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HIGHLIGHT

SERPINA1 Mutations in Bronchiectasis: Screening for Alpha-1 Antitrypsin Deficiency

Sildenafil + Ambrisentan as Initial Therapy in Chronic Thromboembolic Pulmonary Hypertension

Air Pollution, Respiratory Risks, and Risk Communication in Rio de Janeiro

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Envisioning the future of the Jornal Brasileiro de Pneumologia

Marcia Margaret Menezes Pizzichini, Denise Rossato Silva

The golden jubilee of the *Jornal Brasileiro de Pneumologia* (JBP) marks a significant achievement for nearly 4,000 members of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association). To celebrate this milestone, the JBP is publishing four editorials reflecting on its history and outlining our aspirations for the future.

The journey of the JBP has been characterized by many unexpected developments, revealing a distinct trend toward consolidating its success. For example, over the past decade, we have made considerable advances in the quality of our publications, as evidenced by our improved rankings from the National Council for Research (Qualis-CNPq) and international recognition from prestigious organizations such as Scimago Journal & Country Rank, Journal Citation Report (JCR), and Scopus. In 2024, the JBP achieved a notable milestone by ranking in the Q2 quadrant among 105 international scientific journals in Respiratory Medicine, securing the 42nd position, a journal impact factor of 3.0, and an H-index of 52. Our citation index, as reported by Scopus, currently stands at 4.0, underscoring the relevance of our publications over the past five years, with 78% of original articles cited.

The JBP ranks 9th among 391 journals across all disciplines in Brazil. Additionally, our publications have considerably attracted significant attention, averaging approximately 6,000 views per paper. Notably, the 2020 Brazilian Thoracic Association recommendations for asthma management have achieved an impressive 238,532 views to date, demonstrating our potential for growth and broader reach beyond our Association and Brazil.

Despite such promising advancements, the current and former Editors of the JBP, along with our team of Associate Editors, recognize that we are only at the beginning of our journey towards greater international recognition and visibility. We envision a future when the JBP transcends its regional identity by adopting a name in English. This change aims to attract scientific manuscripts from around the globe and to facilitate the dissemination of free-of-charge translational research in respiratory and pulmonary health.

We acknowledge that this transformation may initially result in a decline in our JCR ranking and citation counts for a period of three years. However, we are fully committed to this investment in the long-term growth of the Journal. It is important to clarify that this does not reflect a decrease in the quality of our publications; on the contrary, it is the result of transitioning to a new name, which may split citations between "*Jornal Brasileiro de Pneumologia*" and "the new title to be chosen."

As we embark on this transformative journey, we want to emphasize our unwavering commitment to maintaining the high standards of scholarly excellence that have defined the JBP for the past fifty years. Our rich history is an indication to the dedication of our editorial team and reviewers, as well as the invaluable contributions of our authors, who have consistently expanded the frontiers of knowledge in pulmonary medicine. This collaborative spirit has fostered an environment conducive to innovation and rigorous scientific inquiry. To strengthen our international reach further, we will be implementing strategies to enhance the visibility of our Journal. These include increased promotional efforts at international conferences, partnerships with global research networks, and an expanded presence on digital platforms. By doing so, we aim not only to attract more submissions from around the globe but also to ensure that our research findings reach a wider audience, thereby maximizing the impact of our work.

Moreover, we are committed to fostering an inclusive platform that welcomes diverse perspectives and encourages international collaborations. This commitment aligns with our mission to advance research that addresses key challenges in respiratory health, particularly in underrepresented populations and settings. We believe that a more inclusive approach will enrich the quality of our publications and better reflect the global nature of research today.

To support our emerging vision, we are also exploring the implementation of new initiatives, such as special issues focused on cutting-edge topics in pulmonology, as well as webinars and workshops aimed at educating authors on best practices for manuscript submission and publication. Our goal is to create a supportive ecosystem that empowers researchers at all stages of their careers, enhancing both the quality and quantity of contributions to our Journal.

In conclusion, as we celebrate this golden jubilee, we stand at a pivotal moment in the evolution of the JBP. With unwavering commitment and a clear vision for the future, we are excited to take the next steps in order to elevate our journal to new heights. We invite all members of the SBPT and the global research community to join us on this journey, as we collectively strive to advance knowledge and improve the health outcomes of individuals affected by respiratory diseases. Together, we will build a stronger, more visible, and impactful JBP for the years to come.

Marcia Margaret Menezes Pizzichini
Editor-in-Chief of the Jornal Brasileiro de Pneumologia
Denise Rossato Silva
Vice-Editor-in-Chief of the Jornal Brasileiro de Pneumologia

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JBP at 50: "It is hard work, but deeply rewarding"

José Roberto Jardim[1]

Fifty years have passed since the first issue of the *Jornal de Pneumologia*, later renamed to *Jornal Brasileiro de Pneumologia* (JBP), was published, and the first thought that comes to mind is: *"How quickly time passes!"* Out of curiosity, this reminds me of an article written by a Brazilian basic science researcher who discussed whether that statement was actually true. He explained that, of course, a day always has 24 hours, a week always has seven days, and a month always has about thirty days. The perception of time passing faster, he argued, is due to the accumulation of knowledge—as people grow older, their understanding of the world makes learning easier and faster. There is a clear parallel between that explanation and the history of the JBP. A scientific journal is a living organism, and the remarkable growth of the JBP over these 50 years is certainly grounded in the increasing expertise and experience of the Editors who have followed one another, of the support teams, and, of course, in the maturation of Brazilian researchers.

The JBP has a rich history, widely recounted through the testimonies of its various Editors-in-Chief when the Journal celebrated its 40th anniversary. Some of those testimonies were titled *"The JBP I Lived."* At the time, for personal reasons, I was unable to write about my own experience with the *Jornal de Pneumologia*. I am deeply grateful to the current Editor-in-Chief of the JBP for this honorable invitation on the occasion of its 50th anniversary. I now feel compelled to share *"The JBP I Lived"* with our readers.

Let us go back in time 43 years. In 1982, I was invited to serve as the Editor-in-Chief of the *Jornal de Pneumologia,* and I officially took office at the closing session of the Brazilian Congress of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT), held in São Paulo, Brazil. The *Jornal de Pneumologia* was in its early years, and previous Editors had already made it a reality, keeping it alive and growing. The incoming SBPT board at that time established that the *Jornal de Pneumologia* should encourage Brazilian researchers to publish their studies in it, ensure regular publication, increase the number of articles published, and become the primary national source of information in respiratory medicine.

Several initiatives were then developed. During my two terms as Editor-in-Chief, we discussed the need to create a permanent board of peer reviewers. Until then, manuscripts were reviewed either by the Editor or by a pulmonologist invited on an ad hoc basis, without a formal peer review process or clear editorial guidelines. Even in those early days, the *Jornal de Pneumologia* was concerned about the misuse of common but incorrect terms, such as calling a disease a *pathology*—a word that properly refers to a medical specialty, not to a disease itself.

Not all authors submitting their manuscripts had prior research experience, and it was common for articles to lack a proper description of the Methods section or a well-structured Discussion. I recall one author who cited his own article as a reference in a foreign publication. I phoned him to explain that we could not publish an already published paper, to which he replied, "But it's not the same article—it was published abroad *without* the photos!" To guide authors, the editorial team routinely sent reviewer comments accompanied by educational notes.

At that time, our journal was published only in Portuguese, with a few articles per issue—often including a series of educational review articles (for example, on physiology). It was printed using offset techniques, with photolithography (transparent film pages) and metal plates for the covers and content, allowing reprints when needed. It was an almost artisanal process, demanding great dedication from the graphic producer and printer. I must here express special thanks to Dr. Alexandre Moroz, a college contemporary from my days at *Escola Paulista de Medicina* and a fellow high hurdles competitor in academic contests, who served as a graphic producer from Volume 4 to Volume 10 of the Journal. Interestingly, after graduation, he also completed a fellowship in our Pulmonology Department, thus becoming a pulmonologist himself.

With approval from the SBPT board, Dr. Moroz and I developed a strategy to increase the Journal's visibility: we mailed each new issue to all medical school and major hospital libraries in Brazil. Although this had financial costs, we believed it was worth it—and indeed, the number of manuscript submissions gradually began to increase.

During my tenure, the *Jornal de Pneumologia* applied for indexation in MEDLINE/PubMed for the first time. At that time, BIREME—the Regional Library of the Pan-American Health Organization—had a staff member directly linked to PubMed, who guided us through the application process. We sent a detailed letter describing SBPT, its objectives, achievements, and the Journal's history, along with the four most recent volumes. The response, though polite, informed us that the Journal was yet to be eligible for indexation and advised us on the steps to be followed in the coming years. Those recommendations were gradually implemented, maintained, and improved upon by subsequent editorial teams. Finally, in 2006—after nearly 22 years—the JBP achieved PubMed indexation. It was a long gestation,

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but a necessary one, ensuring that the Journal met the rigorous standards of PubMed and that both the JBP Editors and SBPT leadership could sustain them.

Scientific journals are the open doors of professional societies, allowing them to reach the most distant parts of their countries and beyond. Each field of health science has its own journals, usually published by its respective professional societies, which aim to disseminate knowledge and best practices. In some countries, there is a strong integration among health professions, leading to joint publications and shared diagnostic and treatment guidelines. In Brazil, this integration is still far from ideal. Different societies often work in parallel toward similar goals, duplicating efforts and costs. I believe our Journal, the JBP, has the experience and credibility to serve as a unifying platform—one that promotes knowledge sharing across all respiratory health disciplines and fosters collaboration among medical specialties.

The next 50 years of the JBP have already begun. The current SBPT Board and Editor-in-Chief, Dr. Márcia Pizzichini, have set new challenges that build upon those faced and overcome by previous Editors-in-Chief. The Journal's growing international recognition should further increase its impact factor; its leadership in Latin America will continue; the team of associate editors will expand; and publications grounded in rigorous scientific methodology will form the basis for new therapeutic recommendations, national guidelines, and public health strategies. These, in turn, will strengthen primary care practices and support Brazil's Unified Health System.

Reflecting on my two terms as Editor-in-Chief, I once told a colleague—who had just been invited to take on the same role and asked if it was a lot of work—"Yes, it is hard work, but deeply rewarding." I am certain that every Editor has felt the same way. Our Society (SBPT) deserves that work.

José Roberto Jardim

Editor-in-Chief of the *Jornal de Pneumologia*, 1982–1984 and 1984–1986

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Navigating change: the trajectory of the Jornal Brasileiro de Pneumologia in a dynamic scientific landscape and its international recognition

Bruno Guedes Baldi[1,2], Rogério Souza[1]

Over the fifty years of the foundation of the *Jornal Brasileiro de Pneumologia* (JBP), initially named *Jornal de Pneumologia*, it has evolved from a national to an international scope, especially in the last two decades. The JBP followed the continuous transformation of science and adapted itself to emerging trends, shifting paradigms and evolving methodologies in the research of respiratory diseases. The main objectives of the JBP are publishing changes and highlights in respiratory medicine, as well as to act as a source of dissemination of the Brazilian and international research in respiratory medicine and correlated areas, with a progressive increase in its scientific rigor. Additionally, the Journal has an important role in improving clinical care on respiratory health internationally, with a particular focus on Brazil and other countries in Latin America.

The JBP is currently the major Latin American journal in the respiratory medicine field and a continuous and robust source of knowledge and support in this region. Several demands are covered by the JBP, such as the publication of guidelines primarily addressing diagnosis and treatment, and epidemiological and daily life studies that help clinical practice, including some diseases prevalent in our environment, such as tuberculosis and other infectious diseases.[1] In addition, the studies published in the Journal helped the implementation of public health policies and the approval of prescribing high-cost medications by regulatory agencies in Brazil.[2,3]

It is pivotal to highlight not only the national impact of the JBP, but also the progressive increase in its international recognition, currently the Journal being placed among the major Brazilian medical journals and at a significant position within the respiratory medicine journals in the major international indexes agencies, such as Scimago Journal & Country Rank (SJR) and Journal Citation Reports (JCR).[4,5] Several achievements were obtained by the JBP in its history towards greater visibility, recognition, and internationalization. The journal was included in the SciELO database in 2002 and indexed in PubMed/MEDLINE, which is sponsored by the United States National Library of Medicine, in 2006, making the Journal accessible for foreign readers and increasing the visibility and citation potential of its articles.[6] The Journal achieved other milestones when it was indexed in the Institute for Scientific Information (ISI) Web of Knowledge in 2009, and when its first impact factor was published in the JCR in 2012.[7] In recent years, there has been a progressive increase in impact factor of the JBP in the main databases, culminating at a score of 3.0 in the JCR 2024, published this year, reinforcing its scientific excellence and its international recognition in the respiratory medicine.[4] The combined role of authors, reviewers, and editorial board members, with the expansion of representatives from other countries, in addition to the support of the staff and board of directors of the Brazilian Thoracic Society, was fundamental to the growth and progressive increase of the international relevance of the JBP.

Several important manuscripts have been published and received a relevant number of citations in the JBP in recent years, such as those related to tuberculosis and other mycobacteria, COVID-19, smoking, obstructive diseases, among others. It is also essential to emphasize the adaptations that the JBP had to make in order to face the challenges determined by COVID-19. The Journal received an increasing number of COVID-19-related submissions and was required to determine those that would be approved carefully, without forgetting the importance to continue publishing manuscripts on other topics.[8-10] Then, it was necessary to make the editorial processes faster during the pandemics, without losing scientific rigor.[10]

It is also important to highlight the increasing number of guidelines, review articles, and meta-analyses published in the JBP, reinforcing its commitment to updating topics for the practice of pulmonologists and other related professionals. The number of articles published by international authors, including editorials, has also progressively increased over the years.[11] Another aspect that reinforces the greater internationalization of the JBP is the consolidated partnership with other relevant journals in respiratory medicine, such as the Pulmonology Journal and the *Archivos de Bronconeumologia*. Other factors that contributed to the greater visibility and submission of articles to the JBP include its the open access, as well as the submission and publication of articles free of charge and only in English, the increase in social media dissemination of information, and the continuous publication of manuscripts.

In summary, several transformations have been implemented in the JBP since its first release in 1975, leading to its consolidation as a relevant journal in the field of respiratory diseases and an important source of reference for pulmonologists in Brazil and abroad. In this context, the Journal has highlighted pivotal contributions that helped to shape the knowledge and

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our understanding of lung diseases over the years. It is hoped that the JBP will increasingly inspire future generations of researchers, pulmonologists, and other health professionals over the next 50 years, with a commitment to achieve a progressively higher quality and maintaining scientific rigor without forgetting to address important topics for the daily practice of respiratory care professionals.

REFERENCES

1. Silva DR, Santos AP, Visca D, Bombarda S, Dalcomo MMP, Galvão T, et al. Brazilian Thoracic Association recommendations for the management of post-tuberculosis lung disease. J Bras Pneumol. 2023;49(6):e20230269. https://doi.org/10.36416/1806-3756/e20230269
2. Athanazio RA, Tanni SE, Ferreira J, Dalcin PTR, Fuccio MB, Esposito C, et al. Brazilian guidelines for the pharmacological treatment of pulmonary symptoms of cystic fibrosis. Official document of the Sociedade Brasileira de Pneumologia e Tisiologia (SBPT, Brazilian Thoracic Association). J Bras Pneumol. 2023;49(2):e20230040. https://doi.org/10.36416/1806-3756/e20230040
3. Carvalho-Pinto RM, Cançado JED, Pizzichini MMM, Fiterman J, Rubin AS, Cerci Neto A, et al. 2021 Brazilian Thoracic Association recommendations for the management of severe asthma. J Bras Pneumol. 2021;47(6):e20210273. https://doi.org/10.36416/1806-3756/e20210273
4. Journal Citation Reports: Science Edition [homepage on the Internet]. Philadelphia (PA): Clarivate Analytics; c2025. 2024 Journal Impact Factor. Available from: https://jcr.clarivate.com/jcr-jp/journal-profile?journal=J%20BRAS%20PNEUMOL&year=2024&fromPage=%2Fjcr%2FhomeA
5. SJR Scimago Journal & Country Rank [homepage on the Internet]. Scimago Lab, c2007-2025. Jornal Brasileiro de Pneumologia. Available from: https://www.scimagojr.com/journalsearch.php?q=4500151503&tip=sid&clean=0A
6. Martinez JAB. A national scientific treasure. J Bras Pneumol. 2009;35(12):1165-1167. https://doi.org/10.1590/S1806-37132009001200001
7. Carvalho CRR. My time at JBP. J Bras Pneumol. 2015;41(5):403. https://doi.org/10.1590/S1806-37132015000500007
8. Costa PN, Pereira JO, Canigral AH, Quintana EM, Sanchez-Nieto JM, Delis PB, et al. Vaccination status and outcomes in critical COVID-19 patients. J Bras Pneumol. 2024;50(1):e20230116. https://doi.org/10.36416/1806-3756/e20230116
9. Sousa MLA, Shimizu IS, Patino CM, Torres-Duque CA, Zabert I, Zabert GE, et al. COVID-19 knowledge, attitudes, and practices among health care workers in Latin America. J Bras Pneumol. 2022;48(5):20220018. https://doi.org/10.36416/1806-3756/e20220018
10. Baldi BG, Pizzichini MMM. Repercussions of the COVID-19 pandemic for science and for the management of the Jornal Brasileiro de Pneumologia. J Bras Pneumol. 2022;48(6):20220429. https://doi.org/10.36416/1806-3756/20220429
11. Pizzichini M, Baldi BG. The new metrics and additional objectives of the Jornal Brasileiro de Pneumologia. J Bras Pneumol. 2024;50(4):e20240284. https://doi.org/10.36416/1806-3756/e20240284

Celebrating our heritage: the *Jornal Brasileiro de Pneumologia* and the *Sociedade Brasileira de Pneumologia e Tisiologia*

Ricardo de Amorim Corrêa[1,2]

At times like these, it is essential to recall important moments in history. In October 1974, the Brazilian Society of Pulmonology was founded. Fifty years ago, in 1975, a visionary group of Brazilian pulmonologists, led by the *Sociedade Brasileira de Pneumologia*, recognized the urgent need for a specialized scientific platform to share research and clinical experiences focused on respiratory diseases. On October 18, 1978, the Brazilian Society of Pulmonology and the Brazilian Federation of Tuberculosis and Respiratory Diseases Societies merged into a single institution. The new society was renamed the Brazilian Society of Pulmonology and Phthisiology and adopted the founding date of the Brazilian Federation of Tuberculosis and Respiratory Diseases Societies, which is 1937.It is, in fact, the sum of the experience, successes, struggles, and greatness of two entities that, in the past, brought together lung specialists from across our country. From that commitment to excellence was born the *Jornal de Pneumologia* (JP)—a publication destined to become the leading scientific voice of pulmonary medicine in Brazil and a reference for the Portuguese-speaking world.[1]

From its earliest issues, the JP reflected the most pressing public health challenges in Brazil, such as the relentless fight against tuberculosis, which was the main cause of respiratory morbidity and mortality at the time. The journal played a pioneering role in disseminating regional research, clinical advances, and public health strategies, contributing directly to educational efforts and the improvement of respiratory care across the country.[2]

As Brazilian pulmonology—along with the SBPT and its committees—progressed, so too did the JP. In the 1980s and 1990s, it expanded its scope to include a wide array of topics—ranging from asthma and COPD to the increasing burden of smoking-related diseases, interstitial lung conditions, and advances in diagnostic and therapeutic techniques. The creation of new editorial sections and the embrace of thematic issues demonstrated the journal's agility and ongoing commitment to the respiratory community.[1,2]

At the dawn of the new millennium, the JP decisively moved toward internationalization. In 2004, on the basis of a survey of SBPT members, it was decided that the journal would be renamed the *Jornal Brasileiro de Pneumologia* (JBP).[1] The adoption of an electronic submission system, publication in Portuguese and English, and the journal's inclusion in major scientific databases such as SciELO (since 2002), PubMed/MEDLINE (since 2006), and Scopus (since 2012) greatly expanded its visibility and influence.[2,3] This global recognition culminated recently in the remarkable achievement of an impact factor of 3.0,[2,3] a testament to the growing relevance and excellence of the research published within its pages. This milestone places the JBP among the most respected journals in respiratory medicine worldwide and reflects both the quality of Brazilian science and the dedication of its editorial leadership.[4]

Recent years have tested and confirmed the journal's vital role. During public health emergencies—from the H1N1 influenza epidemic to the COVID-19 pandemic—the JBP offered timely, free access to life-saving research, national guidelines, and new clinical insights, thus becoming an essential resource for practitioners and policymakers alike.[5-7]

The trajectory of the JBP is inseparable from that of the SBPT and the broader respiratory medicine community in Brazil. From the early days of typewritten manuscripts to its present era as a fully digital, internationally recognized scientific journal, the JBP has been defined by rigor, independence, and a profound commitment to the advancement of respiratory health.[1-3]

As we commemorate five decades of achievements, we honor everyone who has contributed to this legacy: the editors-in-chief, associate editors, peer reviewers, authors, dedicated readers, and SBPT members. We also remember and thank the founders who imagined and built this platform, paving the way for future generations.

Looking ahead, we reaffirm our mission: to foster scientific excellence, promote lifelong education, and advocate for stronger respiratory health policies. The challenges that await us—emerging diseases, environmental threats, and barriers to access—only strengthen our resolve to innovate and collaborate, led by the strong and respected voice of our journal.

May the JBP continue to illuminate our path, strengthen professional bonds, and inspire pulmonologists throughout Brazil and the world.

Congratulations to all who are part of this remarkable journey!

REFERENCES

1. Sociedade Brasileira de Pneumologia e Tisiologia. [homepage on the Internet]. Brasília: SBPT; [cited 2024 Aug 5]. História. Available from: https://sbpt.org.br/portal/historia/
2. Carvalho CR. The Brazilian Journal of Pulmonology and international

1. Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
2. Sociedade Brasileira de Pneumologia e Tisiologia – SBPT – Brasília (DF) Brasil. (President, 2025-2026)

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databases. J Bras Pneumol. 2013;39(5):529-31. https://doi.org/10.1590/S1806-37132013000500001

3. Carvalho CR, Baldi BG, Jardim CV, Caruso P. Publication of the impact factor of the Brazilian Journal of Pulmonology: a milestone on a long and arduous journey. J Bras Pneumol. 2012;38(4):417-8. https://doi.org/10.1590/S1806-37132012000400001
4. Carvalho CR, Baldi BG, Jardim CV, Caruso P, Souza R. New steps for the international consolidation of the Brazilian Journal of Pulmonology. J Bras Pneumol. 2014;40(4):325-6. https://doi.org/10.1590/S1806-37132014000400001
5. Lenzi L, Mello ÂM, Silva LR, Grochocki MH, Pontarolo R. Pandemic influenza A (H1N1) 2009: risk factors for hospitalization. J Bras Pneumol. 2012;38(1):57-65. https://doi.org/10.1590/S1806-37132012000100009
6. Ramos FJDS, Atallah FC, Souza MA, Ferreira EM, Machado FR, Freitas FGR. Determinants of death in critically ill COVID-19 patients during the first wave of COVID-19: a multicenter study in Brazil. J Bras Pneumol. 2022;48(5):e20220083. https://doi.org/10.36416/1806-3756/e20220083
7. Ceccato A, Luna CM, Artigas A. The COVID-19 challenge. What have we learned? J Bras Pneumol. 2022;48(5):e20220361. https://doi.org/10.36416/1806-3756/e20220361

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Searching for alpha-1 antitrypsin deficiency in patients with bronchiectasis: reducing idiopathic cases

Sara Qutubuddin[1], Rodrigo Cavallazzi[1]

There has been substantial progress in our understanding of bronchiectasis in recent years. It is well established that bronchiectasis is characterized by a neutrophilic airway inflammation, but a new finding is the recognition that 20% of patients with bronchiectasis have an eosinophilic profile, which has implications in the risk of exacerbations.[1] Research on microbiome has illustrated the importance of microbial interactions and the potential role of commensal microbes in the pathogenesis of exacerbation.[2] Multicenter cohorts have informed us about the most common causes of bronchiectasis in different areas of the globe (Figure 1).[3-6] In South America, the most common causes of bronchiectasis in a study[4] that included 651 patients were post-infective (40.3%), idiopathic (31.3%), primary ciliary dyskinesia (9%), airway disease (5.1%), rheumatologic disease (4.3%), and other causes (10%).In that cohort, the post-infective etiology included both tuberculosis and other lung infections.[4]

One of the etiologies of bronchiectasis is alpha-1-antitrypsin (A1AT) deficiency, an autosomal codominant disease characterized by a mutation leading to an amino acid change in the A1AT. This results in misfolding of the protein, rendering it unable to perform its usual function of inhibiting proteinases. Unchecked, the proteinases may lead to lung parenchymal damage and immune dysfunction. Furthermore, the polymerization of the enzyme in the hepatocytes can cause liver disease. In addition to emphysema and liver disease, patients are also at an increased risk of developing bronchiectasis and necrotizing panniculitis.[7]

In a registry cohort of 418 patients with the genotype PiZZ A1AT deficiency who underwent chest CT scanning, the results of which were abnormal in 82% of the patients.[8] The most common abnormalities included emphysema alone in 45%, bronchiectasis plus emphysema in 27%, and bronchiectasis alone in 9% of the patients. Overall, bronchiectasis was present in 36% of the patients.[8] In a clinic for patients with COPD in Brazil, 27 patients with A1AT compatible mutation were identified. Of these, bronchiectasis was present in 14 patients (52%).[9] A corollary to these findings is the prevalence of A1AT deficiency in patients with bronchiectasis. This clinically relevant question is expected to be influenced by the prevalence of A1AT deficiency in the general population where patients are being seen.

In a multinational study,[10] 2,620 dried blood or buccal swab samples from patients in Brazil with suspected A1AT deficiency underwent allele-specific genotyping for the 14 most common deficiency variants of the *SERPINA1* gene. Further testing with gene sequencing was conducted if no mutation was found, or if a mutation was found in the heterozygous status and the A1AT level

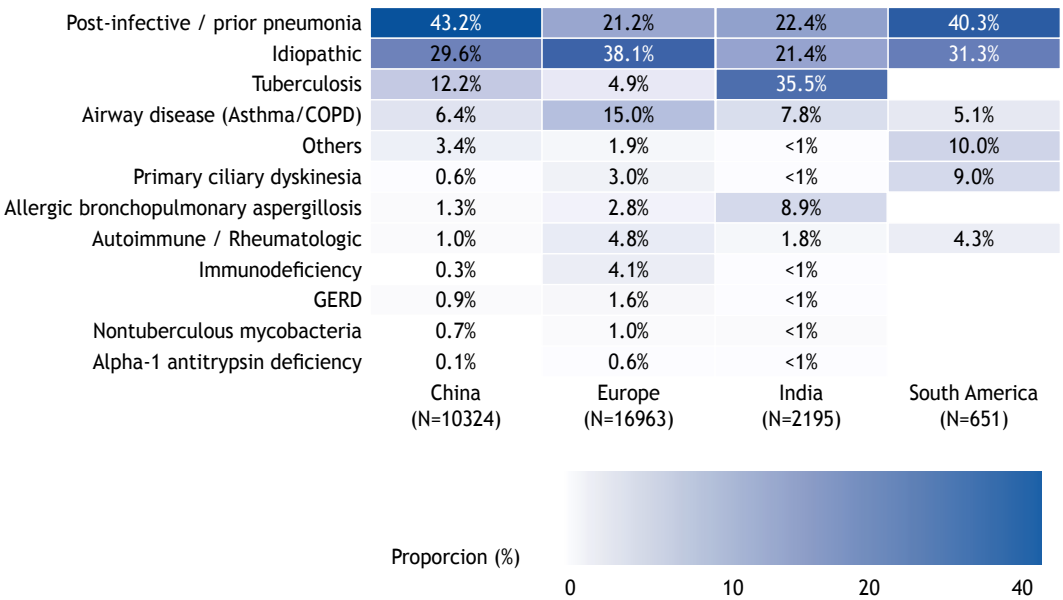

Figure 1. Heatmap graph showing the etiology of bronchiectasis in different cohorts across the globe.

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Chart 1. Recommendations for alpha-1 antitrypsin testing for patients with bronchiectasis in different guidelines or consensus.

Chalmers et al.[12]	"Alpha-1 antitrypsin testing should not be performed routinely but should be considered in patients with suggestive clinical and radiological features such as basal emphysema or severe airflow obstruction."
Pereira et al,[15]	Alpha-1 antitrypsin testing is part of the recommended investigation in the algorithm for the diagnosis and etiologic investigation of bronchiectasis.
Hill et al.[13]	"Consider testing for alpha 1 antitrypsin deficiency in patients with coexisting basal panacinar emphysema."
Chang et al.[14]	"consider the following: Alpha-1-antitrypsin levels if there is evidence of chronic obstructive pulmonary disease/emphysema"

was lower than 60 mg/dL, or per clinician request. An A1AT deficiency mutation was present in 28% of the samples. The most frequent genotypes were PiMS (12.7%), PiMZ (7.4%), PiSS (0.8%), PiSZ (1.6%), and PiZZ (3%). Allele percentages were S (15.2%), Z (12.6%), rare alleles (2.5%), null alleles (0.2%), and new alleles (0.2%). Bronchiectasis was the second most common reason for testing patients for A1AT. The prevalence of mutation in the Brazilian cohort was higher than that of other South American countries for which data were available (Argentina, Chile, and Colombia), but the non-random nature of data collection precludes an accurate comparison among countries. For example, in the Brazilian cohort, a substantially higher proportion of patients were tested due to a family history of A1AT deficiency in a biological relative.[10]

Another important study conducted in Brazil evaluated the prevalence of A1AT deficiency and the allele frequency in 926 patients with COPD from five states covering four Brazilian regions.[11] All patients had A1AT levels measured in dried spot blood samples. For those with dried spot blood A1AT levels < 2.64 mg/dL, measurement of A1AT levels in the serum was conducted. For those with serum A1AT levels < 113 mg/dL, genotyping was performed. Genetic sequencing was conducted when serum A1AT levels were < 113 mg/dL, but no S and Z alleles were detected in genotyping. The prevalence of A1AT deficiency was 2.8%, whereas that of the PiZZ genotype was 0.8%. In patients with serum A1AT levels < 113 mg/dL, the most frequent allele was Z (53.8%). The authors of the study pointed out that the prevalence of A1AT deficiency in Brazil was similar to that of other countries.[11] However, it is possible that the prevalence of A1AT deficiency in Brazilian patients with COPD is even higher than what was reported in that study, because genotyping was only triggered when serum A1AT levels were < 113 mg/dL.

In this issue of the *Jornal Brasileiro de Pneumologia*, Sokoloski et al.[12] included 136 adult outpatients without cystic fibrosis who were seen in an academic referral center in Southern Brazil in their study. Patients underwent A1AT level measurement in serum and genotyping of the *SERPINA1* gene for 14 common variants from buccal swab samples. Serum A1AT levels were classified as normal (≥ 116 mg/dL), intermediate (57-115 mg/dL), and severely reduced (< 57 mg/dL). The authors of the study considered A1AT deficiency as a definitive etiology for bronchiectasis in the presence of genotypes that cause severe A1AT deficiency, such as PiZZ, PiSZ, and PiZM(Malton). Serum levels of A1AT were < 116 mg/dL in 28 patients (20.6%) of the cohort. The levels were < 57 mg/dL in 3 patients (2.2%) and between 57 and 115 mg/dL in 25 patients (18.4%). At least one *SERPINA1* mutation was detected in 35 patients (25.7%). Pathogenic A1AT variants were detected in 17.4% of patients with serum A1AT levels ≥ 116 mg/dL, 64% of whom with levels between 57 and 115 mg/dL, and in 100% of patients with levels < 57 mg/dL. The overall cohort had a high proportion of patients with emphysema (33%). However, the proportion of emphysema was not significantly different between patients with A1AT mutations and those without it (28.6% vs. 34.7%). Additionally, among the patients with A1AT mutations and emphysema, only 30% had the panlobular type of emphysema. A1AT deficiency, as per author's definition, was the etiology of bronchiectasis in 2.9% of patients.[12]

There are important take-home messages from the study by Sokoloski et al.[12] that apply to this particular cohort of patients with bronchiectasis: (1) normal A1AT levels did not exclude pathogenic variant alleles; (2) emphysema was not more prevalent in patients with A1AT mutations; (3) the typical panlobular pattern of emphysema was not always present in patients who had A1AT mutations and emphysema; (4) the systematic investigation for A1AT is the likely reason why the prevalence of A1AT deficiency was higher than that reported in the major international cohorts of patients with bronchiectasis[3-6]; and (5) the comprehensive genotyping allowed the authors to detect a rare genotype (Pi*MI) in a young patient with a normal A1AT level and bronchiectasis of undetermined etiology. The study has limitations that the authors recognized. For example, its single-center nature limits generalizability, particularly in a large and diverse country as Brazil. The relatively small sample size undermines the precision of the estimates. The proportion of patients with emphysema was higher than that in the major published cohorts of patients with bronchiectasis,[3-6] highlighting the unique aspects of the practice where the study was conducted.

The study has important clinical implications. Currently, most guidelines or consensus on

bronchiectasis recommend testing A1AT deficiency conditional on the presence of emphysema or basal emphysema or panlobular emphysema.[13-15] The exception is the Brazilian consensus, which recommends routine investigation for A1AT deficiency in such patients (Chart 1).[16] However, if the investigation for A1AT deficiency is predicated on the presence of emphysema, many patients (probably the majority) with A1AT mutations will be missed. A more reasonable approach would be to test patients with bronchiectasis for A1AT deficiency in the presence of emphysema or if the cause of bronchiectasis has yet to be clearly established. As shown in Figure 1, large multicenter cohorts of patients with bronchiectasis consistently show that an etiology for bronchiectasis cannot be established in approximately one third of patients. Another important implication is that reliance on isolated A1AT levels is likely to miss many patients with pathogenic A1AT variants, which illustrates the importance of adding genotyping to the investigation. Moving forward, it will be interesting to conduct a similar study in a multicenter Brazilian cohort, as well as a comparison of the prevalence of pathogenic variants in the general population with that of patients with bronchiectasis, which will provide a better understanding of the magnitude of A1AT deficiency as an etiology of bronchiectasis.

CONFLICTS OF INTEREST

None of the authors report any conflict of interest pertaining to this work.

REFERENCES

1. Shoemark A, Shteinberg M, De Soyza A, Haworth C, Richardson H, Gao Y, et al. Characterisation of Eosinophilic Bronchiectasis: A European Multicohort Study. Am J Respir Crit Care Med. 2022;205(8):894-902. https://doi.org/10.1183/13993003.congress-2021.OA1307
2. Mac Aogáin M, Narayana JK, Tiew PY, Ali N, Yong VFL, Jaggi TK, et al. Integrative microbiomics in bronchiectasis exacerbations. Nat Med. 2021;27(4):688-99. https://doi.org/10.1038/s41591-021-01289-7
3. Dhar R, Singh S, Talwar D, Mohan M, Tripathi SK, Swarnakar R, et al. Bronchiectasis in India: results from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and Respiratory Research Network of India Registry. Lancet Glob Health. 2019;7(9):e1269-e1279. https://doi.org/10.1016/S2214-109X(19)30327-4
4. Athanazio R, Pereira MC, Gramblicka G, Cavalcanti-Lundgren F, de Figueiredo MF, Arancibia F, et al. Latin America validation of FACED score in patients with bronchiectasis: an analysis of six cohorts. BMC Pulm Med. 2017;17(1):73. https://doi.org/10.1186/s12890-017-0417-3
5. Xu JF, Zheng HZ, Lu HW, Wang LW, Wu B, Lv XD, et al. Baseline characteristics of patients in the Chinese Bronchiectasis Registry (BE-China): a multicentre prospective cohort study. Lancet Respir Med. 2025;13(2):166-76. https://doi.org/10.1016/S2213-2600(24)00364-3
6. Chalmers JD, Polverino E, Crichton ML, Ringshausen FC, De Soyza A, Vendrell M, et al. Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC). Lancet Respir Med. 2023;11(7):637-49. https://doi.org/10.1016/S2213-2600(23)00093-0
7. Feitosa PHR, Castellano M, Costa CHD, Cardoso A, Pereira LFF, Fernandes FLA, et al. Recommendations for the diagnosis and treatment of alpha-1 antitrypsin deficiency. J Bras Pneumol. 2024;50(5):e20240235. https://doi.org/10.36416/1806-3756/e20240235
8. Stockley RA, Pye A, De Soyza J, Turner AM, Miravitlles M. The prevalence of bronchiectasis in patients with alpha-1 antitrypsin deficiency: initial report of EARCO. Orphanet J Rare Dis. 2023;18(1):243. https://doi.org/10.1186/s13023-023-02830-2
9. Felisbino MB, Fernandes FLA, Nucci M, Pinto RMC, Pizzichini E, Cukier A. The patient profile of individuals with Alpha-1 antitrypsin gene mutations at a referral center in Brazil. J Bras Pneumol. 2018;44(5):383-9. https://doi.org/10.1590/s1806-37562017000000420
10. Lopez-Campos JL, Osaba L, Czischke K, Jardim JR, Fernandez Acquier M, Ali A, et al. Feasibility of a genotyping system for the diagnosis of alpha1 antitrypsin deficiency: a multinational cross-sectional analysis. Respir Res. 2022;23(1):152. https://doi.org/10.1186/s12931-022-02074-x
11. Russo R, Zillmer LR, Nascimento OA, Manzano B, Ivanaga IT, Fritscher L, et al. Prevalence of alpha-1 antitrypsin deficiency and allele frequency in patients with COPD in Brazil. J Bras Pneumol. 2016;42(5):311-6. https://doi.org/10.1590/S1806-37562015000000180
12. Sokoloski CS, Canan MGM, Leitão CA, Storrer KM. Prevalence of SERPINA1 mutations in a bronchiectasis cohort: implications of extended screening for alpha-1 antitrypsin deficiency. J Bras Pneumol. 2025;51(5):e20250181. https://doi.org/10.36416/1806-3756/e20250181
13. Chalmers JD, Haworth CS, Flume P, Long MB, Burgel PR, Dimakou K, et al. European Respiratory Society Clinical Practice Guideline for the Management of Adult Bronchiectasis. Eur Respir J. 2025: 2501126. https://doi.org/10.1183/13993003.01126-2025
14. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn SJ, Floto AR, et al. British Thoracic Society Guideline for bronchiectasis in adults. Thorax. 2019;74(Suppl 1):1-69. https://doi.org/10.1136/thoraxjnl-2018-212463
15. Chang AB, Bell SC, Byrnes CA, Dawkins P, Holland AE, Kennedy E, et al. Thoracic Society of Australia and New Zealand (TSANZ) position statement on chronic suppurative lung disease and bronchiectasis in children, adolescents and adults in Australia and New Zealand. Respirology. 2023;28(4):339-49. https://doi.org/10.1111/resp.14479
16. Pereira MC, Athanazio RA, Dalcin PTR, Figueiredo MRF, Gomes M, Freitas CG, et al. Brazilian consensus on non-cystic fibrosis bronchiectasis. J Bras Pneumol. 2019;45(4):e20190122. https://doi.org/10.1590/1806-3713/e20190122

J Bras Pneumol. 2025;51(5):e20250354
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Peripheral longitudinal consolidations

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

A 21-year-old man complained of a dry cough, progressive dyspnea, and fever for two months. He had peripheral eosinophilia of 1,800/mm³ (27%). A CT scan showed peripheral longitudinal bands of consolidation in the upper lobes (Figure 1). The final diagnosis was chronic eosinophilic pneumonia (CEP).

Peripheral consolidations can occasionally occur in some infections (H1N1, COVID-19, leptospirosis, etc.), non-thrombotic embolisms (fat, silicone), and sarcoidosis, among others. However, in these conditions, the clinical and laboratory findings are usually sufficient for diagnosis. The main differential diagnoses in our case, once these conditions were ruled out, would be organizing pneumonia and CEP. The main aspect for the differential diagnosis was the presence of significant eosinophilia in peripheral blood.

Eosinophilic lung diseases are a diverse group of diseases characterized by lung opacities associated with tissue or peripheral eosinophilia. Diagnosis of eosinophilic lung disease can be made if any of the following findings are present: (a) lung opacities with peripheral eosinophilia, (b) tissue eosinophilia confirmed by open lung biopsy or transbronchial biopsy, or (c) increased eosinophils in BALF. Eosinophilic lung diseases are generally classified as those of unknown cause (simple pulmonary eosinophilia, acute eosinophilic pneumonia, CEP, idiopathic hypereosinophilic syndrome) and those of known causes (allergic bronchopulmonary aspergillosis, bronchocentric granulomatosis, parasitic infection, drug reaction), as well as eosinophilic vasculitis (allergic angiitis, granulomatosis).[1,2]

Most patients with CEP have a history of asthma or atopy. It is characterized by respiratory symptoms for 2 to 4 weeks, diffuse pulmonary alveolar consolidation with air bronchogram and/or ground-glass opacities, eosinophilia in BALF (≥ 40% eosinophils) or eosinophilia in peripheral blood (≥ 1,000/mm³), and absence of other known causes of eosinophilic pneumonia. Symptoms may persist for more than one month and include cough, fever, night sweats, progressive dyspnea, malaise, and weight loss. Blood eosinophilia is present in 90% of patients, and sputum eosinophilia in 50%. Imaging studies may show linear, band-like opacities parallel to the pleural surface. The combination of this imaging finding, the presence of eosinophilia, and response to steroid treatment are usually sufficient for diagnosis, obviating the need for lung biopsy.[1,2]

The disease responds very well to steroids, and the opacities resolve within 7 to 10 days after starting corticosteroid therapy, although recurrence rate is high.

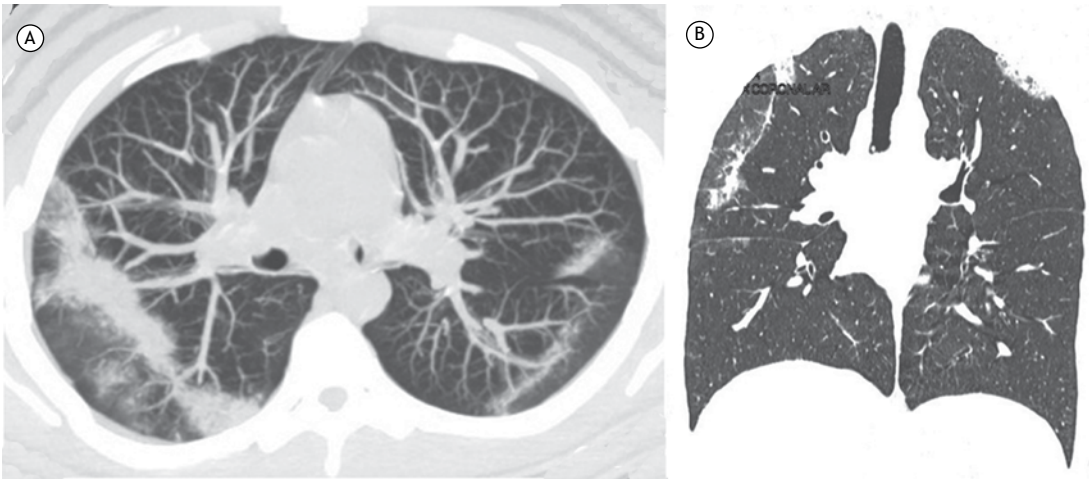

Figure 1. In A, axial chest CT scan showing band-like pulmonary consolidations, longitudinal to the pleural surface, in the upper lobes, predominantly on the right. In B, coronal reconstruction demonstrating the extent of the consolidations.

REFERENCES

1. Carbone RG, Puppo F, Mattar E, Roden AC, Hirani N. Acute and chronic eosinophilic pneumonia: an overview. Front Med (Lausanne) 2024:11:1355247. https://doi.org/10.3389/fmed.2024.1355247
2. Jeong YJ, Kim KI, Seo IJ, Lee CH, Lee KN, Kim KN, et al. Eosinophilic Lung Diseases: A Clinical, Radiologic, and Pathologic Overview. Radiographics 2007;27:617-37. https://doi.org/10.1148/rg.273065051

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Artificial intelligence transforming healthcare research: opportunities, risks, and responsible use

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PRACTICAL SCENARIO

A team of early career researchers is developing a proposal for a clinical trial testing a new treatment for interstitial lung disease. They must write the introduction section and describe the randomization process, but the deadline for submitting is midnight of that day. With little time and uncertain about what to write, they turned to an artificial intelligence (AI) tool for assistance. The output appeared polished, accurate, and trustworthy, so they pasted it directly into their proposal and submitted it. However, during peer review, it was found that some references were nonexistent, and the description of randomization was incorrect and unsuitable for the trial design. What began as a minor shortcut has now compromised the validity of the proposal and the probability of getting funding.

OPPORTUNITIES OF AI IN RESEARCH

AI is a field of computer science that develops systems capable of learning, reasoning, understanding human language, perceiving, and making decisions in ways that mimic human cognition. Common applications include voice assistants, chatbots, and large language models (LLMs), such as ChatGPT, Gemini, and DeepSeek, which are trained in massive datasets that can understand, process, and generate human-like language.

AI has been rapidly integrated across multiple stages of the scientific process, through natural language processing (NLP) and machine learning. Specialized tools (open or subscription-based) assist in searching, summarizing, and extracting data from published literature. Examples include Elicit, Consensus, among others (Figure 1). These platforms are useful to identify relevant studies quickly, explore evidence, and address clinical or scientific questions in an efficient and evidence-informed manner.

Beyond literature review, AI offers additional capabilities. It can process and analyze large study datasets, generate code for statistical platforms, such as R or Python, and identify patterns or associations that might otherwise be overlooked. LLMs can be used to rewrite text, proving editorial support. At the publication stage, journals are increasingly adopting AI-based systems for research integrity checks and automatically screen manuscripts for potential plagiarism or fabricated information with high accuracy.

RISKS AND LIMITATIONS

Despite its promising landscape, there are many concerns. One of the most relevant is "hallucination," whereby LLMs generate plausible but inaccurate or fabricated information. In our fictitious clinical scenario, the AI generated an eloquent introduction but included inexistent references. Hallucination rates for ChatGPT have been reported between 10-40%, depending on the model version.[1] Overreliance on AI, therefore, may lead to errors that undermine the rigor and validity of research. Also, AI reports may be constructed in studies with biases, presenting incorrect answers to clinic or research questions based on disparities according to sex, race, or ethnic origin of patients.[1]

Another risk is the potential for AI to accelerate a phase of science, in which we may "produce more but understand

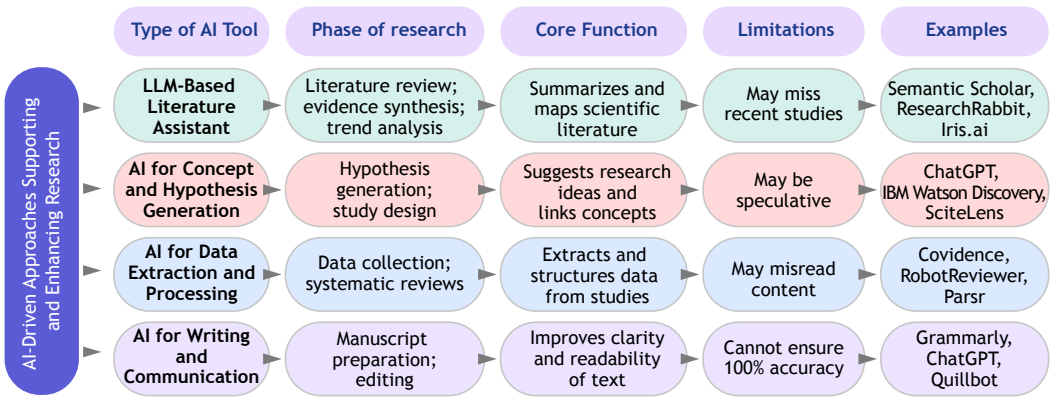

Figure 1. Artificial intelligence (AI)-driven tools supporting different phases of the research process. LLM: large language model.

