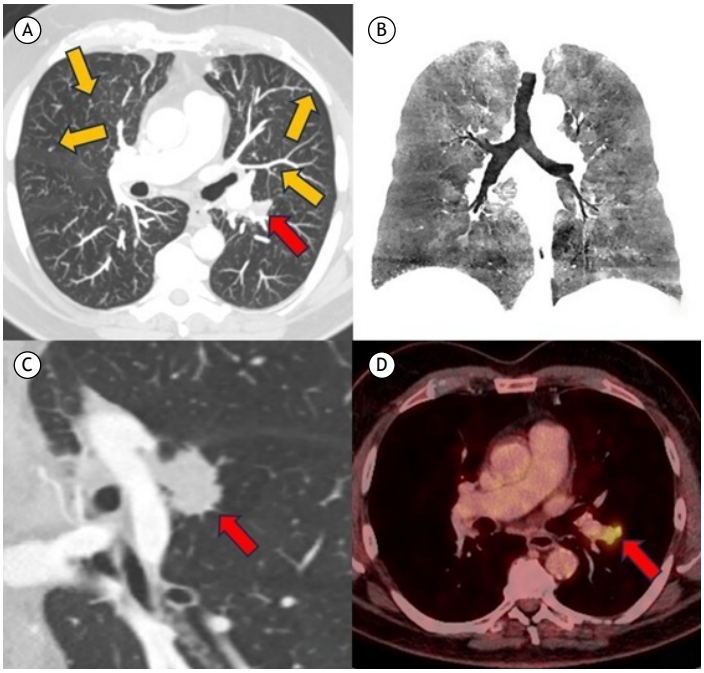

Figure 1. A: an axial CT image in lung window setting reformatted in maximum intensity projection depicts multiple lung nodules (yellow arrows) in line with the diagnosis of diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH); the main lesion is shown in A (red arrow). In B, a coronal CT image in lung window setting reformatted in minimal intensity projection demonstrates mosaic attenuation in the lungs, commonly found in DIPNECH. In C, a coronal CT image in lung window setting shows the morphological characteristic of irregular margins of the main lesion (red arrow), which distinguishes it from the other lesions. In D, a fusion PET-CT image demonstrates focal glycolytic hypermetabolism in the lesion (red arrow); none of the other smaller nodules showed significant ^{18}F-fluorodeoxyglucose uptake.

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Complicated tracheal diverticulitis

Izabel de Oliveira Karam[1], Daniel Vaccaro Sumi[1], Eduardo Kaiser Ururahy Nunes Fonseca[1]

A 64-year-old female presented to the emergency department with neck pain and swelling. Further CT investigation revealed a hypodense mass in the right tracheoesophageal sulcus with mild peripheral enhancement and adjacent fat stranding (Figure 1A). The diagnosis of a tracheal diverticulum abscess was confirmed after reviewing a 9-year prior CT that revealed a tiny uncomplicated diverticulum at the same site (Figure 1B). An MRI confirmed the diagnosis showing significant restriction in diffusion-weighted images (Figures 1C and 1D). The patient then underwent echoendoscopy and bronchoscopy (Figure 1E), which revealed purulent secretion in the airway.

Tracheal diverticula are divided by their origin into congenital and acquired, both being mostly asymptomatic and incidentally found during imaging exams.[1] When present, the most common symptoms are cough, dyspnea, stridor, dysphagia, local tenderness, and dysphonia due to local compression.[2] Hospitalization or emergency treatment is rarely required.[3]

AUTHOR CONTRIBUTIONS

DVS and EKUNF reported the case and idealized the article. All authors wrote and reviewed the article, reviewed the literature, and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