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less," prioritizing efficiency over comprehension and making science less innovative and more vulnerable to error and bias.[2] In academic research, plausibility and the explanatory pathway are mandatory for scientific reasoning. Ethical considerations also extend to issues of bias, reproducibility, and accountability. Recognizing these risks does not diminish the utility of AI, but rather underscores the need for cautious, transparent, and informed use.

As a result, ethical and transparent use of AI in research reporting is now emphasized by leading editorial bodies. The International Committee of Medical Journal Editors (ICMJE) recommends that authors disclose any use of AI in writing, data analysis, or figure generation, typically in the acknowledgments section.[3] Importantly, chatbots or LLMs cannot be credited as authors, as they lack accountability for accuracy, integrity, and originality, which are essential criteria for authorship.

AI has already transformed research by streamlining literature searches, supporting data analysis, enhancing quality control, and improving manuscript preparation, particularly for non-native English speakers. However, AI should be regarded as a support tool rather than a substitute for scientific judgment or a co-author. Final decisions and interpretations must always rest with the researcher. By combining AI's capabilities with human expertise and adhering to ethical guidelines, investigators can harness its strengths while safeguarding research integrity and reproducibility.

REFERENCES

1. Chelli M, Descamps J, Lavoué V, Trojani C, Azar M, Deckert M, et al. Hallucination Rates and Reference Accuracy of ChatGPT and Bard for Systematic Reviews: Comparative Analysis. J Med Internet Res. 2024;26:e53164. https://doi.org/10.2196/53164
2. Messeri L, Crockett MJ. Artificial intelligence and illusions of understanding in scientific research. Nature. 2024;627(8002):49-58. https://doi.org/10.1038/s41586-024-07146-0
3. International Committee of Medical Journal Editors (ICMJE) [homepage on the Internet]. Philadelphia, PA: ICMJE; [cited 2025 Oct 11]. Recommendations. Defining the Role of Authors and Contributors. Available from: https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

The role of the pulmonary function laboratory in the assessment of adults with neuromuscular disease

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BACKGROUND

Neuromuscular disease (NMD) can affect all respiratory muscle groups, and respiratory complications are the major cause of morbidity and mortality.[1] The duration of symptoms varies depending on the underlying diagnosis. NMD can be acute (e.g., Guillain-Barré syndrome; acute spinal cord or phrenic nerve trauma or infarction; epidural abscess; acute poisoning; drug-related NMD; metabolic disturbances; tetanus or other infections; and acute myasthenic crisis) or present slowly over months (e.g., amyotrophic lateral sclerosis, multiple sclerosis, spinal cord tumors, myasthenia gravis, syringomyelia, muscular dystrophy, and myotonic dystrophy). In the latter context, pulmonary function tests (PFTs) play a prominent role in objectively assessing respiratory muscle strength and potential consequences of weakness of the respiratory system (Figure 1).

OVERVIEW

A 55-year-old overweight man (BMI = 27 kg/m^2) with a history of heavy smoking (30 pack-years) was referred for a pulmonology consultation because of long-standing sporadic inclusion body myositis. He reported having experienced leg pain and weakness since he was in his 30s and 40s, respectively. Although there were no respiratory symptoms during wakefulness (with a modified Medical Research Council scale score of 1, with no cough or phlegm) or daytime somnolence (an Epworth Sleepiness Scale score of 6), the patient did report episodes of nocturnal choking and frequent rhonchi. Moderate left convex scoliosis was observed on physical examination. PFTs indicated a restrictive ventilatory defect (an FVC of 62% of the predicted value and a TLC of 68% of the predicted value) and respiratory muscle weakness (an MIP of 57% of the predicted value and an MEP of 69% of the predicted value). Of note, RV and the RV/TLC ratio were within and above the upper limit of normal, respectively. A proportional reduction in DL_{CO} (60% of the predicted value) and alveolar volume (V_A; 65% of the predicted value) corresponded to a carbon monoxide transfer coefficient (K_{CO}) within normal ranges (94% of the predicted value = a z-score of −0.30). Diffuse myocardial hypokinesis (a left ventricular ejection fraction of 49%) was observed on echocardiography. Mild obstructive respiratory disorder was observed during overnight polysomnography (an apnea-hypopnea index of 14.6 events/h), with significant CO_2 retention (mean partial pressure of end-tidal CO_2 = 39, with peaks of 51 mmHg).

Restriction is the typical finding in patients with respiratory muscle weakness. It is suggested by reduced FEV_1 and FVC with a preserved FEV_1/FVC ratio and confirmed by a reduced TLC. In cases of preserved FVC, a fall > 15% in FVC from the sitting position to the supine position supports a diagnosis of diaphragm weakness.[2] This threshold can be higher in the presence of concomitant ventilatory defects.[3] A high RV/TLC ratio was a consequence of a low TLC (rather than a high RV), in keeping with restriction. Nevertheless, when the expiratory muscles are involved, RV and RV/TLC may be increased, resulting in complex restriction (reduced FVC relative to TLC).[4] DL_{CO} is reduced in extraparenchymal restriction as a result of reduced V_A, which would lead to a supranormal K_{CO} (DL_{CO}/V_A). A "normal" K_{CO} with preserved V_A/TLC indicates some degree of concomitant intraparenchymal restriction.[5] In the current case, it was attributed to alveolar fibrosing sequelae from repeated episodes of pulmonary congestion caused by cardiomyopathy. Arterial blood gas analysis should be routinely obtained to determine whether daytime hypercapnia is present. Hypercapnia, however, may be evident during sleep only, when polysomnography with end-tidal or transcutaneous capnography is useful.

CLINICAL MESSAGE

PFTs are regularly recommended for patients with NMD who may exhibit varying rates of decline in lung function.[1] Objective testing is important because there is no correlation between respiratory muscle weakness and the degree of peripheral muscle weakness in several conditions.[6] Functional testing helps identify patients who need specific therapies, such as assisted cough, airway clearance, and ventilatory support.[1]

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

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SPIROMETRY

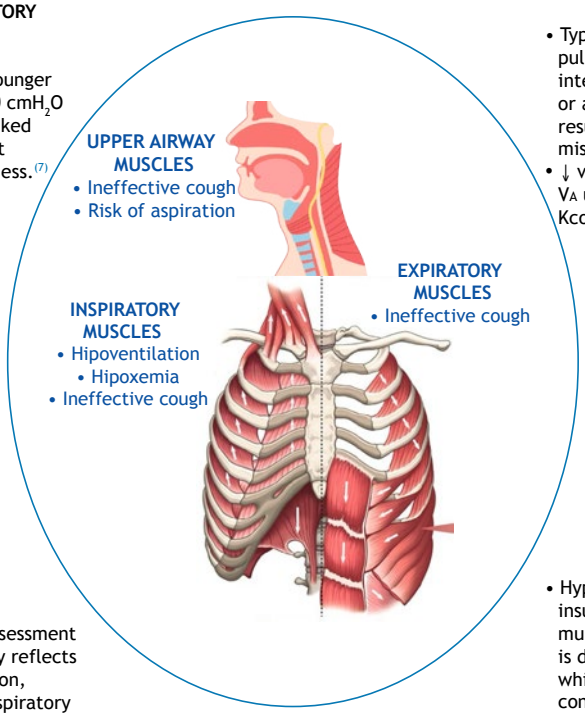
- ↓ FEV_1 and FVC with ↔ FEV_1/FVC ratio suggest restriction, the typical ventilatory defect in patients with respiratory muscle weakness.
- A fall in FVC > 15% from the sitting position to the supine position suggests diaphragmatic weakness.
- ↓ measured MVV in comparison with estimated MVV (= FEV_1 × 40) indicates ↓ respiratory muscle endurance.

BODY PLETHYSMOGRAPHY

- TLC < LLN is the gold standard for restriction.
- Patients with predominantly expiratory muscle weakness may demonstrate a ↓ expiratory reserve volume and an ↑ RV, leading to an ↑ RV/TLC ratio (complex restriction).

MAXIMAL INSPIRATORY PRESSURE

- Absolute values < -50-60 cmH_2O in younger individuals and < -40 cmH_2O in the elderly are linked with a higher pretest probability of weakness.[7]
- Severe bulbar dysfunction may cause difficulty performing the tests due to the lack of a tight seal of the lips around the mouthpiece. In these situations, the operator can assist by manually ensuring a tight seal for the patient.
- Alternatively, sniff nasal inspiratory pressure (SNIP) may be used to indicate respiratory muscle weakness.
- SNIP is a dynamic assessment that more accurately reflects diaphragm dysfunction, whereas maximal inspiratory pressure is more influenced by the recruitment of accessory inspiratory muscles.



DLco

- Typically preserved if no coexisting pulmonary parenchymal (e.g., interstitial lung disease, emphysema or atelectasis), or vascular disease resulting in ventilation/perfusion mismatch.
- ↓ values may occur due to reduced V_A usually resulting in supranormal Kco (DLco/V_A).

ARTERIAL BLOOD GAS ANALYSIS

- Hypercapnia is the hallmark of inadequate ventilation.
- Early in the course of chronic disease, ventilation may be adequate to maintain a normal $PaCO_2$. However, under stress (e.g., sleep, fever, infection) or with disease progression, ventilation cannot be sufficiently increased, and $PaCO_2$ rises.
- Hypoxemia frequently accompanies insufficient ventilation and is multifactorial. A small contribution is due to insufficient ventilation, while a more significant contribution is typically due to atelectasis-induced shunt from rapid, shallow breathing.

MAXIMAL EXPIRATORY PRESSURE

- Values < 60 cm H_2O suggest that the patient's cough is ineffective.
- A peak cough flow < 160 L/min identifies patients with an ineffective cough. Values between 160-270 L/min. indicate an increased risk for respiratory tract infections
- The absence of transient increases in peak cough expiratory flow (i.e., cough spikes) above the maximal flow-volume loop in spirometry indicates decreased cough effectiveness.

USE OF NONINVASIVE VENTILATION[1]

- The clinical indications for noninvasive ventilation can vary depending on NMD, age, and rate of disease progression.
- Any fall in FVC to < 80% of predicted with symptoms or FVC to < 50% of predicted without symptoms or SNIP /maximal inspiratory pressure to < -40 cmH_2O or hypercapnia would support initiation of noninvasive ventilation or further testing as clinically indicated for individual NMD.

RECOMMENDATIONS FOR LUNG VOLUME RECRUITMENT (BREATH STACKING) AND ASSISTED COUGH TECHNIQUES/DEVICES[1]

- For patients with NMD and hypoventilation, ↓ lung function or ↓ cough effectiveness.

Figure 1. Involvement of inspiratory, expiratory, and/or upper airway muscles in patients with neuromuscular disease (NMD) determines the predominating clinical presentation (in blue). Different pulmonary function tests (in black) can reveal functional impairments and support the indication of specific therapies (in red). MVV: maximal voluntary ventilation; LLN: lower limit of normal; ↓: decreased; ↑: increased; ↔: preserved; V_A: alveolar volume; and K_{CO}: carbon monoxide transfer coefficient.

REFERENCES

1. Khan A, Frazer-Green L, Amin R, Wolfe L, Faulkner G, Casey K, et al. Respiratory Management of Patients With Neuromuscular Weakness: An American College of Chest Physicians Clinical Practice Guideline and Expert Panel Report. Chest. 2023;164(2):394-

413. https://doi.org/10.1016/j.chest.2023.03.011

2. Poddighe D, Van Hollebeke M, Rodrigues A, Hermans G, Testelmans D, Kalkanis A, et al. Respiratory muscle dysfunction in acute and chronic respiratory failure: how to diagnose and how to treat? Eur Respir Rev. 2024;33(174):240150. https://doi.org/10.1183/16000617.0150-2024
3. Allen SM, Hunt B, Green M. Fall in vital capacity with posture. Br J Dis Chest. 1985;79(3):267-71. https://doi.org/10.1016/0007-0971(85)90047-6
4. Clay RD, Iyer VN, Reddy DR, Siontis B, Scanlon PD. The "Complex Restrictive" Pulmonary Function Pattern: Clinical and Radiologic Analysis of a Common but Previously Undescribed Restrictive Pattern. Chest. 2017;152(6):1258-1265. https://doi.org/10.1016/j.chest.2017.07.009
5. D'Cruz J, Neder-Serafini I, Zapotichny A, Neder JA. Exposing the Roots of Restriction: When the Transfer Coefficient Makes the Difference. Ann Am Thorac Soc. 2024;21(2):343-350. https://doi.org/10.1513/AnnalsATS.202305-484CC
6. Burakgazi AZ, Höke A. Respiratory muscle weakness in peripheral neuropathies. J Peripher Nerv Syst. 2010;15(4):307-13. https://doi.org/10.1111/j.1529-8027.2010.00293.x
7. Rodrigues A, Da Silva ML, Berton DC, Cipriano G Jr, Pitta F, O'Donnell DE, et al. Maximal Inspiratory Pressure: Does the Choice of Reference Values Actually Matter? Chest. 2017;152(1):32-39. https://doi.org/10.1016/j.chest.2016.11.045

Long-term impact of the 10-valent pneumococcal conjugate vaccine on nonvaccine pneumococcal serotypes: implications for practice and surveillance

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BACKGROUND

Pneumonia remains one of the leading causes of death in children under five years of age worldwide. It is estimated that approximately 700,000 deaths occur annually, and *Streptococcus pneumoniae* is the bacterial agent that is most frequently implicated. The risk is even greater among children with preexisting cardiovascular or respiratory diseases, which makes prevention essential. In this context, pneumococcal conjugate vaccines (PCVs) have radically changed the landscape of public health. The first PCV, the 7-valent PCV, was introduced in 2000, followed by broader formulations such as the 10-valent PCV (PCV10), the 13-valent PCV (PCV13), the 15-valent PCV, and the 20-valent PCV. In Brazil, PCV10 was incorporated into the Brazilian National Immunization Program in 2010, covering ten serotypes but not including 19A.[1,2]

In the years following the introduction of PCV10, the results were remarkable: according to the Information Technology Department of the Brazilian Unified Health Care System, hospitalizations for pneumonia in children dropped from 2,157.5 to 1,441.5 per 100,000 population between 2010 and 2018 (a reduction of 33.2%). This clearly demonstrates the short-term positive impact of the vaccine. However, the trajectory did not remain linear. Starting in 2019, a reversal trend emerged, culminating with rates of 1,553.7 per 100,000 population in 2023, i.e., a 7.8% increase in comparison with the lowest rate observed in 2018 (Figure 1A).

WHAT EXPLAINS THIS CHANGE?

The phenomenon of serotype replacement is the main candidate. When the vaccine dramatically reduces the targeted serotypes, other serotypes find space to spread.[3]

Serotype 19A became the most relevant in Brazil after the introduction of PCV10. Epidemiological analysis showed an average annual increase of 6.06 cases of 19A, with statistical significance (95% CI, 1.39-10.73; $p < 0.01$; Figure 1B). In practical terms, this means that, even when vaccinated, many children remained vulnerable to severe pneumonia, now caused by a serotype not included in the formulation adopted in the country.

This pattern is not unique to Brazil. In other Latin American countries, an increase in serotype 19A has also been documented following the adoption of PCV10.[4,5] In places such as the United States, England, and Wales, a similar trajectory of 19A growth was observed, often associated with complicated pneumonia and penicillin resistance. The difference is that in those countries, the introduction of PCV13, which includes serotype 19A, led to significant declines in its prevalence. In the United States, there was a reduction of approximately 40% among children under five years of age. In Israel, the incidence of invasive respiratory disease caused by 19A fell from 5 to 1.6 per 100,000 population after the introduction of PCV13. These data reinforce that the choice of vaccine formulation has a direct impact on epidemiological dynamics and clinical outcomes.[2,3]

From a clinical and public health perspective, the Brazilian experience with PCV10 shows that vaccines are not static in their effects. The initial impact was significant: a one-third reduction in hospitalizations for childhood pneumonia. However, this protection did not remain uniform over time, as the phenomenon of serotype replacement brought new challenges. The most striking example is serotype 19A, which is not included in PCV10 and has become a common cause of pneumonia, often associated with severe cases and antimicrobial resistance. This means that, in clinical practice, pediatricians and primary care physicians should remain aware that children vaccinated with PCV10 are still at risk for pneumonia caused by nonvaccine serotypes. In severe cases, especially those of hospitalization, it is necessary to consider the possibility of infection by serotype 19A and adjust therapeutic management to local patterns of resistance. This reinforces the importance of integrating clinical reasoning into epidemiological surveillance, given that the prevalence of serotypes may vary across regions and change rapidly.[6]

For policymakers and health authorities, the lesson is equally clear: the success of a vaccine depends on the ability to monitor the dynamics of disease. Transitioning to higher-valency vaccines, such as PCV13, the 15-valent PCV, and the 20-valent PCV, offers broader protection and represents an opportunity to resume the reductions observed in the first decade after PCV10 was introduced. International experience confirms this path. Countries that

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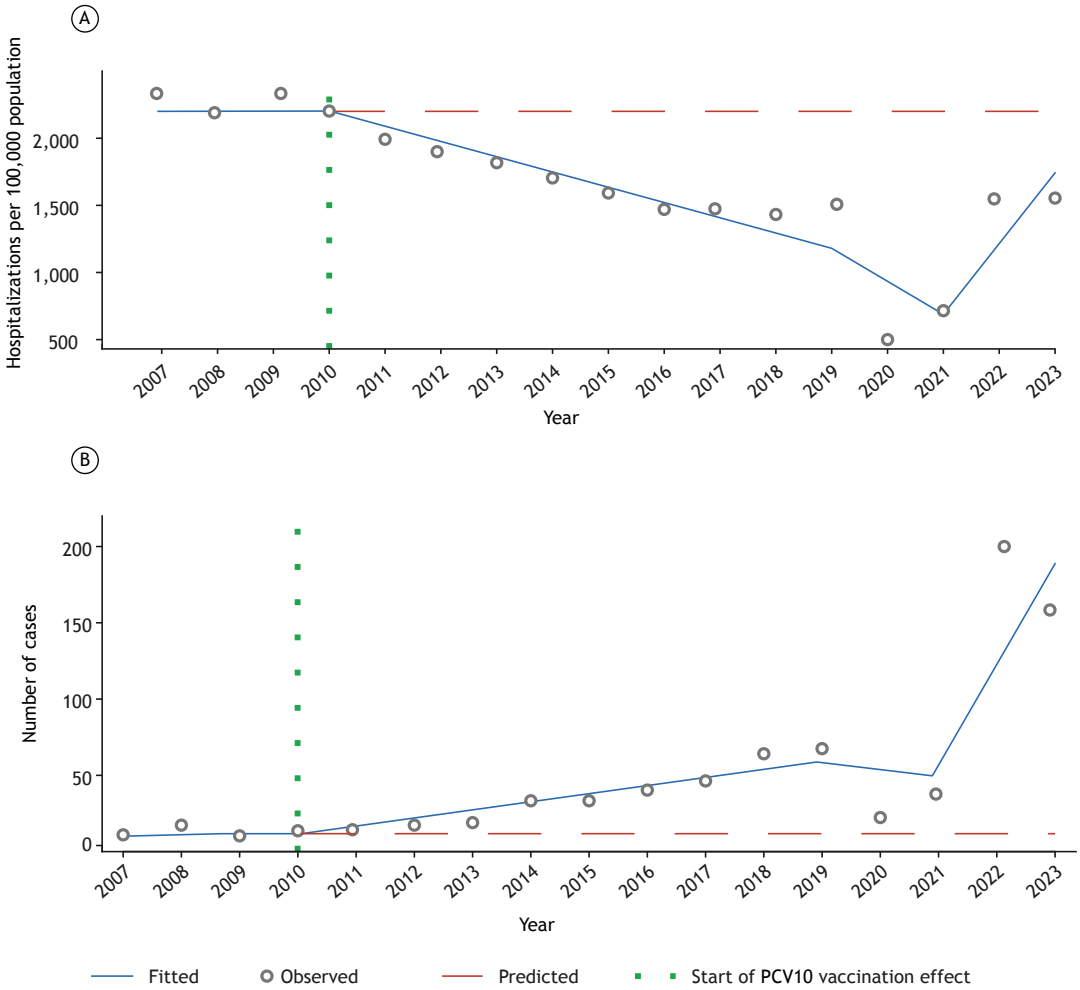

Figure 1. Long-term impact of the 10-valent pneumococcal conjugate vaccine (PCV10) on nonvaccine pneumococcal serotypes. In A, hospitalizations for pneumonia. In B, absolute cases of *Streptococcus pneumonia* serotype 19A.

adopted PCV13 saw marked declines in the prevalence of serotype 19A, including cases of invasive disease. This effect is not limited to reducing hospitalizations but also impacts antimicrobial resistance, given that 19A is known for presenting higher resistance profiles.

Another important aspect for practice is understanding that continuous surveillance should not be seen as the sole responsibility of central public health authorities. Physicians, hospitals, and laboratories play an active role in feeding information systems and identifying changes in the clinical profile of diseases. Accurate reporting and collection of microbiological data are essential components to guide effective vaccination policies.

Finally, the discussion on pneumococcal serotypes illustrates a broader point: immunization strategies must be constantly updated to respond to the dynamic behavior of microorganisms. Scientific advances have allowed the development of vaccines covering 15 to 20 serotypes, with the potential to include not only 19A but also emerging serotypes such as 22F and 33F. Incorporating these options is not just a technical decision but also a strategic one, capable of preventing setbacks and ensuring long-term protection for children.

In summary, the lesson is that pneumococcal vaccination should be regarded as a constantly evolving process. Although PCV10 has brought concrete benefits, the current epidemiological reality demands expansion of the vaccine arsenal. Updating immunization strategies, adopting higher-valency vaccines, and maintaining active surveillance are fundamental steps to consolidate protection against severe pneumonia and ensure that the progress achieved in the past decade is not compromised by emerging serotypes.

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AUTHOR CONTRIBUTIONS

LFX, GB, PBB, EH, MP, and CM: data curation, formal analysis, investigation, methodology, and writing—original draft. MB, FF, MCS, and LAP: conceptualization, formal analysis, methodology, project administration, and writing—review and editing. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Kim GL, Seon SH, Rhee DK. Pneumonia and Streptococcus pneumoniae vaccine. Arch Pharm Res. 2017;40(8):885-893. https://doi.org/10.1007/s12272-017-0933-y.
2. UNICEF Data [homepage on the Internet]. New York City: UNICEF; [updated 2024 Nov; cited 2023 Jan 15]. Pneumonia. A child dies of pneumonia every 43 seconds. Available from: https://data.unicef.org/topic/child-health/pneumonia/
3. Kawaguchiya M, Urushibara N, Aung MS, Ohashi N, Tsutida S, Kurashita K, et al. Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolated from children in Japan, 2023. New Microbes New Infect. 2024:62:101513. https://doi.org/10.1016/j.nmni.2024.101513
4. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018;18(11):1191-1210. https://doi.org/10.1016/S1473-3099(18)30310-4
5. Senders S, Klein NP, Tamimi N, Thompson A, Baugher G, Trammel J, et al. A Phase Three Study of the Safety and Immunogenicity of a Four-dose Series of 20-Valent Pneumococcal Conjugate Vaccine in Healthy Infants. Pediatr Infect Dis J. 2024;43(6):596-603. https://doi.org/10.1097/INF.0000000000004334
6. Camacho-Moreno G, Leal AL, Patiño-Niño J, Vasquez-Hoyos P, Gutiérrez I, Beltrán S, et al. Serotype distribution, clinical characteristics, and antimicrobial resistance of pediatric invasive pneumococcal disease in Colombia during PCV10 mass vaccination (2017–2022). Front Med (Lausanne). 2024;11:1380125. https://doi.org/10.3389/fmed.2024.1380125

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Effect of combined strength and endurance training in adults with asthma: a randomized controlled trial

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ABSTRACT

Objective: Pulmonary rehabilitation programs, including exercise training, have an established role in the treatment of chronic respiratory diseases but are not routinely used in asthma. Most studies of individuals with asthma have focused on endurance training, and there is therefore limited data available on strength training. The aim of this study was to evaluate the effects that adding strength training to a program of endurance training and education has on the quality of life of such individuals. **Methods:** In this single-center, parallel-group randomized controlled trial, adults with moderate-to-severe asthma admitted for in-hospital pulmonary rehabilitation between June of 2021 and October of 2022 were randomized to either a study group (SG) or a control group (CG). The SG received strength training alongside endurance training and education, whereas the CG received the same endurance training and education, along with sham mobility exercise training instead of strength training. The primary outcome was the change in the Asthma Quality of Life Questionnaire (AQLQ) score from hospital admission to discharge. **Results:** A total of 61 participants were randomized, with 31 being assigned to the SG and 30 being assigned to the CG. At discharge, the AQLQ score showed significant improvement in both groups ($p < 0.001$ for the SG and $p = 0.02$ for the CG), albeit without a significant difference between the groups ($p > 0.99$). In contrast, peripheral muscle strength improved significantly from admission to discharge only in the SG, with a significant difference between the groups in terms of quadriceps strength ($p = 0.03$). **Conclusions:** Adding strength training to endurance training and education does not seem to result in further improvement in the quality of life of individuals with moderate-to-severe asthma.

Keywords: Rehabilitation; Asthma; Exercise therapy; Resistance training; Exercise tolerance; Quality of life.

(ClinicalTrials.gov identifier: NCT04935125 [http://www.clinicaltrials.gov/])

INTRODUCTION

Asthma is one of the most common chronic respiratory diseases, affecting an estimated 262 million people globally in 2019.[1] Although drug therapy is effective in most cases, the disease can remain less than optimally controlled in some cases, partly because of incorrect usage of or reduced adherence to pharmacological treatment.[2] These individuals might not be able to perform activities of daily living and can suffer from poor health-related quality of life. This highlights the need for additional, nonpharmacological interventions,[3] and exercise training could be a highly effective strategy. In particular, studies showed that exercise training is associated with a reduction in symptoms, improved asthma control, better lung function, and enhanced quality of life.[4,5] Nevertheless, although pulmonary rehabilitation programs that include exercise training have an established role in the treatment of chronic respiratory diseases, they are not routinely employed in individuals with asthma and there are no specific recommendations on the intensity, frequency, or duration of the exercise.[6–8] However, the latest update to the GINA guidelines on asthma management and prevention recommends that individuals with asthma and reduced functional capacity be referred to a pulmonary rehabilitation program.[9] Although more research is needed to establish the optimal exercise regimen and strong recommendations are currently unavailable, endurance training (ET) is the most widely studied and recommended exercise modality for individuals with asthma.[8-11] Strength training (ST), which involves repetitive lifting of increasing loads to strengthen muscle groups, is another exercise modality recognized for its importance in promoting healthy aging.[12-14] In addition, ST is known to improve not only muscle strength in the limbs, hand grip, and depression but also quality of life in older people,[14] as well as being indicated in individuals with chronic respiratory diseases.[6] However, there are few data on the effect of ST on quality of life in individuals

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with asthma. Therefore, the aim of this trial was to evaluate the short- and long-term effects that adding ST to a program of ET and education has on quality of life in individuals with moderate-to-severe asthma.

METHODS

This was a single-center, parallel-group randomized controlled trial, approved by the Research Ethics Committee of the *Istituti Clinici Scientifici Maugeri* (Reference no. 2525 CE 08-June-2021), in the city of Tradate, Italy. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Participants gave written informed consent, and data were treated confidentially. The study was registered with ClinicalTrials.gov (identifier: NCT04935125; http://www.clinicaltrials.gov/). The reporting adhered to the Consolidated Standards of Reporting Trials guidelines.[15] The interventions were described following the Consensus on Exercise Reporting Template (CERT).[16]

We evaluated all individuals with asthma, diagnosed in accordance with the GINA guidelines,[9] who were admitted to the *Istituti Clinici Scientifici Maugeri* Rehabilitation Hospital of Tradate for in-hospital pulmonary rehabilitation between June of 2021 and October of 2022. The inclusion criteria were as follows: being between 18 and 80 years of age; having severe asthma, as defined by GINA steps 4 and 5 under inhalation therapy[9]; presenting with symptoms, as evidenced by an Asthma Control Test score between 20 and 24[17]; and being able to perform and complete the study procedures and the pulmonary rehabilitation program. Subjects were excluded if they met any of the following criteria: having COPD; being a current or former smoker with a smoking history of more than 10 pack-years; having a BMI ≥ 30 kg/m^2; having a change in medication within the last 30 days before randomization; presenting with cognitive impairment, as evidenced by a Mini-Mental State Examination score < 22[18]; and having a history of cancer, neurological disorder, cardiovascular disease, musculoskeletal impairment, or any condition that would preclude exercise testing and pulmonary rehabilitation.

After baseline evaluations, the eligible participants were enrolled. The randomization list, with a 1:1 ratio, was computer-generated by an independent statistician using dedicated software (https://www.randomizer.org/). Allocation to the study group (SG) or control group (CG) was determined by a researcher not involved in the study, who drew sealed, opaque envelopes, each containing a group code. Participants in the SG underwent ET and education with the addition of ST, whereas those in the CG underwent the same ET and education program along with a sham intervention, which consisted of unloaded exercises for the upper and lower limbs.

Measurements

The following data and assessments were recorded or performed at admission, designated time zero (T0): demographics; anthropometrics; asthma severity according to the GINA guidelines[9]; comorbidities, assessed with the Cumulative Illness Rating Scale Severity and Comorbidity Index[19]; the Asthma Control Test score[17]; steroid use and number of exacerbations in the previous 12 months; dynamic lung volumes according to standards[20] using the predicted values established by Quanjer et al.[21]; arterial blood gases; and airway inflammation, identified by measuring the fractional exhaled nitric oxide (FeNO).[22] At discharge (T1), we also applied the Global Perceived Effect scale.[23]

At T0, at T1, and at 12 months after discharge (T2), the following were evaluated[24-29]:

- Health-related quality of life, by application of the Asthma Quality of Life Questionnaire (AQLQ)
- Disease control, as characterized by the score on the six-item Asthma Control Questionnaire (ACQ-6)
- Functional capacity, as determined by the distance covered on the six-minute walk test; that is, the six-minute walk distance (6MWD)
- Isometric maximal voluntary contraction (MVC) of the quadriceps and biceps, as assessed with a hand-held dynamometer

At T2, the number of exacerbations during the previous 12 months was recorded. Exacerbations were defined as a progressive increase in symptoms and decrease in lung function, requiring a change in medications.[30] The assessors who conducted the evaluations were blinded to the group allocation. Details of the measurements, including their minimal clinically important difference (MCID) values for outcome measures, are shown in the supplementary material.

Pulmonary rehabilitation

All interventions were supervised by a team consisting of chest physicians, nurses, physical therapists, dieticians, and psychologists.

The ET program consisted of 14 daily 30-min sessions (six days per week) of supervised incremental cycling on a cycle ergometer (Ergoselect 4 or Ergoselect 5; Ergoline GmbH, Bitz, Germany). The initial workload was set at 50-70% of the maximal load, calculated on the basis of the baseline 6MWD, as described by Hill et al.[31] The progression was individualized based on perceived effort: if participants rated their dyspnea or leg fatigue as < 4 on the modified Borg scale,[32] the workload was increased by 5 watts; if their Borg scale score was 4 or 5, the workload remained unchanged; and if their Borg scale score was > 5, the workload was reduced. Peripheral oxygen saturation, heart rate, arterial blood pressure, perceived dyspnea, and perceived fatigue were monitored during sessions. The total weekly ET volume was 180 min.

The ST program targeted peripheral limb muscle and was performed six times per week in 30-min supervised sessions. Each participant completed the same exercise protocol, performing three sets

per exercise, beginning with 8 repetitions per set for the first 4-5 days, then increasing to at least 12 repetitions per set on the following days. The initial load was set to induce moderate fatigue or dyspnea (Borg scale score of 3 or 4). The progression was based on perceived effort: if participants rated their fatigue or dyspnea as < 4 on the Borg scale, the resistance was increased by 0.5-1.0 kg; if the Borg scale score was 4 or 5, the load remained unchanged; and if the Borg scale score was > 5, the resistance was reduced. The training session was conducted one-on-one under the supervision of a physical therapist. The weekly training volume was adjusted based on tolerance and performance, ensuring a progressive overload approach.

The sham training consisted of unloaded mobilization exercises for the upper and lower limbs, performed in small groups under the supervision of a physical therapist. Sessions lasted 30 min, six times per week, and each exercise was performed for three sets of 8-12 repetitions, without any progression in load or intensity.

Additional details on the exercise training modalities can be found in the supplementary material.

Education, provided by chest physicians, nurses, and physical therapists, consisted of at least three individual 20-min sessions on asthma characteristics, drug/inhalation therapy, physical activity, and lifestyle. In addition, a minimum of three 45-min group sessions on diet and nutrition, anxiety, depression and stress control,[33] were provided by a dietitian and a psychologist.

Full treatment adherence was defined as 80% participation, as assessed by counting the number of sessions completed by each subject.

Before discharge, each subject received written instructions on how to behave at home and how to maintain their exercise training. Specifically, all patients were instructed to perform ET, with ST for those in the SG and sham mobility exercises for those in the CG (more details in the supplementary material).

Statistical analysis

The primary outcome measure of this study was the change in the AQLQ score from T0 to T1. Secondary outcome measures were the changes in the ACQ-6 score, in the 6MWD, in the quadriceps MVC, and in the biceps MVC—between T0 and T1 and between T0 and T2—in both groups.

The sample size calculation was based on the primary outcome of the study. Data from 29 subjects per group were required to test the null hypothesis of no difference in the AQLQ score from T0 and T1 between the SG—expected mean change, 1.03 ± 0.62 points[34]—and the CG—expected mean change, 0.52 ± 0.41 points[35]—with a significance level of $\alpha = 0.05$ and a statistical power $(1 - \beta)$ of 0.95 (two-tailed t-test for independent samples). The total sample size of 58 subjects was rounded up to 60. Sample size calculations were performed with the G*Power software tool, version 3.1.9.2 (Heinrich-Heine-Universität, Düsseldorf, Germany).

All participants were included in the intention-to-treat analysis. Participants who completed the program with available measures at all-time points were included in the per-protocol analysis. Quantitative variables are expressed as mean and standard deviation, or as median and interquartile range when their distribution deviated significantly from the normality assumptions ($p < 0.05$ on the Shapiro-Wilk test) or in the case of discrete numeric variables. Categorical variables are expressed as absolute and relative frequency. Linear quantile mixed models were applied to estimate the change over time in outcomes between time points and to compare estimates between the SG and CG. The Bonferroni correction was applied to adjust for multiple comparisons. The significance level was set at $\alpha = 0.05$. Statistical analyses were performed with R software, version 4.2.2 (www.r-project.org). A detailed description of the statistical methods can be found in the supplementary material.

RESULTS

We evaluated 61 participants, 31 in the SG and 30 in the CG. Although all participants were included in the intention-to-treat analysis, 7 were excluded from the per-protocol analysis (Figure 1). As shown in Table 1, there were no significant differences between the two groups in terms of the demographic, anthropometric, physiological, or clinical characteristics, or in terms of the medications used. The only statistically significant difference was in the FeNO, which was higher in the SG. In addition, none of the enrolled subjects had any clinically significant respiratory conditions other than asthma.

At T0, 4 of the participants in the SG had very high FeNO values (> 100 ppb), which were not observed in any of the participants in the CG. Values exceeding the threshold for eosinophilic inflammation, defined as 25 ppb,[22] were observed in 17 (55%) of the participants in the SG and in 12 (40%) of those in the CG, with no significant difference between the groups ($p = 0.16$). Because of technical and organizational constraints, in comparison with the registered protocol, the results of the assessment of the FeNO at T1 and T2 were registered in very few participants, as were those of the cardiopulmonary exercise testing at T0, T1, and T2. Therefore, those data are not reported or commented upon.

The mean number of ET sessions completed was 12 (IQR: 11-15) in the SG and 12 (IQR: 12-14) in the CG ($p = 0.92$). Participants in the SG also completed 13 ST sessions (IQR: 11-14), whereas those in the CG completed 13 sham training sessions (IQR: 7-14), and the difference was not significant ($p = 0.47$). Full treatment adherence, defined as completing at least 80% of the 14 sessions, was achieved by 24 (77%) of the participants in the SG and by 20 (67%) of

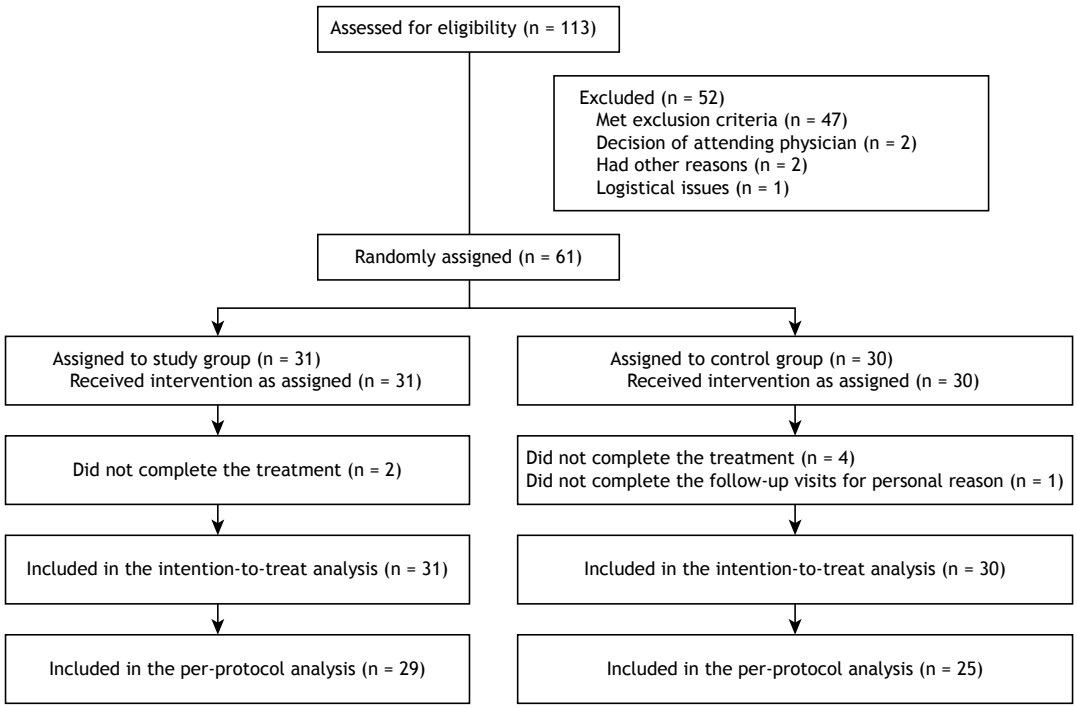

Figure 1. Consolidated Standards of Reporting Trials flow diagram.

Table 1. Baseline characteristics of the participants.

Variable	Study group (n = 31)	Control group (n = 30)	p
Male	9 (29)	4 (13)	0.21
Age, years	63 (58-71)	62 (54-72)	0.72
BMI, kg/m^2	27.1 (23.6-29.0)	26.3 (21.0-29.0)	0.54
GINA step 5	21 (68)	14 (48)	0.20
ACT score	20 (17-21)	20 (16-21)	0.97
Current or former smoker	10 (32)	5 (17)	0.24
Smoking history, pack-years	0 (0-1)	0 (0-0)	0.28
CIRS Severity Index score	1.5 (1.3-1.8)	1.7 (1.4-1.9)	0.19
CIRS Comorbidity Index score	3 (2-5)	4 (2-6)	0.43
Previous exacerbation, n	0 (0-1)	0 (0-1)	0.44
At least one exacerbation in the previous year	12 (39)	14 (47)	0.53
Steroid use in previous 12 months, mg	0.00 (0.00-0.56)	0.00 (0.00-1.08)	0.33
FEV_1, % pred	85.13 ± 21.53	86.45 ± 24.17	0.82
FVC, % pred	95.39 ± 15.52	92.45 ± 15.35	0.46
PaO_2, mmHg	80.97 ± 9.79	81.19 ± 12.34	0.94
$PaCO_2$, mmHg	37.3 (35.3-39.6)	37.2 (35.7-41.1)	0.40
pH	7.41 (7.41-7.43)	7.42 (7.40-7.43)	0.99
FeNO[a], ppb	40.5 (21.8-88.5)	23 (15.3-37.5)	0.01
AQLQ score	5.75 (5.08-6.04)	5.20 (4.38-5.90)	0.16
ACQ-6 score	1.33 (0.50-1.83)	1.42 (0.74-1.66)	0.66
6MWD, m	483.9 ± 71.9	461.9 ± 99.0	0.33
6MWD, % pred	85.1 ± 11.2	79.5 ± 17.3	0.15
Isometric MVC, kg			
Biceps	13.7 (11.8-16.4)	12.3 (9.3-15.1)	0.21
Quadriceps	22.3 ± 7.1	22.4 ± 8.4	0.95

Data are reported as n (%), mean ± SD, or median (IQR). ACT: Asthma Control Test; CIRS: Cumulative Illness Rating Scale; FeNO: fractional exhaled nitric oxide; AQLQ: Asthma Quality of Life Questionnaire; ACQ-6: six-item Asthma Control Questionnaire; 6MWD: six-minute walk distance; and MVC: maximal voluntary contraction. [a] Data available for only 52 subjects (26 in the study group and 26 in the control group).

those in the CG, without any statistically significant difference between groups (p = 0.35). No adverse events occurred in either group over the course of the study.

Primary outcome measure

As shown in Table 2, the AQLQ score improved significantly from T0 to T1 in both groups, without any statistically significant difference between the groups (p > 0.99). The number of participants reaching the MCID on the AQLQ was 18 (62%) in the SG and 12 (46%) in the CG (p = 0.28).

Secondary outcome measures

The improvement gained in AQLQ scores by T1 was lost in both groups by T2 (Figure 2). From T0 to T1, the quadriceps and biceps MVC values improved significantly only in the SG participants. In particular, the change estimated in terms of quadriceps MVC was significantly higher in the SG than in the CG (interaction p = 0.03). From T0 to T1, all other outcomes improved significantly in both groups, although without statistically significant differences between the groups. Such benefits were lost by T2 (Table 2 and Supplementary Figures S1-S5). At T1, the median score on the Global Perceived Effect scale was 2 (IQR: 1-2) in the SG and in the CG, with no significant difference between the two groups (p = 0.65). During the year following randomization, there was no significant change in the exacerbation rate in either group. The results adjusted for baseline values (Figures S1-S7 and Table S1) and obtained from the per-protocol analysis (Tables S2 and S3) were similar to those obtained from the unadjusted intention-to-treat analysis.

Figure 3 shows the proportion of participants reaching the MCID for each outcome. A significant difference was found only for quadriceps MVC: the proportion of participants reaching the MCID was significantly higher in the SG (p = 0.02).

DISCUSSION

To our knowledge, this is the first randomized controlled trial to evaluate the effects of adding ST to a program of ET and education in individuals with moderate-to-severe asthma. We found an improvement in the primary and secondary outcome measures in the SG and the GC at T1, with no significant differences between groups, except for the quadriceps and biceps MVC, which improved only in the SG. However, the

Table 2. Results from linear quantile mixed models according to the intention-to-treat analysis.

Outcome measure(s)	Study group (n = 31)		Control group (n = 30)		Interaction p-value[c]
	Estimate (95% CI)[a]	p[b]	Estimate (95% CI)[a]	p[b]	
Primary					
Δ T0-T1					
AQLQ score	0.63 (0.27 to 0.98)	< 0.001	0.55 (0.07 to 1.02)	0.02	> 0.99
Secondary					
Δ T0-T1					
ACQ-6 score	−0.69 (−1.18 to −0.21)	0.002	−0.74 (−1.08 to −0.40)	< 0.001	> 0.99
6MWD, m	31.04 (9.79 to 52.28)	0.001	41.21 (16.64 to 65.78)	< 0.001	0.81
6MWD, % pred	6.55 (2.87 to 10.23)	< 0.001	5.93 (2.02 to 9.84)	< 0.001	> 0.99
Isometric MVC, kg					
Quadriceps	6.27 (3.65 to 8.90)	< 0.001	2.35 (−0.77 to 5.47)	0.24	0.03
Biceps	2.39 (0.47 to 4.30)	0.008	1.98 (−0.16 to 4.12)	0.08	> 0.99
Δ T0-T2					
AQLQ score	0.01 (−0.37 to 0.39)	> 0.99	0.36 (−0.20 to 0.91)	0.43	0.36
ACQ-6 score	−0.31 (−0.71 to 0.10)	0.23	−0.53 (−1.00 to −0.05)	0.02	0.72
6MWD, m	17.04 (−14.97 to 49.04)	0.72	27.41 (−10.08 to 64.90)	0.27	> 0.99
6MWD, % pred	2.53 (−2.58 to 7.65)	0.85	2.87 (−3.11 to 8.86)	0.91	> 0.99
Isometric MVC, kg					
Quadriceps	−0.16 (−3.22 to 2.91)	> 0.99	−2.24 (−5.84 to 1.37)	0.48	0.50
Biceps	−0.01 (−2.01 to 1.98)	> 0.99	−0.75 (−2.83 to 1.32)	> 0.99	> 0.99
Exacerbations, n	−0.17 (−0.65 to 0.32)	0.88	−0.63 (−1.32 to 0.06)	0.08	0.18

T0: time zero (admission); T1: time one (discharge); T2: time two (12 months after discharge); AQLQ: Asthma Quality of Life Questionnaire; ACQ-6: six-item Asthma Control Questionnaire; 6MWD: six-minute walk distance; and MVC: maximal voluntary contraction. [a]Change between time points estimated by linear quantile mixed models and corresponding Bonferroni-corrected 95% CI, adjusted by four tests (AQLQ; ACQ-6; 6MWD, m; 6MWD, % pred; biceps MVC; and quadriceps MVC) or by two tests (exacerbations).[b]Bonferroni-corrected p-value, adjusted by four tests (AQLQ; ACQ-6; 6MWD, m; 6MWD, % pred; biceps MVC; and quadriceps MVC) or by two tests (exacerbations), corresponding to the estimate deriving from linear quantile mixed models.[c]Bonferroni-corrected p-value, adjusted by two tests (AQLQ; ACQ-6; 6MWD, m; 6MWD, % pred; biceps MVC; and quadriceps MVC) or unadjusted (exacerbations) for the interaction between time and group.

observed benefits of training were lost by one year after randomization in both groups.

We have assessed individuals with moderate-to-severe asthma according to the GINA guidelines.[9] It has been shown that individuals with asthma at any GINA step can benefit from pulmonary rehabilitation programs including ET.[36] Our study is unique in that it adds evidence to support pulmonary rehabilitation programs that also include ST, at least for individuals with moderate-to-severe asthma. Another original result of our study is the improvement in peripheral muscle strength, as evidenced by greater biceps and quadriceps MVC, in the participants receiving ET plus ST but not in those undergoing ET without ST. This result shows the specificity of the training programs we used. To determine the workload for the ST, we adopted a symptom-driven approach rather than the more commonly used method based on a percentage of the one-repetition maximum.[7] As well as being simpler and more pragmatic, this approach allows the training intensity to be more individualized, enhancing adherence and optimizing functional adaptations. That may have contributed to the observed improvements in muscle strength, because individual adjustments ensured an appropriate yet challenging workload for each participant. All other outcomes improved in both groups. The lack of statistically significant between-group differences in terms of the post-program changes in outcome measures is not surprising given that both groups performed ET, which is associated with improvements in those outcomes.[36] In addition, the lack of significant differences in the scores on the AQLQ may be partly due to the broad nature of its questions, which assess muscle strength only indirectly, through a few items on physical limitations in daily life. However, this is a common feature of quality-of-life questionnaires, where such aspects are generally assessed only marginally.

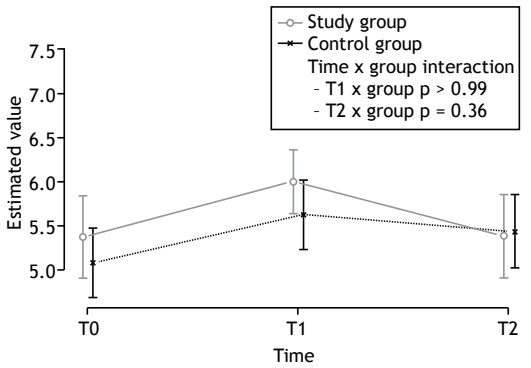

Figure 2. Estimated Asthma Quality of Life Questionnaire scores, by group and time point, in the intention-to-treat analysis. Points show the conditional medians from linear quantile mixed model regression, with the bars representing 95% confidence intervals (no Bonferroni correction). T0: time zero (admission); T1: time one (discharge); and T2: time two (12 months after discharge).

In the present study, the benefits observed at T1 were lost by T2, despite the fact that each participant

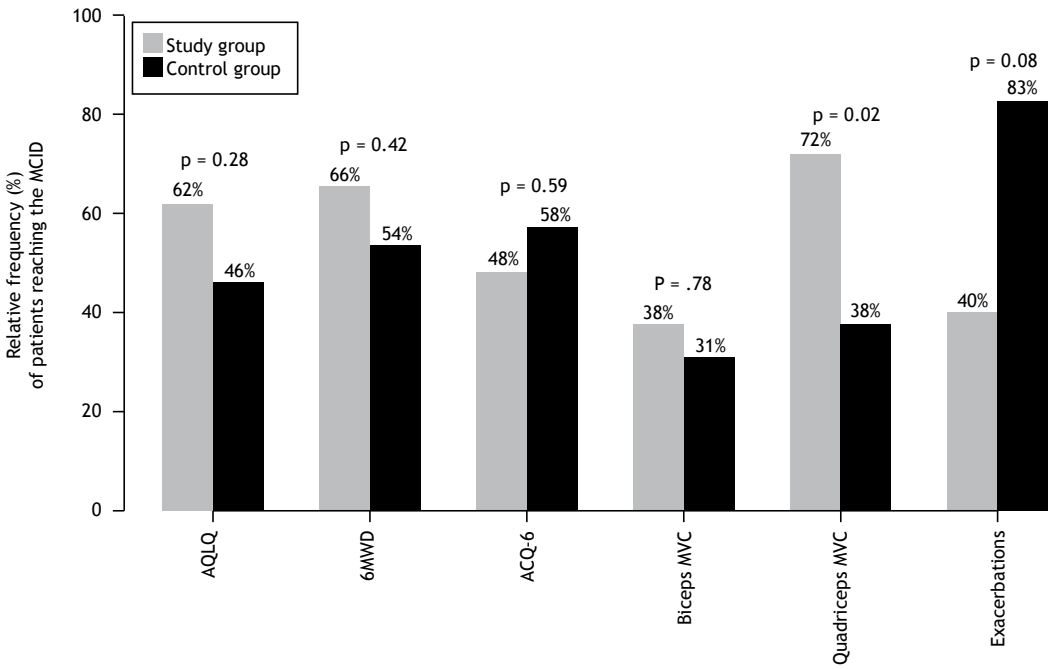

Figure 3. Relative frequency of patients reaching the minimal clinically important difference (MCID) for each outcome, in the study group (n = 31) and in the control group (n = 30). AQLQ: Asthma Quality of Life Questionnaire; 6MWD: six-minute walk distance; ACQ-6: six-item Asthma Control Questionnaire; and MVC: (isometric) maximal voluntary contraction. Frequency of patients reaching the MCID at discharge, for each outcome, except for exacerbations, which were evaluated at 12 months after discharge. Exacerbations were analyzed in a subset of 22 subjects who had at least one exacerbation in the 12 months before randomization and available data on exacerbations during the 12 months after randomization. Values of p are from chi-square tests.

received a written maintenance program at T1. That finding confirms what has been reported in previous studies.[37] Recent technological advances may facilitate the organization of such programs.[38]

The lack of changes in exacerbation rates in the year following the program in both groups is not surprising. Given the very low rate in the year before the study, further improvement would be highly improbable in a population also enrolled in an educational program.

We are confident that the duration of the program applied in the present study (at least 12 training sessions) was sufficient to reach the plateau of exercise tolerance, as previously shown in individuals with COPD admitted for in-hospital pulmonary rehabilitation.[39] In fact, a study comparing the functional benefits and relative costs of a short-term intensive inpatient pulmonary rehabilitation program with those of a longer outpatient program for individuals with chronic airway obstruction, concluded that the shorter inpatient program provides improvements in exercise tolerance similar to those of the longer outpatient program, but at a lower cost.[39]

Our study has some limitations. First, there was a statistically significant difference between the SG and CG in terms of the FeNO at baseline. That can be explained by the presence of a few SG participants with very high FeNO values, despite the fact that the proportion of participants in whom eosinophilic inflammation exceeded the 25 ppb threshold did not differ significantly between the two groups. In addition, a recent meta-analysis concluded that FeNO-guided asthma treatment probably results in fewer exacerbations but may not have clinically relevant effects on other asthma outcomes.[40] Therefore, we are confident that this difference has not biased our results. Furthermore, the use of anklets and wristbands in place of gym machines (unavailable at our facility), particularly for the lower extremity exercises, may have limited the effectiveness of the ST. However, the combination of simple, low-cost equipment and the detailed description of the treatment following the CERT guidelines[16] makes our program easily replicable and adaptable, even in home or resource-limited settings. Another limitation of our study is the use of the exacerbation rate as the only long-term outcome measure. However, collecting additional relevant outcomes, such as health care resource utilization and lost workdays, would have required a health care data collection system that is not readily available in our country. Finally, the single-center design may have limited the generalizability of the results. However, the use of nonparametric statistical methods and repeated analyses, employing both intention-to-treat and per-protocol approaches, with and without adjustments for baseline values, increased the robustness of our results.

In conclusion, the results of this study, while confirming the benefits of exercise training, show that adding ST to a program of ET and education does not result in further improvement in quality of life for individuals with moderate-to-severe asthma in comparison with ET and education alone. However, the observed improvement in peripheral muscle strength in participants also undergoing ST suggests that it could be a valuable addition to pulmonary rehabilitation programs, particularly for subjects with muscle weakness at the initial assessment.

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AUTHOR CONTRIBUTIONS

NA, MT, and EZ contributed to the conception or design of the study and have directly assessed and verified the data reported in the manuscript. GLB, FMO, AM, and AZ contributed to the acquisition, analysis, or interpretation of data. All of the authors drafted, critically revised, and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-1222. https://doi.org/10.1016/S0140-6736(20)30925-9
2. Camarinha C, Fernandes M, Alarc Úo V, Franco J, Mana oas ME, B írbara C, et al. Determinants associated with uncontrolled asthma in Portugal: A national population-based study. Pulmonology. 2023;29(1):29-41. https://doi.org/10.1016/j.pulmoe.2020.02.014
3. Clemente-Suárez VJ, Mielgo-Ayuso J, Ramos-Campo DJ, Beltran-Velasco AI, Martínez-Guardado I, Navarro Jimenez E, et al. Basis of preventive and non-pharmacological interventions in asthma. Front Public Health. 2023;11:1172391. https://doi.org/10.3389/fpubh.2023.1172391
4. Hansen ESH, Pitzner-Fabricius A, Toennesen LL, Rasmusen HK, Hostrup M, Hellsten Y, et al. Effect of aerobic exercise training on asthma in adults: a systematic review and meta-analysis. Eur Respir J. 2020;56(1):2000146. https://doi.org/10.1183/13993003.00146-2020
5. Freeman AT, Staples KJ, Wilkinson TMA. Defining a role for exercise training in the management of asthma. Eur Respir Rev. 2020;29(156):190106. https://doi.org/10.1183/16000617.0106-2019
6. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An Official American Thoracic Society/European Respiratory Society Statement: Key Concepts and Advances in Pulmonary Rehabilitation. [published correction appears in Am J Respir Crit Care Med. 2014 Jun 15;189(12):1570]. Am J Respir Crit Care Med. 2013;188(8):e13-e64. https://doi.org/10.1164/rccm.201309-1634ST
7. Gloeckl R, Zwick RH, Fürlinger U, Jarosch I, Schneeberger T, Leitl D, et al. Prescribing and adjusting exercise training in chronic respiratory diseases - Expert-based practical recommendations. Pulmonology. 2023;29(4):306-314. https://doi.org/10.1016/j.pulmoe.2022.09.004

8. British Thoracic Society, Scottish Intercollegiate Guidelines Network [site on the Internet]. Edinburgh: Scottish Intercollegiate Guidelines Network [updated 2019 Jul; cited 2024 Sep 1]. BTS/SIGN158 British Guideline on the Management of Asthma. Available from: https://www.brit-thoracic.org.uk/document-library/guidelines/asthma/btssign-guideline-for-the-management-of-asthma-2019/
9. Global Initiative for Asthma [homepage on the internet]. Bethesda: Global Initiative for Asthma; c2023 [cited 2024 Dec 29]. Global Strategy for Asthma Management and Prevention (2024 update). Available from: https://ginasthma.org/
10. Evaristo KB, Mendes FAR, Saccomani MG, Cukier A, Carvalho-Pinto RM, Rodrigues MR, et al. Effects of Aerobic Training Versus Breathing Exercises on Asthma Control: A Randomized Trial. J Allergy Clin Immunol Pract. 2020;8(9):2989-2996.e4. https://doi.org/10.1016/j.jaip.2020.06.042
11. Jaakkola JJK, Aalto SAM, Hernberg S, Kiihamäki SP, Jaakkola MS. Regular exercise improves asthma control in adults: A randomized controlled trial. Sci Rep. 2019;9(1):12088. https://doi.org/10.1038/s41598-019-48484-8
12. Hurley BF, Hanson ED, Sheaff AK. Strength training as a countermeasure to aging muscle and chronic disease. Sports Med Auckl NZ. 2011 1;41(4):289-306. https://doi.org/10.2165/11585920-000000000-00000
13. Marcos-Pardo PJ, Orquin-Castrillón FJ, Gea-García GM, Menayo-Antúnez R, González-Gálvez N, Vale RG de S, et al. Effects of a moderate-to-high intensity resistance circuit training on fat mass, functional capacity, muscular strength, and quality of life in elderly: A randomized controlled trial. Sci Rep. 2019;9(1):7830. https://doi.org/10.1038/s41598-019-44329-6
14. Khodadad Kashi S, Mirzazadeh ZS, Saatchian V. A Systematic Review and Meta-Analysis of Resistance Training on Quality of Life, Depression, Muscle Strength, and Functional Exercise Capacity in Older Adults Aged 60 Years or More. Biol Res Nurs. 2023;25(1):88-106. https://doi.org/10.1177/10998004221120945
15. Schulz KF. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Ann Intern Med. 2010;152(11):726. https://doi.org/10.7326/0003-4819-152-11-201006010-00232
16. Slade SC, Dionne CE, Underwood M, Buchbinder R. Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. Br J Sports Med. 2016;50(23):1428-37. https://doi.org/10.1136/bjsports-2016-096651
17. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113(1):59-65. https://doi.org/10.1016/j.jaci.2003.09.008
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." J Psychiatr Res. 1975;12(3):189-98. https://doi.org/10.1016/0022-3956(75)90026-6
19. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16(5):622-6. https://doi.org/10.1111/j.1532-5415.1968.tb02103.x
20. Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932-46. https://doi.org/10.1183/09031936.04.00014304
21. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43. https://doi.org/10.1183/09031936.00080312
22. American Thoracic Society, European Respiratory Society. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. Am J Respir Crit Care Med. 2005;171(8):912-30. https://doi.org/10.1164/rccm.200406-710ST
23. Kamper SJ, Ostelo RW, Knol DL, Maher CG, de Vet HC, Hancock MJ. Global Perceived Effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. J Clin Epidemiol. 2010;63(7):760-766.e1. https://doi.org/10.1016/j.jclinepi.2009.09.009
24. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax. 1992 1;47(2):76-83. https://doi.org/10.1136/thx.47.2.76
25. Juniper EF, O□byrne PM, Guyatt G h, Ferrie P j, King D r. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902. https://doi.org/10.1034/j.1399-3003.1999.14d29.x
26. Meys R, Janssen SMJ, Franssen FME, Vaes AW, Stoffels AAF, Van Hees HWH, et al. Test-retest reliability, construct validity and determinants of 6-minute walk test performance in adult patients with asthma. Pulmonology. 2023;29(6):486-94. https://doi.org/10.1016/j.pulmoe.2022.10.011
27. Delbressine JM, Jensen D, Vaes AW, Li PZ, Bourbeau J, Tan WC, et al. Reference values for six-minute walk distance and six-minute walk work in Caucasian adults. Pulmonology. 2023;29(5):399-409. https://doi.org/10.1016/j.pulmoe.2023.02.014
28. Zampogna E, Ambrosino N, Centis R, Cherubino F, Migliori GB, Pignatti P, et al. Minimal clinically important difference of the 6-min walking test in patients with asthma. Int J Tuberc Lung Dis. 2021;25(3):215-21. https://doi.org/10.5588/ijtld.20.0928
29. Meldrum D, Cahalane E, Conroy R, Fitzgerald D, Hardiman O. Maximum voluntary isometric contraction: Reference values and clinical application. Amyotroph Lateral Scler. 2007;8(1):47-55. https://doi.org/10.1080/17482960601012491
30. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations: Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. Am J Respir Crit Care Med. 2009;180(1):59-99. https://doi.org/10.1164/rccm.200801-060ST
31. Hill K, Jenkins SC, Cecins N, Philippe DL, Hillman DR, Eastwood PR. Estimating Maximum Work Rate During Incremental Cycle Ergometry Testing From Six-Minute Walk Distance in Patients With Chronic Obstructive Pulmonary Disease. Arch Phys Med Rehabil. 2008;89(9):1782-7. https://doi.org/10.1016/j.apmr.2008.01.020
32. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-81. https://doi.org/10.1249/00005768-198205000-00012
33. Gibson PG, Powell H, Wilson A, Abramson MJ, Haywood P, Bauman A, et al. Self-management education and regular practitioner review for adults with asthma. Cochrane Database Syst Rev. 2003(1):CD001117. https://doi.org/10.1002/14651858.CD001117
34. França-Pinto A, Mendes FAR, de Carvalho-Pinto RM, Agondi RC, Cukier A, Stelmach R, et al. Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: a randomised controlled trial. Thorax. 2015;70(8):732-9. https://doi.org/10.1136/thoraxjnl-2014-206070
35. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994;47(1):81-7. https://doi.org/10.1016/0895-4356(94)90036-1
36. Zampogna E, Paneroni M, Cherubino F, Pignatti P, Rudi M, Casu G, et al. Effectiveness of a Pulmonary Rehabilitation Program on Persistent Asthma Stratified for Severity. Respir Care. 2019;64(12):1523-30. https://doi.org/10.4187/respcare.06761
37. Foglio K, Bianchi L, Bruletti G, Battista L, Pagani M, Ambrosino N. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. Eur Respir J. 1999;13(1):125-32. https://doi.org/10.1183/09031936.99.13112599
38. Silva J, Hipólito N, Machado P, Flora S, Cruz J. Technological features of smartphone apps for physical activity promotion in patients with COPD: A systematic review. Pulmonology. 2025;31(1): 2416796. https://doi.org/10.1016/j.pulmoe.2023.06.005
39. Clini E, Foglio K, Bianchi L, Porta R, Vitacca M, Ambrosino N. In-Hospital Short-term Training Program for Patients With Chronic Airway Obstruction. Chest. 2001;120(5):1500-5. https://doi.org/10.1378/chest.120.5.1500
40. Korevaar DA, Damen JA, Heus P, Moen MJ, Spijker R, van Veen IH, et al. Effectiveness of FeNO-guided treatment in adult asthma patients: A systematic review and meta-analysis. Clin Exp Allergy J. 2023;53(8):798-808. https://doi.org/10.1111/cea.14359

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https://dx.doi.org/10.36416/1806-3756/e20250181

Prevalence of *SERPINA1* mutations in a bronchiectasis cohort: implications of extended screening for alpha-1 antitrypsin deficiency

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ABSTRACT

Objective: To evaluate the prevalence of alpha-1 antitrypsin (AAT) variants through SERPINA1 genotyping in patients with non-cystic fibrosis bronchiectasis, and assess their clinical, functional and radiological characteristics. AAT deficiency is underdiagnosed, and an etiology to be considered when evaluating bronchiectasis. **Methods:** A cross-sectional study was conducted at an outpatient clinic focused on bronchiectasis in a tertiary hospital. Data from patients followed between 2005 and 2023 were collected. Genotyping for AAT was performed. Demographic, clinical, pulmonary function tests, serum AAT levels and chest CT data were analyzed. **Results:** A total of 136 patients were included, predominantly female (72.1%), with a median age of 56.6 years. The prevalence of *SERPINA1* gene mutations was 25.7% (n=35). Among the detected variant genotypes were Pi*MS (15.4%), Pi*MZ (5,1%), Pi*SS (1,5%), Pi*ZZ (1,5%), Pi*MI (0,7%), Pi*SZ (0,7%) and Pi*ZMMalton (0,7%). When comparing patients with and without *SERPINA1* mutations, significant differences were observed in AAT serum levels, emphysema type (panlobular) and distribution (diffuse and lower-lobe predominant). No other clinical, microbiological, functional or radiological differences were found, including emphysema presence or absence. Notably, 16 (45.7%) of individuals carrying *SERPINA1* mutations exhibited normal serum AAT levels. **Conclusions:** AAT variants are not uncommon among patients with bronchiectasis. Presence of panlobular, diffuse or lower-lobe predominant emphysema should prompt AATD diagnostic consideration. However, the absence of emphysema does not exclude the diagnosis. Moreover, *SERPINA1* variants may occur along with normal AAT serum levels. Clinicians should consider genotyping in patients with normal AAT levels, particularly when bronchiectasis remains unexplained.

Keywords: Alpha 1-antitrypsin deficiency; Bronchiectasis; Genotype; Mutation; Alleles

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a still underdiagnosed autosomal codominant disorder caused by mutations in the *SERPINA1* gene, resulting in reduced serum levels of alpha-1 antitrypsin (AAT) and increased susceptibility to chronic pulmonary and liver diseases.[1] AAT is the main circulating serine protease inhibitor, and its deficiency promotes a protease–antiprotease imbalance, favoring lung tissue damage to occur.[2] Although AATD is typically associated with emphysema, recent studies have also linked the condition to other lung diseases, such as asthma and non-cystic fibrosis bronchiectasis.[3-5]

Bronchiectasis is a chronic suppurative lung disorder, caused by a heterogenic group of diseases, characterized by permanent bronchial dilation, typically presenting with chronic cough, sputum production, dyspnea and recurrent respiratory infections. Identifying the underlying etiology is critical to guide management and prognosis.[6] Despite thorough evaluation, 24-40% of bronchiectasis cases remain undetermined worldwide.[7,8] Therefore, AATD should be systematically considered as a possible cause of bronchiectasis.[3,6]

Although the prevalence of AATD is unknown in most countries and varies across populations, it is most frequently observed in individuals of European ancestry,[3] with estimates of up to 1 in 5,000 people in Europe.[9] In Brazil, epidemiological data of AATD in general population are lacking.[10] A cross-sectional study involving 926 patients with COPD from five different Brazilian regions found an overall prevalence of 2.8% for AATD.[11] However, to our knowledge, there are no published data specifically addressing the prevalence of AAT variants among patients with bronchiectasis in Brazil.

This study aims to evaluate the prevalence of AAT variants in a population of patients with bronchiectasis using *SERPINA1* gene mutation testing, and to assess their clinical, functional and radiological characteristics compared to those without mutations.

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METHODS

This was a cross-sectional study, performed at the non-cystic fibrosis bronchiectasis referral center of the Federal University of Paraná, southern Brazil. Between 2005 and 2023, 239 patients were followed at the outpatient clinic. Data were evaluated and collected from July 2022 to December 2023. The present study was approved by the Committee for Ethics in Research on Human Beings under the opinion 5.464.008, and written informed consent was obtained from all participants.

Patients aged 18 years or older with bronchiectasis diagnosed by clinical and tomographic criteria, who had undergone genotyping for AAT variants were included. Patients with insufficient data or a diagnosis of cystic fibrosis were excluded.

Diagnosis and etiology of bronchiectasis were defined according to specific diagnostic criteria.[6,12] For this study, etiology was grouped as follows: post-tuberculosis, post-infectious (other), common variable immunodeficiency, immunoglobulin A deficiency, related to HIV virus infection, other immunodeficiency, related to auto-immune diseases (collagen and inflammatory bowel diseases), primary ciliary dyskinesia, AATD-related, undefined (or idiopathic), and others (involving the diagnosis: Williams-Campbell syndrome, Scimitar syndrome, allergic bronchopulmonary aspergillosis, chronic aspiration).

Clinical, laboratory, and imaging data were retrieved from electronic medical records and hospital information systems and compiled for analysis. Data related to the following were collected:

- Clinical variables: age, sex, race, smoking status, BMI, long-term oxygen therapy, number of exacerbations and hospitalizations in the previous 12 months of follow-up, comorbidities (asthma and prior tuberculosis), and E-FACED bronchiectasis severity score (calculated based on occurrence of severe exacerbation in the previous year, FEV_1 % predicted, age, chronic infection by *Pseudomonas aeruginosa*, radiological extent, and dyspnea by modified Medical Research Council scale).
- Laboratory variables: serum AAT level, *SERPINA1* genotype, sputum culture microbiology.
- Pulmonary function: FEV_1, FVC, FEV_1/FVC ratio, DL_{CO} (absolute and % predicted) and bronchodilator response were evaluated. FEV_1 was considered very severely reduced when <30% predicted; severely reduced when 30–49% predicted; moderately reduced when 50–79% predicted and mildly reduced when ≥80% predicted.
- CT scan variables: images were acquired in a multidetector scanner (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan), with a high-resolution protocol (1-mm slice thickness and 0.5-mm increments), and assessed by a chest radiologist. Evaluated parameters included presence, type and distribution of emphysema and bronchiectasis, number of affected lobes, bronchial wall thickening, mucus plugging, tree-in-bud opacities, and prior surgical resections.

AAT measurement and genotyping

Serum AAT levels were measured by turbidimetry in peripheral venous blood samples. The reference range for this method was 90–200 mg/dL. By protocol, measurements were performed during clinically stable periods, as AAT is an acute-phase reactant and may be elevated during inflammatory or infectious exacerbations.[3,10]

Serum AAT concentrations were stratified into three categories according to the AATD diagnostic algorithm[3,10] and the internationally recognized threshold for severe deficiency[13]: ≥116 mg/dL (normal), 57–115 mg/dL (intermediate levels), and <57 mg/dL (severely reduced levels).

Genotyping of the *SERPINA1* gene was performed, regardless of AAT serum levels. It was used a buccal swab collection kit (ORAcollect OCR-100; DNA Genotek, Inc, Ottawa, Canada), preserved in bacteriostatic stabilizing solution. Samples were shipped at room temperature and analyzed by Progenika Biopharma S.A. (a Grifols company, Derio, Spain). DNA was extracted and amplified by PCR, followed by hybridization with allele-specific probes targeting 14 common variants in exons II, III, and V, using Luminex xMAP technology (Luminex Corp., Austin, TX, USA).

Genetic diagnosis of AAT variants was confirmed when a mutation was detected in at least one allele.[3,10] AATD was considered a definite etiology of bronchiectasis when severe genotypes were found, such as Pi*ZZ, Pi*SZ and Pi*ZM(Malton).[14]

Statistical analysis

Exploratory analysis of quantitative variables was performed by calculating means and standard deviations (mean ± SD) or medians and interquartile ranges (IQR), according to data distribution. Categorical variables were expressed as absolute and relative frequencies. Association analysis between nominal, ordinal, or discrete variables were evaluated using the Chi-square test or Fisher's exact test, when appropriate. For contingency tables with more than two categories and low expected frequencies, the Fisher-Freeman-Halton exact test was used to ensure statistical validity. For continuous outcome variables, normally distributed data were analyzed using one-way ANOVA, while the Kruskal–Wallis and Mann–Whitney U tests were used for non-normally distributed variables. All statistical analyses were performed with the IBM SPSS Statistics software package, version 29.0 (IBM Corporation, Armonk, NY, USA). A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

Of 239 patients with non-cystic fibrosis bronchiectasis followed at the outpatient referral center between 2005 and 2023, 136 met the eligibility criteria and were included in the study (Figure 1).

Study population characteristics can be seen in Table 1. The majority were female (72.1%) and

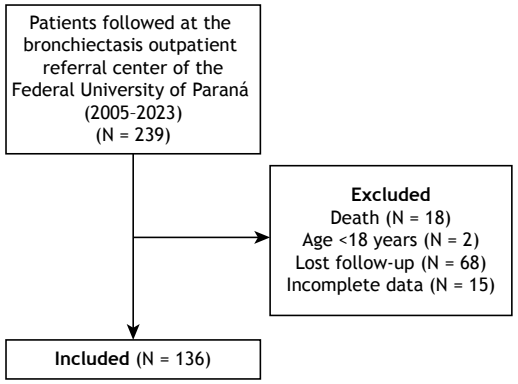

Figure 1. Study flow chart.

White (86.8%). Ages ranged from 18 to 85 years, with a median of 59.5 years (IQR: 45.0–67.8). Only 10.3% were underweighted. Most patients were never smokers (71.3%), and from those who were current or former smokers (28.6%), median smoking history was 20 pack-years (IQR: 7-50).

Chronic hypoxemic respiratory failure requiring long-term oxygen therapy was present in 15 patients (11%). In terms of clinical outcomes, 28.6% had two or more exacerbations in the last year requiring antibiotic treatment, and 16.9% required hospitalization due to severe exacerbation. According to the E-FACED severity score, 34.5% had severe or moderate disease.

Microbiological analysis of spontaneous sputum cultures showed that 57.4% of patients did not have chronic bronchial infection. Among those with infection, *Pseudomonas aeruginosa* was the most prevalent pathogen (23.5%).

Pulmonary function tests revealed obstructive ventilatory disorder in 78.3% of patients. Most patients had moderate (35.8%) and severe (30.6%) reduction in forced expiratory volume in one second (FEV_1).

Considering chest CT, emphysema was identified in 33.3% of patients. When present, it predominantly involved the upper lobes, and centrilobular emphysema was the most frequent pattern. Bronchiectasis was predominantly located in the lower lobes (45.4%) and most frequently cylindrical (42.4%). Extensive lobar involvement (all lobes) was seen in 48.5% of cases. Bronchial wall thickening (68.2%), mucus plugging (70.4%), and centrilobular tree-in-bud opacities (65.9%) were also common.

Regarding etiology (Table 2), post-tuberculosis bronchiectasis was the most common identified cause (21.3%), followed by post-infectious bronchiectasis due to other pathogens (16.9%). Only 2.9% were attributed to AATD.[15] The etiology remained undefined in 40.4% of cases, despite extensive investigation.

AAT levels and genotyping

Twenty-eight individuals with bronchiectasis (20.6%) had low serum levels of AAT (≤116mg/dL), including 2.2% with severe deficiency (<57mg/dL) and 18.4% with intermediate concentrations (57-115mg/dL). Furthermore, 35 (25.7%) had at least one *SERPINA1* mutation identified (Table 3).

Presence of *SERPINA1* mutations was found in 100% of patients with severely reduced AAT levels. However, pathogenic variants were also identified in individuals with serum levels ≥57 mg/dL, including some above normal threshold.[3,10]

Comparison between patients with and without SERPINA1 gene mutations

When the cases were stratified by the presence or absence of *SERPINA1* gene mutations (Table 4), significant differences were found for AAT serum levels, emphysema distribution and emphysema type. The median serum AAT level was 107 mg/dL (IQR: 91–130) among mutation carriers, compared to 146 mg/dL (IQR: 131–171) in non-carriers ($p < 0.001$). Although the overall frequency of emphysema was similar between groups, among patients with AAT mutations, emphysema was more frequently located in lower lobes (57.1%) or diffusely distributed (20%). Panlobular emphysema was observed exclusively in patients with *SERPINA1* mutations (3 cases, 8.6%).

No statistically significant differences were observed in other demographic, clinical, microbiological, functional, or radiological features.

DISCUSSION

To our knowledge, this is the first study to report the prevalence of AAT variants in a population of patients with non-cystic fibrosis bronchiectasis in Brazil, in which *SERPINA1* gene mutations were identified in 25.7% of the individuals. It is important to highlight that AATD is a genetically determined condition more commonly observed in Caucasian populations. Given Brazil's racial admixture and continental dimensions, along with historical differences in regional immigration patterns, it is plausible that the prevalence of AAT variants may vary across regions of the country.

In Brazil, the prevalence of AAT variants was previously assessed only in a cohort of 926 individuals with COPD from five different regions.[11] In that study, genetic analysis was performed only in the individuals with reduced serum AAT levels identified during initial screening. In contrast, the present study conducted genotyping in the entire sample of patients with non-cystic fibrosis bronchiectasis, which may partially explain the higher prevalence of *SERPINA1* mutations observed (25.7% vs. 2.8%).

When compared to studies focusing on bronchiectasis populations, our findings also revealed a higher frequency of *SERPINA1* mutations. In Italy, a study that investigated the prevalence of AAT variants by genotyping in a population with bronchiectasis found a frequency of 7.7%.[15] In the United Kingdom, AATD prevalence among 1,600 patients with bronchiectasis was 0.5%, through initial evaluation of serum levels, followed by phenotyping when levels were

Table 1. Clinical, functional, and radiological characteristics of the study population.

Characteristic(s)	(N = 136*)
Clinical-epidemiological	
Female sex, n (%)	98 (72.1)
Age (years), median (IQR)	59.5 (45-67.75)
White race, n (%)	118 (86.8)
Smoking status, n (%)	
Smoker	4 (2.9)
Former smoker	35 (25.7)
Never smoker	97 (71.3)
Smoking history (pack-years), median (IQR)	20 (7-50)
BMI (kg/m^2), median (IQR)	24.5 (21.92-28)
Underweight, n (%)	14 (10.3)
Normal weight, n (%)	57 (41.9)
Overweight, n (%)	45 (33.1)
Obese, n (%)	20 (14.7)
Long-term oxygen therapy, n (%)	15 (11)
E-FACED-based bronchiectasis severity	
Mild, n (%)	89 (65.4)
Moderate, n (%)	39 (28.7)
Severe, n (%)	8 (5.8)
Agent of chronic bronchial infection, n (%)	
None detected	78 (57.4)
Staphylococcus aureus	7 (5.1)
Pseudomonas aeruginosa	32 (23.5)
Haemophilus influenzae	3 (2.2)
Other, n (%)	1 (0.7)
No data, n (%)	15 (11)
Pulmonary exacerbation in the last year, n (%)	
0	52 (38.2)
1	45 (33.1)
2	24 (17.6)
≥ 3	15 (11)
Hospitalization for severe exacerbation, n (%)	23 (16.9)
Asthma (comorbidity), n (%)	50 (36.8)
Prior tuberculosis, n (%)	38 (27.9)
Alpha-1 antitrypsin serum level ≤ 116 mg/dL, n (%)	28 (20.6)
Lung function†	
Obstructive ventilatory defect, n (%)	105 (78.3)
FEV_1 % predicted, median (IQR)	54.8 (36.7-76.0)
FVC % predicted, median (IQR)	70.6 (56.2-88.1)
FEV_1 % predicted - stratified, n (%)	
< 30%	20 (14.9)
30-49%	41 (30.6)
50-79%	48 (35.8)
≥ 80%	25 (18.6)
DL_{CO} % predicted, median (IQR)	93.1 (73.9-114.2)
Radiological‡	
Emphysema, n (%)	44 (33.3)
Predominant distribution of emphysema, n (%)	
Upper lobes	29 (21.9)
Lower lobes	11 (8.3)
Diffuse	4 (3.0)
Predominant type of emphysema, n (%)	
Paraseptal	10 (7.5)
Centrilobular	31 (23.4)
Panlobular	3 (2.3)
Predominant distribution of bronchiectasis, n (%)	
Upper lobes	32 (24.2)
Lower lobes	60 (45.4)
Diffuse	40 (30.3)
Predominant type of bronchiectasis, n (%)	
Cylindrical	56 (42.4)
Varicose	50 (37.8)
Cystic	26 (19.7)

Continue...▶

Table 1. Clinical, functional, and radiological characteristics of the study population. (Continued...)

Characteristic(s)	(N = 136*)
Number of lobes affected by bronchiectasis, n (%)	
1	7 (5.3)
2	22 (16.6)
3	19 (14.4)
4	20 (15.1)
5	64 (48.5)
Other, n (%)	
Bronchial wall thickening	90 (68.2)
Mucus plugging	93 (70.4)
Tree-in-bud opacities	87 (65.9)
Previous pulmonary resection	9 (6.8)

E-FACED: Exacerbation frequency, FEV_1, Age, Colonization, Extension, and Dyspnea (bronchiectasis severity score). *Varies for some characteristics, as noted below. †Data available for only 134 patients for all characteristics except DL_{CO}, for which data were available for only 57 patients. ‡Data available for only 132 patients.

Table 2. Etiology of non-cystic fibrosis bronchiectasis.

Etiology	(N = 136)
Undefined/idiopathic, n (%)	55 (40.4)
Post-tuberculosis, n (%)	29 (21.3)
Post-infectious (other), n (%)	23 (16.9)
Common variable immunodeficiency, n (%)	5 (3.7)
Alpha-1 antitrypsin deficiency*, n (%)	4 (2.9)
Related to auto-immune diseases, n (%)	3 (2.2)
Immunoglobulin A deficiency, n (%)	2 (1.5)
Other immunodeficiency†, n (%)	3 (2.2)
Primary ciliary dyskinesia, n (%)	2 (1.5)
Related to HIV infection, n (%)	2 (1.5)
Other‡, n (%)	8 (5.9)

*Considering only the Pi*ZZ, Pi*ZMMalton, and Pi*SZ genotypes. †Anti-pneumococcal polysaccharide antibody deficiency or immunodeficiency secondary to neoplasm. ‡Williams-Campbell syndrome, Scimitar syndrome, allergic bronchopulmonary aspergillosis, or chronic aspiration.

Table 3. Alpha-1 antitrypsin levels and genotyping in a sample of patients with non-cystic fibrosis bronchiectasis.

Genotype	Serum alpha-1 antitrypsin level*			
	Severe < 57 mg/dL (n = 3) n (%)	Intermediate 57-115 mg/dL (n = 25) n (%)	Normal ≥ 116 mg/dL (n = 108) n (%)	Total n (%)
Pi*MM†	0 (0)	9 (6.6)	92 (67.7)	101 (74.3)
AATD variants	3 (2.2)	16 (11.7)	16 (11.7)	35 (25.7)
Pi*MS	0 (0)	7 (5.2)	14 (10.3)	21 (15.5)
Pi*MZ	0 (0)	7 (5.2)	0 (0)	7 (5.2)
Pi*MI	0 (0)	0 (0)	1 (0.7)	1 (0.7)
Pi*SS	0 (0)	1 (0.7)	1 (0.7)	2 (1.4)
Pi*SZ	0 (0)	1 (0.7)	0 (0)	1 (0.7)
Pi*ZMMalton	1 (0.7)	0 (0)	0 (0)	1 (0.7)
Pi*ZZ	2 (1.4)	0 (0)	0 (0)	2 (1.4)

AATD: alpha-1 antitrypsin deficiency. *Determined by turbidimetry. †Healthy genotype.

low.[16] In France, AATD diagnosis based directly on phenotyping method in a population of 202 patients with bronchiectasis showed a frequency of 18.81%.[17]

When comparing the two groups—those with and without *SERPINA1* mutations—significant differences were found only in serum AAT levels, predominant pattern of emphysema distribution (lower lobes or diffuse), and emphysema type (panlobular). These findings are consistent with previous reports suggesting that AATD should be suspected in patients with bronchiectasis who exhibit low serum AAT levels and imaging features of basal or panlobular emphysema.[18] However, it is noteworthy that emphysema was present in only 26.8% of mutation carriers in this sample, and only 30% of these cases had panlobular emphysema. Both cases carrying Pi*ZZ genotype did not have emphysema. Therefore, the absence of emphysema—especially of the panlobular or basal type—should not preclude investigation for AATD. This is further supported by data from the European Alpha-1 Research Collaboration (EARCO) international registry, in which 9.1% of Pi*ZZ carriers presented with bronchiectasis in the absence of radiological emphysema.[4]

Table 4. Comparative analysis between individuals with and without *SERPINA1* gene mutations in a sample of patients with non-cystic fibrosis bronchiectasis.[a]

Characteristic(s)	*SERPINA1* mutation		p-value
	No (n = 101)	Yes (n = 35)	
Clinical-demographic			
Age (years)	60 (48-66)	59 (40-70)	0.823*
Female sex, n (%)	72 (71.3)	26 (74.3)	0.829†
BMI (kg/m^2)	25 (22.3-27.8)	24 (21.6-28.6)	0.615*
Smoking status, n (%)			0.193‡
Smoker	4 (3.9)	0 (0.0)	
Former smoker	29 (28.7)	6 (17.1)	
Never smoker	68 (67.3)	29 (82.8)	
Smoking history (pack-years)	15 (7-40)	30 (12-50)	0.412*
E-FACED score	3 (1-4)	2 (1-4)	0.456*
Pulmonary exacerbation(s) in the last year of follow-up	1 (0-2)	1 (0-2)	0.971*
Hospitalization for severe exacerbation in the last year of follow-up	0 (0-0)	0 (0-0)	0.90*
Chronic bronchial infection by *P. aeruginosa*, n (%)	26 (25.7)	6 (17.1)	0.361†
Long-term oxygen use, n (%)	13 (12.9)	2 (5.7)	0.353†
Prior tuberculosis, n (%)	30 (29.7)	8 (22.9)	0.516†
Serum AAT level (mg/dL)	146 (131-171)	107 (91-130)	< 0.001*
Pulmonary function			
FEV_1/FVC	0.63 (0.52-0.73)	0.63 (0.54-0.75)	0.632*
FEV_1 (% predicted)	49 (36-73)	57 (46-78)	0.205*
DL_{CO} (% predicted)	84.0 (71.9-112.7)	99.6 (85.3-117.6)	0.095*
Chest CT			
Number of lobes affected by bronchiectasis	4 (3-5)	5 (2-5)	0.698*
Predominant type of bronchiectasis, n (%)			0.689§
Cylindrical	39 (40.2)	17 (48.6)	
Varicose	38 (39.2)	12 (34.2)	
Cystic	20 (20.6)	6 (17.1)	
Predominant distribution of bronchiectasis, n (%)			0.208§
Upper lobes	24 (24.7)	8 (22.9)	
Lower lobes	40 (41.2)	20 (57.1)	
Diffuse	33 (34)	7 (20.0)	
Emphysema, n (%)	34 (34.7)	10 (28.6)	0.539†
Predominant distribution of emphysema, n (%)			0.014‡
Upper lobes	26 (76.5)	3 (30.0)	
Lower lobes	6 (17.6)	5 (50.0)	
Diffuse	2 (5.9)	2 (20.0)	
Predominant type of emphysema, n (%)			0.014‡
Paraseptal	8 (23.5)	2 (20.0)	
Centrilobular	26 (76.5)	5 (50.0)	
Panlobular	0 (0.0)	3 (30.0)	
Other, n (%)			
Bronchial wall thickening	70 (71.4)	20 (57.1)	0.143†
Mucus plugging	72 (73.5)	21 (60.0)	0.197†
Tree-in-bud opacities	66 (67.3)	21 (60.0)	0.535†
Previous pulmonary resection	6 (6.1)	3 (8.6)	0.696†

AAT: alpha-1 antitrypsin; and E-FACED: Exacerbation frequency, FEV_1, Age, Colonization, Extension, and Dyspnea (bronchiectasis severity score). [a]Results expressed as median (IQR), except where otherwise indicated. *Mann-Whitney test. †Fisher's Exact test. ‡Fisher-Freeman-Halton exact test. §Chi-square test.

Although serum AAT levels were lower in the mutation group, normal values did not exclude the presence of AAT variants. In fact, 16 (45.7%) of the 35 patients with *SERPINA1* gene mutations had serum concentrations above the normal threshold.[3] Of note, 14 of these 16 patients carried the Pi*MS genotype. The remaining two patients had the following genotypes: Pi*MI and Pi*SS. Although the Pi*MS genotype alone is not historically considered a significant risk factor for the development of pulmonary disease,[14,19] and therefore cannot be considered a definitive etiological factor for bronchiectasis, it is conceivable that cumulative

exposure to other risk factors—such as smoking, occupational exposures, and recurrent respiratory infections—might modulate this risk. Interestingly in the present study, one patient with the Pi*MS genotype and undefined etiology for bronchiectasis presented with panlobular emphysema affecting a lower lobe, despite never having smoked.

A rare genotype identified in our cohort was Pi*MI, involving the I allele, which is classified as a variant of uncertain clinical significance.[3] This was in a young adult, never-smoker, with a serum AAT level of 141 mg/dL, who presented with bronchiectasis of indeterminate etiology, along with coexistent upper lobe emphysema. Pulmonary function was markedly impaired (FEV_1 = 38% of predicted), and the patient also had evidence of chronic liver disease of unknown cause. This case raises the possibility that certain rare *SERPINA1* variants, although not classically associated with severe deficiency, may contribute to complex phenotypes involving both pulmonary and extrapulmonary manifestations. Notably, despite serum AAT levels within the normal range, the functional activity of the molecule may be impaired, as described for certain variants that produce structurally unstable or dysfunctional proteins.[19,20]

Another point to be considered is that chronic inflammation, a hallmark of bronchiectasis,[21] may increase AAT concentrations due to its role as an acute-phase reactant.[10,20] Thus, diagnosing AATD solely on the basis of the initial serum AAT level, without subsequent confirmation using complementary diagnostic tools (such as genotyping, phenotyping, or gene sequencing), may lead to underdiagnosis in this population.

Regarding microbiology findings, data from the U.S. Bronchiectasis Registry previously demonstrated increased nontuberculous mycobacterial (NTM) infections in patients with AATD.[14] This may be explained by at least two mechanisms: AAT enhances macrophage-mediated clearance of intracellular mycobacteria through increased phagolysosomal fusion and autophagy,[22] and it potentiates TNF-α activity. Thus, low serum AAT levels may reduce TNF-α–mediated immune responses, increasing susceptibility to mycobacterial infections.[23] Although this pathophysiological rationale exists, no significant differences were observed in AAT variant carriers in this study.

In the present study, no other clinical, laboratory, or radiological variables differed significantly between patients with and without *SERPINA1* variants. Thus, apart from low serum AAT levels, diffuse or basal emphysema distribution, and panlobular emphysema, no consistent pattern could be identified to suggest the presence of *SERPINA1* mutations in individuals with bronchiectasis. Importantly, these findings should not be used as exclusive criteria to guide genetic investigation, since, as previously discussed, a substantial proportion of individuals carrying *SERPINA1* mutations may present with normal serum AAT levels and without radiological evidence of emphysema.

This study has limitations. This is a cross-sectional analysis based on consecutive patients evaluated in a referral center over a defined period. As such, no formal sample size calculation was performed. The single-center nature of the study limits the generalizability of the findings. Furthermore, the rarity of bronchiectasis associated with AATD led to a relatively small number of cases, potentially reducing the statistical power for detecting significant associations. Additionally, serum AAT levels were measured using turbidimetry, which, although the method available at our center, is known to be less sensitive than nephelometry—the technique preferably indicated by consensus.[3] This lower sensitivity is particularly relevant for detecting subtle differences at lower AAT concentrations. Despite these limitations, our study provides a comprehensive clinical, microbiological, radiological, and genetic characterization of a significant population of patients with non-cystic fibrosis bronchiectasis in a referral center. Although numerous studies have explored bronchiectasis among individuals with AATD, investigations focusing on screening for AAT variants in populations with primary bronchiectasis, especially at referral centers, remain scarce.

In conclusion, our findings suggest that AAT variants are not uncommon among patients with bronchiectasis. Clinicians should consider genotyping or further diagnostic evaluation even in patients with normal AAT levels, particularly when bronchiectasis remains unexplained. Although the identification of a *SERPINA1* mutation alone may not always define the etiology of bronchiectasis, it should be considered an additional risk factor that may act synergistically with other environmental or infectious exposures to influence disease expression.