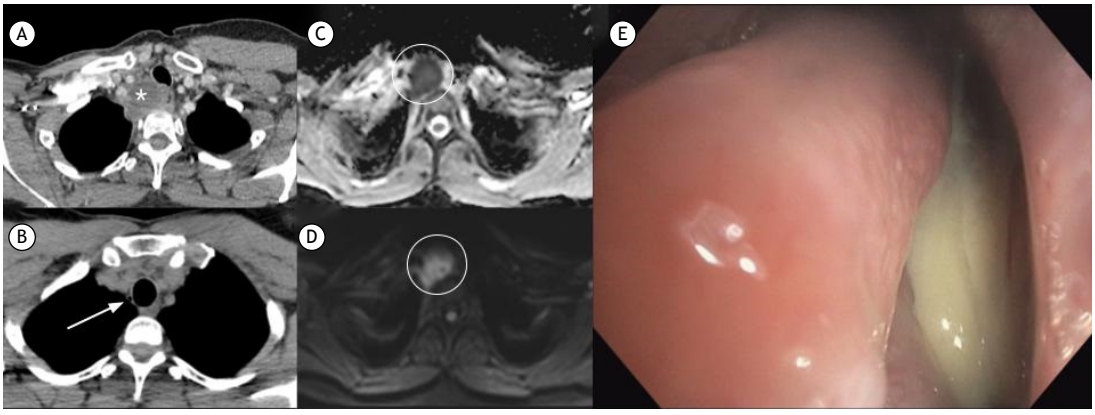

Figure 1. Panel A shows a hypodense mass (asterisk) in the right tracheoesophageal sulcus with mild peripheral enhancement and adjacent fat densification, suggestive of an abscess. A 9-year prior chest CT revealed an uncomplicated diverticulum at the same site (arrow in panel B). A diffusion-weighted MR image (panel C) and an apparent diffusion coefficient map (panel D) also confirmed the diagnosis of an abscess (circle in both panels). A bronchoscopy image (panel E) shows purulent secretion in the airway.

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Correspondence about the article: Trends on the Brazilian asthma mortality rate: a call for a standardized protocol analysis from the DATASUS databases

Marcos Otávio Antunes[1], Frederico Friedrich[1], Paulo Pitrez[2]

DEAR EDITOR:

We appreciate the recent article by Pinheiro et al. (2024), entitled "Asthma in the Brazilian Unified Health Care System: an epidemiological analysis from 2008 to 2021", published in the *Jornal Brasileiro de Pneumologia*, which provides valuable insights into the epidemiology of asthma in Brazil.[1] However, we have some concerns regarding the interpretation of the asthma mortality data, which warrants further attention.

Pinheiro et al.[1] reported lower mortality rates than those previously documented in Brazil, which totaled 2,047 in 2013.[2] Between 2008 and 2021, Pinheiro et al.[1] reported 8,497 deaths from asthma, whereas other official mortality data sources indicate that this number was approximately 34,000. Upon reproducing this data, we found that the values presented by the authors were derived from TabNet, which focuses exclusively on deaths related to hospitalizations. Relying on data from this platform may lead to a significant underestimation of asthma-related deaths, as it does not account for deaths occurring outside the hospital setting, including those in non-hospital healthcare facilities.

The presentation of this data using the term "mortality rate" implies that all deaths from the disease in Brazil are included, as already described in both national and international literature. For this reason, we consider the use of underlying cause of death data, available in the Mortality Information System (SIM), to be the most appropriate choice to avoid underreporting. Furthermore, the lack of population adjustment based on the most recent IBGE census (2022) may have led to an overestimation of the population, thereby impacting the mortality rate calculation, as the 2010 projections referenced in the study have an estimated error of approximately 10 million inhabitants.

Our results, submitted for publication in this journal in April 2024 (ID: JBPNEU-2024-0138), indicate that after a long-term historical decline, there was an increasing trend in asthma mortality after 2014. We highlight that the data analyzed in our report (detailed information available at: https://github.com/mobrant94/asthma_mortality) took the following key factors into account: 1) Brazilian population growth from 2014 to 2021; 2) Exclusion of cases related to the COVID-19 pandemic in 2020 and 2021; and 3) Exclusion of the number of registered deaths in individuals aged ≤ 6 years. Our findings in terms of numbers and mortality rates align with the trends reported by the World Health Organization (WHO) Mortality Database platform for the period between 2014 and 2020.[3] We recommend that future research on asthma mortality in Brazil utilize the same data sources for general asthma mortality, specifically the DATASUS Mortality Information System (SIM), which encompasses all causes of death and allows for a reliable analysis of mortality.