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AUTHOR CONTRIBUTIONS

CSS, MGMC, and KMS: study conception and design; drafting and reviewing the manuscript. CAL: drafting and reviewing the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Miravitlles M, Dirksen A, Ferrarotti I, Koblizek V, Lange P, Mahadeva R, et al. European Respiratory Society statement: Diagnosis and treatment of pulmonary disease in Alfa1-antitrypsin deficiency. Eur Respir J. 2017;50(5):1700610. https://doi.org/10.1183/13993003.00610-2017
2. Stockley RA, Parr DG. Antitrypsin deficiency; still more to learn about the lung after 60 years. ERJ Open Res. 2024;10(4):00139-2024. https://doi.org/10.1183/23120541.00139-2024
3. Feitosa PHR, Castellano MVCO, Costa CHD, Cardoso ADRO, Pereira LFF, Fernandes FLA, et al. Recommendations for the diagnosis and treatment of alpha-1 antitrypsin deficiency. J Bras Pneumol. 2024;50(5): e20240235. https://doi.org/10.36416/1806-3756/e20240235
4. Stockley RA, Pye A, De Soyza J, Turner AM, Miravitlles M. The prevalence of bronchiectasis in patients with alpha-1 antitrypsin deficiency: initial report of EARCO. Orphanet J Rare Dis. 2023;18(1):1-8. https://doi.org/10.1186/s13023-023-02830-2
5. Soyza J De, Ellis BP, Newnham M, Rickard L, Turner MAM. Bronchiectasis Occurs Independently of Chronic Obstructive Pulmonary Disease in Alpha-1 Antitrypsin Deficiency. Chronic Obstr Pulm Dis. 2024;11(5):507-514. https://doi.org/10.15326/jcopdf.2024.0526
6. Pereira MC, Athanazio RA, Dalcin PTR, Figueiredo MRF, Gomes M, Freitas CG, et al. Brazilian consensus on non-cystic fibrosis bronchiectasis. J Bras Pneumol. 2019;45(4):e20190122. https://doi.org/10.1590/1806-3713/e20190122
7. Lonni S, Chalmers JD, Goeminne PC, Mcdonnell MJ, Dimakou K, De Soyza A, et al. Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. Ann Am Thorac Soc. 2015;12(12):1764-70. https://doi.org/10.1513/AnnalsATS.201507-472OC
8. Olveira C, Padilla A, Martínez-García MÁ, De La Rosa D, Girón RM, Vendrell M, et al. Etiology of Bronchiectasis in a Cohort of 2047 Patients. An Analysis of the Spanish Historical Bronchiectasis Registry. Arch Bronconeumol. 2017;53(7):366-374. https://doi.org/10.1016/j.arbres.2016.12.003
9. Orphanet Report Series [homepage on the Internet]. Paris: Orphanet; c2024. Prevalence and incidence of rare diseases: Bibliographic data. [Adobe Acrobat doc. 194p.].. Available from: http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf
10. Jardim JR, Casas-Maldonado F, Fernandes FLA, Castellano MVCO, Torres-Durán M, Miravitlles M. Update on and future perspectives for the diagnosis of alpha-1 antitrypsin deficiency in Brazil. J Bras Pneumol. 2021;47(3):e20200380. https://doi.org/10.36416/1806-3756/e20200380
11. Russo R, Zillmer LR, Nascimento OA, Manzano B, Ivanaga IT, Fritscher L, et al. Prevalence of alpha-1 antitrypsin deficiency and allele frequency in patients with COPD in Brazil. J Bras Pneumol. 2016;42(5):311-6. https://doi.org/10.1590/S1806-37562015000000180
12. Araújo D, Shteinberg M, Aliberti S, Goeminne PC, Hill AT, Fardon T, et al. Standardised classification of the aetiology of bronchiectasis using an objective algorithm. Eur Respir J. 2017;50(6):3-6. https://doi.org/10.1183/13993003.01289-2017
13. Miravitlles M, Anzueto A, Barrecheguren M. Nine controversial questions about augmentation therapy for alpha-1 antitrypsin deficiency: a viewpoint. Eur Respir Rev. 2023;32(170):1-12. https://doi.org/10.1183/16000617.0170-2023
14. Eden E, Choate R, Barker A, Addrizzo-Harris D, Aksamit TR, Daley CL, et al. The Clinical Features of Bronchiectasis Associated with Alpha-1 Antitrypsin Deficiency, Common Variable Immunodeficiency and Primary Ciliary Dyskinesia--Results from the U.S. Bronchiectasis Research Registry. Chronic Obstr Pulm Dis. 2019;6(2):145-153. https://doi.org/10.15326/jcopdf.6.2.2018.0156
15. Aliberti S, Gramegna A, Seia M, Malvestiti F, Mantero M, Sotgiu G, et al. Alpha1-Antitrypsin Inherited Variants in Patients With Bronchiectasis. Arch Bronconeumol. 2023;59(6):401-2. https://doi.org/10.1016/j.arbres.2023.01.004
16. Carreto L, Morrison M, Donovan J, Finch S, Tan GL, Fardon T, et al. Utility of routine screening for alpha-1 antitrypsin deficiency in patients with bronchiectasis. Thorax. 2020;75:592-3. https://doi.org/10.1136/thoraxjnl-2019-214195
17. Cuvelier A, Muir JF, Hellot MF, Benhamou D, Martin JP, Bénichou J, et al. Distribution of α1-antitrypsin alleles in patients with bronchiectasis. Chest. 2000;117(2):415-9. https://doi.org/10.1378/chest.117.2.415
18. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn S, Floto RA, et al. BTS Guidelines for Bronchiectasis 2018. Thorax. 2019;74(1):1-69. https://doi.org/10.1136/thoraxjnl-2018-212468
19. Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. 2006 Oct 27 [updated 2023 Jun 1]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2025. PMID: 20301692.
20. Franciosi AN, Fraughen D, Carroll TP, McElvaney NG. Alpha-1 antitrypsin deficiency: clarifying the role of the putative protective threshold. Eur Respir J. 2022;59(2):1-12. https://doi.org/10.1183/13993003.01410-2021
21. Long MB, Chotirmall SH, Shteinberg M, Chalmers JD. Review Rethinking bronchiectasis as an inflammatory disease. Lancet Respir. 2024;2600(24):1-14. https://doi.org/10.1016/S2213-2600(24)00176-0
22. Bai X, Bai A, Honda JR, Eichstaedt C, Musheyev A, Feng Z, et al. Alpha-1-Antitrypsin Enhances Primary Human Macrophage Immunity against Non-tuberculous Mycobacteria. Front Immunol. 2019;10:1417. https://doi.org/10.3389/fimmu.2019.01417
23. De Smet S, Dierick J, Steyaert S, Schurgers M, Van Steenkiste C, Loof S. Alfa-1-antitrypsin deficiency: a predisposing factor leading to invasive infections? Infect Dis (Auckl). 2020;52(2):130-4. https://doi.org/10.1080/23744235.2019.1690163

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ORIGINAL ARTICLE

Development and preliminary tests of a portable volumetric capnograph for outpatient use

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Study carried out at the Instituto Federal de Educação, Ciência e Tecnologia de São Paulo and at the Universidade Estadual de Campinas, both located in the city of Campinas (SP) Brasil.

ABSTRACT

Objective: To develop and validate a portable volumetric capnograph for collecting data on ventilatory mechanics during spontaneous breathing for outpatient use. **Methods:** The device was developed by integrating the following commercially available sensors: a Hamilton® flow sensor (variable orifice; Hamilton Medical AG, Graubünden, Switzerland); an SDP810-125PA differential pressure sensor (Sensirion AG, Stäfa, Switzerland); and a Capnostat 5 CO_2 sensor (Philips Respironics, Murrysville, PA, USA). An Arduino UNO-R3® microcontroller (Arduino, Monza, Italy) was used as an interface between the sensors and a laptop computer, and a Python application was used to acquire data at 10 ms intervals (100 Hz). Validation included static tests (flow: 0-45 L/min; partial pressure of CO_2: 0-100 mmHg) and tests with five healthy volunteers (n = 115 respiratory cycles), in comparison with the reference equipment (a CO_2SMO Plus® DX-8100 oxycapnograph; Philips Respironics). **Results:** The static tests showed excellent linear correlation for flow and CO_2 concentration. For the tests conducted with the five volunteers, no significant differences were observed between the portable volumetric capnograph and the reference equipment for any of the variables analyzed. Intracycle variability was observed in the capnography curves, reflecting the physiological characteristics of spontaneous breathing. **Conclusions:** Our portable volumetric capnograph demonstrated the ability to collect accurate data on flow and partial pressure of CO_2 during spontaneous breathing, with performance equivalent to that of the reference equipment. The variability in the capnography curves represents an intrinsic characteristic of spontaneous breathing that must be considered when developing algorithms for calculating physiological indicators.

Keywords: Volumetric capnography, microcontroller, respiratory monitoring, spontaneous breathing, portable device.

INTRODUCTION

Chronic respiratory diseases are increasing significantly worldwide and represent a global public health challenge, affecting millions of people annually.[1,2] Among the main conditions are asthma and COPD, which impose a significant socioeconomic burden worldwide.[3] In the United States, approximately 14.2 million adults were diagnosed with COPD in 2021, highlighting the magnitude of this problem.[4]

Spirometry has traditionally been considered the gold standard for assessing lung function.[5,6] However, this method has important limitations, including dependence on the ability of patients to perform forced expiratory maneuvers[7] and a shortage of qualified professionals to perform it.[8,9] Spirometry requires maximum expiratory effort, which can be difficult or impossible for patients with severe dyspnea, chest pain, or cognitive limitations.[10]

Volumetric capnography is emerging as a promising alternative for the diagnosis and monitoring of chronic lung diseases.[11-14] While temporal capnography measures CO_2 concentration over time, volumetric capnography incorporates information on expired volume, providing more comprehensive data on respiratory function.[15,16] This technique offers significant advantages, including the fact that it is noninvasive, has low cost, and requires only 10 ventilatory cycles at rest, without the need for patient effort.[17]

The main feature of volumetric capnography in an outpatient setting is the analysis of spontaneous breathing, which is very different from the forced maneuvers used in spirometry. During spontaneous breathing, natural variability in breathing patterns is observed, with cycle-to-cycle fluctuations in tidal volume, breathing times, and transpulmonary pressures.[18,19] Although this variability represents an analytical challenge, it can provide additional diagnostic information on respiratory function.[20]

Volumetric capnography has proven cost-effective for monitoring patients with chronic respiratory diseases in outpatient settings. Because volumetric capnography is a

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noninvasive technique, its use can reduce the need for more complex tests and optimize resource allocation, serving as a complementary tool to spirometry in longitudinal patient monitoring.[21]

Most of the volumetric capnography devices that are currently available have been developed for use with mechanical ventilators in the ICU. There is a significant gap regarding portable devices for outpatient use. Therefore, the objective of the present study was to develop and validate a portable volumetric capnograph for collecting data on ventilatory mechanics in spontaneously breathing individuals in an outpatient setting.

METHODS

The study was conducted following all ethical principles set forth in Brazilian National Health Council Resolution No. 466/2012. The project was approved by the Research Ethics Committee of the *Universidade Estadual de Campinas*, located in the city of Campinas, Brazil (Protocol no. 6,897,044), and all volunteers gave written informed consent.

Hardware development

A portable volumetric capnograph was developed by integrating well-established, commercially available sensors for medical use. For respiratory flow measurement, the mainstream mode (all respiratory flow) was adopted with differential pressure measurement by variable orifice. The selected components were as follows:

- a Hamilton® pediatric/adult flow sensor (variable orifice; Hamilton Medical AG, Graubünden, Switzerland)
- an SDP810-125PA differential pressure sensor (Sensirion AG, Stäfa, Switzerland) with an I2C digital output
- a Capnostat 5 CO_2 sensor (Philips Respironics, Murrysville, PA, USA) with an RS232 digital output
- an Arduino UNO-R3® microcontroller with an Atmega328P® processor (Arduino, Monza, Italy)

Figure 1 illustrates the main components used in developing the device.

The Arduino UNO-R3® is a microcontroller development board based on the ATmega328P chip, one of the most popular and widely used versions of the Arduino platform. It is especially used for prototyping; rapid development of automation concepts and sensor control (data reading and processing); and projects involving the internet of things.

The differential pressure sensor was connected to the variable orifice flow meter via two flexible tubes, with an I2C digital communication protocol with the Arduino UNO-R3® microcontroller. The CO_2 sensor was connected to the same microcontroller via a 1.5 m cable using an RS232-TTL converter at 19200 baud. A USB port was used to connect the microcontroller to a laptop computer.

Firmware and software development

Firmware is a special type of low-level software that is permanently stored in hardware components—in the present study, the Arduino UNO-R3® microcontroller—and provides basic instructions for the operation and control of electronic devices.

In the present study, the set of instructions was written in the C++ programming language to manage communications, initialization, and data capture by the sensors. The sampling frequency was set at 100 Hz (10 ms), limited by the maximum rate available on the Capnostat 5. The flow sensor, with an internal resolution of 0.5 ms, had its mean values calculated for each 10 ms window.

The user interface was developed in the Python programming language, with local storage (computer) of data in CSV files. Flow (L/min) and partial pressure of CO_2 (PCO_2, in mmHg) were recorded with synchronized timestamps of 10 ms. The volume of CO_2 exhaled per cycle (VCO_2/br) was calculated by equation 1, as follows:

$$VCO_2/br = \int_{II}^{FE} \frac{VT(t).PCO_2(t)\,dt}{Patm} \quad (1)$$

where *II* is the beginning of inspiration; *FE* is the end of expiration; VT is the tidal volume; Patm is the atmospheric pressure, the time differential used for integration being = 10 ms.

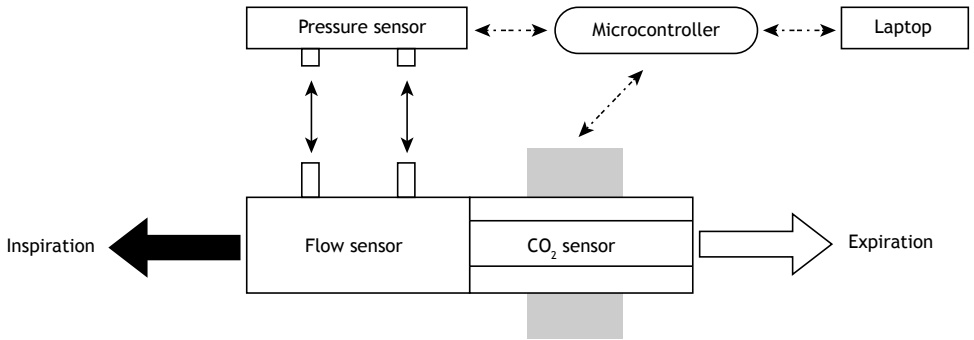

Figure 1. Illustration of the main components of our portable volumetric capnograph: a flow sensor connected to a differential pressure transducer, and a CO_2 transducer connected to a microcontroller. The transducers have a digital output that integrates them with the microcontroller, which is connected to a laptop computer.

Static tests

Static tests were performed in the Ultrasound and Biomedical Instrumentation Laboratory of the Biomedical Engineering Center at the *Universidade Estadual de Campinas* under controlled temperature conditions (i.e., 24 ± 2°C).

Inspiratory and expiratory flows were tested at 0, 5, 10, 15, 20, 25, 30, 35, 40, and 45 L/min, with 5 repetitions per point (totaling 100 measurements). Concentrations of CO_2 were measured in steady state (constant CO_2 concentration), with mixing performed from a cylinder. Medical air and CO_2 flows were regulated with the aid of two needle valves and adjusted at each point using a Fluke VT650 gas analyzer (Fluke Biomedical, Everett, WA, USA) to adjust the flow and a CO_2SMO Plus® DX-8100 oxycapnograph (Philips Respironics) to adjust the CO_2 concentration. The following CO_2 concentrations were tested: 0, 5, 10, 20, 30, 40, 50, 60, 70, 80, and 100 mmHg, with constant flows of 5, 10, 15, 20, and 30 L/min; three measurements were taken at each point, totaling 165 measurements.

Tests with volunteers

Five healthy volunteers were recruited in accordance with the following inclusion criteria: being in the 18- to 40-year age bracket; having no respiratory diseases; being a nonsmoker. Exclusion criteria included pregnancy, use of respiratory medications, and recent respiratory infection.

Each volunteer performed between 15 and 35 spontaneous breathing cycles in a sitting position, a total of 115 cycles being analyzed. The portable volumetric capnograph was connected in series with the reference equipment for simultaneous data capture.

Statistical analysis

The data were analyzed with Minitab software, version 19 (Minitab Inc., State College, PA, USA). For the static tests, the linear correlation coefficient (R^2) was estimated for the confidence and prediction intervals, both with a 95% confidence level.

Inspiration and expiration cycles were separated on the basis of the reversal of the respiratory flow in the table of raw data. Inspiration time (Ti) and expiration time (Te) were calculated by the time difference between the last and first measurements in each cycle. End-tidal CO_2 ($ETCO_2$) was obtained when the expiratory volume reached its maximum value (end of exhalation). Inspiration volume (Vi) and expired volume (Ve) were calculated by numerical integration of flow over time for each cycle, and VCO_2/br was calculated by equation 1.

For the tests with the five volunteers, the Mann-Whitney test was used to compare the means of respiratory parameters ($ETCO_2$, Ti, Te, Vi, Ve, PEF, and VCO_2/br). A value of $p < 0.05$ was considered significant.

RESULTS

Our portable volumetric capnograph was integrated into a compact box (15 × 10 × 5 cm) weighing 350 g. Total consumption was 1.4 W, powered via the computer USB port, with a startup time of 8 s. Figure 2 shows a photograph of the finished device.

The characterization of the flow sensor demonstrated linear behavior with an $R^2 = 0.995$ (95% CI, 0.993-0.997). A factor for correcting the slope of the line with a value of 1.438 was implemented in the firmware.

The validation of the CO_2 sensor showed an $R^2 = 0.995$ (95% CI, 0.994-0.996), confirming equivalence with the reference equipment.

Figures 3A and 3B illustrate the linear regression graphs of flow and CO_2 concentration with the respective references.

Table 1 shows the comparative results between our portable volumetric capnograph and the reference equipment, with no significant differences between the two ($p > 0.05$) in any of the parameters analyzed.

Figures 4A, 4B, 4C, and 4D illustrate examples of capnography curves with the respective positions of slope III, calculated between 40% and 80% of tidal volume[22,23] and showing the intercycle variability characteristic of spontaneous breathing.

DISCUSSION

The development of our portable volumetric capnograph represents an advance in the availability of volumetric capnography technology for data acquisition during spontaneous ventilation in an outpatient setting. The choice of well-established, commercially available components, integrated through a microcontroller platform, offers a good cost-benefit ratio.

There is growing interest in the application of volumetric capnography for the diagnosis and monitoring of lung diseases,[11,14,16,24] especially with the development of machine learning techniques.[7,9,25]

Zech et al.[26] demonstrated that volumetric capnography can be reliably used in spontaneously breathing patients, showing a mean difference of −0.9 mmHg in the measurement of expired PCO_2, with a correlation coefficient of 0.98 for reproducibility. The study supports the technical feasibility of the

Figure 2. Photograph of our portable volumetric capnograph with sensors and connections.

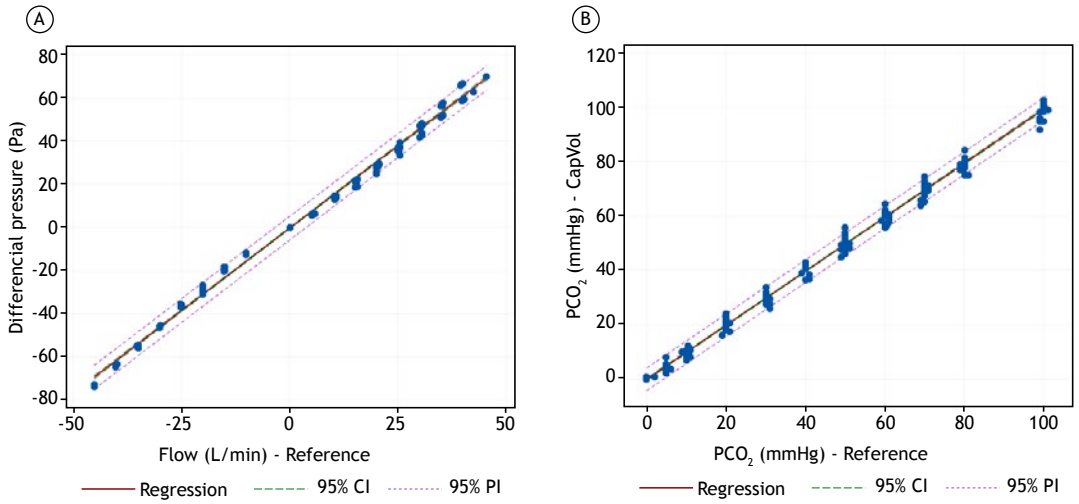

Figure 3. Graphs comparing our portable volumetric capnograph (CapVol) with a CO_2SMO Plus® DX-8100 oxycapnograph (Philips Respironics, Murrysville, PA, USA; reference equipment). In A, differential pressure (Pa) vs. flow for the reference equipment. In B, partial pressure of CO_2 (PCO_2) for CapVol vs. the reference equipment. PI: prediction interval.

Table 1. Results of a comparison between intracycle means of respiratory parameters of volunteers using a portable volumetric capnograph and a CO_2SMO Plus® DX-8100 oxycapnograph (Philips Respironics, Murrysville, PA, USA).[a]

Variable	Volunteer				
	1 (n = 22)	2 (n = 34)	3 (n = 24)	4 (n = 18)	5 (n = 17)
$ETCO_2$, mmHg					
CapVol	34.9 ± 0.8	32.1 ± 0.9	36.3 ± 1.2	36.5 ± 1.3	34.0 ± 1.0
CO_2SMO	34.9 ± 0.8	32.3 ± 0.9	36.4 ± 1.4	35.8 ± 1.3	34.0 ± 1.2
p	0.37	0.11	0.82	0.13	0.68
Ti, s					
CapVol	1.8 ± 0.1	1.3 ± 0.2	2.5 ± 0.2	3.0 ± 0.5	2.3 ± 0.3
CO_2SMO	1.8 ± 0.1	1.3 ± 0.2	2.5 ± 0.3	3.1 ± 0.6	2.3 ± 0.3
p	0.43	0.63	0.58	0.57	0.80
Te, s					
CapVol	2.4 ± 0.2	1.6 ± 0.1	3.1 ± 0.4	3.4 ± 0.6	3.3 ± 0.5
CO_2SMO	2.4 ± 0.3	1.6 ± 0.1	3.1 ± 0.4	3.2 ± 0.5	3.4 ± 0.3
p	0.40	0.85	0.77	0.64	0.66
Vi, mL					
CapVol	844 ± 56	561 ± 76	1,041 ± 151	989 ± 289	986 ± 202
CO_2SMO	824 ± 50	554 ± 75	1,032 ± 135	1,065 ± 233	1,046 ± 180
p	0.21	0.69	0.93	0.66	0.40
Ve, mL					
CapVol	787 ± 99	544 ± 59	1,009 ± 149	1,069 ± 237	857 ± 102
CO_2SMO	798 ± 89	548 ± 53	1,053 ± 154	1,128 ± 242	920 ± 124
p	0.53	0.78	0.31	0.53	0.11
PEF, mmHg					
CapVol	32.5 ± 3.0	34.5 ± 3.2	28.9 ± 3.8	28.6 ± 4.4	23.0 ± 2.4
CO_2SMO	31.5 ± 2.4	34.1 ± 2.5	30.1 ± 2.9	28.7 ± 3.8	24.0 ± 2.2
p	0.38	0.74	0.39	0.77	0.21
VCO_2/br, mL					
CapVol	18.7 ± 3.6	11.2 ± 2.0	28.5 ± 6.3	33.2 ± 9.0	21.1 ± 3.9
CO_2SMO	19.5 ± 3.3	11.8 ± 1.8	30.5 ± 6.2	33.8 ± 8.0	22.8 ± 4.5
p	0.67	0.08	0.26	0.82	0.27

n: number of respiratory cycles; $ETCO_2$: end-tidal carbon dioxide; CapVol: portable volumetric capnograph; Ti: inspiration time; Te: expiration time; Vi: inspired volume per cycle; Ve: expired volume per cycle; VCO_2/br: volume of CO_2 expired per cycle. [a]Data expressed as mean ± SD.

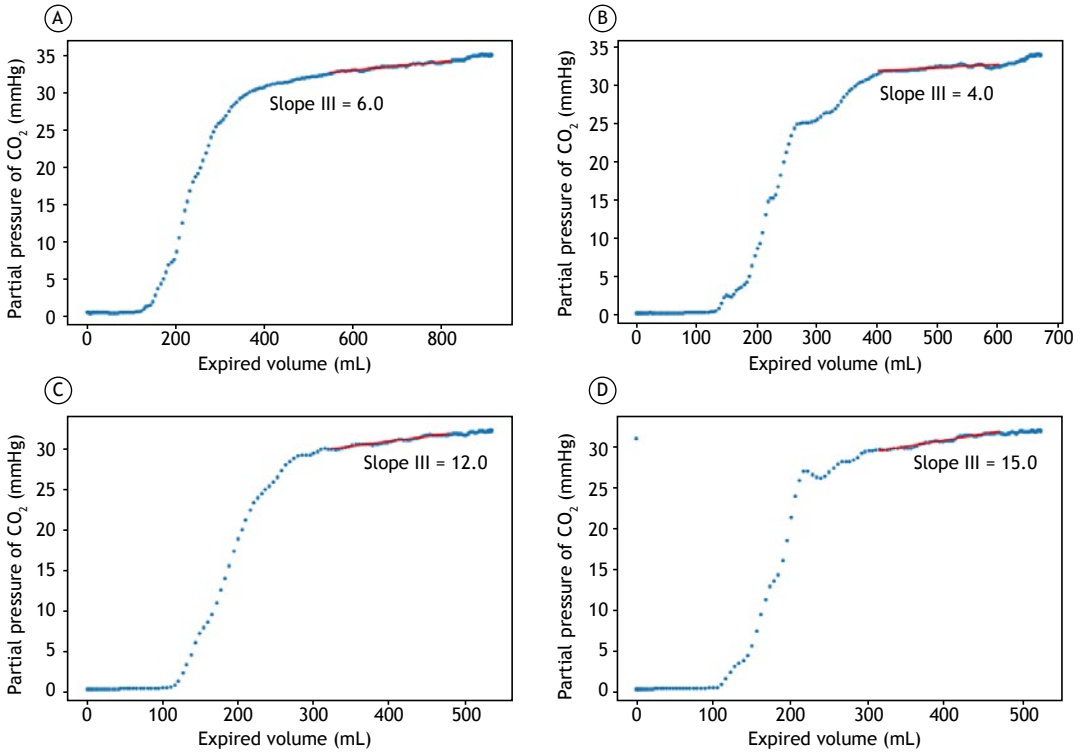

Figure 4. Capnography curves. In A, tidal volume vs. partial pressure of CO_2 (PCO_2), highlighting the position of slope III (volunteer 3, expiratory cycle 2). In B, tidal volume vs. PCO_2, highlighting the position of slope III (volunteer 3, expiratory cycle 8). In C, tidal volume vs. PCO_2, highlighting the position of slope III (volunteer 2, expiratory cycle 17). In D, tidal volume vs. PCO_2, highlighting the position of slope III (volunteer 2, expiratory cycle 27).

approach adopted in developing our portable volumetric capnograph, which achieved statistical equivalence with the reference equipment in all parameters evaluated.

Kellerer et al.[17] showed that volumetric capnography is a viable alternative when spirometry cannot be performed reliably. It allows the degree of functional impairment to be assessed in patients with obstructive pulmonary diseases, including COPD, asthma, and cystic fibrosis. This application is particularly relevant considering that our device does not require forced maneuvers by the patient, unlike spirometry, and its portability facilitates examination, benefiting severe lung disease patients who have difficulty moving and traveling to perform traditional ancillary tests, such as CT.

Slope III indicator, calculated from the volumetric curve, has established clinical utility for the assessment of multiple lung diseases. Almeida et al.[27] identified an increase in the slope of phase III normalized by tidal volume in asthma patients, suggesting ventilatory heterogeneity in the distal air spaces that may reflect chronic structural changes or acute reversible changes. Ribeiro et al.[28] demonstrated the use of volumetric capnography for early detection of peripheral pulmonary obstruction in patients with cystic fibrosis, whereas Jarenbäck et al.[10] validated its use for the diagnosis and grading of COPD. Moreira et al.[29,30] described applications in the assessment of pulmonary thromboembolism, demonstrating the clinical versatility of indicators derived from volumetric capnography.

The development of specific devices for spontaneous breathing is based on documented physiological differences between this modality and mechanical ventilation. Wolff et al.[31] demonstrated that dead space ventilation is reduced during spontaneous breathing when compared with mechanical ventilation, this phenomenon being explained by a reduction in anatomical dead space and increased alveolar CO_2 efficiency.

Romero et al.[32] showed that volumetric capnography can be used as an alternative to assess the severity of functional disorders in patients with COPD when spirometry cannot be performed reliably, reinforcing the need for specific devices for each ventilatory modality.

Our technical validation showed a performance equivalent to that of the reference equipment, with an $R^2 = 0.995$ for flow and CO_2 measurements. These results are consistent with those reported for high-cost commercially available devices.[33,34]

The sampling rate of 100 Hz (10 ms) used in our portable volumetric capnograph exceeds the 50 Hz reported by Talker et al.[9] for a device regulated in the European Union for COPD assessment. Higher sampling rates are especially better for slope II calculations, where the variation in PCO_2 as a function of tidal volume is very pronounced.

Sassmann et al.[35] reported a resolution of 5 ms in high-fidelity equipment, suggesting that devices

with higher time resolution provide more accurate analysis of expired CO_2 kinetics. The best sampling rate for our device was limited by Capnostat 5, with no possibility of reducing the data acquisition time.

The key finding of the present study was the variability of capnography curves during spontaneous breathing. Unlike controlled mechanical ventilation, where patterns are reproducible, spontaneous breathing has natural fluctuations that affect traditional physiological indicators. Although this variability represents a technical challenge for data processing, it contains valuable clinical information on individual breathing patterns and pulmonary heterogeneity. Tolnai et al.[36] demonstrated that different respiratory rates in patients with spontaneous breathing produce significant variations in capnography indices, including changes in the slopes of phases II and III of the capnogram, corroborating the findings of the present study.

Slope III, an important indicator for assessing obstructive diseases,[27,28] showed intracycle variations of 25-50% and reflects the natural heterogeneity of spontaneous ventilation. Artificial intelligence algorithms can extract diagnostic information from this variability, as demonstrated in recent studies achieving an AUC of 0.93-0.99 for the classification of respiratory diseases.[37]

The prospects of our portable volumetric capnograph are promising in terms of development driven by miniaturization and portability, providing access to medical offices and clinics, with progressive cost reduction and democratization of access to these technologies. It establishes a technological basis for future studies focused on the following: clinical validation in patients with COPD, asthma, and other respiratory diseases; development of artificial intelligence algorithms for automated analysis of respiratory variability; and integration with telemedicine systems for remote monitoring.

The incorporation of artificial intelligence in the automatic interpretation of capnograms is supported by recent studies. Feng et al.[25] described growing applications of artificial intelligence and machine learning in chronic airway diseases, focusing on asthma and COPD.

Zhou et al.[7] demonstrated prediction of pulmonary function parameters based on combined algorithms, suggesting that the integration of volumetric capnography data with machine learning techniques can significantly amplify the clinical utility of ambulatory devices, democratizing the use of technology and significantly improving safety in monitoring patients during outpatient procedures.

The design of a prototype, as proposed in the present study, represents only the first step in the development of an industrialized medical device. The transition to a commercially available product requires the implementation of a quality management system specific to medical devices,[38] rigorous verification, validation, and biocompatibility processes.[39]

Because this was a preliminary study, it has limitations. One limitation is that the study included only five healthy volunteers, thus limiting its generalization to larger populations and those with respiratory diseases. Validation was performed in a controlled environment, and additional studies are needed in real outpatient conditions. In addition, no specific algorithms were developed for analyzing respiratory variability.

In conclusion, our portable volumetric capnograph demonstrated technical capability for accurate flow and PCO_2 measurements with a sampling rate of 100 Hz (10 ms), showing statistical equivalence with the commercially available reference equipment. The architecture based on commercially available components integrated by a microcontroller offers a cost-effective solution for ambulatory volumetric capnography.

Although the variability observed in capnography curves during spontaneous breathing is challenging for traditional algorithms, it offers opportunities for the development of new respiratory indicators through artificial intelligence techniques.

Future studies should focus on the development of adaptive algorithms for respiratory variability analysis and clinical validation in populations with respiratory diseases.

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AUTHOR CONTRIBUTIONS

FUVJ: design and planning of the study; interpretation of findings; and approval of the final version of the manuscript. DAM, NCRS, MAGOR, and IMV: design and planning of the study; and interpretation of findings. MMM and ETC: design and planning of the study; and revision of all preliminary drafts, as well as of the final version of the manuscript. IAP: design and planning of the study.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Hashimoto N, Wakahara K, Sakamoto K. The Importance of Appropriate Diagnosis in the Practical Management of Chronic Obstructive Pulmonary Disease. Diagnostics. 2021;11(4):618. https://doi.org/10.3390/diagnostics11040618

2. Tan CL, Chan Y, Candasamy M, Chellian J, Madheswaran M, Sakthivel LP, et al. Unravelling the molecular mechanisms underlying chronic respiratory diseases for the development of novel therapeutics via in vitro experimental models. Eur J Pharmacol. 2022;919. https://doi.org/10.1016/j.ejphar.2022.174821
3. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. Clin Sci (Lond). 2017;131(13):1541-58. https://doi.org/10.1042/CS20160487
4. CDC. Chronic Obstructive Pulmonary Disease (COPD) Statistics. Centers for Disease Control and Prevention.
5. Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, Weinberger S, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2007;147(9):633-8. https://doi.org/10.7326/0003-4819-147-9-200711060-00008
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [homepage on the Internet]. Bethesda: GOLD. 2020 Global Strategy for Prevention, Diagnosis and Management of COPD: 2023 Report. Available from: https://goldcopd.org/2023-gold-report-2/
7. Zhou R, Wang P, Li Y, Mou X, Zhao Z, Chen X, et al. Prediction of Pulmonary Function Parameters Based on a Combination Algorithm. Bioengineering. 2022;9(4):136. https://doi.org/10.3390/bioengineering9040136
8. Exarchos KP, Beltsiou M, Votti CA, Kostikas K. Artificial intelligence techniques in asthma: a systematic review and critical appraisal of the existing literature. Eur Respir J. 2020;56(3):2000521. https://doi.org/10.1183/13993003.00521-2020
9. Talker L, Dogan C, Neville D, Lim RH, Broomfield H, Lambert G, et al. Diagnosis and Severity Assessment of COPD Using a Novel Fast-Response Capnometer and Interpretable Machine Learning. COPD. 2024;21(1):2321379. https://doi.org/10.1080/15412555.2024.2321379
10. Jarenbäck L, Tufvesson E, Ankerst J, Bjermer L, Jonson B. The Efficiency Index (EFFi), based on volumetric capnography, may allow for simple diagnosis and grading of COPD. Int J Chron Obstr Pulm Dis. 2018;13:2033-9. https://doi.org/10.2147/COPD.S161345
11. Diniz OHG. Volumetric Capnography: History, Function and Clinical Uses. Open Access Library Journal. 2022;9:e175. https://doi.org/10.4236/oalib.1109175
12. Howe TA, Jaalam K, Ahmad R, Sheng CK, Nik Ab Rahman NH. The use of end-tidal capnography to monitor non-intubated patients presenting with acute exacerbation of asthma in the emergency department. J Emerg Med. 2011;41(6):581-9. https://doi.org/10.1016/j.jemermed.2008.10.017
13. Jaffe MB. Using the features of the time and volumetric capnogram for classification and prediction. J Clin Monit Comput. 2017;31(1):19-41. https://doi.org/10.1007/s10877-016-9830-z
14. Kremeier P, Böhm SH, Tusman G. Clinical use of volumetric capnography in mechanically ventilated patients. J Clin Monit Comput. 2020;34(1):7-16. https://doi.org/10.1007/s10877-019-00325-9
15. Talker L, Neville D, Wiffen L, Selim AB, Haines M, Carter JC, et al. Machine diagnosis of chronic obstructive pulmonary disease using a novel fast-response capnometer. Respir Res. 2023;24(1):150. https://doi.org/10.1186/s12931-023-02460-z
16. Siobal MS, Ong H, Valdes J, Tang J. Calculation of Physiologic Dead Space: Comparison of Ventilator Volumetric Capnography to Measurements by Metabolic Analyzer and Volumetric CO2 Monitor. Respir Care. 2013;58(7):1143-51. https://doi.org/10.4187/respcare.02116
17. Kellerer C, Klütsch K, Husemann K, Sorichter S, Jörres RA, Schneider A. Capnovolumetry in combination with clinical history for the diagnosis of asthma and COPD. Prim Care Respir Med. 2020;30(1):32. https://doi.org/10.1038/s41533-020-00190-z
18. Veronez LF. Capnografia volumétrica na avaliação de doenças crônicas pulmonares [thesis]. Campinas: Universidade Estadual de Campinas; 2014.
19. Mauri T, Cambiaghi B, Spinelli E, Langer T, Grasselli G. Spontaneous breathing: a double-edged sword to handle with care. Ann Transl Med. 2017;5(14):292. https://doi.org/10.21037/atm.2017.06.55
20. Yoshida T, Amato MBP, Kavanagh BP. Understanding spontaneous vs. ventilator breaths: impact and monitoring. Intensive Care Med. 2018;44(12):2235-8. https://doi.org/10.1007/s00134-018-5145-5
21. Kodali BS. Capnography Outside the Operating Room. Survey Anesthesiol. 2014;58(3):150. https://doi.org/10.1097/01.SA.0000446377.07385.e3
22. Tang Y, Turner MJ, Baker AB. Systematic errors and susceptibility to noise of four methods for calculating anatomical dead space from the CO2 expirogram. Bri J Anaesth. 2007;98(6):828-34. https://doi.org/10.1093/bja/aem090
23. Kars AH, Bogaard JM, Stijnen T, Vries J de, Verbraak AF, Hilvering C. Dead space and slope indices from the expiratory carbon dioxide tension-volume curve. European Respir J. 1997;10(8):1829-36. https://doi.org/10.1183/09031936.97.10081829
24. Verscheure S, Massion PB, Verschuren F, Damas P, Magder S. Volumetric capnography: lessons from the past and current clinical applications. Crit Care. 2016;20(1):184. https://doi.org/10.1186/s13054-016-1377-3
25. Feng Y, Wang Y, Zeng C, Mao H. Artificial Intelligence and Machine Learning in Chronic Airway Diseases: Focus on Asthma and Chronic Obstructive Pulmonary Disease. Int J Med Sci. 2021;18(13):2871-89. https://doi.org/10.7150/ijms.58191
26. Verschuren F, Heinonen E, Clause D, Zech F, Reynaert MS, Liistro G. Volumetric capnography: reliability and reproducibility in spontaneously breathing patients. Clin Physiol Funct Imaging. 2005;25(5):275-80. https://doi.org/10.1111/j.1475-097X.2005.00620.x
27. Almeida CCB, Almeida-Júnior AA, Ribeiro MÂGO, Nolasco-Silva MT, Ribeiro JD. Volumetric capnography to detect ventilation inhomogeneity in children and adolescents with controlled persistent asthma. J Pediatr (Rio J). 2011;87:163-8. https://doi.org/10.2223/JPED.2077
28. Ribeiro MÂGO, Silva MTN, Ribeiro JD, Moreira MM, Almeida CCB, Almeida-Junior AA, et al. Volumetric capnography as a tool to detect early peripheric lung obstruction in cystic fibrosis patients. J Pediatr (Rio J). 2012;88:509-17. https://doi.org/10.2223/JPED.2233
29. Moreira MM, Martins LC, Metze K, Pereira MV, Paschoal IA. Near-fatal pulmonary embolism: capnographic perspective. J Bras Pneumol. 2018;44(6):525-8. https://doi.org/10.1590/s1806-37562018000000080
30. Moreira MM, Terzi RGG, Paschoal IA, Martins LC, Oliveira EP da L, Falcão ALE. Thrombolysis in massive pulmonary embolism based on the volumetric capnography [Article in Portuguese]. Arq Bras Cardiol. 2010;95(4):e97-9. https://doi.org/10.1590/S0066-782X2010001400025
31. Wolff G, Brunner J, Grädel E. Gas exchange during mechanical ventilation and spontaneous breathing. Intermittent mandatory ventilation after open heart surgery. Chest. 1986 1;90:11-7. https://doi.org/10.1378/chest.90.1.11
32. Romero PV, Rodriguez B, de Oliveira D, Blanch L, Manresa F. Volumetric capnography and chronic obstructive pulmonary disease staging. Int J Chron Obstruct Pulmon Dis. 2007;2(3):381-91.
33. Jaffe MB. Infrared Measurement of Carbon Dioxide in the Human Breath: "Breathe-Through" Devices from Tyndall to the Present Day. Anesth Analg. 2008;107(3):890-904. https://doi.org/10.1213/ane.0b013e31817ee3b3
34. Schmalisch G. Current methodological and technical limitations of time and volumetric capnography in newborns. Biomed Eng Online. 2016;15(1):104. https://doi.org/10.1186/s12938-016-0228-4
35. Sassmann T, Kovacs G, Douschan P, Foris V, Gumpoldsberger M, John N, et al. Detection of structural pulmonary changes with real-time and high-fidelity analysis of expiratory CO2. [cited 2024 Jun 13]. https://doi.org/10.21203/rs.3.rs-3894602/v1
36. Tolnai J, Rárosi F, Tóth I, Babik B, Novák Z, Peták F, et al. Relationships between capnogram parameters by mainstream and sidestream techniques at different breathing frequencies. Sci Rep. 2024;14(1):25443. https://doi.org/10.1038/s41598-024-75808-0
37. McDowell A, Kang J, Yang J, Jung J, Oh YM, Kym SM, et al. Machine-learning algorithms for asthma, COPD, and lung cancer risk assessment using circulating microbial extracellular vesicle data and their application to assess dietary effects. Exp Mol Med. 2022;54(9):1586-95. https://doi.org/10.1038/s12276-022-00846-5
38. Kramer DB, Xu S, Kesselheim AS. How Does Medical Device Regulation Perform in the United States and the European Union? A Systematic Review. PLOS Med. 2012;9(7):e1001276. https://doi.org/10.1371/journal.pmed.1001276
39. Williams DF. On the mechanisms of biocompatibility. Biomaterials. 2008;20(29):2941-53. https://doi.org/10.1016/j.biomaterials.2008.04.023

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Upfront combination therapy with sildenafil and ambrisentan in patients with chronic thromboembolic pulmonary hypertension

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ABSTRACT

Objective: Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of acute pulmonary embolism, being characterized by persistent obstruction of pulmonary vessels and leading to increased pulmonary vascular resistance and right ventricular failure. Although pulmonary endarterectomy is the preferred treatment, medical therapies may offer clinical benefits in specific settings. We sought to evaluate the clinical and hemodynamic response of CTEPH patients treated with sildenafil and ambrisentan upfront combination therapy. **Methods:** This was a retrospective cohort study including patients with operable and inoperable CTEPH. The patients were followed from 2019 to 2022 and were treated with sildenafil and ambrisentan as first-line therapy. **Results:** Functional and hemodynamic data were analyzed at baseline and after a minimum of six months of therapy. Following treatment, there was a notable improvement in functional class, natriuretic peptide levels, and invasive hemodynamics. **Conclusions:** The combined use of sildenafil and ambrisentan appears to be associated with clinical, functional, and hemodynamic improvement in patients with CTEPH.

Keywords: Pulmonary Embolism; Drug therapy, combination; Hypertension, pulmonary.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare complication of acute pulmonary embolism,[1] being characterized by chronic obstruction of the pulmonary vasculature by organized thrombi and leading to increased pulmonary vascular resistance (PVR) and right ventricular failure.[2] Progressive remodeling of the distal pulmonary arteries and arterioles[3] may also occur. This is due to several factors, including high pulmonary vascular pressure and shear stress associated with persistent fibrothrombotic remodeling, local inflammation, and circulating vascular mediators.[3,4] These changes are similar to those observed in patients with pulmonary arterial hypertension (PAH), including intimal thickening and plexiform lesion development.[5] These changes lead to progressive vascular remodeling, which modifies vascular endothelial cell responses, compromises fibrinolysis, and affects annexin expression[6,7] and heat shock protein regulation,[7] ultimately causing vascular disruption in patients with CTEPH.

The preferred treatment for CTEPH is pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA) being the treatment of choice for inoperable patients.[8,9] However, mechanical interventions are not always feasible, being dependent on thrombus accessibility, coexisting comorbidities, and patient preference.[10] For ineligible patients, medical therapies represent an option for clinical and hemodynamic improvement. In patients with inoperable CTEPH, the use of bosentan (an endothelin receptor antagonist) has been reported to reduce PVR without significantly affecting the six-minute walk distance (6MWD).[11] Conversely, the use of riociguat (an oral stimulator of soluble guanylate cyclase) has been reported to increase the 6MWD by 36 m in inoperable patients and in patients with residual PAH following PEA.[12] In a phase 2 study, macitentan (an endothelin receptor antagonist) was shown to have a positive effect on the 6MWD.[13] A prospective study of ambrisentan was discontinued in 2019 because of low recruitment.[14]

There is substantial evidence to support the use of medical therapies in selected patients with CTEPH; however, the role of different treatment strategies has yet to be addressed in this setting. In patients with PAH, upfront combination therapy has become the standard of care,[15,16] which is largely due to the results of a study comparing the effects of combined therapy with ambrisentan and tadalafil against monotherapy and demonstrating the superiority of dual oral therapy.[17] In patients with CTEPH, the five-year survival rate for those receiving combination therapy has been reported to be similar to that of those receiving monotherapy.[18]

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However, there is a lack of data regarding the use of combination therapy as an upfront treatment strategy.

The objective of the present study was to evaluate the clinical and hemodynamic response of CTEPH patients treated with sildenafil and ambrisentan upfront combination therapy.

METHODS

This was a retrospective cohort study of patients followed at our institution—a referral center for CTEPH management—from 2019 to 2022. Because of the COVID-19 pandemic, the number of PEA procedures was drastically reduced. Given the clinical or hemodynamic severity, medical therapy was initiated during the evaluation of a potential surgical intervention at the discretion of the attending physician, with patients being classified as operable or inoperable at the time of medical treatment initiation. The diagnosis of CTEPH was based on established guidelines.[19] The inclusion criterion was having received upfront combination therapy with sildenafil and ambrisentan. The study variables included functional class, B-type natriuretic peptide (BNP) levels, and hemodynamic data from right heart catheterization, collected before and after a minimum of six months of treatment with sildenafil and ambrisentan. The present study was approved by the local research ethics committee (Protocol no. CAAE 11032919.8.0000.0068).

The Wilcoxon signed-rank test was used in order to compare continuous variables before and after medical therapy. Fisher's exact test was used in order to compare categorical variables. Data distribution was tested for normality with the Kolmogorov-Smirnov test. Continuous variables were expressed as median and interquartile range. All statistical analyses were performed with GraphPad Prism software, version 9.0 (GraphPad Software, Inc., San Diego, CA, USA), with values of $p < 0.05$ being considered significant.

RESULTS

A total of 32 CTEPH patients receiving sildenafil and ambrisentan were included in the present study, with a mean age of 50 years. Most of the patients were in functional class III or IV, showing severe hemodynamic impairment (Table 1). All patients were started on sildenafil at a dose of 20 mg three times a day; however, during the follow-up period the dose was increased at the discretion of the attending physician. At the follow-up evaluation, 13 patients were receiving 20 mg of sildenafil three times a day; 11 were receiving 40 mg three times a day; 5 were receiving 60 mg three times a day; and 3 were receiving 80 mg three times a day. All patients were concurrently treated with ambrisentan at a dose of 10 mg/day.

After a median treatment follow-up of 13.2 months (IQR, 10-22), we observed a significant improvement in functional class, with the proportion of patients in functional class III or IV decreasing from 87.5% to 31.2% ($p < 0.001$). Prior to treatment, 50% of the patients were classified as being high-risk patients. Following treatment, only 3.10% remained in the high-risk category, with the majority transitioning to intermediate risk (Figure 1). This was accompanied by a significant decrease in BNP levels and an improved hemodynamic profile (Figure 2 and Table 2), including a 38% reduction in PVR, driven by a 43% increase in cardiac output, a 7% decrease in mean pulmonary artery pressure (mPAP; Figure 2), and a 29% reduction in right atrial pressure (Table 2). All patients underwent hemodynamic assessment before and after treatment. BNP levels were available for all patients at baseline but only for 26 at the follow-up evaluation. Neither rehabilitation nor angioplasty was performed. No severe side effects were observed during the follow-up period.

Table 1. Baseline characteristics of the study population.[a]

Characteristic	Baseline (N = 32)
Female	17 (53.1)
Age, years	50.3 ± 14.9
Anticoagulant, DOAC	18 (56.2)
NYHA functional class	
I	0
II	4 (12.5)
III	22 (68.7)
IV	6 (18.7)
BNP, pg/dL	337.5 [140.3-603.5]
Hemodynamic parameters	
RAP, mmHg	17.0 [11.5-20.0]
PAOP, mmHg	11.5 [8.0-15.0]
mPAP, mmHg	59.5 [52.5-64.7]
Cardiac output, L/min	2.9 [2.1-3.9]
PVR, dyn • s^{-1} • cm^{-5}	1,258 [832-1,558]

DOAC: direct oral anticoagulant; NYHA: New York Heart Association; BNP: B-type natriuretic peptide; RAP: right atrial pressure; PAOP: pulmonary artery occlusion pressure; mPAP: mean pulmonary artery pressure; and PVR: pulmonary vascular resistance. [a]Data presented as n (%), mean ± SD, or median [IQR].

DISCUSSION

Our study demonstrated that patients with CTEPH experienced significant clinical and hemodynamic improvement following upfront combination therapy with sildenafil and ambrisentan. To the best of our knowledge, this is the first study to investigate the role of ambrisentan used in combination with sildenafil in this context.

In an international registry of patients in Europe and Canada,[20] 50.1% of the patients were male, with a mean age of 63 years. Hemodynamic results showed an mPAP of 47 mmHg, a PVR of 709 dyn • s^{-1} • cm^{-5}, and a cardiac index of 2.2 L • min^{-1} • m^{-2}.[20] Similarly, in a study reporting results from the United Kingdom National Cohort,[21] the mean age was 57 years, with

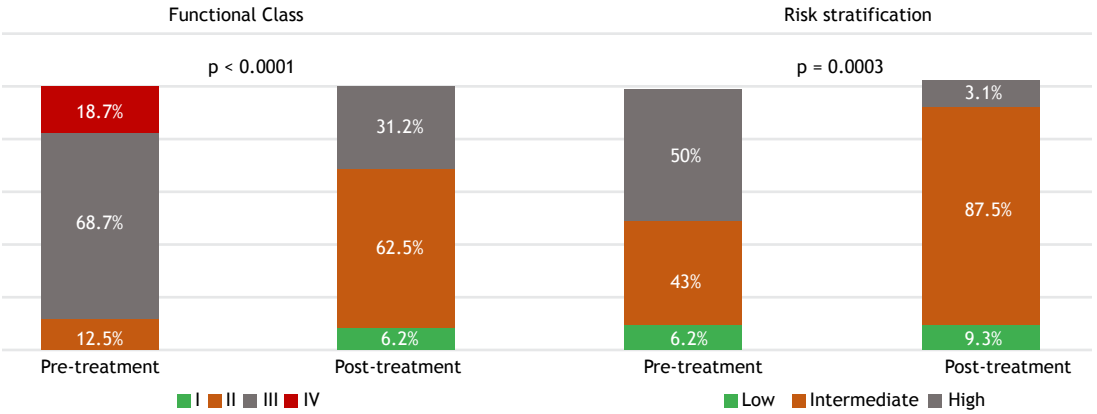

Figure 1. Pre- and post-treatment functional class and risk stratification.

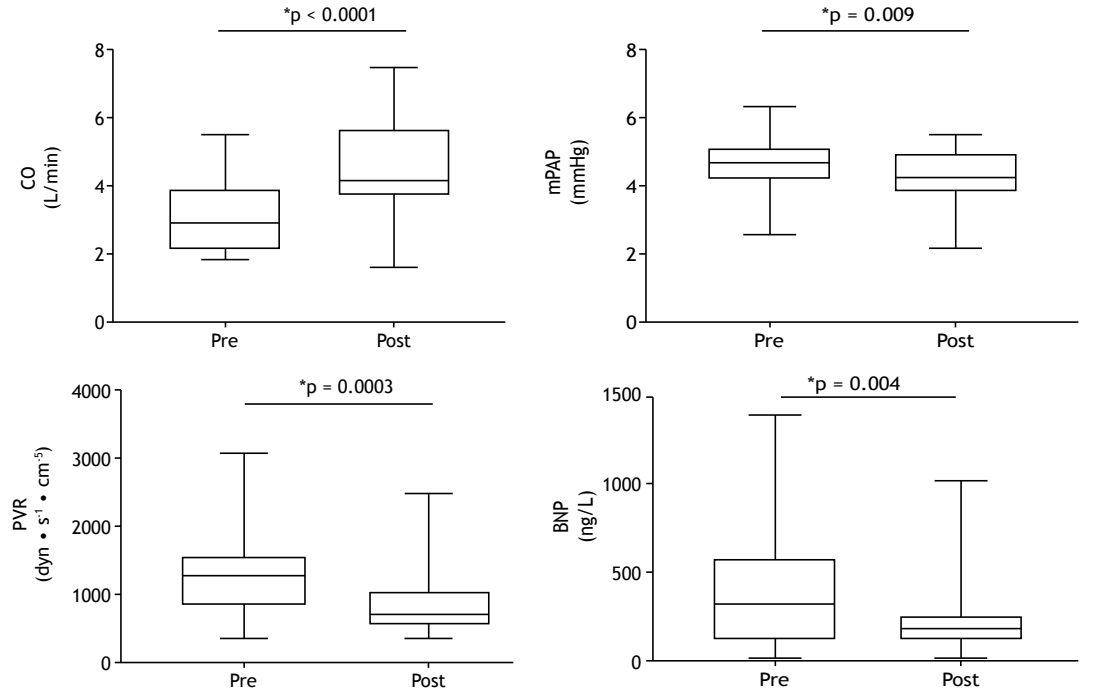

Figure 2. Pre- and post-treatment evaluation of hemodynamics (n = 32) and B-type natriuretic peptide (BNP) levels (n = 26). CO: cardiac output; mPAP: mean pulmonary artery pressure; and PVR: pulmonary vascular resistance.

Table 2. Pre- and post-treatment evaluation.[a]

	Pre-treatment	Post-treatment	p-value
BNP, ng/L (n = 26)	426.9 [140.3-603.5]	186 [109-292.8]	p = 0.0004
RAP, mmHg	17.0 [11.5-20.0]	12.0 [8.0-17.2]	p = 0.009
CO, L/min	2.9 [2.1-3.9]	4.1 [3.7-5.6]	p < 0.0001
mPAP, mmHg	59.5 [52.5-64.7]	53.5 [48.2-62.0]	p = 0.009
PVR, dyn • s^{-1} • cm^{-5}	1,258 [832-1,558]	718.5 [528-1,034]	p = 0.0003

BNP: B-type natriuretic peptide; RAP: right atrial pressure; CO: cardiac output; mPAP: mean pulmonary artery pressure; and PVR: pulmonary vascular resistance. [a]Data presented as median [IQR].

53% of the patients being male. Hemodynamic findings included a mean baseline mPAP of 47 mmHg and a PVR of 830 dyn • s^{-1} • cm^{-5}.[21] Although our patient population was younger, they presented with more severe hemodynamic impairment and were therefore selected for medical treatment prior to PEA.

Recently, a worldwide CTEPH registry demonstrated that the use of targeted medical therapy prior to mechanical intervention was significantly more common before BPA (63%) than before PEA (25%).[22] The most frequently used medications were phosphodiesterase type 5 inhibitors and endothelin receptor antagonists,

although without a description of their combined use.[22] Our study introduced this therapeutic approach as a potential strategy for patients with CTEPH.

Medical therapy as a bridge to PEA has been shown to delay the surgical procedure without clear evidence of improved patient outcomes.[23] However, this might not apply to patients with severe hemodynamic impairment at diagnosis. In a trial of BPA vs. riociguat for the treatment of inoperable CTEPH,[8] riociguat administered before BPA in patients with higher hemodynamic impairment was associated with fewer adverse events, highlighting the potential benefit of medical therapy in more severe cases. At the 7th World Symposium on Pulmonary Hypertension, the proposed treatment algorithm included medical therapy prior to BPA for patients with mPAP ≥ 40 mmHg or PVR > 4 Wood units,[24] further emphasizing the importance of medical therapy in patients with significant hemodynamic impairment. Nevertheless, combination therapy for CTEPH, particularly as upfront treatment and including operable patients, remains a poorly explored area. Despite evidence supporting combination strategies in patients with PAH, data for patients with CTEPH are scarce and mostly limited to inoperable cases or monotherapy trials.[18] In a previous study, our group demonstrated that patients with CTEPH and a preoperative cardiac output of < 3.75 L/min had poorer postoperative outcomes.[25] In such cases, medical therapy was associated with improved overall survival after PEA, which justified the use of combination therapy in our cohort to optimize hemodynamics for future surgical interventions.

A recent study evaluating the use of selexipag in inoperable patients with CTEPH or patients with residual PAH after PEA was discontinued because of futility. The trial failed to demonstrate a treatment effect on the primary endpoint of PVR.[26] Ambrisentan had previously been tested in the same setting, showing a trend of improvement in the 6MWD and a reduction in PVR as a secondary endpoint.[14] However, the study was terminated early because of low enrollment.[14] In a study published in 2013,[12] riociguat resulted in a significant (31%) reduction in PVR of 226 dyn • s^{-1} • cm^{-5}. In a trial assessing the use of bosentan,[11] there was a 24.1% reduction in PVR, although without improvement in the 6MWD, a coprimary endpoint of the study. Similarly, in a phase II study assessing the use of macitentan exclusively in inoperable patients,[13,27] there was a reduction of 206 dyn • s^{-1} • cm^{-5} (16%) in the treatment group and a reduction of 86 dyn • s^{-1} • cm^{-5}. (8%) in the control group, the efficacy and safety of macitentan being also demonstrated in the extension study.[27] In our study, patients receiving dual therapy showed a 38% reduction in PVR, corresponding to a reduction of 494 dyn • s^{-1} • cm^{-5}. and exceeding the aforementioned reductions. This finding is consistent with the hemodynamic effects of combination therapy in patients with PAH, such as those observed in a study demonstrating a reduction of approximately 50% in PVR with dual or triple upfront therapy.[28] Our findings raise the question of the most appropriate strategy to be employed when medical therapy is considered in patients with CTEPH, a topic that warrants thorough investigation in future prospective trials.

Other key findings in our study include improvements in functional class and BNP levels, which are consistent with those of other studies.[11,12] One of the aforementioned studies[11] showed a 622 ng/L reduction in N-terminal pro-BNP levels, whereas the other[12] showed a 291 ng/L reduction, both being consistent with our observed improvements in BNP levels and functional class.[11,12]

Our study has several limitations that must be acknowledged. First, the study was conducted at a single center, although it is the largest center for CTEPH management in Brazil. Second, given the constraints imposed by the COVID-19 pandemic, patients could not be classified as operable or inoperable prior to initiation of medical therapy, the decision of initiating medical treatment being solely based on clinical and hemodynamic severity, thus potentially creating a selection bias for treating the most severe cases with upfront combination therapy. Nevertheless, patients with more severe hemodynamic profiles are the most likely to benefit from a more aggressive therapeutic approach prior to mechanical intervention. Third, the fact that six-minute walk tests were not regularly performed during the COVID-19 pandemic prevented an analysis of the impact of the sildenafil-ambrisentan combination on the exercise capacity of patients. Although riociguat remains the only approved medical therapy for CTEPH, its unavailability in our region justified the use of sildenafil and ambrisentan in the present study. Another limitation of the present study is the absence of a standardized protocol for sildenafil dosing, which may have influenced the hemodynamic response to medical treatment. Finally, during follow-up, only a few of the patients undergoing PEA underwent invasive hemodynamic assessment after surgery, which prevented an analysis of the potential benefit of the sildenafil-ambrisentan combination on surgical outcomes. In addition, this was a retrospective observational study without a control group. Being a before-and-after analysis, it is subject to several biases such as missing data and nonstandardized documentation. Ideally, therapeutic efficacy should be evaluated in a prospective randomized controlled trial.

In conclusion, patients with CTEPH showed significant clinical, functional, and hemodynamic improvement with the combined use of sildenafil and ambrisentan as medical therapy. Our findings suggest that this combination may be a valuable addition to the treatment strategy for CTEPH and should be further evaluated in future prospective studies.

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AUTHOR CONTRIBUTIONS

WSF and RS were responsible for the study concept and design; statistical analysis; and drafting of the manuscript. TMV, YPPN, and LST contributed to the analysis of data. JLAJ performed all right heart catheterizations and contributed to the analysis of data. CJCF, CVPJ, and MTF were involved in the study conception; analysis of data; and drafting of the manuscript. All authors critically revised the manuscript for important intellectual content and provided final approval of the version to be published.

CONFLICTS OF INTEREST

William Salibe-Filho has received lecture fees from Bayer. José Leonidas Alves-Junior has received consultancy and lecture fees from Bayer, Janssen, MSD, and Gossamer Bio. Caio Julio Cesar Fernandes has received lecture fees from Bayer, Janssen, and MSD. Rogerio Souza has received consultancy and lecture fees from Janssen, Bayer, MSD, Keros Therapeutics, and Pulmovant. Mario Terra-Filho has received consultancy fees from Bayer. Tulio Martins Vieira, Yally Priscila Pessôa Nascimento, Luiza Sarmento Tatagiba, and Carlos Viana Poyares Jardim have nothing to disclose.

REFERENCES

1. Marti D, Gomez V, Escobar C, Wagner C, Zamarro C, Sanchez D, et al. Incidence of symptomatic and asymptomatic chronic thromboembolic pulmonary hypertension [Article in Spanish]. Arch Bronconeumol. 2010;46(12):628-33. https://doi.org/10.1016/S1579-2129(10)70137-3
2. Fernandes C, Ota-Arakaki JS, Campos F, Correa RA, Gazzana MB, Jardim CVP, et al. Brazilian Thoracic Society recommendations for the diagnosis and treatment of chronic thromboembolic pulmonary hypertension. J Bras Pneumol. 2022;46(4):e20200204. https://doi.org/10.36416/1806-3756/e20200204
3. Lang IM, Dorfmuller P, Vonk Noordegraaf A. The Pathobiology of Chronic Thromboembolic Pulmonary Hypertension. Ann Am Thorac Soc. 2016;13 Suppl 3:S215-21. https://doi.org/10.1513/AnnalsATS.201509-620AS
4. Sharma S, Hofbauer TM, Ondracek AS, Chausheva S, Alimohammadi A, Artner T, et al. Neutrophil extracellular traps promote fibrous vascular occlusions in chronic thrombosis. Blood. 2021;137(8):1104-16. https://doi.org/10.1182/blood.2020005861
5. Dorfmuller P, Gunther S, Ghigna MR, Thomas de Montpreville V, Boulate D, Paul JF, et al. Microvascular disease in chronic thromboembolic pulmonary hypertension: a role for pulmonary veins and systemic vasculature. Eur Respir J. 2014;44(5):1275-88. https://doi.org/10.1183/09031936.00169113
6. Fassel H, Chen H, Ruisi M, Kumar N, DeSancho M, Hajjar KA. Reduced expression of annexin A2 is associated with impaired cell surface fibrinolysis and venous thromboembolism. Blood. 2021;137(16):2221-30. https://doi.org/10.1182/blood.2020008123
7. Salibe-Filho W, Araujo TLS, G Melo E, B C T Coimbra L, Lapa MS, Acencio MMP, et al. Shear stress-exposed pulmonary artery endothelial cells fail to upregulate HSP70 in chronic thromboembolic pulmonary hypertension. PLoS One. 2020;15(12):e0242960. https://doi.org/10.1371/journal.pone.0242960
8. Jais X, Brenot P, Bouvaist H, Jevnikar M, Canuet M, Chabanne C, et al. Balloon pulmonary angioplasty versus riociguat for the treatment of inoperable chronic thromboembolic pulmonary hypertension (RACE): a multicentre, phase 3, open-label, randomised controlled trial and ancillary follow-up study. Lancet Respir Med. 2022;10(10):961-71. https://doi.org/10.1016/S2213-2600(22)00214-4
9. Kawakami T, Matsubara H, Shinke T, Abe K, Kohsaka S, Hosokawa K, et al. Balloon pulmonary angioplasty versus riociguat in inoperable chronic thromboembolic pulmonary hypertension (MR BPA): an open-label, randomised controlled trial. Lancet Respir Med. 2022;10(10):949-60. https://doi.org/10.1016/S2213-2600(22)00171-0
10. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. Eur Respir J. 2019;53(1):1801915. https://doi.org/10.1183/13993003.01915-2018
11. Jais X, D'Armini AM, Jansa P, Torbicki A, Delcroix M, Ghofrani HA, et al. Bosentan for treatment of inoperable chronic thromboembolic pulmonary hypertension: BENEFiT (Bosentan Effects in iNopErable Forms of chronIc Thromboembolic pulmonary hypertension), a randomized, placebo-controlled trial. J Am Coll Cardiol. 2008;52(25):2127-34. https://doi.org/10.1016/j.jacc.2008.08.059
12. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med. 2013;369(4):319-29. https://doi.org/10.1056/NEJMoa1209657
13. Ghofrani HA, Simonneau G, D'Armini AM, Fedullo P, Howard LS, Jais X, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med. 2024;12(4):e21-e30. https://doi.org/10.1016/S2213-2600(24)00029-8
14. Escribano-Subias P, Bendjenana H, Curtis PS, Lang I, Vonk Noordegraaf A. Ambrisentan for treatment of inoperable chronic thromboembolic pulmonary hypertension (CTEPH). Pulm Circ. 2019;9(2):2045894019846433. https://doi.org/10.1177/2045894019846433
15. Chin KM, Gaine SP, Gerges C, Jing ZC, Mathai SC, Tamura Y, et al. Treatment algorithm for pulmonary arterial hypertension. Eur Respir J. 2024;64(4)2401325. https://doi.org/10.1183/13993003.01325-2024
16. Fernandes CJ, Calderaro D, Assad APL, Salibe-Filho W, Kato-Morinaga LT, Hoette S, et al. Update on the Treatment of Pulmonary Arterial Hypertension. Arq Bras Cardiol. 2021;117(4):750-64. https://doi.org/10.36660/abc.20200702
17. Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. N Engl J Med. 2015;373(9):834-44. https://doi.org/10.1056/NEJMoa1413687
18. van Thor MCJ, Snijder RJ, Kelder JC, Mager JJ, Post MC. Does combination therapy work in chronic thromboembolic pulmonary hypertension? Int J Cardiol Heart Vasc. 2020;29:100544. https://doi.org/10.1016/j.ijcha.2020.100544
19. Frost A, Badesch D, Gibbs JSR, Gopalan D, Khanna D, Manes A, et al. Diagnosis of pulmonary hypertension. Eur Respir J. 2019;53(1):1801904. https://doi.org/10.1183/13993003.01904-2018
20. Pepke-Zaba J, Delcroix M, Lang I, Mayer E, Jansa P, Ambroz D, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): results from an international prospective registry. Circulation. 2011;124(18):1973-81. https://doi.org/10.1161/CIRCULATIONAHA.110.015008
21. Cannon JE, Su L, Kiely DG, Page K, Toshner M, Swietlik E, et al. Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort. Circulation. 2016;133(18):1761-71. https://doi.org/10.1161/CIRCULATIONAHA.115.019470
22. Delcroix M, Pepke-Zaba J, D'Armini AM, Fadel E, Guth S, Hoole SP, et al. Worldwide CTEPH Registry: Long-Term Outcomes With Pulmonary Endarterectomy, Balloon Pulmonary Angioplasty, and Medical Therapy. Circulation. 2024;150(17):1354-65. https://doi.org/10.1161/CIRCULATIONAHA.124.068610
23. Pepke-Zaba J, Ghofrani HA, Hoeper MM. Medical management of chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2017;26(143):160107. https://doi.org/10.1183/16000617.0107-2016
24. Kim NH, D'Armini AM, Delcroix M, Jais X, Jevnikar M, Madani MM, et al. Chronic thromboembolic pulmonary disease. Eur Respir J. 2024;64(4):2401294. https://doi.org/10.1183/13993003.01294-2024
25. Castro MA, Piloto B, Dos Santos Fernandes CJC, Jardim C, Filho WS, Oleas FG, et al. Use of medical therapies before pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension patients with severe hemodynamic impairment. PLoS One. 2020;15(5):e0233063. https://doi.org/10.1371/journal.pone.0233063
26. Kim NH, Channick R, Delcroix M, Madani M, Pepke-Zaba J, Borissoff JI, et al. Efficacy and safety of selexipag in patients with inoperable or persistent/recurrent CTEPH (SELECT randomised trial). Eur Respir J. 2024;64(4):2400193. https://doi.org/10.1183/13993003.00193-2024
27. Kim NH, D'Armini AM, Howard LS, Jenkins DP, Jing ZC, Mayer E, et al. Long-Term Safety and Efficacy of Macitentan in Inoperable Chronic Thromboembolic Pulmonary Hypertension: Results from MERIT and its Open-Label Extension. Pulm Ther. 2025;11(1):101-116. https://doi.org/10.1007/s41030-024-00276-w
28. Chin KM, Sitbon O, Doelberg M, Feldman J, Gibbs JSR, Grunig E, et al. Three- Versus Two-Drug Therapy for Patients With Newly Diagnosed Pulmonary Arterial Hypertension. J Am Coll Cardiol. 2021;78(14):1393-403. https://doi.org/10.1016/j.jacc.2021.07.057

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ORIGINAL ARTICLE

Risk communication, respiratory health risks, and air pollution forecasting in the city of Rio de Janeiro, Brazil

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ABSTRACT

Objective: Although communicating air pollution risks is critical for protecting public health, particularly in low- and middle-income countries (LMICs), its effectiveness remains underexplored. This study evaluated current risk communication practices in the city of Rio de Janeiro, Brazil, by assessing the associations between short-term exposure to pollutants and respiratory-related hospital admissions; the ability of the Brazilian national *índice de qualidade do ar* (IQAr, air quality index) to reflect health risks; and the accuracy of pollutant forecasts in comparison with monitored concentrations. **Methods:** Exposure and health data for the 2014-2019 period were obtained through a research partnership with local government officials. Poisson generalized linear models were employed to determine whether IQAr values and short-term exposure to air pollutants, including nitrogen dioxide (NO_2) and particulate matter (PM), were associated with daily hospital admissions for respiratory disease. Bias-corrected, forecasted daily concentrations of individual air pollutants from the Goddard Earth Observing System Composition Forecast Composition Forecast (GEOS-CF) model were employed to assess the performance of existing forecasting tools for use in risk communication. **Results:** Significant associations were consistently observed between hospital admissions for respiratory disease and short-term exposures to NO_2 and coarse PM, with excess risks of 5.1% (95% CI: 1.3-8.9%) and 5.6% (95% CI: 1.5-9.9%), respectively, per interquartile range increases in lag day 0-1 exposures. Values of IQAr were not significantly associated with respiratory health events, likely due to their failure to capture the health risks associated with NO_2. Bias-corrected forecasts from the GEOS-CF model showed strong correlations with observed pollutant concentrations. **Conclusions:** These findings indicate that adopting a health-based, multi-pollutant index, combined with improved forecasting tools, could substantially strengthen risk communication in the city of Rio de Janeiro and other LMIC settings.

Keywords: Air pollutants/analysis; Air pollution/adverse effects; Nitrogen dioxide; Particulate matter; Developing countries; Respiratory tract diseases/epidemiology.

INTRODUCTION

Respiratory diseases linked to outdoor air pollution represent a significant public health burden worldwide, particularly in low- and middle-income countries (LMICs) such as Brazil. Although air quality indices are widely used to communicate pollution levels, their effectiveness in conveying short-term health risks remains underexplored. This issue is especially critical in cities that are less studied, like Rio de Janeiro, Brazil, where diverse pollution sources, unique urban geography, and socioeconomic disparities create distinct exposure patterns and health responses.[1,2]

The Rio de Janeiro *Secretaria Municipal do Ambiente e Clima* (SMAC, Municipal Secretary of the Environment and Climate) has implemented the Rio de Janeiro Air Quality Monitoring Program (MonitorAR-Rio) to inform the public of air pollution risks through dissemination of the Brazilian national *índice de qualidade do ar* (IQAr, air quality index). These efforts include informing the public of the air quality in the city through an online air quality bulletin that is updated daily with concentration values of major pollutants that the WHO has classified as having serious impacts on human health.[3] However, the current approach using the IQAr, which is based on the pollutant with the highest calculated index value each day, has not been quantitatively assessed to determine its accuracy in reflecting population-level health risks in a way that can lead to effective decision-making by individuals regarding behavior modification.

This study, designed and carried out in collaboration with local civil servants within the city government, addresses three key aspects of air quality risk communication: quantifying the associations between short-term exposure to pollutants and population-level health risks; evaluating the ability of the current IQAr to reflect those risks;

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and exploring the potential of a forecasting-based approach to enhance communication of next-day pollutant concentrations. Collectively, these findings will directly inform future decisions on how to best communicate health risks associated with outdoor air pollution in Rio de Janeiro and will provide actionable insights for air quality management in LMICs.

METHODS

Exposure data

For the 2014-2019 period, hourly air pollution data and IQAr values for the city of Rio de Janeiro were obtained from the SMAC. The IQAr has a theoretical range from 0 to 400, with higher values indicating higher levels of air pollution and therefore greater harm to human health. Table S1 shows the IQAr values and associated levels of health concern in accordance with the national air quality standards. Daily IQAr values are reported to the public based on the highest value associated with concentrations of the monitored pollutants.

Pollution data for this study were collected from four central monitoring stations (Centro, Irajá, São Cristóvão, and Tijuca) managed by MonitorAR-Rio. These stations were selected in consultation with local experts based on their similar geographical, meteorological, and socioeconomic characteristics to ensure consistency in exposure and health assessments. The hourly concentrations of monitored air pollutants—particulate matter with a diameter ≤ 10 μm (PM_{10}), particulate matter with a diameter ≤ 2.5 μm ($PM_{2.5}$), ground-level ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2)—were aggregated into daily exposure variables using various averaging times (see Table 1). Missing data were handled with multivariate imputation by chained equations and predictive mean matching. Hourly meteorological data, such as temperature, relative humidity, and precipitation, also provided by the SMAC (Table 1), were aggregated into daily (24-h) average variables.

Forecasted daily concentrations of individual air pollutants from the publicly available U.S. National Aeronautics and Space Administration Goddard Earth Observing System Composition Forecast (GEOS-CF) model were employed to assess the suitability of a quantitative tool in predicting pollutant concentrations,[4] compared with the current qualitative approach.[5] The forecasting capabilities of the GEOS-CF were further enhanced with bias correction methods that integrate local observations through machine learning (ML).[4] With that approach, an ML model was trained to improve upon the capabilities of the GEOS-CF model in accounting for local atmospheric trends at each monitor.[4,6] Coefficients of determination (R^2) were calculated for the 2018-2019 period, comparing daily monitored pollutant concentrations with forecasted concentrations from the bias-corrected GEOS-CF model.

Health data

Daily hospital admissions for respiratory diseases during the 2014-2016 period were obtained from the data platform of the Brazilian Unified Health Care System[7] and provided by Rio de Janeiro city officials at the Pereira Passos Institute. That period was selected in order to retain other years for independently developing and evaluating potential revisions to the current IQAr. Respiratory diseases were defined by the following ICD-10 codes: J01-J06 (acute upper respiratory infections, excluding the common cold); J18 (pneumonia, unspecified organism); J20-J22 (other acute lower respiratory infections); J30-J39 (other diseases of the upper respiratory tract); J40-J47 (chronic lower respiratory disease, including COPD and asthma); J80-J84 (other respiratory diseases principally affecting the interstitium); J86 (suppurative and necrotic conditions of the lower respiratory tract); and J90/J92-J94 (other diseases of the pleura). After patients who could not be linked back to any monitors, because of missing geographical data, had been excluded, the study sample comprised 10,431 admissions (an average of approximately 10 admissions per day).

Statistical analysis

Time-series analyses with Poisson generalized linear models were used in order to assess the associations that the daily IQAr and individual air pollutant concentrations had with hospital admissions for respiratory disease in the city of Rio de Janeiro. Poisson generalized linear models are well-suited for

Table 1. Descriptive statistics of air pollution and meteorological data in the city of Rio de Janeiro, Brazil. Combined data from four monitoring stations, 2014-2016.

Variable	Mean ± SD	Median (range)	IQR
NO_2, 1-h maximum (ppb)	37.0 ± 17.3	34.0 (6.91-126.0)	20.7
O_3, 8-h maximum (ppb)	21.7 ± 10.2	20.1 (3.74-66.3)	13.1
PM_{10}, 24-h (μg/m³)	34.5 ± 14.1	32.0 (8.0-102.0)	17.0
$PM_{2.5}$*, 24-h (μg/m³)	17.9 ± 10.7	15.0 (0.0-84.0)	12.0
SO_2, 24-h (ppb)	1.99 ± 1.38	1.72 (0.0-13.4)	1.72
Temperature (°C)	25.3 ± 3.6	25.0 (16.0-33.7)	5.3
Daily precipitation (mm)	0.06 ± 0.26	0.0 (0.0-3.0)	0.0
Relative humidity (%)	64.6 ± 9.79	64.5 (37.3-92.5)	13.3

NO_2: nitrogen dioxide, O_3: ozone, PM_{10}: particulate matter with a diameter ≤ 10 μm, $PM_{2.5}$: particulate matter with a diameter ≤ 2.5 μm; SO_2: sulfur dioxide. *$PM_{2.5}$ data were available from only one of the four monitoring stations.

analyzing count data, such as daily hospital admissions, in relation to environmental exposures. They allow the assessment of short-term associations while accounting for temporal patterns, confounding factors, lagged effects, and overdispersion, providing interpretable results, such as relative risks and excess risks, that are directly applicable to public health decisions.[8]

Optimal degrees of freedom (df) for covariates, such as temperature and seasonality, were determined by assessing model fit with the pseudo-R^2 and residual sum of squares. The regression model included a linear indicator for each day of the week; smooth functions of time (using natural splines) to control for seasonality and long-term trends (df = 6 per year), same-day temperature (df = 3), average temperature at lag 1-3 (df = 3), same-day relative humidity (df = 3), same-day precipitation (df = 3); and a binary indicator to control for the Rio de Janeiro 2016 Summer Olympics. Models were specified for each pollutant at individual lag days 0-5 and average lag days 0-1. Excess risks were calculated per interquartile range increase in individual pollutant concentrations and IQAr. Stability of the overall model was confirmed through sensitivity analyses of alternative df values for meteorological and seasonality variables. Two-pollutant models included a second pollutant that uses the same lag variables and indicators used in the single-pollutant model. Each possible pollutant pair was tested in the analysis. All analyses conducted were completed with RStudio, version 2022.07.1.[9]

RESULTS

The overall air quality of the study area in the city of Rio de Janeiro was defined by the IQAr as "good" on the vast majority of days during the study period, as "moderate" on a much smaller portion of days, and as "bad" or "very bad" on only 2% of days. More specifically, there were no days during the study period on which the NO_2 concentrations were reported as being anything other than "good" (Table 2).

Despite the overall air quality of the study area in the city being reported as generally healthy on most days, there were still observed increases in respiratory health risks associated with short-term exposures to NO_2 and PM_{10}. The single-pollutant models demonstrated a significant association between hospital admission for respiratory disease and air pollution exposure at lag day 0 and 1 (Figure 1). Significant, positive associations were observed for NO_2 and PM_{10} but were not consistently found for other pollutants (O_3 or SO_2). Each interquartile-range (21-ppb) increase in the NO_2 concentration was associated with an excess risk of hospital admission for respiratory disease of 5.1% (95% CI: 1.3-8.9%) at lag day 0-1; and each interquartile-range (17-μg/m^3) increase in PM_{10} was associated with an excess risk of such admission of 5.6% (95% CI: 1.5-9.9%) at lag day 0-1. In two-pollutant models, the associations observed for NO_2 and PM_{10} (Figures S1 and S2, respectively) were positive but attenuated when adjusted for each other. Because $PM_{2.5}$ exposure was monitored at only one station and showed low correlation coefficients (< 0.60) with other pollutants and meteorological variables (data not shown), $PM_{2.5}$ was excluded from the regression analysis.

Daily IQAr values reported to the public were not found to be significantly associated with population-level respiratory morbidity risks (Figure 1). During the study period, the pollutant with the highest calculated index value (Table 3), also known as the primary driver pollutant, was most commonly PM_{10} (on 611 of the 1,150 days with a primary driver pollutant) followed by O_3 (on 353 of such days). NO_2 was the primary driver pollutant on 14 days (Table 3), all of which were classified as having "good" air quality (Table 2) on the IQAr scale.

The analysis of the capability of the bias-corrected GEOS-CF model in forecasting pollutant concentrations revealed strong correlations between monitored concentrations and the bias-corrected GEOS-CF estimates (Figure 2). Those correlations were particularly strong for NO_2 and O_3 (R^2 = 0.83 and 0.90, respectively). PM_{10} was excluded from the analysis because estimates of PM10 were not available in the GEOS-CF model at the time of the study.

DISCUSSION

This study makes significant, novel contributions to the field of environmental epidemiology by evaluating

Table 2. Range of the Brazilian national air quality index values (IQAr) and daily classifications for NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2 in the city of Rio de Janeiro, Brazil, 2014-2016. The Irajá monitoring station was selected as representative of the worst air quality in the region.

IQAr range	Classification	NO_2 (% of days)	O_3 (% of days)	PM_{10} (% of days)	$PM_{2.5}$ (% of days)	SO_2 (% of days)
0-40	Good	96.0	85.0	76.0	76.0	91.0
41-80	Moderate	0.0	10.0	18.0	17.0	0.1
81-120	Unhealthy	0.0	1.7	1.4	1.6	0.0
121-200	Very unhealthy	0.0	0.3	0.0	0.1	0.0
201-400	Terrible	0.0	0.0	0.0	0.0	0.0
Missing data		4.0	3.0	4.2	5.8	8.7
Total days		1,096	1,096	1,096	1,096	1,096

NO_2: nitrogen dioxide, O_3: ozone, PM_{10}: particulate matter with a diameter ≤ 10 μm; $PM_{2.5}$: particulate matter with a diameter ≤ 2.5 μm; SO_2: sulfur dioxide.

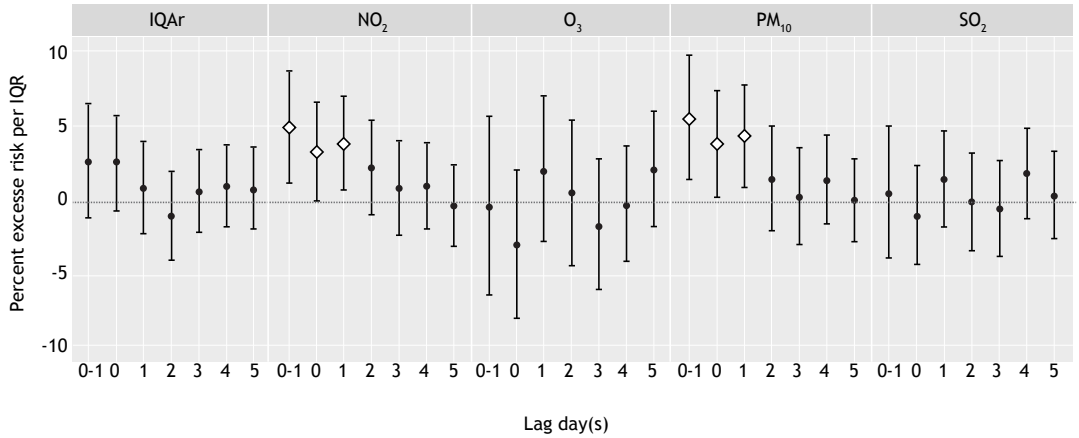

Figure 1. Percent excess risks of hospital admission for respiratory disease per interquartile-range increase in the Brazilian national air quality index (IQAr) and in concentrations of nitrogen dioxide (NO_2), ozone (O_3), particulate matter with a diameter ≤ 10 μm (PM_{10}), and sulfur dioxide (SO_2), by lag structure, in the city of Rio de Janeiro, Brazil, 2014-2016. Open diamonds indicate statistical significance ($p < 0.05$), and filled circles indicate statistical insignificance ($p \geq 0.05$). IQAr: *índice de qualidade do ar* (air quality index).

Table 3. Number of days on which NO_2, O_3, PM_{10}, $PM_{2.5}$, and SO_2 were the primary driver pollutant—which determines the Brazilian national air quality index values (IQAr)—or the secondary driver pollutant in the city of Rio de Janeiro, Brazil (from the Centro, Irajá, São Cristóvão, and Tijuca monitoring stations), 2014-2016.

Monitored pollutant	Primary driver (days)	Secondary driver (days)
NO_2	14	11
O_3	353	243
PM_{10}	611	894
$PM_{2.5}$	146	32
SO_2	26	23
Total days*	1,150	1,203

NO_2: nitrogen dioxide, O_3: ozone, PM_{10}: particulate matter with a diameter ≤ 10 μm; $PM_{2.5}$: particulate matter with a diameter ≤ 2.5 μm; SO_2: sulfur dioxide. *The total number of days for primary and secondary drivers differs because there were some days on which two pollutants had the same calculated IQAr value.

the effectiveness of the IQAr in communicating short-term health risks in the city of Rio de Janeiro and proposing a more robust forecasting-based approach to improve risk communication in the city. Although traditional air quality indices have been widely used,[10] this study is among the first to rigorously assess the inadequacies of such indices in accurately reflecting population-level health risks in an LMIC context. Although many adverse health outcomes are associated with short-term increases in ambient air pollution, respiratory morbidity has been identified as the most promising target for individual behavior modification.[11] Therefore, respiratory morbidity was used in order to evaluate the performance of the IQAr in the present study.

The observed significant associations between short-term exposures to NO_2 and PM_{10} and increased risks of hospital admission for respiratory disease in the city of Rio de Janeiro align closely with the findings of other studies conducted in Latin America. Previous epidemiological investigations in urban areas, such as Mexico City, Mexico and Quito, Ecuador, have similarly demonstrated that traffic-related pollutants, particularly NO_2, are among the strongest predictors of respiratory morbidity.[8,12] Those studies suggest that NO_2 often serves as a marker for emissions from vehicles and other sources of combustion, which are prevalent in densely populated cities with high traffic volume in LMICs.[13] Similarly, the association between PM and respiratory health outcomes has been consistently observed across Latin America, with PM often linked to a broad range of respiratory effects due to its ability to penetrate the respiratory tract and trigger inflammation.[14-16] This underscores the importance of targeting reductions in NO_2 and PM in air quality management strategies across Latin America.

Our finding that the IQAr values, driven predominantly by PM or O_3 concentrations, fail to reflect the significant respiratory risks associated with exposure to NO_2 is particularly striking. As previously stated, while 14 days of the three-year period had index values primarily driven by NO_2, all of these days, however, were classified as having "good" air quality according to the IQAr classifications. This underscores the need for a health-based, multi-pollutant approach tailored to the unique urban and socioeconomic characteristics of cities like Rio de Janeiro (e.g., the strong associations between NO_2 exposure and adverse health effects), in order to improve the effectiveness of informed behavior modification decisions to reduce exposures and health risks.

Our results highlight the need for a comprehensive risk communication framework that, at a minimum, includes the pollutants that are currently underrepresented in the IQAr system. Given that NO_2 concentrations in Rio de Janeiro were classified as "good" under the IQAr for the entire study period, despite significant

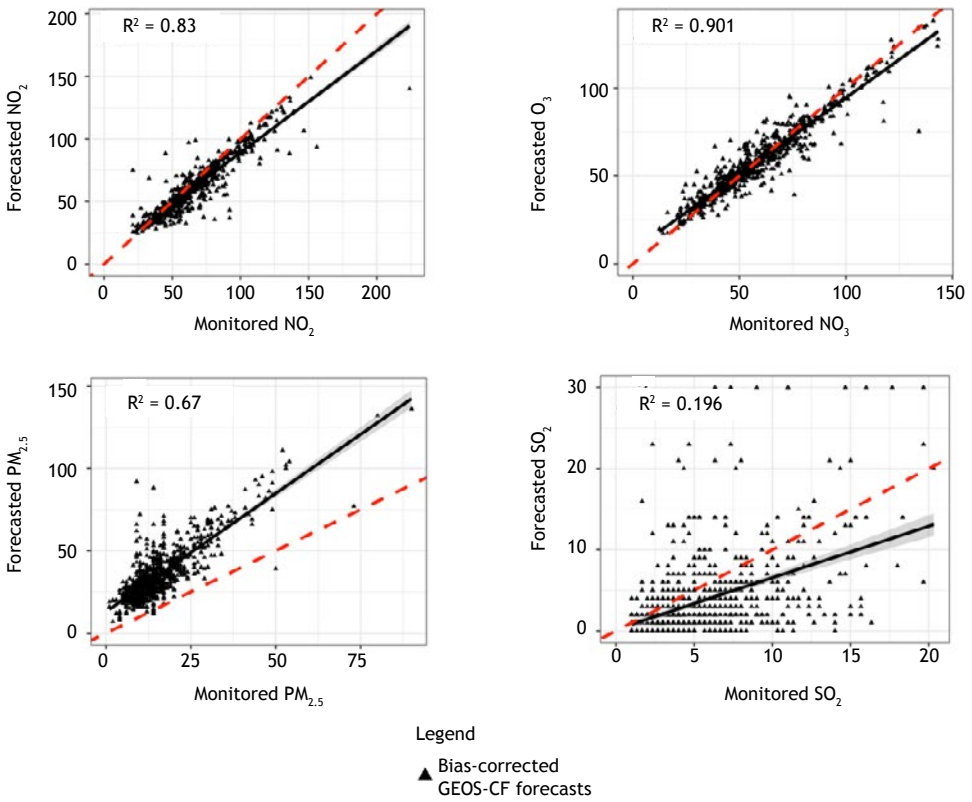

Figure 2. Correlation plots between monitored and forecasted levels of nitrogen dioxide (NO_2), ozone (O_3), particulate matter with a diameter ≤ 2.5 μm ($PM_{2.5}$), and sulfur dioxide (SO_2), in the city of Rio de Janeiro, Brazil, 2014-2016. Daily forecast levels of air pollutants are derived from the bias-corrected Goddard Earth Observing System Composition Forecast (GEOS-CF) model with 1-day lead time. Coefficients of determination (R^2) are presented on each plot.

health risks, the current system may fail to adequately inform the public of potential harms.

The absence of significant associations between short-term O_3 exposure and respiratory morbidity in our study is consistent with the findings of studies conducted in other LMIC contexts, including urban centers in other Latin America countries. Although significant associations between O_3 and respiratory health outcomes are frequently observed in studies conducted in high-income regions, such as North America, they are less commonly reported in LMICs.[17-19] It is noteworthy that the typical O_3 concentrations in the city of Rio de Janeiro are substantially lower than the levels typically found in urban areas where positive associations are observed.

The lack of significant associations observed for exposure to O_3 in the present study does not negate the potential health risks of such exposure but rather highlights the need for further research to understand the specific conditions under which O_3 poses a threat to respiratory health in LMIC settings. The strong influence of O_3 on daily IQAr values represents a major opportunity to improve the health protection offered by risk communication approaches in Brazil. Although continued monitoring and analysis of O_3 concentrations and their potential health impacts is important, ensuring that all relevant pollutants are adequately accounted for in public health frameworks is critical to refining risk communication strategies.

Our data demonstrate the potential of advanced ML-enhanced forecasting tools, such as the bias-corrected GEOS-CF model, to dramatically improve the accuracy of pollutant predictions.[20,21] The present study provides robust evidence that real-time forecasting tools could replace the reliance on the current qualitative approach in predicting future pollutant concentrations. This could not only enhance the precision of air quality assessments but also allow more timely, actionable health messaging, thus addressing a critical limitation of current practices.

Our study has some limitations. The fact that the health outcome data used in the study did not include emergency department visits limited the statistical power of the analysis as there are typically a greater number of emergency department visits when compared with that of hospital admissions. In addition, acknowledging the diverse geographical and meteorological characteristics of the city of Rio de Janeiro, we limited the study area to only a portion of the city, and, thus, this study may not fully reflect health risks associated with air quality in other regions.

The findings of the present study have far-reaching implications for air quality management and public

health communication in LMICs. Traditional single-pollutant air quality indices have long been criticized for their inability to capture the synergistic health effects of multiple pollutants at moderate or low levels.[23-27] This study supports a growing body of evidence advocating for the development and adoption of multi-pollutant, health-based air quality indices tailored to local contexts.[26,28-32] By leveraging the collaborative involvement of local civil servants, this research exemplifies how partnerships between researchers and policymakers can lead to actionable solutions that improve public health outcomes.

As cities worldwide face increasing challenges from air pollution and climate variability, integrating advanced forecasting technologies with health-based indices has the potential to revolutionize air quality management and risk communication strategies. This study serves as a foundational step toward such advances, paving the way for further innovations in air pollution epidemiology and public health interventions.

Effective risk communication for outdoor air pollution requires accurate forecasting of pollutant concentrations and comprehensive consideration of the combined health risks posed by multiple pollutants. This study highlights significant gaps in the current IQAr employed in the city of Rio de Janeiro, including its inability to reflect the health risks associated with individual pollutants, specifically NO_2, while overweighting the impact of O_3, which was not found to be associated with increased respiratory health risks in our study. These limitations hinder the ability of the IQAr to effectively inform timely public health actions.

The results of this study provide a roadmap for specific actions that can be taken to improve risk communication in the city of Rio de Janeiro.[33] First, our findings demonstrate the potential of advanced forecasting tools, such as the bias-corrected GEOS-CF model, to substantially improve the accuracy of pollutant predictions. High-quality forecasts for NO_2 and PM should be immediately prioritized for use in calculating next-day index values for risk communication purposes. In addition, incorporating these tools, alongside the development of a validated, health-based multi-pollutant index, could greatly enhance the reliability of air quality information communicated to the public. There is an urgent need for improved weighting of pollutant values that better reflects the observed respiratory health risks of exposure to NO_2 and PM. Such an advance would not only support better individual decision-making but also contribute to broader efforts to reduce the public health burden of air pollution in the city of Rio de Janeiro and similar urban settings in this and other LMICs.