In summary, it is important that future epidemiological studies on asthma mortality employ standardized methods and reliable data sources to avoid misinterpretations. We appreciate the opportunity to discuss these issues and hope to contribute to a better understanding of asthma mortality trends in Brazil.

AUTHOR CONTRIBUTIONS

M.O.A. participated in the conception and design of the study, elaborating the letter and reviewing it critically. F.F. and P.M.P. participated in the design of the study, interpretation of data, writing the article, and reviewing it critically. All authors approved the final version to be published.

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◄ Voltar ao sumário
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Author's Reply about the article: Asthma in the Brazilian Unified Health Care System: An Epidemiological Analysis from 2008 to 2021.

David Halen Araújo Pinheiro[1], João Victor Hermógenes de Souza[1], Alberto Fernando Oliveira Justo[2], Regina Maria Carvalho-Pinto[3], Fabiano Francisco de Lima[1], Celso R. F. Carvalho[1]

We received with great interest the correspondence "Trends on the Brazilian asthma mortality rate: a call for a standardized protocol analysis from DATASUS databases" (ID: JBPNEU-2024-0162), which includes comments from Antunes et al. regarding our study, "Asthma in the Brazilian Unified Health Care System: an epidemiological analysis from 2008 to 2021".[1] They suggest that our results may lead to an underestimation of the number of deaths reported in our study. However, we disagree, as our study aimed to "analyze the number of hospitalizations, the length of hospital stay, and mortality due to asthma". Therefore, it could not underestimate the total number of deaths in Brazil. In addition, we utilized the Information Technology Department of the Brazilian Unified Health Care System (DATASUS), a secure public platform provided by the Ministry of Health, which specifically reports the mortality of hospitalized patients, as clearly stated in our study. The results presented by Antunes et al. are not contradictory but rather complementary. For instance, while their findings highlight an increase in the number of deaths, this observation alone raises concern without explaining the underlying causes. On the other hand, our findings on the reduced mortality in hospitalized patients strongly suggests that the increased mortality may be due to inadequate pharmacological treatment for those not hospitalized.

We acknowledge that there is a discrepancy in the number of deaths reported in 2013 in our study compared to the findings of Cardoso et al.[2] However, we emphasize that this comparison is inappropriate, as they are analyzing entirely different populations. Furthermore, our study indicated in the limitations section that the data analyzed were collected from electronic records, which may vary from other sources. Regarding the pandemic period, we also noted that the reduction in the number of hospitalizations from 2020 to 2021 could be associated with the restriction measures recommended by the World Health Organization (WHO) due to COVID-19.

In addition, the *Sociedade Brasileira de Pneumologia e Tisiologia* recently published data regarding asthma in Brazil (also collected from DATASUS), indicating that in 2022, there were 83,155 hospitalizations due to asthma and 524 deaths. The report states that the "extension of care and access to medications... led to a significant drop in asthma medication".[3] Consistent with our findings, the authors also assert that the "expansion of care and access to medications led to a significant drop in hospitalizations for asthma".[1] We agree with the authors that it is crucial for future epidemiological studies on asthma mortality to employ standardized methods and reliable data sources. Finally, contrary to the statement made by Antunes et al., the number of patients was standardized according to population growth based on data from the *Instituto Brasileiro de Geografia e Estatística* (IBGE, Brazilian Institute of Geography and Statistics) website. Therefore, we look forward to carefully analyzing the results that will be published by Antunes et al., as they will contribute to a better understanding of asthma mortality in Brazil.

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Brasilia, December 18, 2024

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"... ergometric treadmill (model ESD-01; FUNBEC, São Paulo, Brazil) ..."

In the case of products from the USA or Canada, the name of the state or province should also be cited. For example:

"... guinea pig liver tTg (T5398; Sigma, St. Louis, MO, USA) ..."

Manuscript preparation

Title Page: The title page should include the title (in Portuguese and in English); the full names, highest academic degrees and institutional affiliations of all authors; complete address, including telephone number, fax number and e-mail address, of the principal author; and a declaration of any and all sources of funding.

Abstract: The abstract should present the information in such a way that the reader can easily understand without referring to the main text. Abstracts should not exceed 250 words. Abstracts should be structured as follows: Objective, Methods, Results and Conclusion. Abstracts for review articles may be unstructured.

Abstracts for brief communications should not exceed 100 words.

Summary: An abstract in English, corresponding in content to the abstract in Portuguese, should be included.

Keywords: Three to six keywords in Portuguese defining the subject of the study should be included as well as the

corresponding keywords in English. Keywords in Portuguese must be based on the Descritores em Ciência da Saúde (DeCS, Health and Science Keywords), published by Bireme and available at: http://decs.bvs.br, whereas keywords in English should be based on the National Library of Medicine Medical Subject Headings (MeSH), available at: http://www.nlm.nih.gov/mesh/MBrowser.html.

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Original articles: For original articles, the text (excluding the title page, abstracts, references, tables, figures and figure legends) should consist of 2000 to 3000 words. Tables and figures should be limited to a total of five. The number of references should not exceed 30. Original articles should be divided into the following sections: Introduction, Methods, Results, Discussion, Acknowledgments, and References. The Methods section should include a statement attesting to the fact the study has been approved by the ethics in human research committee or the ethics in animal research committee of the governing institution. There should also be a section describing the statistical analysis employed, with the respective references. In the Methods and Results sections, subheadings may be used, provided that they are limited to a reasonable number. Subheadings may not be used in the Introduction or Discussion.

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Legends: Legends should accompany the respective figures (graphs, photographs and illustrations) and tables. Each legend should be numbered with an Arabic numeral corresponding to its citation in the text. In addition, all abbreviations, acronyms, and symbols should be defined below each table or figure in which they appear.

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Abstracts

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

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

Electronic publications

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

Homepages/URLs

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

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A responsabilidade pela determinação da conduta terapêutica para cada paciente é do médico e sua equipe. O aplicativo apenas facilita a utilização das estratégias de avaliação de risco. As informações apresentadas pelo aplicativo não devem ser utilizadas isoladamente.

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1. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J. 2017 Aug 3;50(2):1700889. 2. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119. 3. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J. 2017 Aug 3;50(2):1700740. 4. Delcroix M, et al. Risk assessment in medically treated chronic thromboembolic pulmonary hypertension patients. Eur Respir J. 2018 Nov 8;52(5):1800248. 5. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, McGoon MD, Pasta DJ, Selej M, Burger CD, Frantz RP. Predicting Survival in Patients With Pulmonary Arterial Hypertension: The REVEAL Risk Score Calculator 2.0 and Comparison With ESC/ERS-Based Risk Assessment Strategies. Chest. 2019 Aug;156(2):323-337. 6. Benza RL, Kanwar MK, Raina A, Scott JV, Zhao CL, Selej M, Elliott CG, Farber HW. Development and Validation of an Abridged Version of the REVEAL 2.0 Risk Score Calculator, REVEAL Lite 2, for Use in Patients With Pulmonary Arterial Hypertension. Chest. 2021 Jan;159(1):337-346.

PP-VEN-BR-0037-1 | Fevereiro 2022

Chegou: EGURINEL® (pirfenidona)

O primeiro similar de pirfenidona do Brasil!

Egurinel® (pirfenidona) é bioequivalente ao medicamento referência![1]

Referência: 1. Vespasiano CFP, Accennato VAC, Costa F, Riccio MF, Bernasconi G, et al. (2020) Bioequivalence between Two Capsules of Pirfenidona in Healthy Subjects under Fed Condition. J Bioeq Stud 6(1): 101.