AUTHOR CONTRIBUTIONS

KC: conceptualization, methodology, supervision, and writing—review and editing. KP: methodology, formal analysis, and writing—original draft. LG: methodology and initial analysis. NL: formal analysis and data curation. GG: initial analysis. LHBS and BBF: data curation. FCM and KEK: writing—review and editing. All authors have read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Cazorla M. Air quality over a populated Andean region: Insights from measurements of ozone, NO, and boundary layer depths. Atmos Pollut Res. 2016;7(1):66-74. https://doi.org/10.1016/j.apr.2015.07.006
2. Gouveia N, Kephart JL, Dronova I, McClure L, Granados JT, Betancourt RM, et al. Ambient fine particulate matter in Latin American cities: Levels, population exposure, and associated urban factors. Sci Total Environ. 2021;772:145035. https://doi.org/10.1016/j.scitotenv.2021.145035
3. Rio Prefeitura. MonitorAR Rio[homepage on the Internet]. Rio de Janeiro: Rio Prefeitura [updated 2024 Jan 26; cited 2025 Apr 1]. Boletim da Qualidade do Ar. Available from: https://jeap.rio.rj.gov.br/je-metinfosmac/boletim?data=1/26/2024
4. Keller CA, Knowland KE, Duncan BN, Liu J, Anderson DC, Das S, et al. Description of the NASA GEOS Composition Forecast Modeling System GEOS-CF v1.0. J Adv Mod Earth Syst. 2021;13(4):e2020MS002413. https://doi.org/10.1029/2020MS002413
5. Duncan BN, Malings CA, Knowland KE, Anderson DC, Prados AI, Keller CA, et al. Augmenting the Standard Operating Procedures of Health and Air Quality Stakeholders With NASA Resources. GeoHealth. 2021;5(9):e2021GH000451. https://doi.org/10.1029/2021GH000451
6. Malings C, Knowland KE, Keller Christoph A, Shah V, Wayman C, Cohn S, et al. Creating and Using Open Global and Local Air Quality Data at NASA GMAO. In: Center NGSF, editor: NASA; Goddard Space Flight Center; 2023.
7. Brasil, Ministério da Saúde. DATASUS [homepage on the Internet]. Brasília: Ministério da Saúde [cited 2025 Apr 1]. Sistema de Informações Hospitalares do SUS (SIH/SUS). Available from: https://datasus.saude.gov.br/acesso-a-informacao/producao-hospitalar-sih-sus/
8. Zhou J, Gladson L, Díaz Suárez V, Cromar K. Respiratory Health Impacts of Outdoor Air Pollution and the Efficacy of Local Risk Communication in Quito, Ecuador. Int J Environ Res Public Health. 2023;20(14):6326. https://doi.org/10.3390/ijerph20146326
9. RStudio Team [homepage on the Internet]. Boston, MA: Rstudio, c2015 [cited 2024 Nov 27]. RStudio: Integrated Development Environment for R. Available from: http://www.rstudio.com/
10. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2024 [updated 2023 Feb 17; cited 2025 Apr 1]. Risk communication of ambient air pollution in the WHO European Region: review of air quality indexes and lessons learned. Available from: https://www.who.int/publications/i/item/WHO-EURO-2023-6885-46651-67825
11. World Health Organization (WHO) [homepage on the Internet]. Geneva: WHO; c2024 [updated 2020 Sep 4; cited 2025 Apr 1]. Personal interventions and risk communication on air pollution. Available from: https://www.who.int/publications/i/item/9789240000278
12. Cromar K, Gladson L, Jaimes Palomera M, Perlmutt L. Development of a Health-Based Index to Identify the Association between Air Pollution and Health Effects in Mexico City. Atmosphere. 2021;12(3):372. https://doi.org/10.3390/atmos12030372
13. WHO Regional Office for Europe. Review of evidence on health aspects of air pollution - REVIHAAP Project: Technical Report. Acknowledgements. Copenhagen: WHO Regional Office for Europe; 2013. Available from: https://www.ncbi.nlm.nih.gov/books/

NBK361806/

14. Alvarez Miño L, Salazar Ceballos A. Respiratory symptoms and lung function in children aged 6-14 years and their relationship with particulate matter PM10 in Santa Marta, Colombia [Article in Spanish]. Rev Esp Salud Publica. 2013;87(3):239-46. https://doi.org/10.4321/S1135-57272013000300003
15. Rodríguez-Villamizar LA, Rojas-Roa NY, Blanco-Becerra LC, Herrera-Galindo VM, Fernández-Niño JA. Short-Term Effects of Air Pollution on Respiratory and Circulatory Morbidity in Colombia 2011-2014: A Multi-City, Time-Series Analysis. Int J Environ Res Public Health. 2018;15(8):1610. https://doi.org/10.3390/ijerph15081610
16. Romieu I, Gouveia N, Cifuentes LA, de Leon AP, Junger W, Vera J, et al. Multicity study of air pollution and mortality in Latin America (the ESCALA study). Res Rep Health Eff Inst. 2012(171):5-86.
17. O'Lenick CR, Chang HH, Kramer MR, Winquist A, Mulholland JA, Friberg MD, et al. Ozone and childhood respiratory disease in three US cities: evaluation of effect measure modification by neighborhood socioeconomic status using a Bayesian hierarchical approach. Environ Health. 2017;16(1):36. https://doi.org/10.1186/s12940-017-0244-2
18. Fraga J, Botelho A, Sá A, Costa M, Quaresma M. The lag structure and the general effect of ozone exposure on pediatric respiratory morbidity. Int J Environ Res Public Health. 2011;8(10):4013-24. https://doi.org/10.3390/ijerph8104013
19. Strosnider HM, Chang HH, Darrow LA, Liu Y, Vaidyanathan A, Strickland MJ. Age-Specific Associations of Ozone and Fine Particulate Matter with Respiratory Emergency Department Visits in the United States. Am J Respir Crit Care Med. 2019;199(7):882-90. https://doi.org/10.1164/rccm.201806-1147OC
20. Bi J, Knowland KE, Keller CA, Liu Y. Combining Machine Learning and Numerical Simulation for High-Resolution PM(2.5) Concentration Forecast. Environ Sci Technol. 2022;56(3):1544-56. https://doi.org/10.1021/acs.est.1c05578
21. Gladson LA, Cromar KR, Ghazipura M, Knowland KE, Keller CA, Duncan B. Communicating respiratory health risk among children using a global air quality index. Environ Int. 2022;159:107023. https://doi.org/10.1016/j.envint.2021.107023
22. Geraldino CGP, Arbilla G, da Silva CM, Corrêa SM, Martins EM. Understanding high tropospheric ozone episodes in Bangu, Rio de Janeiro, Brazil. Environ Monit Assess. 2020;192(3):156. https://doi.org/10.1007/s10661-020-8119-3
23. Perlmutt L, Stieb D, Cromar K. Accuracy of quantification of risk using a single-pollutant Air Quality Index. J Expo Sci Environ Epidemiol. 2017;27(1):24-32. https://doi.org/10.1038/jes.2015.43
24. Sicard P, Lesne O, Alexandre N, Mangin A, Collomp R. Air quality trends and potential health effects - Development of an aggregate risk index. Atmos Environ. 2011;45(5):1145-53. https://doi.org/10.1016/j.atmosenv.2010.12.052
25. Sicard P, Talbot C, Lesne O, Mangin A, Alexandre N, Collomp R. The Aggregate Risk Index: An intuitive tool providing the health risks of air pollution to health care community and public. Atmos Environ. 2012;46:11-6. https://doi.org/10.1016/j.atmosenv.2011.10.048
26. Tan X, Han L, Zhang X, Zhou W, Li W, Qian Y. A review of current air quality indexes and improvements under the multi-contaminant air pollution exposure. J Environ Manage. 2021;279:111681. https://doi.org/10.1016/j.jenvman.2020.111681
27. Pengelly D, Campbell M, Macfarlane R, Li-Muller A. Toronto air quality index health links analysis. Canada: Toronto Public Health, Toronto, ON (Canada); 2001.
28. Stieb DM, Burnett RT, Smith-Doiron M, Brion O, Shin HH, Economou V. A new multipollutant, no-threshold air quality health index based on short-term associations observed in daily time-series analyses. J Air Waste Manag Assoc. 2008;58(3):435-50. https://doi.org/10.3155/1047-3289.58.3.435
29. Maio S, Fasola S, Marcon A, Angino A, Baldacci S, Bilò MB, et al. Relationship of long-term air pollution exposure with asthma and rhinitis in Italy: an innovative multipollutant approach. Environ Res. 2023;224:115455. https://doi.org/10.1016/j.envres.2023.115455
30. Chen MJ, Leon Guo Y, Lin P, Chiang H-C, Chen PC, Chen YC. Air quality health index (AQHI) based on multiple air pollutants and mortality risks in Taiwan: Construction and validation. Environ Res. 2023;231:116214. https://doi.org/10.1016/j.envres.2023.116214
31. Cao R, Wang Y, Huang J, Zeng Q, Pan X, Li G, et al. The construction of the air quality health index (AQHI) and a validity comparison based on three different methods. Environ Res. 2021;197:110987. https://doi.org/10.1016/j.envres.2021.110987
32. Adebayo-Ojo TC, Wichmann J, Arowosegbe OO, Probst-Hensch N, Schindler C, Künzli N. A New Global Air Quality Health Index Based on the WHO Air Quality Guideline Values With Application in Cape Town. Int J Public Health. 2023;68:1606349. https://doi.org/10.3389/ijph.2023.1606349
33. Laumbach RJ, Cromar KR, Adamkiewicz G, Carlsten C, Charpin D, Chan WR, et al. Personal Interventions for Reducing Exposure and Risk for Outdoor Air Pollution: An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc. 2021;18(9):1435-43. https://doi.org/10.1513/AnnalsATS.202104-421ST

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Treatment completion rates and adverse effects of three months of once-weekly isoniazid plus rifapentine for latent tuberculosis infection

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ABSTRACT

Objective: Preventive treatment of active tuberculosis is one of the main strategies for reducing the incidence of tuberculosis. We sought to evaluate the rates of latent tuberculosis infection (LTBI) treatment completion with three months of once-weekly isoniazid plus rifapentine (3HP) and compare them with those for six to nine months of daily isoniazid (6H/9H). **Methods:** This was a retrospective cross-sectional study. Consecutive patients undergoing LTBI treatment with 3HP or 6H/9H were included in the study. Treatment completion rates and adverse effects were analyzed. **Results:** A total of 226 patients were included in the study: 113 in the 3HP group and 113 in the 6H/9H group. The frequency of adverse effects was not significantly different between the 3HP and 6H/9H groups. The 3HP group had a higher treatment completion rate (93.8%) than did the 6H/9H group (84.1%), the difference being significant. **Conclusions:** The rates of LTBI treatment completion appear to be higher with 3HP than with 6H/9H. Health care professionals should be vigilant in managing adverse effects to further maximize LTBI treatment completion.

Keywords: Tuberculosis, pulmonary; Latent tuberculosis/prevention & control; Mycobacterium tuberculosis.

INTRODUCTION

Most people infected with *Mycobacterium tuberculosis* are asymptomatic, a condition known as latent tuberculosis infection (LTBI). According to the WHO, approximately 2-3 billion people worldwide are infected with *M. tuberculosis*, and 5-15% will progress from LTBI to active symptomatic disease during their lifetime. Reactivation of LTBI accounts for a large proportion of the incidence of active tuberculosis, making diagnosis and treatment crucial, especially in high-risk groups.[1,2]

Preventive treatment of active tuberculosis is one of the main strategies for reducing the incidence of tuberculosis. There are several regimens for treating LTBI. However, since 2021, the Brazilian National Ministry of Health has recommended three months of once-weekly isoniazid plus rifapentine (3HP) as the first choice of treatment. There are at least four randomized clinical trials[3-6] demonstrating that the 3HP regimen is as effective as isoniazid monotherapy, with higher treatment completion rates. The 3HP regimen is used once a week for three months, for a total of 12 doses. Its efficacy and toxicity are similar to those of six months of daily isoniazid (6H), the main advantage being reduced treatment time.[7]

Despite the advantages of the 3HP regimen, some patients may experience influenza-like symptoms or hypersensitivity reactions. Although these are less common than symptoms such as pruritus, rash, nausea, and vomiting, they remain a cause for concern among patients and physicians alike regarding the use of the 3HP regimen.[8] One study demonstrated that patients using 3HP are at an increased risk of adverse effects leading to treatment discontinuation.[9] In Brazil, there have been no studies evaluating 3HP treatment completion rates or the profile of adverse events associated with the 3HP regimen. Therefore, the objective of the present study was to evaluate the rates of LTBI treatment completion with 3HP and compare them with those of LTBI treatment completion with 6H or nine months of daily isoniazid (9H).

METHODS

Study design and setting

This was a retrospective cross-sectional study conducted in the city of Alvorada, in southern Brazil. The study was

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approved by the local institutional review board on October 11, 2023 (Protocol no. 6.423.958).

Patients and data collection

Consecutive patients undergoing LTBI treatment with 3HP or 6H/9H were included in the study. We included all of the patients who initiated treatment with the 3HP regimen and the same number of patients initiating treatment with the 6H/9H regimen. The exclusion criterion was having undergone LTBI treatment with four months of rifampin. We collected the following data: demographic data (including age, sex, and race); smoking status; alcohol abuse; drug use; comorbidities; LTBI treatment regimen; adverse effects of LTBI treatment; and treatment outcome (completion or abandonment).

Statistical analysis

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

In order to calculate the sample size, we used treatment completion rates of approximately 90% for the 3HP regimen and 70% for the 6H/9H regimen.[5,10] Thus, considering a 95% confidence interval and a study power of 80%, we calculated a sample size of 54 patients per group.

RESULTS

A total of 226 patients were included in the present study. Of those, 113 were included in the 3HP group and 113 were included in the 6H/9H group. The characteristics of the study population, by treatment regimen, are shown in Table 1. The mean age was 41.2 ± 18.7 years in the 3HP group and 40.3 ± 18.6 years in the 6H/9H group ($p = 0.738$). In the 3HP and 6H/9H groups, 53.1% and 58.4% were male, respectively. Current smoking, alcohol abuse, and drug use were reported in the 6H/9H group only, by 2.7%, 2.7%, and 1.8%, respectively. The prevalence of comorbidities was not significantly different between the 3HP and 6H/9H groups (23.0% vs. 19.5%; $p = 0.626$). HIV infection was present in 7 (6.2%) of the patients in the 3HP group and in 9 (8.0%) of those in the 6H/9H group ($p = 0.795$).

The frequency of adverse effects was not significantly different between the 3HP and 6H/9H groups. However, nausea/vomiting was more common in the 6H/9H group (in 22 [91.7%]) than in the 3HP group (in 16 [55.2%]; $p = 0.009$). In contrast, abdominal pain and headache were more common in the 3HP group than in the 6H/9H group ($p = 0.004$ and $p = 0.003$, respectively). Seven (6.2%) of the patients in the 3HP group and 18 (15.9%) of those in the 6H/9H group defaulted from treatment, the difference being statistically significant ($p = 0.034$). The 3HP group had a higher treatment completion rate (93.8%) than did the 6H/9H group (84.1%).

DISCUSSION

In this cross-sectional study, we found that patients using the 3HP regimen had a higher treatment completion rate (93.8%) than did those using the 6H/9H regimen (84.1%). In addition, nausea/vomiting was more common in the 6H/9H group, whereas abdominal pain and headache were more common in the 3HP group.

Treating LTBI is crucial to prevent it from developing into active tuberculosis, LTBI treatment being an

Table 1. Comparison of patients with latent tuberculosis infection treated with three months of once-weekly isoniazid plus rifapentine or six to nine months of daily isoniazid.[a]

Characteristic	Group		p
	3HP (n = 113)	6H/9H (n = 113)	
Age, years	41.2 ± 18.7	40.3 ± 18.6	0.738
Male	60 (53.1)	66 (58.4)	0.503
White	46 (40.7)	49 (43.4)	0.788
Current smoking	0	3 (2.7)	0.247
Alcohol abuse	0	3 (2.7)	0.247
Drug use	0	2 (1.8)	0.498
Comorbidities	26 (23.0)	22 (19.5)	0.626
HIV infection	7 (6.2)	9 (8.0)	0.795
Adverse effects	29 (25.7)	24 (21.2)	0.530
Nausea/vomiting	16 (55.2)	22 (91.7)	0.009
Abdominal pain	14 (48.3)	2 (8.3)	0.004
Headache	9 (31.0)	0	0.003
Default from treatment	7 (6.2)	18 (15.9)	0.034

3HP: three months of once-weekly isoniazid plus rifapentine; and 6H/9H: six to nine months of daily isoniazid. [a]Data presented as n (%) or mean ± SD.

important component of tuberculosis control and elimination.[11] Until recently, the treatment of choice for LTBI in Brazil was six to nine months of daily isoniazid. Problems such as hepatotoxicity, as well as the long duration of treatment, contribute to low rates of treatment completion with 6H/9H, ranging from 30% to 64%.[5] Thus, shorter treatment regimens for LTBI are very welcome. In this sense, studies[5,6] have shown that the 3HP regimen has a higher treatment completion rate than does the 9H regimen, as well as having similar effectiveness. In an open-label, randomized noninferiority trial, the rates of treatment completion were 82.1% in the 3HP group and 69.0% in the 9H group.[5] In another study, treatment completion was higher with 3HP (89%) than with 9H (64%).[6] In our study, treatment completion rates were higher than the aforementioned rates in both groups, although ours was a pragmatic study without the ideal conditions of a clinical trial.

Nausea and vomiting were more common in the 6H/9H group than in the 3HP group in the present study. It is well known that gastrointestinal effects constitute the most common group of reactions and can be attributed to any drug. A major concern with isoniazid is the possibility of hepatitis. During treatment, as many as 10% to 20% of patients treated with isoniazid have mild, asymptomatic elevations in liver enzymes, but hepatitis is rare. Nausea and vomiting are also symptoms of hepatitis, in addition to fatigue, poor appetite, jaundice, and abdominal pain.[12] In our study, we did not have any cases of hepatitis.

Abdominal pain and headache were more common among patients in the 3HP group than among those in the 6H/9H group. As mentioned above, abdominal pain is part of the set of gastrointestinal symptoms that are the most common group of symptoms and are related to several drugs. Headache is also a common side effect, being usually mild and transient, and most patients are able to complete treatment without interruption. In a study analyzing data on symptoms in 1,002 participants receiving 3HP, the most common symptom was headache (in 29.4%).[13]

Our study has some limitations. First, we recruited patients from a single setting; however, we do not think that this is a limitation for generalizing the results. Second, the study was retrospective, being based on patient medical records, which may compromise the completeness of the data. Finally, adverse effects were not graded, because they were collected in the context of clinical practice rather than for a clinical trial. Despite these concerns, this was the first study in Brazil to evaluate the use of the 3HP regimen in pragmatic conditions.

In conclusion, the rates of LTBI treatment completion with 3HP are higher than those with 6H/9H. Health care professionals should be vigilant in managing adverse effects to further maximize LTBI treatment completion.

AUTHOR CONTRIBUTIONS

THM: conceptualization; methodology; investigation; data curation; project administration; and writing—original draft. GRP, AKS, RSLB, MSS, GSR, APM, and RUBN: conceptualization; methodology; investigation; and writing—review and editing. DRS: conceptualization; methodology; investigation; data curation; project administration; supervision; and writing—original draft. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, et al. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis? A TBNET consensus statement. Eur Respir J. 2009;33(5):956-73. https://doi.org/10.1183/09031936.00120908
2. World Health Organization [homepage on the Internet]. Geneva: WHO; c2022. Global Tuberculosis Report 2022. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022
3. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, et al. Treatment for preventing tuberculosis in children and adolescents: A randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and Isoniazid. JAMA Pediatr. 2015;169(3):247-55. https://doi.org/10.1001/jamapediatrics.2014.3158
4. Martinson NA, Barnes GL, Moulton LH, Msandiwa R, Hausler H, Ram M, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med. 2011;365(1):11-20. https://doi.org/10.1056/NEJMoa1005136
5. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011;365(23):2155-66. https://doi.org/10.1056/NEJMoa1104875
6. Sterling TR, Scott NA, Miro JM, Calvet G, La Rosa A, Infante R, et al. Three months of weekly rifapentine and isoniazid for treatment of Mycobacterium tuberculosis infection in HIV-coinfected persons. AIDS. 2016;30(10):1607-15. https://doi.org/10.1097/QAD.0000000000001098
7. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 1, Prevention : tuberculosis preventive treatment; 2020. 41p.
8. Sadowski C, Belknap R, Holland DP, Moro RN, Chen MP, Wright A, et al. Symptoms and Systemic Drug Reactions in Persons Receiving Weekly Rifapentine Plus Isoniazid (3HP) Treatment for Latent Tuberculosis Infection. Clin Infect Dis. 2023;30329:1-8. https://doi.org/10.1093/cid/ciad083
9. Winters N, Belknap R, Benedetti A, Borisov A, Campbell JR, Chaisson RE, et al. Completion, safety, and efficacy of tuberculosis preventive treatment regimens containing rifampicin or rifapentine: an individual patient data network meta-analysis. Lancet Respir Med. 2023:11(9):782-790. https://doi.org/10.1016/S2213-2600(23)00096-6
10. Chen YM, Liao TL, Chen HH, Chen DY. Three months of once-weekly isoniazid plus rifapentine (3HP) in treating latent tuberculosis infection is feasible in patients with rheumatoid arthritis. Ann Rheum Dis. 2018;77(11):1688-9. https://doi.org/10.1136/annrheumdis-2018-213097
11. World Health Organization [homepage on the Internet]. Geneva: World Health Organization. Guidelines on the management of latent tuberculosis infection 2015. Available from: https://www.who.int/publications/i/item/9789241548908
12. Centers for Disease Control and Prevention (CDC) [homepage on the Internet]. Atlanta: CDC; c2025. Adverse Reactions to LTBI Treatment. Available from: https://www.cdc.gov/tb/webcourses/TB101/page16747.html
13. Sadowski C, Belknap R, Holland DP, Moro RN, Chen MP, Wright A, et al. Symptoms and Systemic Drug Reactions in Persons Receiving Weekly Rifapentine Plus Isoniazid (3HP) Treatment for Latent Tuberculosis Infection. Clin Infect Dis. 2023;76(12):2090-7. https://doi.org/10.1093/cid/ciad083

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ORIGINAL ARTICLE

Impact of new regimens and drugs on rifampin-resistant tuberculosis management in Mexico

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Study carried out at the *Instituto Nacional de Enfermedades Respiratorias* (INER), Mexico City, and at the *Hospital General de Tijuana*, Tijuana, Mexico.

ABSTRACT

Objective: To compare the former tuberculosis treatment regimen including one fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin) and a second-line injectable drug (amikacin, kanamycin, or capreomycin) plus three to five oral drugs (regimen 1) with the current regimen including the three WHO group A drugs (regimen 2) in terms of efficacy and safety at two tuberculosis referral centers in Mexico. **Methods:** This was a retrospective study based on a review of the clinical records of all consecutive rifampin-resistant or multidrug-resistant tuberculosis (RR/MDR-TB) patients treated from January of 2010 to October of 2023. Patients included were microbiologically confirmed cases of RR/MDR-TB with pulmonary involvement and who received at least 30 days of regimen 1 or regimen 2. Outcomes and adverse events were classified in accordance with WHO definitions. **Results:** One hundred and twenty-six RR/MDR-TB patients met the inclusion criteria. Of those, 87 were treated with regimen 1 and 39 received regimen 2. Success rates were not significantly different between the two groups of patients, although those treated with the oral regimen including bedaquiline from regimen 2 had higher success rates. Regimen 2 patients experienced a shorter time to culture conversion, and the regimen length was shortened accordingly, the median duration being 16.1 months [IQR, 15-17.3 months]. In patients receiving the all-oral regimen 2, adverse events were significantly associated with a history of type 2 diabetes mellitus (OR = 15.4; 95% CI, 2.73-87.29; p = 0.002) and were mainly related to linezolid use. **Conclusions:** Oral regimens appear to be effective, although toxicity to linezolid requires strict patient monitoring.

Keywords: Mexico; Tuberculosis, multidrug-resistant; Bedaquiline; Linezolid; Treatment outcome.

INTRODUCTION

Drug-resistant tuberculosis remains a public health concern, particularly in Mexico, where the number of cases of rifampin-resistant or multidrug-resistant tuberculosis (RR/MDR-TB) in 2023 was estimated at 1,300 (range, 0-2,700), although only 444 were reported.[1] During the last decade, significant progress has been achieved on tuberculosis diagnosis and treatment.[2-4] Since 2019 (after the release of the STREAM (*Standardized Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB*) stage 1 study results, the WHO has recommended the use of a shorter (nine-month) regimen for the treatment of selected cases of RR/MDR-TB.[2-4] Nevertheless, the availability of new oral drugs (e.g., bedaquiline) and repurposed drugs (e.g., fluoroquinolones, linezolid, and clofazimine) allowed the WHO to develop a new classification of antituberculosis drugs (groups A, B, and C) on the basis of their effectiveness and safety.[3,5] The WHO approval of the all-oral six-month combinations of bedaquiline, pretomanid, and linezolid, with or without moxifloxacin, i.e., the BPaL/BPaLM regimens,[6] opened new perspectives in the treatment of RR/MDR-TB. However, not all national tuberculosis programs, including the Mexican National Tuberculosis Program, have been able to implement the BPaL/BPaLM regimens (Table 1).

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Before the WHO reclassification of drugs, the standard regimen for RR/MDR-TB cases included one fluoroquinolone and a second-line injectable drug. After the reclassification, the longer regimen including the three group A drugs (levofloxacin or moxifloxacin, bedaquiline, and linezolid) and one group B drug (clofazimine and/or cycloserine)[7] became the standard treatment for RR/MDR-TB cases in Mexico (Table 1). The WHO shorter regimens (of 9-11 months) initially including the use of an injectable drug (and later bedaquiline) were used in very few selected cases for different reasons, including the drug resistance profile of RR/MDR-TB patients in Mexico[8] and the concern raised by the high number of drugs in these regimens, as well as their toxicity and potential impact on treatment adherence.

Given the rapid evolution of regimens and the different approaches followed by countries to adopt the WHO recommendations, in-depth analyses of the effectiveness and safety of the longer all-oral regimens at the programmatic level are scanty.[9]

The objective of the present study was to compare the former regimen including one fluoroquinolone and a second-line injectable drug (regimen 1) with the current regimen including the three group A drugs (regimen 2) in terms of efficacy and safety at two tuberculosis referral centers in Mexico.

METHODS

Study design

This was a retrospective study based on a review of the clinical records of all consecutive RR/MDR-TB patients treated between January of 2010 and October of 2023 at either of two tuberculosis referral centers in Mexico, namely, the *Instituto Nacional de Enfermedades Respiratorias* (INER), located in Mexico City, and the *Hospital General de Tijuana*, located in

Table 1. Comparison of sociodemographic and clinical characteristics of tuberculosis patients enrolled to receive treatment regimen 1 or 2.[a]

Variable	Regimen 1 (n = 87)	Regimen 2 (n = 39)	p
Male	59 (67.8%)	22 (56.4%)	0.217
Age, years	42 [33-55]	37 [28-50]	0.3924
Type 2 diabetes mellitus	43 (49.4%)	14 (35.9%)	0.158
Disease duration	10 [7-14]	9.5 [6.5-19]	0.8284
Glucose at diagnosis, mg/dL[b]	178 [134-252]	186 [142-242]	0.9883
Glycated hemoglobin at diagnosis, %[c]	9.3 [7.9-10.9]	9.4 [7.2-9.9]	0.3819
HIV infection	3/86 (3.5%)	7 (18%)	0.006
CD4 count at diagnosis, cells/mm^3	88 [21-316]	62.5 [30-111]	0.7963
Malnutrition (BMI < 18.5 kg/m^2)	26/85 (30.6%)	9 (23.1%)	0.388
BMI, kg/m^2	20.9 [18.2-24.7]	22 [19.6-24]	0.6551
Hypertension	13/86 (15.1%)	6 (15.4%)	0.969
Chronic kidney disease	11/85 (13%)	2 (5.1%)	0.187
Smoking history	7/28 (25%)	9 (23.1%)	0.856
History of drug abuse	8 (9.2%)	5 (12.8%)	0.536
Previous tuberculosis treatment	76 (87.3%)	21 (53.8%)	0.000
Weight, kg	55 [48-66]	56 [49.5-62.5]	0.6933
Hemoglobin, g/dL[d]	12.4 [10.8-14.1]	11.4 [10.5-13]	0.0945
Lymphocyte count, cells/µL	1.4 [1.3-2]	1.7 [0.9-2.1]	0.9470
Albumin, g/dL[d]	3.3 [2.9-3.7]	3.2 [2.9-3.6]	0.6541
Smear positive at diagnosis	73/86 (84.9%)	23/36 (63.9%)	0.010
Culture positive at diagnosis	85/86 (98.8%)	32 (82%)	0.001
RR[e]	7	12	
MDR	75	26	
Pre-XDR[f]	5	1	
Chest X-ray	86/87[g]	39	0.018
Non cavities	15 (17.4%)	16 (41%)	
Unilateral cavities	38 (44.2%)	13 (33.3%)	
Bilateral cavities	33 (38.4%)	10 (25.6%)	
Cavitary disease	71/86 (82.6%)	23 (59%)	0.005

RR: rifampin resistant; MDR: multidrug resistant (i.e., resistant to rifampin and isoniazid); and pre-XDR: pre-extensively drug resistant (i.e., MDR plus additional resistance to a fluoroquinolone). [a]Data presented as n, n (%), or median [IQR]. [b]Data available for 48 patients. [c]Data available for 49 patients. [d]Data available for 97 patients. [e]5 patients with additional resistance to pyrazinamide (1 receiving regimen 1 and 4 receiving regimen 2). [f]For regimen 1, 4 patients were resistant to ofloxacin and 1 patient was resistant to ofloxacin and moxifloxacin. For regimen 2, 1 patient was resistant to levofloxacin. [g]Two patients had pleural involvement: 1 receiving regimen 1 and 1 receiving regimen 2.

the city of Tijuana. The study was approved by the local research ethics committees. The requirement for informed consent was waived because of the retrospective nature of the study.

Diagnosis

The nationwide programmatic treatment of drug-resistant tuberculosis in Mexico started in 2010, when all presumptive drug-resistant patients were referred to tuberculosis referral centers, such as the INER and the *Hospital General de Tijuana*. Before the introduction of GeneXpert MTB/RIF in 2016, all cases were diagnosed by culture and phenotypic drug susceptibility tests, which were carried out in national referral laboratories. All laboratory procedures were (and still are) conducted in accordance with international guidelines, and drug susceptibility testing is performed using the critical concentrations suggested by the WHO.[10,11]

Treatment

Second-line drugs in Mexico are provided by the Mexican National Tuberculosis Program, all cases being treated in accordance with WHO guidelines and drug susceptibility test results. Before the latest classification of antituberculosis drugs, RR/MDR-TB cases were treated with a regimen of five or six drugs (regimen 1), including one fluoroquinolone (ofloxacin, levofloxacin, or moxifloxacin), one second-line injectable drug (amikacin, kanamycin, or capreomycin), and two or three oral agents (including prothionamide, cycloserine, and para-aminosalicylic acid), with systematic addition of ethambutol and pyrazinamide, the duration of regimen 1 ranging from 18 to 20 months as per the WHO recommendations.[12] Bedaquiline, introduced in Mexico in 2017, has been used nationwide by the Mexican National Tuberculosis Program since 2019. Since then, RR/MDR-TB cases have been treated at referral centers with three group A drugs—levofloxacin/moxifloxacin, bedaquiline, and linezolid—and one or two group B drugs—clofazimine or cycloserine—i.e., regimen 2 (Table 1). The use of clofazimine vs. cycloserine depends on whether there is central nervous system involvement, given that cycloserine has better cerebrospinal fluid penetration.[13] The duration of regimen 2 was initially 18 months as per the WHO recommendations; however, after careful programmatic evaluation, it was reduced to a minimum of 15 months.[3,6] Patients receiving either regimen underwent directly observed treatment.

Treatment monitoring

Patients underwent monthly follow-up visits during the intensive phase and every two months during the treatment maintenance phase. At each visit, blood tests were requested in order to assess adverse events. Since the addition of bedaquiline, a 12-lead electrocardiogram is also performed, and a sputum sample for culture is obtained in order to monitor treatment response.

Study population

All consecutive microbiologically confirmed RR/MDR-TB cases treated for at least 30 days with regimen 1 or regimen 2 were included. All selected cases had pulmonary involvement.

Statistical analysis

Regimen 1 and regimen 2 were compared in terms of efficacy and safety. The WHO definitions for treatment outcomes and adverse events were used. A bivariate analysis of variables (either categorical or numerical depending on their distribution) was conducted. Variables significantly associated with a successful outcome were considered for a multivariate logistic regression analysis including age, sex, HIV status, and type 2 diabetes mellitus (T2DM).

All analyses were performed with the Stata statistical software package, version 13.0 (StataCorp LP, College Station, TX, USA).

RESULTS

Between 2010 and 2023, a total of 126 patients (101 patients at the INER and 25 at the *Hospital General de Tijuana*) met the inclusion criteria. Of those, 117 (92.8%) were culture positive at diagnosis, the remaining being diagnosed on the basis of a positive GeneXpert MTB/RIF test result for rifampin resistance. A total of 96 patients (76.2%) underwent drug susceptibility testing for fluoroquinolones. One hundred and twenty (95.2%) had RR/MDR-TB, with 6 (4.8%) showing additional resistance to a fluoroquinolone (Table 1).

Thirty-nine patients received regimen 2, including bedaquiline and another two group A drugs (Table 2). Clofazimine was included in 37/39 (95%) cases, with 6 patients receiving additional cycloserine because of central nervous system involvement, all of them being coinfected with HIV.

Regimens 1 and 2 were comparable for the variables reported in Table 1, the exception being that more patients receiving regimen 1 reported a history of previous tuberculosis treatment (primary regimen) and more patients receiving regimen 2 were living with HIV. Therefore, cavitary disease was more common in those patients (82.6% vs. 59%; p = 0.005), as were the related parameters (culture and sputum smear positivity).

The prevalence of T2DM was high among drug-resistant cases[13] in the sample as a whole, being = 57 (45.2%), with a median duration of 10 years [IQR, 7-15 years], although no difference was found between patients receiving regimen 1 and those receiving regimen 2 (Table 1).

Success rates were not significantly different between the two groups of patients (p = 0.246); however, cases treated with the oral regimen including bedaquiline (regimen 2) had higher success rates (Table 3). Regimen 2 patients experienced a

Table 2. Former tuberculosis treatment regimen (regimen 1) and the regimen that is currently used in Mexico (regimen 2): drugs and doses.

Variable	REGIMEN 1	REGIMEN 2
Fluoroquinolones		
Ofloxacin	600-800 mg	
Levofloxacin	750-1,000 mg	750-1,000 mg
Moxifloxacin	400-800 mg	400-800 mg
Second-line injectable drugs		
Amikacin	15-20 mg/kg	----------
Kanamycin	15-20 mg/kg	----------
Capreomycin	15-20 mg/kg	----------
Prothionamide	15-20 mg/kg	----------
Cycloserine	10-15 mg/kg	10-15 mg/kg*
Ethambutol	15-25 mg/kg	
Pyrazinamide	25-35 mg/kg	
Bedaquiline	----------	400 mg × 2 weeks 200 mg/3 times per week for 22 weeks
Linezolid		600 mg/day
Clofazimine		100 mg/day
Intensive phase of treatment	6-8 months	24 weeks
Treatment duration	18-20 months	15-18 months

*Used in 6 patients in the present study, all of whom had central nervous system involvement.

Table 3. Regimen 1 and 2 outcomes (bivariate analysis).[a]

	Regimen 1 (n = 87)	Regimen 2 (n = 39)	p
Positive outcome	63 (72.4%)	32 (82%)	0.246
Cure	59	29	
Treatment completion	4	3	
Negative outcome	24 (27.6%)	7 (18%)	0.183
Loss to follow-up	12	3	
Failure	4	1	
Death	8	3	
Intensive phase, months	7.0 [5.9-7.7][b]	5.5 [5.2-5.5][c]	0.0000
Time to culture negative status, months	2.2 [1.2-2.7]	1.7 [1.0-2.1]	0.0221

[a]Data presented as n, n (%), or median [IQR]. [b]Data available for 66 patients. [c]Data available for 16 patients.

shorter time to culture conversion in comparison with regimen 1 patients (1.7 [1.0-2.1] vs. 2.2 [1.2-2.7] months; hazard ratio = 1.75; 95% CI, 1.08-2.83; p = 0.022). Although a history of T2DM was initially associated with a longer time to culture conversion, in the proportional hazards model, after adjustment for cavitary disease, T2DM, and HIV infection, the strength of the association increased (adjusted hazard ratio = 1.81; 95% CI, 1.11-2.95; p = 0.016; Table 4), and the presence of cavitary disease was associated with a longer time to culture conversion (adjusted hazard ratio = 0.57; 95% CI, 0.34-0.96; p = 0.036; Table 4).

Given that the patients who received the oral regimen had a faster sputum culture conversion (Figure 1), the length of the regimen was shortened on the basis of medical evaluation, the mean duration being 16.1 months [IQR, 15-17.3 months].

As can be seen in Table 3, a higher number of patients receiving regimen 1 experienced a negative outcome: loss to follow-up (12 vs. 3); treatment failure (4 vs. 1); or death (8 vs. 3). However, none of these outcomes was statistically significant between the two groups of patients.

The median time elapsed between treatment initiation and loss to follow-up was 4.9 months [IQR, 2.1-6.6 months] for regimen 1 and 5.0 months [IQR, 3.4-6.4 months] for regimen 2. Two patients who had been lost to follow-up were later evaluated and remained bacteriologically negative.

Adverse events are reported in Table 5, by regimen and type. Adverse events were the main reason why patients receiving regimen 1 decided to stop their treatment, whereas, among those receiving regimen 2, one could not be followed because of the COVID-19 pandemic; one had to move to another state; and one had gastrointestinal adverse events only.

Patients treated with regimen 1 reported adverse events mainly related to the use of second-line injectable drugs: nephrotoxicity (an increase in serum creatinine ≥ 0.3 mg/dL) and ototoxicity (Table 5). Although a greater number of patients receiving

Table 4. Hazard ratios for univariate and multivariate analyses.

	HR	95% CI	p	aHR*	95% CI
Sex	0.78	0.52-1.17	0.236	------	--------
T2DM	0.93	0.63-1.37	0.699	------	---------
HIV infection	0.62	0.22-1.71	0.355	------	---------
Cavitary disease	0.64	0.39-1.03	0.068	0.57	0.34-0.96
Regimen	1.75	1.08-2.83	0.022	1.81	1.11-2.95

T2DM: type 2 diabetes mellitus; HR: hazard ratio; and aHR: adjusted HR. *The adjusted model included a history of T2DM, HIV infection, and presence or absence of cavitary disease.

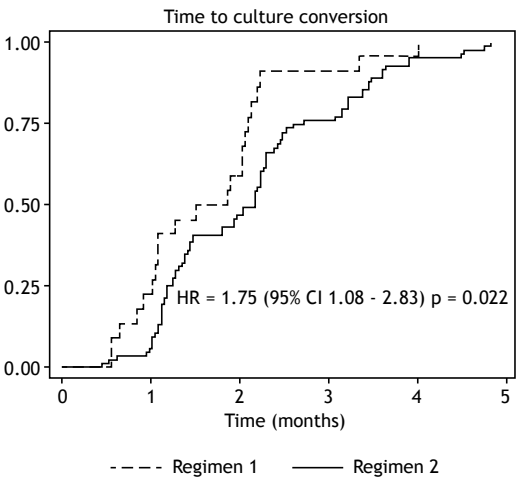

Figure 1. Time to culture conversion in tuberculosis patients treated with regimen 1 or 2. HR: hazard ratio.

regimen 2 developed hepatotoxicity [in 4 (10.3%)], there was no need to stop or modify the regimen.

Among the patients treated with the oral regimen, most of the adverse events were related to linezolid, including neuropathy (clinically assessed) and myelotoxicity, the median time to an adverse event being 5.2 months [IQR, 4.1-8.75 months]. Only 5 patients had to stop the drug even when the linezolid dose was reduced to 300 mg.

Among the patients treated with regimen 2, 6 (15.4%) experienced Fridericia-corrected QT interval prolongation ≥ 500 ms, the median time to this adverse event being 1.05 months [IQR, 1.05-2.7 months]. Bedaquiline had to be removed from the regimen in one case only; in another, the drug was reintroduced at a daily dose of 100 mg.

Skin hyperpigmentation related to the use of clofazimine (regimen 2) was generally mild, being severe in 11 cases (28.2%); however, no patient reported this complaint.

Patients treated with regimen 1 also experienced cutaneous adverse events (6.9%), mostly rash with or without pruritus (easily managed with ancillary medications), although one patient experienced drug rash with eosinophilia and systemic symptoms syndrome caused by levofloxacin.

Adverse events related to second-line antituberculosis treatment were more common among T2DM patients receiving regimen 1 or regimen 2[14] (Table 2). Among the patients treated with regimen 2, a history of T2DM was significantly associated with an increased risk of developing adverse events (neuropathy, myelotoxicity, hepatotoxicity, or QT prolongation; OR = 15.4; 95% CI, 2.73-87.29; p = 0.002). Notably, linezolid-associated neuropathy was more common among T2DM patients (3 vs. 9; p = 0.001). In a multivariate analysis adjusted for sex, age, and T2DM, the development of neuropathy remained associated with a history of T2DM (adjusted OR = 10.67; 95% CI, 1.72-62; p = 0.011). Among the patients receiving regimen 2, we found no difference in time to culture conversion between those with and those without T2DM.[15]

No relapses were reported by patients receiving regimen 1, whereas, among those receiving regimen 2, relapse could only be evaluated at one year, with 30/39 (77%) patients completing their treatment successfully.

DISCUSSION

The objective of the present study was to compare the former regimen including one fluoroquinolone and a second-line injectable drug (regimen 1) with the current regimen including the three group A drugs (regimen 2) in terms of efficacy and safety at two tuberculosis referral centers in Mexico.

Several systematic reviews and meta-analyses have demonstrated the efficacy and safety of the addition of bedaquiline to tuberculosis treatment regimens, highlighting how the inclusion of this drug instead of second-line injectable drugs has enabled the development of fully oral and effective second-line regimens.

The results of our study are different from those of a previous retrospective study conducted in Brazil,[16] where a bedaquiline-containing regimen (similar to regimen 2 in our study but using terizidone instead of clofazimine) was associated with positive outcomes but no shorter time to culture conversion. In our study, despite a smaller sample size and a higher number of patients with T2DM, we observed similar success rates (and proportions of negative outcomes) between the two groups of patients. Notably, patients treated with an all-oral regimen including bedaquiline (regimen 2) had a shorter (nearly 50% shorter) time to culture conversion, thus potentially reducing tuberculosis transmission and treatment duration.

Table 5. Adverse events observed in tuberculosis patients enrolled to receive treatment regimen 1 or 2.[a]

	Regimen 1 (n = 87)	Regimen 2 (n = 39)	p
Hepatotoxicity	2 (2.3%)	4 (10.2%)	0.052
Nephrotoxicity	36 (41.4%)	2 (5.1%)	0.000
Ototoxicity	25 (28.7%)	0	0.000
Hypothyroidism	21 (24.1%)	0	0.001
Psychiatric disorder	14 (16.1%)	1 (2.5%)	0.029
Neuropathy	1 (1.1%)	12 (31%)	0.000
Myelotoxicity	0	4 (10.2%)	0.003
Skin reaction	6 (6.9%)	11 (28.2%)	0.001
QT prolongation	Not evaluated[b]	6 (15.4%)	(*not done*)

[a]Data presented as n (%). [b]Before the introduction of the new drugs, patients were never evaluated for QT prolongation.

Patients receiving either regimen 1 or 2 in the present study were similar for the main variables, with two notable exceptions. Regimen 1 patients more often had a history of previous tuberculosis treatment (81.6% vs. 62%; p = 0.015), probably due to the introduction of GeneXpert MTB/RIF in Mexico as an initial diagnostic tool in 2016, and were less likely to be living with HIV (3.4% vs. 16.6%; p = 0.006).

T2DM is frequently associated with drug-susceptible and drug-resistant tuberculosis in Latin America, especially in Mexico.[14] In our cohort, the prevalence of T2DM was high (44.6%) in comparison with that reported in other studies conducted in Latin America.[16] Although T2DM has a negative effect on MDR-TB outcomes,[17] we found no difference in outcomes between patients with or without T2DM, probably because of the effective management of T2DM at the two tuberculosis referral centers. However, a comprehensive evaluation of the two regimens must consider safety and tolerability. As previously described, patients receiving regimen 1 were mainly affected by nephrotoxicity, ototoxicity (related to second-line injectables drugs) and psychiatric disorders, all of which are commonly observed in T2DM patients.

Patients who received regimen 2 in the present study were mostly affected by linezolid-related toxicity (neuropathy and myelotoxicity). Of all WHO group A drugs, linezolid is considered the most toxic, being responsible for major adverse events such as neuropathy (in 31% of patients), whereas myelotoxicity had a lower impact (9.5%). Tolerance to prolonged use of linezolid has been a significant limitation of new treatment regimens. The 600 mg/day dose used in our group of patients appeared to be the best tolerated, with fewer serious adverse events.[18,19] In fact, linezolid is the drug for which therapeutic drug monitoring is strongly recommended[20]; unfortunately, it is not yet accessible globally, particularly in low- and middle-income countries, where the prevalence of drug-resistant tuberculosis remains elevated.[21] In absence of therapeutic drug monitoring, close clinical follow-up is essential to identify early linezolid-related adverse events.[22]

Tolerance to linezolid is of paramount importance when using shortened regimens (including BPaL/BPaLM) to prevent frequent changes in the regimen. In the present study, the median time to a linezolid-related adverse event was five months; this means that linezolid was used at the full dose for a sufficient duration to ensure a good bactericidal activity, being then either reduced or removed from the regimen. In addition to the dose of linezolid, patient-specific variables such as preexisting comorbidities (e.g., T2DM) play a role in the development of neuropathy.[23]

When discussing the adverse events of fluoroquinolones, we must consider QT prolongation. This adverse event was not considered significant until the introduction of new and repurposed drugs such as bedaquiline, clofazimine, and delamanid. Among fluoroquinolones, moxifloxacin carries the greatest risk of QT prolongation and therefore a higher risk of serious ventricular arrhythmia[24]; this is the main reason why levofloxacin was preferred over moxifloxacin in regimen 2 (37 vs. 2 patients). QT prolongation (> 500 ms) has been reported in approximately 10% of cases of patients receiving bedaquiline-based regimens[25-27]; in our study, the prevalence of this adverse event was mildly higher (14.3%). Bedaquiline is considered safe; in one case only was the drug removed from the regimen, whereas, in another, it was reintroduced at a daily dose of 100 mg.

Within regimen 2, clofazimine has been reported to cause skin hyperpigmentation in approximately 50% of cases.[28] In our study, severe hyperpigmentation was observed in only 11 cases (28.2%), although, interestingly, no patient complained about this adverse event.

The similarities and equal distribution of features potentially hampering treatment outcomes between the two groups (history of previous tuberculosis treatment and HIV coinfection) can be considered a strength, as can the programmatic perspective from two of the main referral centers in a priority country such as Mexico. We were able to evaluate the adverse events of the main drugs from a real-life perspective in Mexico. However, although the information collected was detailed, the retrospective nature of the study is a limitation, as is the lower sample size for regimen 2. Furthermore, despite the efforts of the staff of the

two referral centers, relapse could not be assessed in all patients.

The use of new and repurposed drugs enabled a shift to an oral and effective regimen in Mexico, although toxicity to linezolid requires strict patient monitoring. Recently, the WHO introduced an all-oral nine-month regimen including bedaquiline, linezolid, levofloxacin, clofazimine, and pyrazinamide to treat patients with levofloxacin-sensitive RR/MDR-TB strains.[29,30] This drug regimen of four or five drugs is similar in Mexico, although without pyrazinamide; it appears to be highly bactericidal (given that most cases tested negative by the first month), offering a safer and effective treatment option without adding additional toxicity related to pyrazinamide. Consequently, extending the regimen to 18-20 months is generally unnecessary. Further studies are required to confirm these findings.

In summary, oral regimens appear to be effective, although toxicity to linezolid requires strict patient monitoring.

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AUTHOR CONTRIBUTIONS

MMT had full access to all of the study data and takes responsibility for the integrity of the data, as well as for the accuracy of the data analysis. RLL, JRS, EBV, WCC, FLLL, LAN, RRG, MSP, NS, JCM, LDA, RC, JAC, and GBM contributed to the study design; the analysis and interpretation of data; the writing of the manuscript; and the critical review of the manuscript. All of the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. World Health Organization. Global tuberculosis report 2024. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.
2. Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med. 2019;380(13):1201-1213. https://doi.org/10.1056/NEJMoa1811867
3. World Health Organization. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
4. Pontali E, Raviglione M. Updated treatment guidelines for drug-resistant TB: how safe are clofazimine-based regimens? IJTLD Open. 2024;1(11):486-489. https://doi.org/10.5588/ijtldopen.24.0490
5. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment-2017; Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821-834. https://doi.org/10.1016/S0140-6736(18)31644-1
6. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.
7. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
8. Munoz-Torrico M, Salazar MA, Millán MJM, Martínez Orozco JA, Narvaez Diaz LA, Segura Del Pilar M, et al. Eligibility for the shorter regimen for multidrug-resistant tuberculosis in Mexico. Eur Respir J. 2018;51(3):1702267. https://doi.org/10.1183/13993003.02267-2017
9. Korotych O, Achar J, Gurbanova E, Hovhannesyan A, Lomtadze N, Ciobanu A, et al. Effectiveness and safety of modified fully oral 9-month treatment regimens for rifampicin-resistant tuberculosis: a prospective cohort study. Lancet Infect Dis. 2024;24(10):1151-1161. https://doi.org/10.1016/S1473-3099(24)00228-7
10. World Health Organization. Technical Report on critical concentrations for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.
11. World Health Organization. Technical report on critical concentrations for drug susceptibility testing of isoniazid and the rifamycins (rifampicin, rifabutin and rifapentine). Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
12. World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis, 2016 Update. Geneva: World Health Organization; 2016. WHO/HTM/TB/2016.04
13. Davis A, Meintjes G, Wilkinson RJ. Treatment of Tuberculous Meningitis and Its Complications in Adults. Curr Treat Options Neurol. 2018 Feb 28;20(3):5. https://doi.org/10.1007/s11940-018-0490-9
14. Muñoz-Torrico M, Caminero-Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Diabetes is Associated with Severe Adverse Events in Multidrug-Resistant Tuberculosis. Arch Bronconeumol. 2017;53(5):245-250. https://doi.org/10.1016/j.arbres.2016.10.021
15. Muñoz-Torrico M, Caminero Luna J, Migliori GB, D'Ambrosio L, Carrillo-Alduenda JL, Villareal-Velarde H, et al. Comparison of bacteriological conversion and treatment outcomes among MDR-TB patients with and without diabetes in Mexico: Preliminary data. Rev Port Pneumol (2006). 2017;23(1):27-30. https://doi.org/10.1016/j.rppnen.2016.11.009
16. Santos AP, Benace CJ Jr, de Medeiros Leung JA, Kritski AL, de Queiroz Mello FC. Bedaquiline versus injectable containing regimens for rifampicin-resistant and multidrug-resistant tuberculosis in a reference center in Brazil - a real-world evidence study using a retrospective design. BMC Infect Dis. 2024;24(1):1112. https://doi.org/10.1186/s12879-024-09993-8
17. Xu G, Hu X, Lian Y, Li X. Diabetes mellitus affects the treatment outcomes of drug-resistant tuberculosis: a systematic review and meta-analysis. BMC Infect Dis. 2023;23(1):813. https://doi.org/10.1186/s12879-023-08765-0
18. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline-Pretomanid-Linezolid Regimens for Drug-Resistant Tuberculosis. N Engl J Med. 2022;387(9):810-823. https://doi.org/10.1056/NEJMoa2119430
19. Hasan T, Medcalf E, Nyang'wa BT, Egizi E, Berry C, Dodd M, et al. The Safety and Tolerability of Linezolid in Novel Short-Course Regimens Containing Bedaquiline, Pretomanid, and Linezolid to Treat Rifampicin-Resistant Tuberculosis: An Individual Patient Data Meta-analysis. Clin Infect Dis. 2024;78(3):730-741. https://doi.org/10.1093/cid/ciad653
20. Rao GG, Konicki R, Cattaneo D, Alffenaar JW, Marriott DJE, Neely M; IATDMCT Antimicrobial Scientific Committee. Therapeutic Drug Monitoring Can Improve Linezolid Dosing Regimens in Current Clinical Practice: A Review of Linezolid Pharmacokinetics and Pharmacodynamics. Ther Drug Monit. 2020;42(1):83-92. https://doi.org/10.1097/FTD.0000000000000710
21. Margineanu I, Akkerman O, Cattaneo D, Goletti D, Marriott DJE, Migliori GB, et al. Practices of therapeutic drug monitoring in tuberculosis: an international survey. Eur Respir J. 2022;59(4):2102787. https://doi.org/10.1183/13993003.02787-2021
22. World Health Organization. WHO operational handbook on

tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

23. Song T, Lee M, Jeon HS, Park Y, Dodd LE, Dartois V, et al. Linezolid Trough Concentrations Correlate with Mitochondrial Toxicity-Related Adverse Events in the Treatment of Chronic Extensively Drug-Resistant Tuberculosis. EBioMedicine. 2015;2(11):1627-33. https://doi.org/10.1016/j.ebiom.2015.09.051
24. Cho Y, Park HS. Association of oral ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin with the risk of serious ventricular arrhythmia: a nationwide cohort study in Korea. BMJ Open. 2018 28;8(9):e020974. https://doi.org/10.1136/bmjopen-2017-020974
25. Hatami H, Sotgiu G, Bostanghadiri N, Abadi SSD, Mesgarpour B, Goudarzi H, et al. Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis. J Bras Pneumol. 2022;48(2):e20210384. https://doi.org/10.36416/1806-3756/e20210384
26. Ur Rehman O, Fatima E, Ali A, Akram U, Nashwan A, Yunus F. Efficacy and safety of bedaquiline containing regimens in patients of drug-resistant tuberculosis: An updated systematic review and meta-analysis. J Clin Tuberc Other Mycobact Dis. 2023;34:100405. https://doi.org/10.1016/j.jctube.2023.100405
27. Borisov SE, Dheda K, Enwerem M, Romero Leyet R, D'Ambrosio L, Centis R, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J. 2017;49(5):1700387. https://doi.org/10.1183/13993003.00387-2017
28. Dalcolmo M, Gayoso R, Sotgiu G, D'Ambrosio L, Rocha JL, Borga L, et al. Effectiveness and safety of clofazimine in multidrug-resistant tuberculosis: a nationwide report from Brazil. Eur Respir J. 2017;49(3):1602445. https://doi.org/10.1183/13993003.02445-2016
29. World Health Organization. Key updates to the treatment of drug-resistant tuberculosis: rapid communication, June 2024. Geneva: World Health Organization; 2024. https://doi.org/10.2471/B09123
30. Guglielmetti L, Khan U, Velásquez GE, Gouillou M, Abubakirov A, Baudin E, et al. Oral Regimens for Rifampin-Resistant, Fluoroquinolone-Susceptible Tuberculosis. N Engl J Med. 2025;392(5):468-482. https://doi.org/10.1056/NEJMoa2400327

Global trends, risk factors, and therapeutic associations of fungal pulmonary infections in lung cancer: A systematic review and meta-analysis

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ABSTRACT

Objective: Fungal pulmonary infections are a significant complication in lung cancer, adversely affecting prognosis and treatment outcomes. This meta-analysis aimed to estimate the prevalence of chronic pulmonary aspergillosis (CPA) and *Pneumocystis jirovecii* pneumonia (PJP) in lung cancer patients and to identify associated clinical predictors. **Methods:** A systematic search of EBSCOhost, Embase, PubMed/MEDLINE, Scopus, and Web of Science retrieved 2,823 records, of which 7 studies were eligible (PROSPERO: CRD42024551104). Meta-analyses of proportions and dichotomous and continuous variables were performed using R (meta package) via Jamovi and RevMan 5, with statistical significance set at $p<0.05$. **Results:** Among 15,901 lung cancer patients, 177 had CPA and 135 had PJP. The pooled prevalence was 1% for CPA and 23% for PJP. CPA was significantly associated with male sex, smoking, COPD, interstitial lung disease, tuberculosis, and squamous cell carcinoma, and negatively associated with adenocarcinoma. CPA patients also had significantly lower BMI. Bilobectomy, radiotherapy, and concurrent chemoradiotherapy were additional risk factors for CPA. High-dose corticosteroid use (≥20 mg/day) was significantly associated with PJP. **Conclusion:** CPA occurs in a clinically distinct subset of lung cancer patients with identifiable risk factors, while PJP appears to be strongly linked to immunosuppressive therapy. Improved screening strategies are warranted to mitigate the burden of these infections in vulnerable lung cancer populations.

Keywords: lung cancer; fungal infection; pulmonary infection; aspergillosis; *Pneumocystis jirovecii*; pneumonia.

INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality worldwide. It originates from epithelial cells of the respiratory tract and is broadly classified as small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC), the latter encompassing subtypes such as lung adenocarcinoma (LUAD) and squamous cell carcinoma (SCC).[1] Between 2001 and 2019, over 4 million U.S. patients were diagnosed,[2] and 2.2 million new cases were reported globally in 2020.[3] A 2023 meta-analysis estimated overall lung cancer mortality at 6–16%,[4] though survival plummets to 18.6% in cases of metastatic disease.[5]

Fungal pulmonary infections (FPIs) are underrecognized yet critical complications in lung cancer, with profound effects on morbidity, treatment outcomes, and survival. Cancer-related immunosuppression—caused by chemotherapy, radiation, and targeted therapies—predisposes patients to opportunistic fungi such as *Aspergillus* spp., *Pneumocystis jirovecii*, and *Cryptococcus* spp. These pathogens exploit therapy-induced immune dysfunction, structural lung damage, and impaired mucociliary clearance to establish invasive or chronic infections.[6–11] FPIs often mimic or aggravate cancer-related symptoms, leading to diagnostic delays and complex clinical management.[6,7,9–11]

Chronic pulmonary aspergillosis (CPA), a progressive infection caused by *Aspergillus* species, is particularly prevalent in this population. A Japanese multicenter study reported CPA-complicated lung cancer in patients undergoing anticancer treatment, correlating with poor prognostic factors such as squamous cell histology and low body mass index (BMI).[6] While CPA itself was not a direct cause of mortality, it led to treatment interruptions (e.g., pneumonitis) and a median overall survival of 14.57 months.[6] Similarly, a cross-sectional cohort detected *Aspergillus* colonization in 47.8% of newly diagnosed, non-neutropenic lung cancer patients, with *A. niger* as the dominant species. Notably, *A. niger* showed concentration-dependent cytotoxicity in human lung fibroblasts, suggesting a potential role in accelerating tissue damage and cancer progression.[7] Post-surgical NSCLC patients receiving trimodality therapy also exhibited elevated CPA risk, particularly those with prior adjuvant chemotherapy or radiation pneumonitis.[10] Localized CPA responded well to surgical or antifungal

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intervention, whereas disseminated disease was frequently fatal, underscoring the importance of early diagnosis.[10]

Pneumocystis jirovecii pneumonia (PJP) further complicates lung cancer management. A nested PCR study in Turkey detected *P. jirovecii* DNA in 66.7% of lung cancer patients—threefold higher than in non-cancer controls—with symptoms such as anorexia and weight loss strongly associated with colonization.[8] These findings highlight the importance of systematic screening in symptomatic patients. Moreover, analysis of exhaled breath condensate identified *A. niger*, *A. ochraceus*, or *Penicillium* spp. in 27.9% of lung cancer patients, but not in healthy controls,[11] suggesting environmental or host-related factors may predispose to FPIs.

Despite these insights, significant knowledge gaps remain. Most available evidence stems from small, retrospective studies,[6,9,10] limiting generalizability. FPIs—including CPA and PJP—are associated with prolonged hospitalization, treatment disruptions, and increased mortality, underscoring the need for greater clinical vigilance, routine screening in high-risk subgroups, and integrated management strategies.[6,7,10] The present systematic review synthesizes current evidence on the prevalence, clinical predictors, and treatment-associated risk factors of FPIs in lung cancer patients, aiming to inform optimized diagnostic and therapeutic approaches.

METHODS

Review Question

The objective of this systematic review and meta-analysis was to determine the prevalence of FPIs in lung cancer patients and to identify potential clinical factors associated with these infections. The study question was framed using the PEO structure, as follows:

- Population (P): patients with lung cancer, including small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) subtypes;
- Exposure (E): pulmonary colonization by pathogenic fungal species;
- Outcome (O): prevalence and clinical co-occurrence of FPIs—primarily CPA and PJP—in lung cancer patients.

The decision to focus on CPA and PJP as outcomes of interest was based on a pilot systematic search, which showed that these infections were the only ones consistently addressed as standalone topics in full-length observational studies. Other FPIs were predominantly described in isolated case reports.

Systematic Search Strategy

A systematic literature search was conducted across five major databases: EBSCOhost, Embase, PubMed/MEDLINE, Scopus, and Web of Science. The predefined search strategy combined four primary keyword domains and their synonyms: fungal pulmonary infection, respiratory tract, lung cancer, and clinical outcome. Detailed PubMed/MEDLINE queries are provided in Supplementary Table S1, with corresponding strategies for EBSCOhost, Embase, Scopus, and Web of Science in Supplementary Tables S2–S5.

The review followed a registered protocol (PROSPERO ID: CRD42024551104); however, the present analysis specifically focused on FPIs as a targeted subset of the broader review. The search and reporting processes adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[12]

Eligibility Criteria

Studies were eligible for inclusion if they:

- Investigated the association between clinical factors and fungal pulmonary infections (FPIs) in lung cancer patients;
- Were observational in design, including prospective or retrospective cohorts, case-control studies, or cross-sectional studies, provided they reported data separately for lung cancer patients with and without FPIs;
- Reported data on at least one of the following variables: demographics (age, sex, smoking history), comorbidities (e.g., cardiovascular disease, diabetes, underlying pulmonary disease), interventions (e.g., therapeutic regimens, surgical procedures), tumor histopathology, or cancer stage.

No restrictions were applied with regard to language or publication date. Records other than original research articles—including reviews, perspectives, editorials, and notes—as well as studies lacking the required data were excluded. Case reports were also excluded from the systematic review and meta-analysis in accordance with predefined criteria; however, a separate summary table of these case reports was compiled and included in the Discussion section to provide complementary insights into rare fungal infections and their clinical management.

Study Screening and Data Extraction

Identified records were managed using Mendeley Desktop (version 1.19.8) (Mendeley, Elsevier, The Netherlands). Duplicate records were removed, and the studies were screened in two stages: (a) title and abstract screening to exclude irrelevant studies, and (b) full-text review to confirm eligibility. Data were extracted on study characteristics, effect measures, and relevant variables.

Risk of Bias Assessment

The risk of bias in the included studies was assessed using the Risk Of Bias In Non-randomized Studies–of Interventions (ROBINS-I) tool,[13] and the results were visualized with the RobVis package (https://mcguinlu.shinyapps.io/robvis/) to enhance transparency.[14] ROBINS-I is the recommended instrument for evaluating bias in observational clinical

studies of patient populations with defined conditions and treatment exposures,[13] making it suitable for the present review. The tool covers seven domains: (1) confounding factors; (2) participant selection; (3) classification of interventions; (4) deviations from intended interventions; (5) missing data; (6) measurement of outcomes; and (7) selection of the reported result.[13] Each domain was rated as having low, moderate, serious, or critical risk of bias.

Statistical Analysis

A meta-analysis of proportions was conducted to estimate the prevalence of CPA and PJP in lung cancer patients using the meta package in RStudio (R version 4.2) under a random-effects model. Meta-analyses of dichotomous and continuous variables (clinical predictors) were performed separately for CPA and PJP using RevMan 5 (https://revman.cochrane.org/). A random-effects model was applied for variables exhibiting substantial heterogeneity ($I^2 > 60\%$), while a fixed-effects model was used for those with moderate or low heterogeneity ($I^2 \leq 60\%$). All analyses used the restricted maximum-likelihood (REML) estimator, with statistical significance set at $p<0.05$. Heterogeneity was assessed with the I^2 statistic and its corresponding p-value. Results are presented in data tables and weighted forest plots. CPA and PJP were treated as distinct subgroups in all analyses. Only clinically relevant and statistically significant findings are shown as forest plots in the main text; complete sets of plots for all variables are available in the Supplementary Material.

RESULTS

Systematic Search

Supplementary Figure S1 presents the PRISMA 2020 flowchart of the systematic search. A total of 2,823 records were identified across EBSCOhost, Embase, PubMed/MEDLINE, Scopus, and Web of Science. After the removal of 91 duplicates, 2,732 records remained for title and abstract screening, of which 2,693 were excluded for not meeting the inclusion criteria. The full texts of the remaining 39 publications were reviewed, yielding 36 potentially eligible studies. Of these, 29 were excluded due to the absence of patient grouping based on the presence or absence of FPIs. Ultimately, 7 studies were included for assessment.

Table 1 summarizes the basic characteristics of the 7 included studies, which were published between 2009 and 2024. Most were observational studies conducted in Asian populations, with additional data from the UK, involving a total of 15,901 lung cancer patients, of whom 312 had concurrent FPIs: 177 CPA cases (4 studies) and 135 PJP cases (3 studies). Diagnoses were based on clinical signs and symptoms, supported by computed tomography (CT) imaging and sputum or bronchoalveolar lavage fluid (BALF) testing, including microbial culture and/or PCR. All CPA studies identified *Aspergillus fumigatus* as the

Table 1. Baseline characteristics of the studies included in the systematic review. "Cases" refer to lung cancer patients diagnosed with either chronic pulmonary aspergillosis (CPA) or *Pneumocystis jirovecii* pneumonia (PJP); "controls" refer to lung cancer patients without these infections.

Study	Year	Country	Study Type	Pulmonary Infection Classification			Sample Size		Age	Ref.
				Type	Pathogen	Diagnostic Test(s)	Case	Control	Total		
Whittaker et al.	2024	UK	RSO	CPA	*A. fumigatus*	BALF/Sputum culture *Aspergillus* IgG	11	4,414	4,425	66.7 ± 10.8	(16)
Kim et al.	2022	South Korea	RSO	CPA	*A. fumigatus*	*A. fumigatus* IgG BALF/Sputum culture	93	6,684	6,777	62.7 ± 9.6	(17)
Zaini et al.	2022	Indonesia	CS	PJP	*P. jirovecii*	BALF/Sputum PCR	10	46	56	≥ 18	(18)
Shin et al.	2020	South Korea	RSO	CPA	*A. fumigatus*	*A. fumigatus* IgG BALF/Sputum culture	56	3,367	3,423	62.7 ± 9.4	(19)
Lee et al.	2019	South Korea	RSO	PJP	*P. jirovecii*	BALF/Sputum PCR/DFA	112	336	448	69 (42 - 88)	(20)
Tamura et al.	2015	Japan	RSO	CPA	*A. fumigatus* *A. niger*	Serum precipitin test BALF/Sputum culture	17	458	475	67 (24 - 86)	(15)
Nishigaki et al.	2009	Japan	RSO	PJP	*P. jirovecii*	BALF/Sputum PCR	13	284	297	72 (34 - 99)	(21)
Overall	–	–	–	–	–	–	312	15,589	15,901	–	–

BALF, bronchoalveolar lavage fluid; CPA, chronic pulmonary aspergillosis; CS, cross-sectional; RSO, retrospective observational; CT, computed tomography; DFA, direct fluorescent antibody; IgG, immunoglobulin G; IPA, invasive pulmonary aspergillosis; ODI, optical density index; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii* pneumonia.

causative strain, except Tamura et al.,[15] who also isolated *Aspergillus niger*.

Prevalence of CPA and PJP in Lung Cancer Patients

Meta-analyses of proportions for the CPA and PJP subgroups are presented in Figure 1. The initial analyses, which included all 4 studies on CPA and all 3 on PJP, showed substantial heterogeneity. In order to address this, studies contributing disproportionately to heterogeneity were sequentially excluded until acceptable heterogeneity levels were achieved. The final pooled prevalence estimates were 1% for CPA (95%CI: [0.01–0.02]; I^2 = 10.6%) based on a total sample size of 10,200 patients, and 23% for PJP (95%CI: [0.18–0.29]; I^2 = 23.6%) based on 504 patients.

Prevalence of Demographics and Clinical Factors in CPA and PJP Subgroups of Lung Cancer Patients

Table 2 presents the results of the meta-analysis of proportions for demographic and clinical factors among lung cancer patients with CPA and PJP. Corresponding forest plots are shown in Supplementary Figures S2–S25.

Among the CPA patients, males predominated, with a pooled mean prevalence of 83% (95%CI: [0.69–0.97]). Comorbidities were generally less common in this subpopulation, except for chronic obstructive pulmonary disease (COPD), which had a pooled mean prevalence of 41% (95%CI: [0.31–0.51]). A positive smoking history was highly prevalent

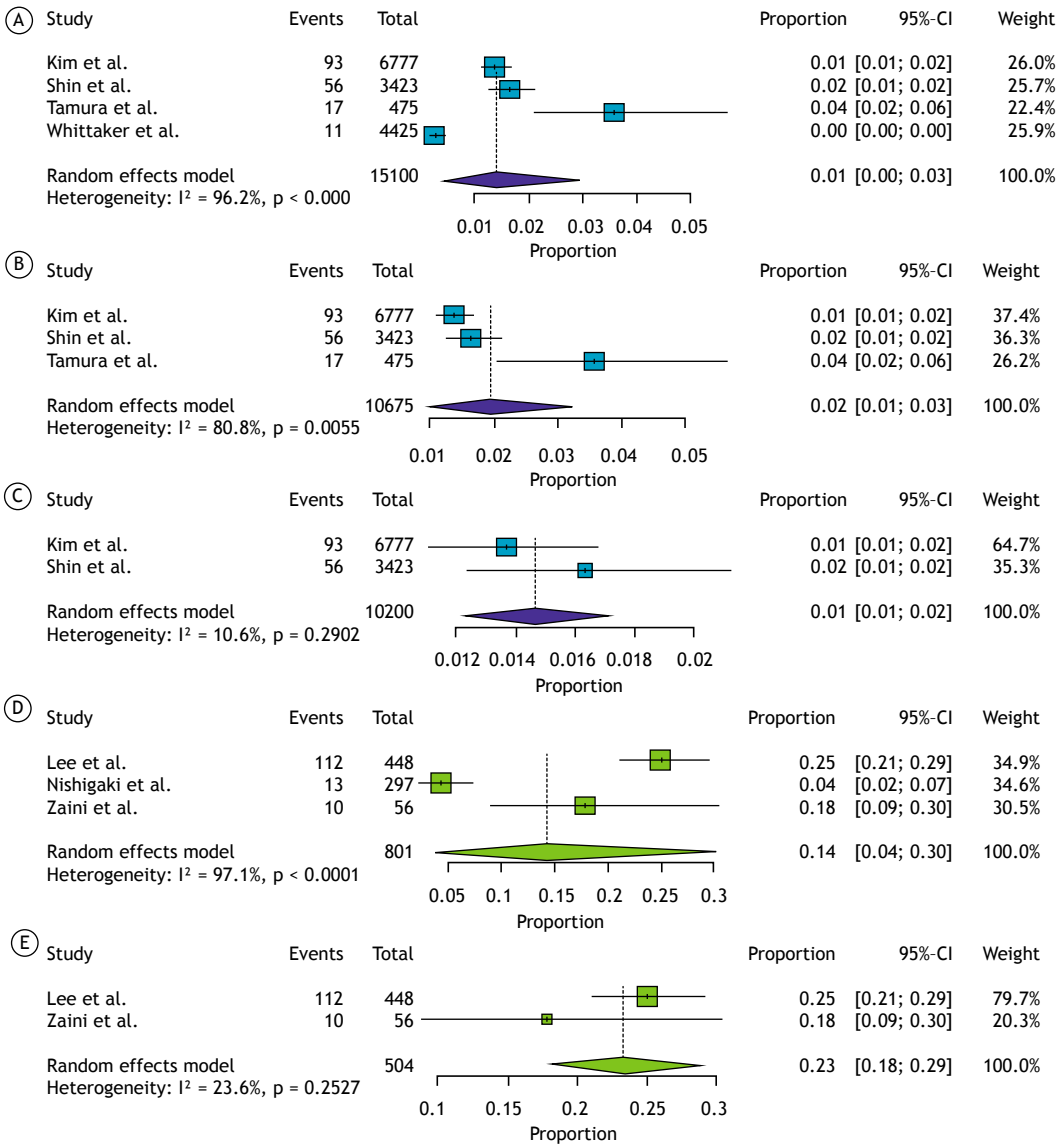


Figure 1. Meta-analysis of proportions for CPA and PJP. Panels A–C present results from 4, 3, and 2 studies on CPA, respectively, while panels D–E present results from 3 and 2 studies on PJP, respectively.

Table 2. Meta-analysis of proportions. Prevalence of demographic and clinical variables among lung cancer patients with chronic pulmonary aspergillosis (CPA) or *Pneumocystis jirovecii* pneumonia (PJP), presented as distinct subgroups.

Subgroup	Variable		Proportion Rate		Statistic		Heterogeneity	
			Mean	95% CI	Z	P	I^2 (%)	P
CPA	Sex	Female	0.17	[0.03, 0.31]	2.30	0.021	85.34	0.019
		Male	0.83	[0.69, 0.97]	11.20	< 0.001	85.34	0.019
	Comorbidity	DM	0.14	[0.08, 0.20]	4.49	< 0.001	24.97	0.296
		COPD	0.41	[0.31, 0.51]	7.95	< 0.001	38.74	0.148
		ILD	0.04	[0.01, 0.08]	2.81	0.005	0.29	0.168
		PTb	0.16	[0.10, 0.21]	5.53	< 0.001	0.00	0.874
		CHD	0.06	[0.02, 0.09]	3.11	0.002	0.10	0.079
		CVD	0.03	[0.00, 0.05]	2.20	0.028	0.00	0.641
	Smoking		0.87	[0.82, 0.97]	34.40	< 0.001	0.00	0.529
	Tumor Location	Left Lung	0.46	[0.38, 0.53]	12.20	< 0.001	0.00	0.805
		Right Lung	0.54	[0.47, 0.62]	14.50	< 0.001	0.00	0.805
		ADC	0.48	[0.41, 0.56]	12.40	< 0.001	0.00	0.816
		SCC	0.41	[0.33, 0.48]	10.80	< 0.001	0.00	0.555
	Tumor Stage	I-II	0.63	[0.48, 0.78]	8.20	< 0.001	73.35	0.020
		III-IV	0.37	[0.22, 0.52]	4.81	< 0.001	73.35	0.020
	Surgical Technique	Lobectomy	0.67	[0.30, 1.00]	3.52	< 0.001	97.89	< 0.001
		Bilobectomy	0.10	[0.05, 0.14]	4.26	< 0.001	0.00	0.641
		Pneumonectomy	0.01	[0.00, 0.03]	1.48	0.139	0.00	0.833
PJP	Sex	Female	0.20	[0.01, 0.40]	2.09	0.037	79.29	0.052
		Male	0.80	[0.60, 0.99]	8.11	< 0.001	79.29	0.052
	Tumor Histopathology	SCLC	0.11	[0.05, 0.16]	4.02	< 0.001	0.00	0.484
		NSCLC	0.89	[0.80, 0.97]	20.40	< 0.001	45.89	0.167
	Tumor Stage	IA-IIIA	0.26	[0.19, 0.34]	6.98	< 0.001	0.00	0.586
		IIIB-IV	0.74	[0.66, 0.81]	19.50	< 0.001	0.00	0.586

Legend: CPA, chronic pulmonary aspergillosis; PJP, *Pneumocystis jirovecii* pneumonia; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PTb, pulmonary tuberculosis; CHD, chronic heart disease; CVD, cerebrovascular disease; ADC, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer.

(87%). Tumor localization and histopathology were largely comparable across patients, while early-stage disease (stages I–II) was more frequent than advanced-stage disease (stages III–IV) (63% vs. 37%, respectively). Surgical management in this subgroup was predominantly lobectomy, with a pooled mean prevalence of 67% (95%CI: [0.30–1.00]). These findings are summarized in Table 2.

Studies involving lung cancer patients with PJP generally reported fewer clinical variables, resulting in a narrower breadth of findings. Similar to CPA, males predominated among PJP patients, with a pooled mean prevalence of 80% (95%CI: [0.60–0.99]; Table 2). Regarding tumor histopathology, NSCLC, including adenocarcinoma (ADC) and squamous cell carcinoma (SCC), was far more frequent than SCLC (89% vs. 11%, respectively). In contrast to CPA, advanced disease was found to be more prevalent in this subgroup, with stage IIIB–IV tumors accounting for 74% of cases.

Meta-Analysis of Clinical Predictors of CPA and PJP in Lung Cancer Patients

A meta-analysis of dichotomous and continuous outcomes comparing CPA vs. non-CPA and PJP vs. non-PJP lung cancer patients is presented in Table 3, with statistically significant findings visualized as forest plots in Figure 2.

Compared with non-CPA patients, CPA patients had significantly higher odds of male sex (OR: 3.11, 95%CI: [1.38–6.98]), smoking (OR: 3.92, 95%CI: [2.56–6.00]), COPD (OR: 2.22, 95%CI: [1.07–4.56]), interstitial lung disease (OR: 4.45, 95%CI: [2.23–8.86]), pulmonary tuberculosis (OR: 1.63, 95%CI: [1.06–2.49]), and squamous cell carcinoma (OR: 2.20, 95%CI: [1.60–2.98]). Conversely, adenocarcinoma was associated with significantly lower odds in CPA patients (OR: 0.41, 95%CI: [0.30–0.55]).

For body mass index (BMI), a continuous variable, the meta-analysis yielded a statistically significant standardized mean difference (SMD) of -0.52 (95%CI: [-0.67 to -0.36]), indicating lower mean BMI in CPA patients compared to non-CPA patients. Heterogeneity was generally low for most statistically significant results, except for male sex and COPD, which showed moderately high levels of heterogeneity (I^2 > 60%).

Table 4 summarizes the results of the meta-analysis of demographic and clinical variables in PJP vs. non-PJP patients. Corresponding forest plots are provided in Supplementary Figures S26–S31. Unlike the CPA/

Table 3. Meta-analysis of demographic and clinical variables in lung cancer patients with fungal pulmonary infections. Comparisons were made between lung cancer patients with chronic pulmonary aspergillosis (CPA) vs. non-CPA (nCPA), and lung cancer patients with *Pneumocystis jirovecii* pneumonia (PJP) vs. non-PJP (nPJP). Odds ratios (OR) and standardized mean differences (SMD) represent dichotomous and continuous outcomes, respectively.

Subgroup	Variable		OR/SMD		Statistic		Heterogeneity	
			Mean	95% CI	Z	P	I^2 (%)	P
CPA	Age		-0.02	[-0.17, 0.12]	-0.328	0.743	0.00	0.966
	Sex	Female	0.32	[0.14, 0.72]	-2.75	0.006	62.72	0.061
		Male	3.11	[1.38, 6.98]	2.75	0.006	62.72	0.061
	BMI (kg/m^2)		-0.52	[-0.67, -0.36]	-6.48	< 0.001	0.00	0.521
	Smoking	Never	0.25	[0.17, 0.39]	6.29	< 0.001	0.00	0.530
		Ex	1.73	[1.25, 2.39]	3.28	0.001	0.00	0.810
		Current	1.88	[1.35, 2.61]	3.75	< 0.001	0.00	0.360
	Comorbidities	DM	1.03	[0.69, 1.54]	0.14	0.888	0.00	0.847
		COPD	2.22	[1.07, 4.56]	2.16	0.031	75.32	0.012
		ILD	4.45	[2.23, 8.86]	4.25	< 0.001	0.00	0.670
		PTb	1.63	[1.06, 2.49]	2.25	0.025	0.00	0.658
		CHD	1.31	[0.47, 3.68]	0.52	0.602	63.09	0.071
		CVD	0.65	[0.28, 1.53]	-0.98	0.327	0.00	0.875
	Tumor Location	Left Lung	1.18	[0.88, 1.59]	1.09	0.274	0.00	0.846
		Right Lung	0.85	[0.63, 1.14]	-1.09	0.274	0.00	0.846
	Tumor Histopathology	ADC	0.41	[0.30, 0.55]	-5.72	< 0.001	0.00	0.899
		SCC	2.18	[1.58, 2.98]	4.87	< 0.001	0.00	0.730
	Tumor Stage	I-II	0.47	[0.14, 1.53]	-0.12	0.210	90.60	< 0.001
		III-IV	2.13	[0.65, 6.98]	1.25	0.210	90.60	< 0.001
	Surgical Procedure	Lobectomy	1.29	[0.87, 1.92]	1.26	0.209	0.00	0.872
		Bilobectomy	2.87	[1.72, 4.79]	4.03	< 0.001	0.00	0.649
		Pneumonectomy	0.43	[0.12, 1.52]	-1.31	0.191	0.00	0.812
PJP	Sex	Female	1.00	[0.61, 1.68]	0.035	0.972	0.00	0.331
		Male	0.99	[0.59, 1.65]	-0.035	0.972	0.00	0.331
	Tumor Histopathology	SCLC	0.83	[0.46, 1.51]	-0.60	0.550	0.00	0.955
		NSCLC	0.90	[0.52, 1.56]	-0.36	0.719	0.00	0.829
	Tumor Stage	IA-IIIA	0.95	[0.62, 1.47]	-0.21	0.835	0.00	0.700
		IIIB-IV	1.06	[0.69, 1.64]	0.26	0.792	0.00	0.716

Legend: CPA, chronic pulmonary aspergillosis; PJP, *Pneumocystis jirovecii* pneumonia; BMI, body mass index; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; PTb, pulmonary tuberculosis; CHD, chronic heart disease; CVD, cerebrovascular disease; ADC, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; OR, odds ratio; SMD, standardized mean difference.

non-CPA analysis, no clinical variables differed significantly between PJP and non-PJP patients. Odds ratios for sex (male/female), tumor histopathology (SCLC/NSCLC), and tumor stage (early/late) were broadly comparable, underscoring the need for further clinical investigations in this particular subgroup.

Treatment-Associated Risk of CPA in Lung Cancer Patients

As shown in Figure 3, chemotherapy was not significantly associated with CPA in patients with lung cancer (OR: 1.29; 95%CI: [0.79–2.09]). In contrast, chest radiotherapy showed a significant association with CPA (p<0.001), with a pooled OR of 3.78 (95%CI: [2.14–6.68]) and negligible heterogeneity (I^2 = 0%). Concurrent chemoradiotherapy (CCRT) also showed a significant association (p=0.001), with a pooled OR of 4.06 (95%CI: [1.75–9.42]), though with substantial heterogeneity (I^2 = 75%).

Bilobectomy—defined as the surgical removal of two tumor-bearing lobes—emerged as a significant predictor of CPA, with a pooled OR of 2.87 (95%CI: [1.72–4.79]) and low heterogeneity (I^2 = 0%). Other surgical procedures, including lobectomy (single-lobe resection) and pneumonectomy, were not significantly associated with CPA (Table 3).

Collectively, these findings suggest that radiotherapy (alone or combined with chemotherapy) and bilobectomy may represent important risk factors for CPA development in lung cancer patients.

Treatment-Associated Risk of PJP in Lung Cancer Patients

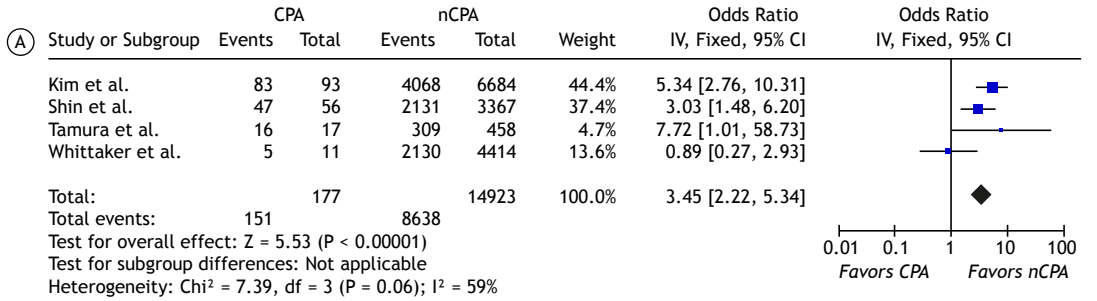
Overall, corticosteroid therapy was not significantly associated with PJP in lung cancer patients (OR: 2.80; 95%CI: [0.44–17.39]; Figure 4). However, high-dose corticosteroid use—defined as a daily dose of ≥20 mg—was significantly associated with increased odds

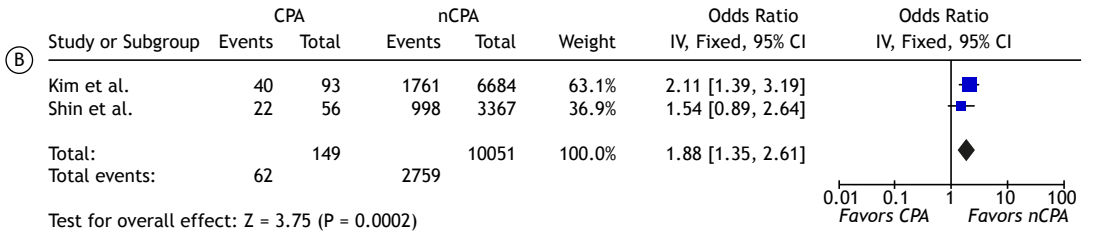
of PJP (p=0.03), with a pooled OR of 3.59 (95%CI: [1.17–11.05]) and moderately high heterogeneity (I^2 = 70%).

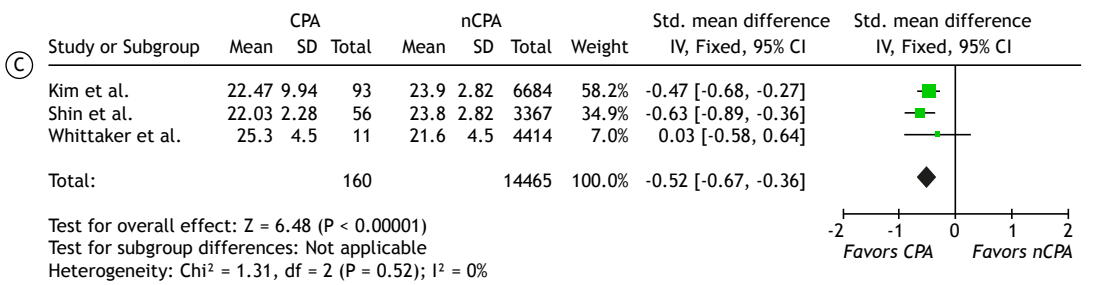
Consistent with the CPA findings, chemotherapy was not significantly associated with PJP (p=0.08). Radiotherapy, on the other hand, showed a borderline significant association with PJP (p=0.05), with a pooled OR of 2.91 (95%CI: [1.02–8.30]) and moderate heterogeneity (I^2 = 64%).

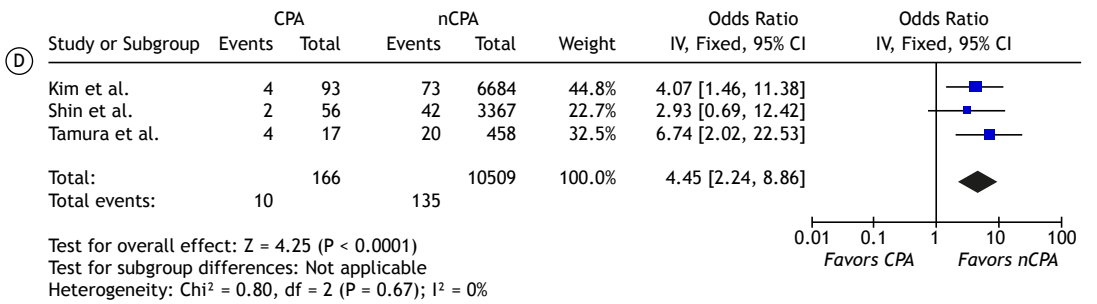
Risk of Bias Assessment

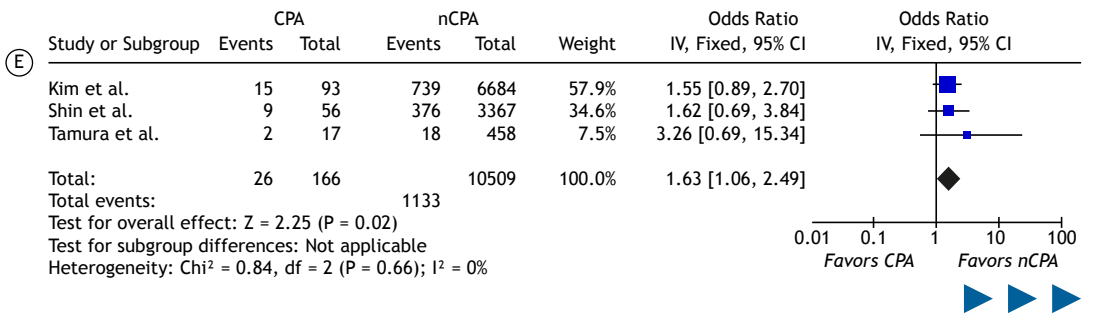
The risk of bias in the included studies was assessed using the ROBINS-I tool. As shown in Supplementary











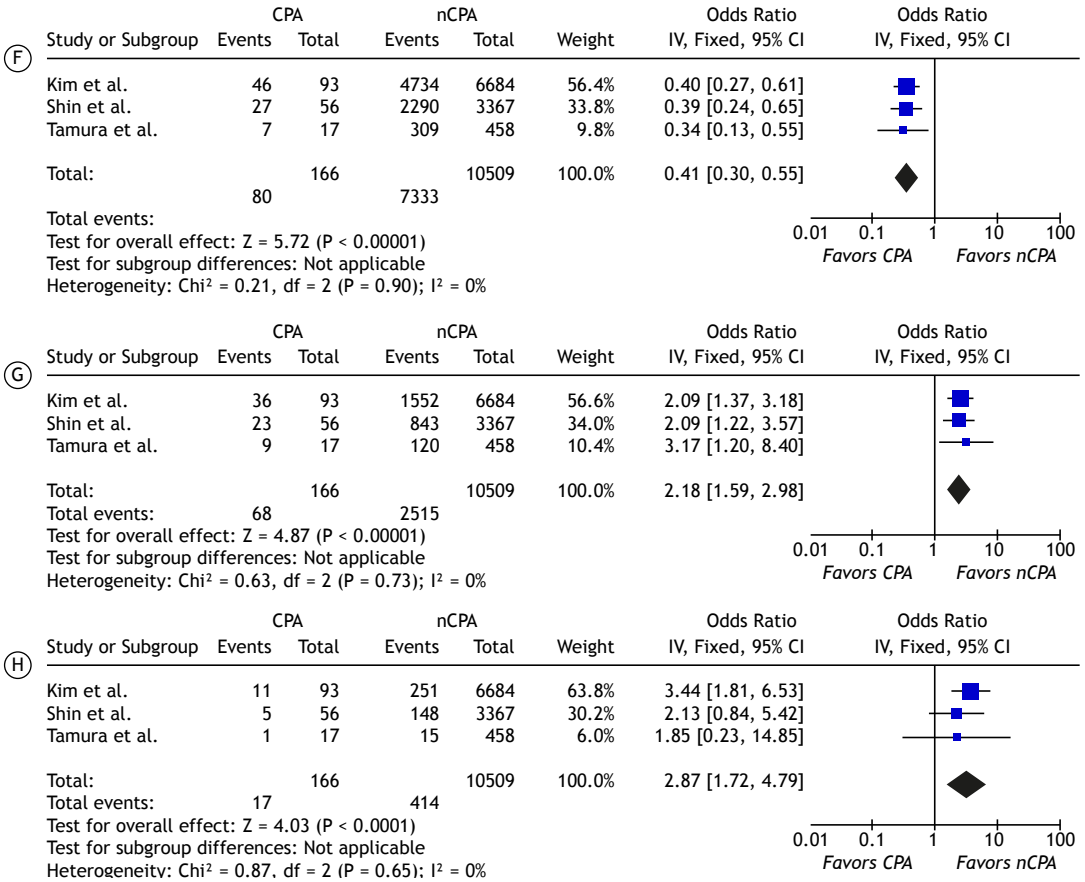


Figure 2. Meta-analysis of demographic and clinical predictors of CPA. Comparative forest plots of clinical and demographic factors showing statistically significant differences between CPA and non-CPA (nCPA) lung cancer patients, with low heterogeneity. Factors include male sex (A), current smoking (B), body mass index (C), interstitial lung disease (D), pulmonary tuberculosis (E), lung adenocarcinoma (F), lung squamous cell carcinoma (G), and bilobectomy (H).

Figure S32, most studies exhibited low risk of bias across the majority of domains. The main concerns were related to confounding factors (D1) and participant selection (D2), where several studies were judged to have moderate risk. Key confounders included age, sex, and smoking history between lung cancer patients with and without FPIs.

Participant selection was deemed to confer serious risk of bias in the study by Lee et al.,[20] which recruited patients with confirmed PJP and compared them with a cohort of lung cancer patients without PJP. Furthermore, the study by Zaini et al.[18] had missing information in certain domains, particularly regarding deviations from intended interventions and classification of interventions, mostly involving surgical procedures and therapeutic regimens in PJP and non-PJP groups. Overall, most studies were considered to have a moderate risk of bias.

DISCUSSION

This systematic review and meta-analysis evaluated the prevalence of fungal pulmonary infections (CPA and PJP) in 15,901 lung cancer patients across seven studies, identifying 312 cases. Key clinical associations were also explored to support risk stratification and management.

Prevalence and Clinical Context

After excluding heterogeneous studies, the pooled prevalence rates were 1% for CPA and 23% for PJP, indicating a higher frequency of PJP. The clinical association between PJP and immunocompromised states[22] contrasts with CPA's association with structural lung damage,[23] which may partly explain the lower prevalence of CPA, despite the widespread use of chemotherapy in lung cancer patients.[24] A Chinese study reported fungal infections in 28.7% of patients based on sputum cultures, with a higher proportion having a history of radiotherapy (31.3% vs. 18.5%).[25] Japanese data showed 31% fungal PCR positivity in lung cancer patients, attributed largely to corticosteroid use.[26] Notably, PJP can arise without prior colonization, as observed in four cases without preceding fungal detection.[27] Emerging antifungal resistance, such as voriconazole resistance in 42.4% of *Aspergillus* isolates in Indonesia,[28] underscores the clinical relevance of FPIs despite the modest 1% prevalence of CPA reported in this meta-analysis.

Table 4. Cases of fungal pulmonary infections (FPIs) in patients with lung cancer reported within the past two decades.