EGURINEL® (pirfenidona) é apresentado em embalagem contendo 270 cápsulas. **Indicações**: EGURINEL® (pirfenidona) está indicado para tratamento de fibrose pulmonar idiopática (FPI). **Posologia**: Adultos: Ao iniciar o tratamento, a dose deve ser escalonada em um período de 14 dias até a dose diária recomendada de nove cápsulas por dia, como se segue: **Dias 1 a 7**: uma cápsula, três vezes por dia (801 mg/dia). **Dias 8 a 14**: duas cápsulas, três vezes por dia (1602 mg/dia). **Dias 15 em diante**: três cápsulas, três vezes por dia (2403 mg/dia). A dose diária recomendada de EGURINEL® para pacientes com FPI é de três cápsulas de 267 mg três vezes por dia com alimentos até um total de 2403 mg/dia. **Contraindicações**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Precauções e Advertências**: Função Hepática: lesão hepática induzida por medicamento (DILI) na forma de elevação transitória e clinicamente silenciosa de transaminases tem sido continuamente reportada em pacientes tratados com EGURINEL® (pirfenidona). Em casos raros, estas elevações foram associadas com elevação concomitante da bilirrubina e consequências clínicas sérias, incluindo casos isolados com desfecho fatal reportados pós-comercialização. Provas de função hepática (ALT, AST e bilirrubinas) devem ser realizadas antes do início do tratamento com EGURINEL® e subsequentemente em intervalos mensais nos 6 primeiros meses e depois a cada 3 meses a partir de então. Reação de hipersensibilidade e erupção cutânea: a exposição direta à luz solar (incluindo bronzeamento artificial) deve ser evitada ou reduzida durante o tratamento com pirfenidona. Os pacientes devem ser orientados a usar bloqueador solar eficaz diariamente, usar roupas que protejam contra a exposição solar e evitar outros medicamentos que reconhecidamente provoquem fotossensibilidade. Os pacientes devem ser orientados a reportar sintomas de fotossensibilidade ou erupção cutânea ao seu médico. Ajustes de dose ou descontinuação temporária de tratamento podem ser necessários no caso de reação de fotossensibilidade ou erupção. Tontura: tonturas têm sido relatadas em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mentais. Em estudos clínicos, a maioria dos pacientes que apresentaram tontura tinham um único evento, e a maioria dos eventos resolvidos, com uma duração média de 22 dias. Se a tontura não melhorar ou se agravar, pode ser necessário um ajuste da dose ou até mesmo a interrupção de pirfenidona. Fadiga: Fadiga tem sido relatada em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mental. Perda de peso: a perda de peso tem sido relatada em pacientes tratados com pirfenidona. Os médicos devem monitorar o peso dos pacientes, e, quando necessário, incentivar o desenvolvimento do consumo de calorias se a perda de peso for considerada de importância clínica. Distúrbios gastrintestinais: nos estudos clínicos, os eventos adversos gastrointestinais como náuseas, diarreia, dispepsia, vômitos, doença do refluxo gastresofágico e dor abdominal foram mais frequentemente relatados pelos pacientes nos grupos de tratamento com pirfenidona do que naqueles que receberam o placebo. **Interações**: EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® **Reações Adversas**: as reações adversas mais comuns, obtidas dos estudos pivotais foram: náuseas (36%); erupção cutânea (30,3%); tosse (27,8%); infecção do trato respiratório superior (26,8%) e diarréia (25,8%). VENDA SOB PRESCRIÇÃO MÉDICA. **Reg. MS- 1.2214.0114. SAC: 08000 016 6575 "Informações adicionais disponíveis aos profissionais de saúde mediante solicitação a Zodiac Produtos Farmacêuticos S.A – www.zodiac.com.br - Para informações completas, consultar a instrução de uso do produto. Contraindicação**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Interação:** EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® .

Egurinel® é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

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