Study	Year	Country	Patient		Lung Cancer		Cancer Treatment History	Fungal Pulmonary Infection			Recommended Treatment	Ref.
			Age	Sex	Type	Stage		Type	Pathogen	Diagnostic Test		
Bai et al.	2024	China	54	Female	ADC	IA	–	PC	*Cryptococcus* spp.	PAS/GMS/MC stain	Fluconazole (PO, 200 mg, OD, 3 months)	(42)
Ng at al.	2024	Malaysia	73	Male	ADC	–	Chemotherapy	Aspergillosis	*A. fumigatus*	PAS/GMS stain	AMB (IV, 2 weeks) Voriconazole (PO, 6 weeks)	(43)
Setiwalidi et al.	2024	China	56	Male	ADC	IIIA	Pralestinib Selpercatinib	Polymicrobial	*A. fumigatus* *C. albicans* *P. jirovecii*	1,3-B-D-Glucan + Galactomannan antigen test	Voriconazole (PO, 12 weeks)	(44)
Guziejko et al.	2022	Poland	54	Female	ADC	IIIA	Etoposide Radiotherapy	CPA	*A. fumigatus* *A. flavus*	ODID	Itraconazole (PO, 200 mg, BID, 3 months) Voriconazole (PO, 200 mg, BID)	(45)
Hiba et al.	2022	Morocco	50	Female	ADC	–	Carboplatin Paclitaxel Pembrolizumab Corticosteroids	PJP	*P. jirovecii*	BALF examination*	TMP/SMX	(46)
Kim et al.	2022	South Korea	64	Male	ADC	IA	Lobectomy	PJP	*P. jirovecii*	BALF PCR	TMP/SMX (IV, 320/160 mg, TID)	(47)
Doello et al.	2020	Spain	59	Male	NSCLC	IIIB	Cisplatin Vinorelbine Radiotherapy	PJP	*P. jirovecii*	BALF examination*	TMP/SMX (IV, 160/800 mg, TID) Voriconazole (PO, 300 mg daily)	(48)
Yao et al.	2020	China	72	Male	SCC	–	–	PC	*Cryptococcus* spp.	Puncture histopathology	Fluconazole (PO, 400 mg daily, 6 months)	(49)
Uehara et al.	2018	Japan	70	Male	SCC	–	Lobectomy	CPA	*A. fumigatus*	1,3-B-D-Glucan + Galactomannan antigen test	Micafungin Voriconazole (PO, 200 mg, BID)	(50)
Boyd et al.	2013	US	48	Male	ADC	IA	–	IPA	*Aspergillus* spp.	Histopathology*	Voriconazole	(51)
Santos et al.	2013	Brazil	76	Male	ADC	–	Cisplatin Dexamethasone Pemetrexed disodium	IPA	*A. fumigatus*	BALF PCR	Voriconazole (IV, 4 mg/kg, BID, 3 weeks) Voriconazole (PO, 200 mg, BID)	(52)
Uchida et al.	2012	Japan	74	Male	SCLC	IIIB	–	Mucormycosis	*C. bertholletiae*	BALF culture	Liposomal AMB (2.5 mg/kg, 1 month)	(53)
Neuville et al.	2011	France	49	Male	ADC	–	Gemcitabine Carboplatin Bevacizumab Pemetrexed disodium	PJP	*P. jirovecii*	BALF PCR	TMP/SMX (IV, 400/80 mg, OD, 3 weeks)	(54)
Velcheti et al.	2007	US	73	Male	NSCLC	–	Gemcitabine Pemetrexed disodium Radiotherapy	PJP	*P. jirovecii*	BALF-DFA	TMP/SMX (IV, 400 mg, QID)	(55)
Itano et al.	2005	Japan	77	Male	ADC	IA	–	IPA	*Aspergillus* spp.	Histopathology*	Itraconazole (PO, 100 mg, OD, 2 weeks)	(56)

Legend: *Exact diagnostic test was not specified. ADC, adenocarcinoma; NSCLC: non-small cell lung cancer; SCC: squamous cell carcinoma; SCLC: small cell lung cancer; PC: pulmonary cryptococcosis; CPA: chronic pulmonary aspergillosis; PJP, *Pneumocystis jirovecii* pneumonia; IPA: invasive pulmonary aspergillosis; SIPA: subacute invasive pulmonary aspergillosis; PAS: periodic acid Schiff; GMS: Gomori methenamine silver; MC: mucicarmine; ODID: Ouchterlony double immunodiffusion; BALF: bronchoalveolar lavage fluid; PCR: polymerase chain reaction; DFA: direct fluorescent antibody; PO: per os (oral); OD: once daily; AMB: amphotericin B; BID: twice daily; TMP/SMX: trimethoprim/sulfamethoxazole; IV: intravenous; TID: three times daily; QID: four times daily.

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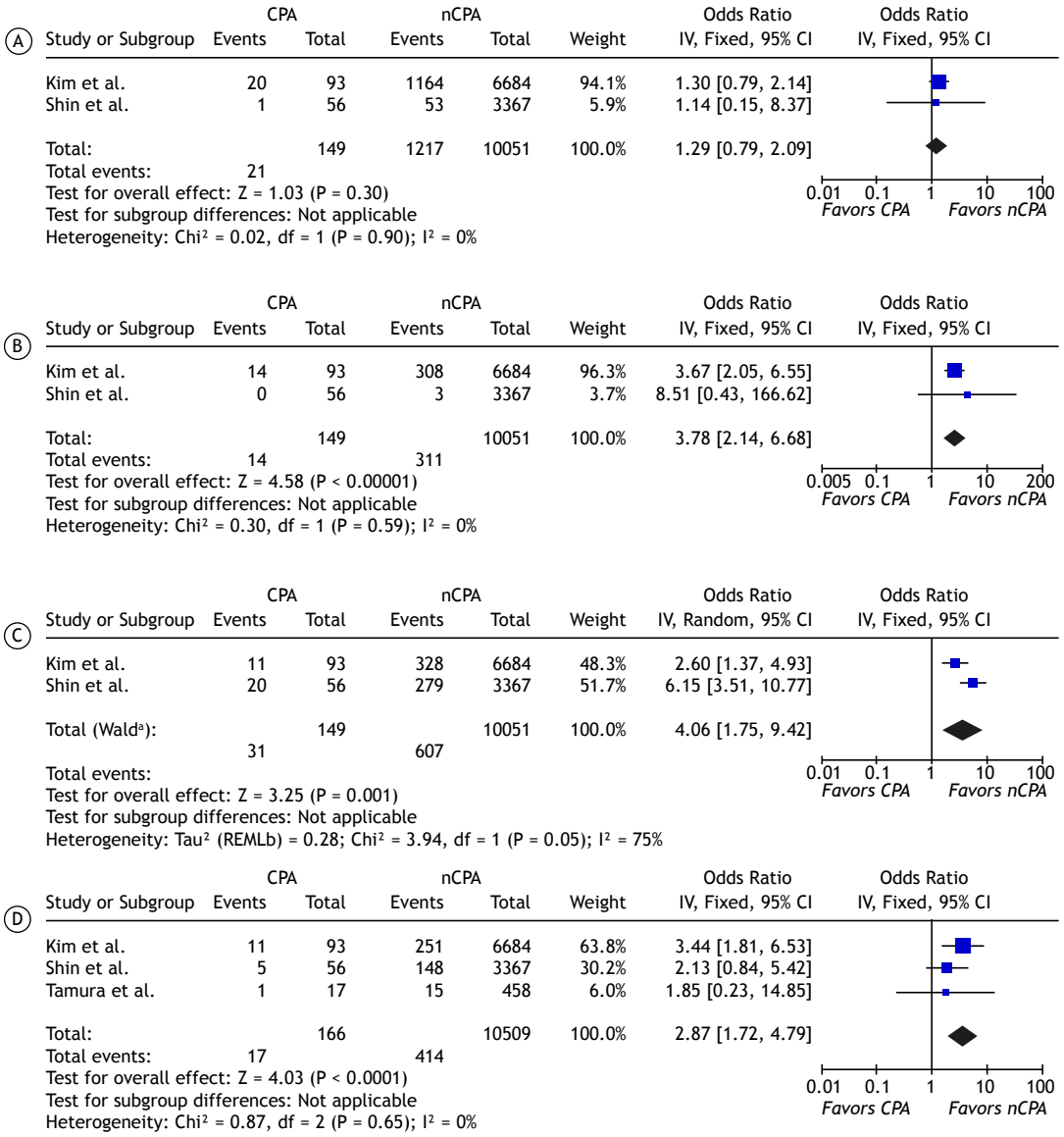

Figure 3. Meta-analysis of therapeutic predictors of CPA. Forest plots comparing chemotherapy (A), radiotherapy (B), concurrent chemoradiotherapy (CCRT) (C), and bilobectomy (D) between CPA and non-CPA lung cancer patients.

Clinical Predictors of CPA

Male sex, COPD, interstitial lung disease (ILD), and SCC histology were positively associated with CPA, while lower BMI showed an inverse correlation. A 2024 cohort study linked lung cancer to CPA, with a hazard ratio of 8.51.[29] Similarly, a nationwide Japanese observational study identified lung cancer, COPD, and ILD as major risk factors for CPA,[30] consistent with our findings. A large-scale French analysis of 17,290 CPA cases over a 10-year period further corroborated these associations.[31] In addition, a Spanish study reported a 9.5-fold increase in mortality among CPA patients with a history of lung cancer.[32] SCC histology and BMI <18.5 kg/m² predicted poorer survival in CPA patients,[6] aligning with our meta-analysis, showing higher odds of SCC and lower BMI in CPA cases. The clinical relevance of low BMI is further supported by an 11-year retrospective study from Brazil involving 91 CPA patients, which found a predominance of underweight individuals, reinforcing the association between low BMI and CPA susceptibility.[33] Notably, a large-scale cohort study of 7,021 patients with advanced NSCLC showed improved overall survival in obese patients receiving chemotherapy or immunotherapy compared with those of normal BMI,[34] further highlighting the prognostic implications of body weight in lung cancer populations.

Treatment-Related Associations

Radiotherapy and CCRT were significantly associated with CPA. Chest radiotherapy, particularly when

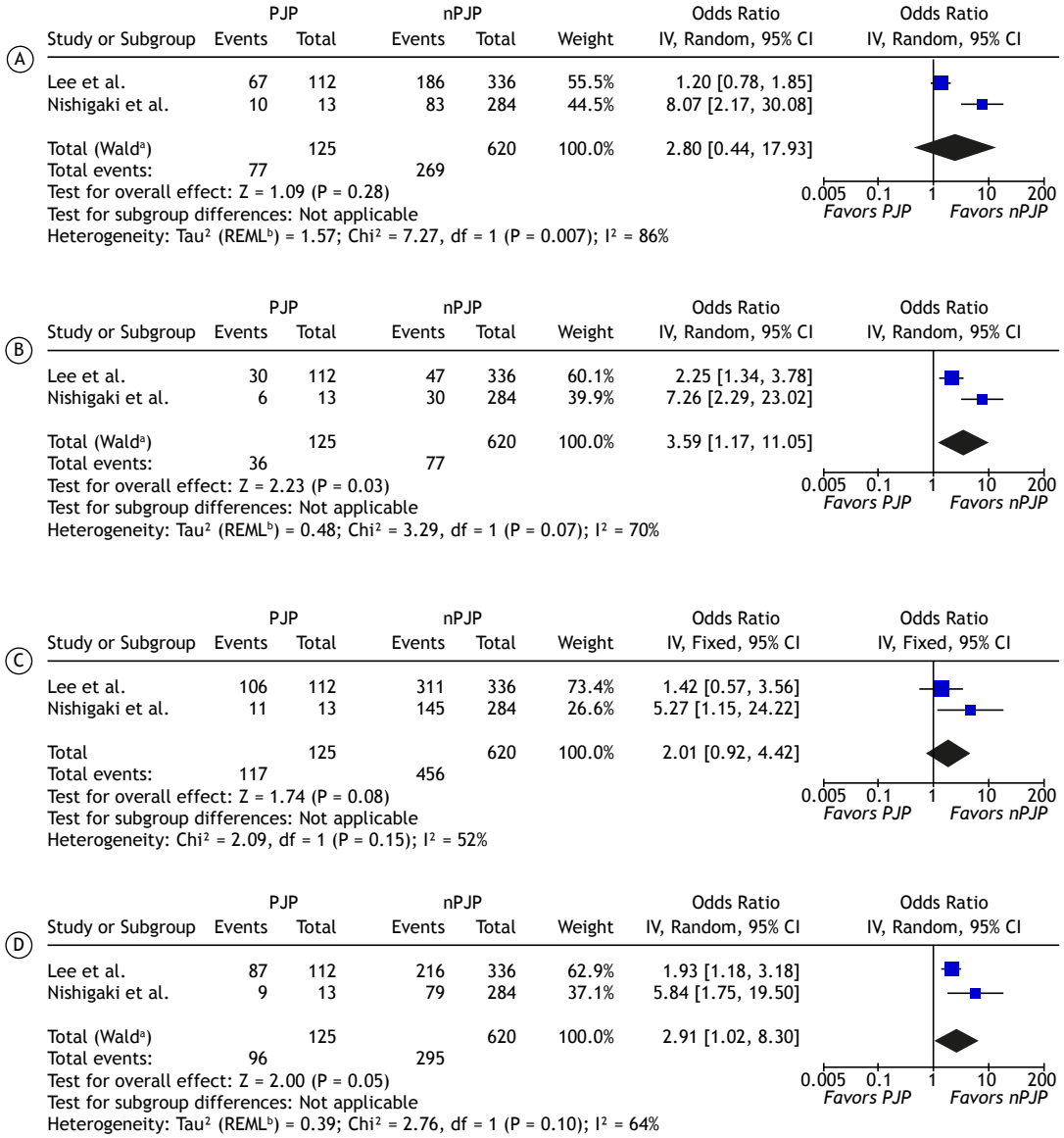

Figure 4. Meta-analysis of therapeutic predictors of PJP. Forest plots comparing corticosteroid therapy (A), high-dose corticosteroid therapy (B), chemotherapy (C), and radiotherapy (D) between PJP and non-PJP lung cancer patients.

combined with chemotherapy, increases the risk of fungal infection, with the highest incidence occurring within three months of treatment initiation.[35] CCRT is especially linked to aspergillosis, with susceptibility peaking during the first three months of treatment. In a cohort of 4,450 patients, fungal infections were reported in 15.9% post-radiotherapy, with markedly higher rates in CCRT patients (60.5% vs. 39.5%).[36] These findings are consistent with our meta-analysis, which showed higher odds of CPA in lung cancer patients with prior CCRT exposure compared to those receiving radiotherapy alone (4.06 vs. 3.78), suggesting that CCRT confers an added risk. A two-year follow-up of 1,872 lung cancer patients undergoing radiotherapy identified CPA in 24 out of 54 cases (44.4%) of chronic pulmonary infections, establishing CPA as the predominant type in this setting.[37] Consistently, a two-decade retrospective survey in Japan of 187 NSCLC patients receiving postoperative CCRT reported CPA in 6 cases (3.2%).[10] This prevalence is approximately three times higher than the 1% weighted mean observed in our meta-analysis, underscoring the contributory role of CCRT in CPA development. The increased odds of CPA following radiotherapy may be partly explained by radiation-induced pneumonitis,[38] compounded by immunosuppression associated with CCRT, further facilitating fungal colonization and the occurrence of CPA.[10]

PJP and Corticosteroid Use

High-dose corticosteroids (≥20 mg/day) were strongly associated with PJP, whereas lower dosages

showed non-significant trends. The association between corticosteroid therapy and PJP is well-established in the literature.[39] Our analysis revealed a pooled mean OR of 2.80 (95%CI: [0.44–17.93]; Figure 4) for PJP in patients with a history of corticosteroid treatment, irrespective of dosage; however, this association did not reach statistical significance. In contrast, daily doses ≥20 mg were significantly associated with PJP. This finding is clinically relevant, as demonstrated by the 2024 PCP-MULTI group study, which reported that among 66 solid tumor patients with PJP, 44 (66.7%) were receiving corticosteroids at daily doses ≥40 mg at the time of infection. High-dose corticosteroid use was linked to significantly lower survival.[40] Collectively, these data support a dose-dependent risk of PJP, highlighting the importance of prophylaxis in patients receiving high-dose corticosteroid therapy.[41]

Potential Implications of Observed Heterogeneity

Several instances of elevated heterogeneity were observed across our analyses, particularly in the meta-analyses of proportions. Initial pooled prevalence estimates for CPA and PJP showed substantial heterogeneity (I^2 > 90%), which was mitigated through subgroup analyses and stepwise exclusion of outlier studies. Residual high heterogeneity was mainly confined to descriptive variables, such as sex distribution and the proportion of lobectomy among CPA patients. While informative, these were not central to our clinical interpretations.

The core of our findings lies in the meta-analyses of binomial outcomes for clinical predictors, where heterogeneity was generally low to moderate. Exceptions include COPD in CPA patients (I^2 = 75%) and tumor stage (I/II vs. III/IV), the latter retaining high heterogeneity (I^2 = 90%) despite *post-hoc* harmonization of stage definitions across a limited number of studies. Corticosteroid use in PJP patients also showed considerable heterogeneity (I^2 = 86%) in the overall analysis, though the association was not statistically significant (p=0.28). In contrast, high-dose corticosteroid use demonstrated a significant association with moderate heterogeneity (I^2 = 70%). These elevated values likely reflect the small number of available studies and the geographical homogeneity of included cohorts, the majority of which were conducted in Asia. Accordingly, we emphasize results with lower heterogeneity, which we consider more reliable and generalizable.

Limitations and Generalizability to Diverse Populations

Our analysis is largely based on retrospective observational studies from Asia, reflecting the limited research on FPIs in lung cancer patients elsewhere. Isolated case reports from Europe, North America, Africa, and South America can be found in the literature. Table 4 provides a summary of pertinent case reports published since 2005, documenting the co-occurrence of pulmonary infections and lung cancer. These reports—spanning diverse histologies (ADC, NSCLC), stages (IA–IIIB), and treatments (platinum regimens, radiotherapy, immunotherapy, corticosteroids)—lack uniform denominators and standardized diagnostic criteria, undermining prevalence estimates outside Asia.

In broader CPA cohorts, 1-year mortality ranges from 7% to 32%, and 5-year mortality from 38% to 52%, with pulmonary cavitation representing the key risk factor and CT imaging plus *Aspergillus* IgG serology remaining central to diagnosis and management.[57] Similarly, non-HIV PJP occurs predominantly in immunocompromised hosts, with malignancy present in up to 46% of cases and systemic glucocorticoids in up to 76%, though without a clearly defined dose threshold.[58] Our identification of high-dose corticosteroids (≥20 mg/day) as a predictor for PJP therefore offers novel, dose-specific insight. Nonetheless, in the absence of prospective cohorts from non-Asian regions applying consistent methodology, the external validity of our pooled prevalence and risk estimates remains constrained, underscoring the need for multinational studies with harmonized diagnostic and treatment protocols.

Assessment of Publication Bias

A formal assessment of publication bias was carried out with caution, as the included outcomes involved <10 studies, which is commonly considered the minimum threshold for meaningful evaluation using funnel plots or Egger's test.[59] Funnel plots for CPA and PJP studies are presented in Supplementary Figures S31–S33. The funnel plot for all CPA studies showed asymmetry, with the study by Whittaker et al.[16] identified as an outlier. Upon exclusion of this study, Egger's regression yielded a Z score of 1.69 (p=0.090), indicating no significant asymmetry or publication bias. Egger's regression for PJP studies produced a Z score of 0.664 (p=0.507), similarly suggesting no evidence of asymmetry or publication bias. Since the Whittaker et al.[16] study was not included in most clinical predictor and treatment-related meta-analyses due to insufficient data (Figures 3–4), we can conclude that publication bias is unlikely to have substantially influenced our findings.

Clinical Remarks and Practical Considerations

In routine practice, FPIs in lung cancer are investigated only when clinical or radiologic findings—such as new infiltrates, persistent fevers, or nodular lesions—raise suspicion, rather than through universal screening.[57,58] For PJP, current guidelines recommend initiating prophylaxis once patients receive the equivalent of ≥20 mg prednisone daily for ≥4 weeks or,[60] according to the 2022 European Alliance of Associations for Rheumatology (EULAR) update, ≥15 mg daily for ≥2 weeks.[57] Trimethoprim-sulfamethoxazole (TMP/SMX) remains the first-line regimen, with dosing adjusted for renal

function and desensitization protocols available for sulfa-allergic patients. Its efficacy is well supported, including in a recent risk-benefit analysis of primary prophylaxis against PJP involving 419 patients receiving TMP/SMX.[61] Within lung cancer-associated case reports (Table 4), TMP/SMX consistently appears as the predominant treatment modality for PJP, reinforcing its central role. By contrast, CPA typically arises from structural lung damage—such as post-radiotherapy pneumonitis or bilobectomy—and routine antifungal prophylaxis is neither standard nor practical given concerns about toxicity, drug interactions, and cost.[57] Instead, our findings suggest a risk-stratified surveillance approach: patients undergoing high-risk interventions, including bilateral lung resections or CCRT, may benefit from scheduled chest imaging or serum biomarkers (e.g., galactomannan, *Aspergillus* PCR; see Table 1) in the months following treatment to enable earlier CPA detection. Together, these observations support targeted PJP prophylaxis and individualized CPA monitoring strategies to optimize fungal infection management in lung cancer care.

CONCLUSION

This systematic review and meta-analysis underscores the prevalence and clinical relevance of fungal pulmonary infections (FPIs) in lung cancer patients, focusing on chronic pulmonary aspergillosis (CPA) and *Pneumocystis jirovecii* pneumonia (PJP). PJP emerged as the predominant infection, with a pooled prevalence of 23% compared to 1% for CPA, reflecting their distinct pathogenic mechanisms—immunosuppression for PJP versus structural lung damage for CPA. Key clinical predictors of CPA included male sex, coexisting COPD or interstitial lung disease, squamous cell carcinoma (SCC) histology, low body mass index (BMI), and prior radiotherapy or chemoradiotherapy. The inverse association between BMI and CPA risk highlights the contribution of nutritional status. For PJP, corticosteroid use was the main risk factor, with daily doses ≥20 mg significantly increasing the risk of infection, reinforcing the need for dose-aware prophylactic strategies.

These findings support a risk-based approach to screening and prophylaxis, emphasizing multidisciplinary collaboration among oncologists, pulmonologists, and infectious disease specialists. Treatment decisions, particularly those involving corticosteroids and radiotherapy, should be carefully balanced against infection risk. Future research should aim to develop validated risk models and evaluate targeted prophylaxis, optimal therapeutic regimens, and long-term outcomes. FPIs represent a clinically significant complication in lung cancer, and tailoring management to their distinct risk profiles may improve prevention and patient care.

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

MS participated in the study conceptualization, data curation, formal analysis, investigation (lead), methodology, writing—original draft (lead), and writing—review & editing. MG participated in the study conceptualization, data curation, formal analysis, investigation, methodology (supporting), and project administration and supervision (supporting). MA participated in the study conceptualization, data curation (supporting), formal analysis (supporting), investigation (supporting), methodology (supporting), project administration and supervision (lead), and writing—review & editing.

REFERENCES

1. Shah A, Hunter-Smith D. Lung Cancer. In: Paulman PM, Taylor RB, Paulman AA, Nasir LS (eds.) Fam. Med., Cham: Springer International Publishing; 2022, p. 1203–10. https://doi.org/10.1007/978-3-030-54441-6_92.
2. Fu Y, Liu J, Chen Y, Liu Z, Xia H, Xu H. Gender disparities in lung cancer incidence in the United States during 2001–2019. Sci Rep. 2023;13:12581. https://doi.org/10.1038/s41598-023-39440-8.
3. Zhang Y, Vaccarella S, Morgan E, Li M, Etxeberria J, Chokunonga E, et al. Global variations in lung cancer incidence by histological subtype in 2020: a population-based study. Lancet Oncol. 2023;24:1206–18. https://doi.org/10.1016/S1470-2045(23)00444-8.
4. Tesfaw LM, Dessie ZG, Mekonnen Fenta H. Lung cancer mortality and associated predictors: systematic review using 32 scientific research findings. Front Oncol 2023;13:1308897. https://doi.org/10.3389/fonc.2023.1308897.
5. Santorsola M, Di Lauro V, Nasti G, Caraglia M, Capuozzo M, Perri F, et al. Tumour Burden Reporting in Phase III Clinical Trials of Metastatic Lung, Breast, and Colorectal Cancers: A Systematic Review. Cancers (Basel). 2022;14:3262. https://doi.org/10.3390/cancers14133262.
6. Morimoto K, Hamashima R, Yamada T, Yokoyama T, Kobayashi T, Tsuyuguchi K, et al. Clinical significance of chronic pulmonary aspergillosis in lung cancer patients undergoing anticancer drug therapy. Thorac Cancer. 2024;15:1882–8. https://doi.org/10.1111/1759-7714.15416.
7. Esmaeel HM, Mohamed SS, Alhewaig AA, Aboul-Nasr MB. Pulmonary Aspergillosis in Naïve Non-neutropenic Lung Cancer Patients. Curr Respir Med Rev. 2023;19:314–22. https://doi.org/10.2174/1573398x19666230816091304.
8. Halidi AG, Ölçen M, Gürbüz E, Ekici A, Aydemir S, Yılmaz H. Investigation of Pneumocystis jirovecii in Lung Cancer Patients with the Nested PCR Method. Turkiye Parazitoloji Derg. 2022;46:276–80. https://doi.org/10.4274/tpd.galenos.2022.44153.
9. Huang J, Lan C, Li H, Chen S, Lin Q, Weng H. Concomitant lung adenocarcinoma and pulmonary cryptococcosis confirmed by

pathologic examinations. Medicine (Baltimore). 2019;98:e18316. https://doi.org/10.1097/MD.0000000000018316.

10. Sugimoto S, Soh J, Suzawa K, Miyoshi K, Otani S, Yamamoto H, et al. Pulmonary aspergillosis as a late complication after surgery for locally advanced non-small cell lung cancer treated with induction chemoradiotherapy. Surg Today. 2020;50:863–71. https://doi.org/10.1007/s00595-020-01960-5.
11. Carpagnano GE, Lacedonia D, Palladino GP, Logrieco G, Crisetti E, Susca A, et al. Aspergillus spp. colonization in exhaled breath condensate of lung cancer patients from Puglia Region of Italy. BMC Pulm Med. 2014;14:22. https://doi.org/10.1186/1471-2466-14-22.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
13. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919.
14. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12:55–61. https://doi.org/10.1002/jrsm.1411.
15. Tamura A, Suzuki J, Fukami T, Matsui H, Akagawa S, Ohta K, et al. Chronic pulmonary aspergillosis as a sequel to lobectomy for lung cancer. Interact Cardiovasc Thorac Surg. 2015;21:650–6. https://doi.org/10.1093/icvts/ivv239.
16. Whittaker G, Taylor M, Chamula M, Granato F, Balata H, Kosmidis C. Chronic Pulmonary Aspergillosis after Surgical Treatment for Non-Small Cell Lung Cancer—An Analysis of Risk Factors and Clinical Outcomes. J Fungi. 2024;10:335. https://doi.org/10.3390/jof10050335.
17. Kim B-G, Choi YS, Shin SH, Lee K, Um S-W, Kim H, et al. Mortality and lung function decline in patients who develop chronic pulmonary aspergillosis after lung cancer surgery. BMC Pulm Med. 2022;22:436. https://doi.org/10.1186/s12890-022-02253-y.
18. Zaini J, Al Maududi AA, Fillahihasanah T, Fadhillah MR, Pradono P, Haryanto B, et al. Pneumocystis jirovecii colonization in bronchoalveolar lavage among naïve non-small cell lung cancer from tertiary respiratory hospital in Jakarta, Indonesia. J Infect Dev Ctries. 2022;16:1643–7. https://doi.org/10.3855/jidc.15840.
19. Shin SH, Kim BG, Kang J, Um SW, Kim H, Kim HK, et al. Incidence and risk factors of chronic pulmonary aspergillosis development during long-term follow-up after lung cancer surgery. J Fungi. 2020;6:1–10. https://doi.org/10.3390/jof6040271.
20. Lee EH, Kim EY, Lee SH, Roh YH, Leem AY, Song JH, et al. Risk factors and clinical characteristics of Pneumocystis jirovecii pneumonia in lung cancer. Sci Rep. 2019;9:2094. https://doi.org/10.1038/s41598-019-38618-3.
21. Nishigaki Y, Fujita Y, Fujiuchi S, Hiramatsu M, Yamamoto Y, Takeda A, et al. Clinical aspects of pneumocystis pneumonia in patients with lung cancer. Japanese J Lung Cancer. 2009;49:241–7. https://doi.org/10.2482/haigan.49.241.
22. Shehbaz M, Aslam S, Arslan M, Nizamuddin S, Ali S, Abbas S. Clinical Characteristics and Outcomes of Pneumocystis jirovecii Pneumonia in Cancer Patients From a Tertiary Care Hospital. Cureus. 2023;15:e51291. https://doi.org/10.7759/cureus.51291.
23. Evans TJ, Lawal AA, Kosmidis C, Denning DW. Chronic Pulmonary Aspergillosis: Clinical Presentation and Management. Semin Respir Crit Care Med. 2024;45:88–101. https://doi.org/10.1055/s-0043-1776914.
24. Abu Rous F, Singhi EK, Sridhar A, Faisal MS, Desai A. Lung Cancer Treatment Advances in 2022. Cancer Invest. 2023;41:12–24. https://doi.org/10.1080/07357907.2022.2119479.
25. Chen J, Chen J, Ding HY, Pan QS, Hong WD, Xu G, et al. Use of an artificial neural network to construct a model of predicting deep fungal infection in lung cancer patients. Asian Pacific J Cancer Prev. 2015;16:5095–9. https://doi.org/10.7314/APJCP.2015.16.12.5095.
26. Mori H, Ohno Y, Ito F, Endo J, Yanase K, Funaguchi N, et al. Polymerase chain reaction positivity of Pneumocystis jirovecii during primary lung cancer treatment. Jpn J Clin Oncol. 2010;40:658–62. https://doi.org/10.1093/jjco/hyq040.
27. Togashi Y, Masago K, Ito Y, Sakamori Y, Okuda C, Fukuhara A, et al. Pneumocystis jiroveci pneumonia and colonization in patients with advanced lung cancer. Oncol Lett. 2013;5:601–4. https://doi.org/10.3892/ol.2012.1052.
28. Zaini J, Al Maududi AA, Annisa Z, Siregar DG, Setianingrum F, Tugiran M, et al. Diversity of Fungal Colonization in Respiratory Tract of Naïve Lung Cancer and The Emergence of Voriconazole Resistant Aspergillus. HAYATI J Biosci. 2023;30:1139–48. https://doi.org/10.4308/hjb.30.6.1139-1148.
29. Zhu ZZ, Hao HX, Tao R, Zhang YW. Identification of prognostic factors of chronic pulmonary aspergillosis: a retrospective cohort of 106 patients. J Thorac Dis. 2024;16:7310–9. https://doi.org/10.21037/jtd-24-831.
30. Kimura Y, Sasabuchi Y, Jo T, Hashimoto Y, Kumazawa R, Ishimaru M, et al. Epidemiology of chronic pulmonary aspergillosis: A nationwide descriptive study. Respir Investig. 2024;62:1102–8. https://doi.org/10.1016/j.resinv.2024.09.015.
31. Maitre T, Cottenet J, Godet C, Roussot A, Carime NA, Ok V, et al. Chronic pulmonary aspergillosis: Prevalence, favouring pulmonary diseases and prognosis. Eur Respir J. 2021;58. https://doi.org/10.1183/13993003.03345-2020.
32. Aguilar-Company J, Martín MT, Goterris-Bonet L, Martinez-Marti A, Sampol J, Roldán E, et al. Chronic pulmonary aspergillosis in a tertiary care centre in Spain: A retrospective, observational study. Mycoses. 2019;62:765–72. https://doi.org/10.1111/myc.12950.
33. de Oliveira VF, Viana JA, Sawamura MVY, Magri ASGK, Benard G, Costa AN, et al. Challenges, Characteristics, and Outcomes of Chronic Pulmonary Aspergillosis: A 11-Year Experience in A Middle-Income Country. Mycopathologia. 2023;188:683–91. https://doi.org/10.1007/s11046-022-00676-z.
34. Nie W, Lu J, Qian J, Wang S-Y, Cheng L, Zheng L, et al. Obesity and survival in advanced non-small cell lung cancer patients treated with chemotherapy, immunotherapy, or chemoimmunotherapy: a multicenter cohort study. BMC Med. 2024;22:463. https://doi.org/10.1186/s12916-024-03688-2.
35. Toussie D, Ginocchio LA, Cooper BT, Azour L, Moore WH, Villasana-Gomez G, et al. Radiation Therapy for Lung Cancer: Imaging Appearances and Pitfalls. Clin Chest Med. 2024;45:339–56. https://doi.org/10.1016/j.ccm.2024.02.007.
36. Terrones-Campos C, Ledergerber B, Specht L, Vogelius IR, Helleberg M, Lundgren J. Risk of Bacterial, Viral, and Fungal Infections in Patients With Solid Malignant Tumors Treated With Curative Intent Radiation Therapy. Adv Radiat Oncol. 2022;7:100950. https://doi.org/10.1016/j.adro.2022.100950.
37. Choi Y, Noh JM, Shin SH, Lee K, Um SW, Kim H, et al. The Incidence and Risk Factors of Chronic Pulmonary Infection after Radiotherapy in Patients with Lung Cancer. Cancer Res Treat. 2023;55:804–13. https://doi.org/10.4143/crt.2022.1305.
38. Vinod SK, Hau E. Radiotherapy treatment for lung cancer: Current status and future directions. Respirology. 2020;25:61–71. https://doi.org/10.1111/resp.13870.
39. Liebling M, Rubio E, Ie S. Prophylaxis for Pneumocystis jiroveci pneumonia: Is it a necessity in pulmonary patients on high-dose, chronic corticosteroid therapy without AIDS? Expert Rev Respir Med. 2015;9:171–81. https://doi.org/10.1586/17476348.2015.1002471.
40. Kamel T, Janssen-Langenstein R, Quelven Q, Chelly J, Valette X, Le MP, et al. Pneumocystis pneumonia in intensive care: clinical spectrum, prophylaxis patterns, antibiotic treatment delay impact, and role of corticosteroids. A French multicentre prospective cohort study. Intensive Care Med. 2024;50:1228–39. https://doi.org/10.1007/s00134-024-07489-2.
41. Luque Paz D, Jouneau S, Tattevin P, Ricordel C. Pneumocystis in metastatic lung cancer, a pragmatic approach in support of prophylaxis. BMJ Case Rep. 2021;14:e232895. https://doi.org/10.1136/bcr-2019-232895.
42. Bai X, Wang H, Tang Y, Xiao C, Gao Y, Tong H, et al. Lung adenocarcinoma concurrent with pulmonary cryptococcosis: a case report and literature review. BMC Pulm Med. 2024;24:416. https://doi.org/10.1186/s12890-024-03242-z.
43. Ng KL, Huan N, Tan WL, Aminudin NHM, Hassan F, Nordin KM. Unravelling lung adenocarcinoma in an immunocompetent patient with endobronchial aspergilloma: A case report. Respirol Case Reports. 2024;12:e01409. https://doi.org/10.1002/rcr2.1409.
44. Setiwalidi K, Li Y, Ma Y, Hao Z, Zhao Y, Zhang Y, et al. Invasive aspergillosis complicated in a patient with non-small cell lung cancer harboring RET fusion during treatment with RET-TKIs: a case report and literature review. Front Oncol. 2024;14:1431908. https://doi.org/10.3389/fonc.2024.1431908.
45. Guziejko K, Klukowska K, Budzińska U, Mróz RM. Case Report: Chronic Pulmonary Aspergillosis—An Unusual Long-Term

Complication of Lung Cancer Treatment. Front Med. 2022;8:777457. https://doi.org/10.3389/fmed.2021.777457.

46. Hiba Z, Abdelmoughit H, Zaynab IH, Hounaida J, Rachida L, Youssef O. Pneumocystis pneumonia in patient with lung adenocarcinoma: early side effects from pembrolizumab. Radiol Case Reports. 2022;17:3979–81. https://doi.org/10.1016/j.radcr.2022.07.083.
47. Kim T-W, Lee J-H, Lee H-J, Kim S-W, Choi H-S. Pneumocystis Pneumonia in a Non-Immunocompromised Lung Cancer Patient after Surgery: A Case Report. Healthcare. 2022;10:2063. https://doi.org/10.3390/healthcare10102063.
48. Doello K, Amezcua V, García J, Valdivia J. Pneumocystis jirovecii pneumonia in a non-small cell lung cancer patient on chemoradiotherapy: A case report. Saudi J Med Med Sci. 2020;8:53–5. https://doi.org/10.4103/sjmms.sjmms_255_18.
49. Yao K, Qiu X, Hu H, Han Y, Zhang W, Xia R, et al. Pulmonary cryptococcosis coexisting with central type lung cancer in an immuocompetent patient: A case report and literature review. BMC Pulm Med. 2020;20:161. https://doi.org/10.1186/s12890-020-01200-z.
50. Uehara Y, Kasai H, Nakajima T, Tanabe N, Tatsumi K, Yoshino I. Aspergillus sternomyelitis developed from chronic pulmonary aspergillosis as a late complication to lobectomy for lung cancer. Intern Med. 2018;57:2991–4. https://doi.org/10.2169/internalmedicine.0334-17.
51. Boyd M, Ojha S, Goyos J, Cragun WH, Rubio E. Invasive pulmonary aspergillosis and lung adenocarcinoma: Case report. Thorac Cancer. 2013;4:212–4. https://doi.org/10.1111/j.1759-7714.2012.00145.x.
52. Santos VM dos, Trindade MC da, Souza DW da S de, Menezes AIC de, Oguma PM, Nascimento ALO. A 76-year-old Man with a Right Lung Adenocarcinoma and Invasive Aspergillosis. Mycopathologia. 2013;176:113–8. https://doi.org/10.1007/s11046-013-9651-2.
53. Uchida Y, Tsukino M, Shigemori W, Hayashi E, Watanabe I, Nakayama T, et al. Diagnosis of pulmonary mucormycosis aiding the diagnosis of small cell lung cancer. J Med Microbiol. 2012;61:1610–3. https://doi.org/10.1099/jmm.0.040766-0.
54. Neuville M, Borie R, Rodier JM, Debray MP, Danel C, Dombret MC, et al. Pneumocystose chez un patient traité par pemetrexed pour adénocarcinome pulmonaire. Rev Mal Respir. 2011;28:97–100. https://doi.org/10.1016/j.rmr.2010.06.029.
55. Velcheti V, Govindan R. Pneumocystis pneumonia in a patient with non-small cell lung cancer (NSCLC) treated with pemetrexed containing regimen. Lung Cancer. 2007;57:240–2. https://doi.org/10.1016/j.lungcan.2007.02.010.
56. Itano H, Andou A, Date H, Shimizu N. Non-small cell lung cancer coexisting with pulmonary aspergilloma. Japanese J Thorac Cardiovasc Surg. 2005;53:513–6. https://doi.org/10.1007/s11748-005-0099-2.
57. Tashiro M, Takazono T, Izumikawa K. Chronic pulmonary aspergillosis: comprehensive insights into epidemiology, treatment, and unresolved challenges. Ther Adv Infect Dis. 2024;11:20499361241253751. https://doi.org/10.1177/20499361241253751.
58. Rhoads S, Maloney J, Mantha A, Van Hook R, Henao-Martinez AF. Pneumocystis jirovecii Pneumonia in HIV-Negative, Non-transplant Patients: Epidemiology, Clinical Manifestations, Diagnosis, Treatment, and Prevention. Curr Fungal Infect Rep. 2024;18:125-35. https://doi.org/10.1007/s12281-024-00482-8.
59. Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018;74(3):785-94. https://doi.org/10.1111/biom.12817.
60. Classen AY, Henze L, von Lilienfeld-Toal M, Maschmeyer G, Sandherr M, Graeff LD, et al. Primary prophylaxis of bacterial infections Pneumocystis jirovecii pneumonia in patients with hematologic malignancies and solid tumors: 2020 updated guidelines of the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology (AGIHO/DGHO). Ann Hematol. 2021;100(6):1603-20. https://doi.org/10.1007/s00277-021-04452-9.
61. Park JW, Curtis JR, Choi SR, Kim MJ, Ha YJ, Kang EH, et al. Risk-Benefit Analysis of Primary Prophylaxis Against Pneumocystis Jirovecii Pneumonia in Patients With Rheumatic Diseases Receiving Rituximab. Arthritis Rheumatol. 2023;75(11):2036-44. https://doi.org/10.1002/art.42541.

Vascular reactivity in post-COVID-19 patients: analysis and correlation with functional capacity

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TO THE EDITOR:

This article discusses a technique for assessing vascular reactivity in post-COVID-19 patients, whose outcomes 4 months after hospital discharge have yet to be fully understood. Understanding vascular reactivity in such patients may help elucidate the relationship of COVID-19 sequelae, prognosis, and long-term functionality.

During the COVID-19 pandemic, critically ill patients frequently required ICU admission, oxygen therapy, and mechanical ventilation, often resulting in complications related to comorbidities and prolonged hospitalization. Vascular alterations, chronic/acute inflammation, and worsening of preexisting conditions have been associated with poor outcomes.[1,2] Patients presenting with any of the aforementioned conditions commonly experience functional decline, muscle loss, ICU-acquired weakness, and reduced independence.[3] In patients with COVID-19, complications such as microthrombi, thromboembolic events, epithelial damage, and elevated proinflammatory cytokines are prevalent, and the dysregulated inflammatory response can lead to vasculitis, coagulation disorders, and impaired gas exchange caused by altered capillary blood flow.[4] Evidence suggests that vascular dysfunction as assessed by near-infrared spectroscopy (NIRS) and vascular occlusion testing (VOT) is associated with endothelial damage, more severe ARDS, and increased mortality.[5] When associated with submaximal tests such as the six-minute walk test (6MWT), NIRS can aid in assessing musculoskeletal, vascular, and pulmonary responses in post-COVID-19 patients, revealing potential associations between cardiovascular and microvascular dysfunction.[6] We sought to evaluate vascular reactivity in post-COVID-19 patients using VOT and to explore the correlation of VOT with the 6MWT and handgrip strength (HGS). This was a prospective observational study conducted at the outpatient clinic of the *Universidade Estadual de Campinas Hospital de Clínicas*, located in the city of Campinas, Brazil. The study was approved by the local research ethics committee (Protocol no. CAAE 34454920.7.0000.5404). Between February and December of 2022, individuals > 18 years of age discharged after RT-PCR-confirmed COVID-19 pneumonia and referred to the post-COVID-19 outpatient clinic were invited by telephone to undergo functional and vascular assessments at our physical therapy and occupational therapy service. Exclusion criteria included upper limb injuries preventing NIRS sensor placement, inability to perform the 6MWT, and cognitive impairment interfering with test understanding. Each participant underwent a single evaluation session including the following: vascular reactivity assessment via NIRS and VOT; HGS testing with a hydraulic dynamometer (Saehan Corporation, Changwon, South Korea); and the 6MWT, performed in a 30-m corridor in accordance with the American Thoracic Society guidelines.[7] The six-minute walk distance (6MWD) was compared with reference equations for the 6MWT in healthy individuals in Brazil.[7]

Before VOT, body fat was measured using an adipometer (Slim Fit; Balmak, Santa Barbara d'Oeste, Brazil) on the dominant arm. Blood pressure was measured with a sphygmomanometer on the contralateral arm (AccuMed, Rio de Janeiro, Brazil). The NIRS sensor (PortaMon; Artinis Medical Systems, Elst, the Netherlands) was secured to the opposite forearm with a black band to reduce ambient light interference. After resting in the supine position for 5 min, a cuff was inflated to 50 mmHg above systolic pressure and maintained for 3 min. A pulse oximeter (G-TECH, Belo Horizonte, Brazil) was placed on the contralateral arm to monitor HR and SpO_2. NIRS data collection continued for 5 min after occlusion, totaling approximately 13 min. The parameters analyzed included desaturation slope, resting saturation, minimum saturation, maximum saturation, resaturation slope, and AUC. Data were transferred via Bluetooth® to a notebook (Lenovo, Beijing, China) and analyzed using DOS-based software.

COVID-19 has systemic repercussions that have yet to be fully understood, especially among hospitalized individuals. We observed that hospital stays longer than 10 days can have a negative impact on resaturation slope values as measured via NIRS during VOT, even in the absence of clearly impaired HGS or 6MWT performance approximately 4 months after discharge.

Of a total of 88 post-COVID-19 patients who had been admitted to our hospital, 47 completed the evaluation protocol (Table 1). All of the study participants achieved more than 80% of the predicted 6MWD (mean, 476.3 ± 98.3 m), and mean HGS was 28.8 ± 11.3 kgf. Mean forearm skinfold thickness was 6.0 ± 10.8 mm. Of the NIRS variables, only the resaturation slope showed a significant correlation with clinical parameters ($r = -0.34$; $p = 0.03$). No significant correlations were

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Table 1. General characteristics of the study sample.[a]

Characteristic	Post-COVID-19 (N = 47)
Sex, female/male	12/35
Age, years	56 ± 1.5
Length of hospital stay, days	
1-5	14 (29.8)
6-10	11 (23.4)
> 10	22 (46.8)
Time since hospital discharge, days	139.6 ± 57.6
Use of corticosteroids, %	44.7
IMV/NIV, %	27.7/4.2
HFNC, %	4.3
Comorbidities	
Hypertension, %	48.9
Smoking, %	34.0
Diabetes, %	29.8
Obesity, %	10.6
6MWD, m	476.3 ± 98.3

IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; and 6MWD: six-minute walk distance. [a]Values expressed as n/n, n (%), or mean ± SD, except where otherwise indicated.

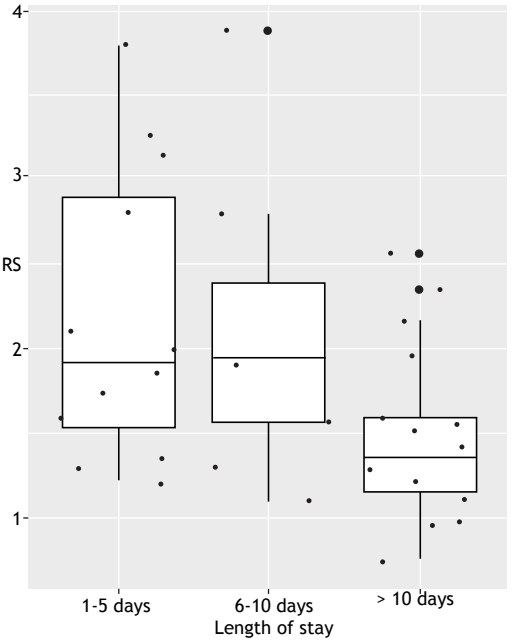

Figure 1. Dispersion of resaturation slope (RS) values, by length of hospital stay.

found between hospital length of stay or time since hospital discharge and vascular or functional outcomes ($p > 0.05$).

VOT showed moderate correlations with the 6MWT: a negative correlation between AUC and resting HR ($r = -0.42$; $p = 0.001$); a positive correlation between AUC and the 6MWD ($r = 0.39$; $p = 0.01$); and a weak but significant positive correlation between the resaturation slope and resting SpO_2 ($r = 0.37$; $p = 0.01$). When patients were stratified by corticosteroid use during hospitalization, significantly lower maximum saturation values (71.74 ± 3.52%) and lower post-6MWT SpO_2 (95.65 ± 2.69%) were observed in the corticosteroid group ($p = 0.03$ and $p = 0.04$, respectively), suggesting a possible impact on microvascular recovery. However, the use of invasive mechanical ventilation did not significantly affect NIRS outcomes.

Patients who had been hospitalized for more than 10 days had significantly lower resaturation slope values (1.47 ± 0.51 %/s) than those who had been hospitalized for 1-5 days or 6-10 days ($p = 0.02$), reinforcing the hypothesis that prolonged hospitalization is associated with impaired microvascular reactivity (Figure 1). Although the functional consequences were not evident in the short term, these findings may indicate long-term risks related to endothelial dysfunction.[8,9] The need for further prospective studies remains critical to clarify the clinical implications of these microcirculatory alterations.

COVID-19 is known to cause significant endothelial dysfunction associated with vasoplegia, systemic inflammation, and prothrombotic responses.[8] Previous studies have demonstrated that microcirculatory changes identified via NIRS may correlate with ARDS severity and poor prognosis.[8] In our analysis, lower resaturation slope values were observed in patients who received corticosteroids during hospitalization, suggesting that microcirculatory recovery may be affected by such interventions.[9] Although a reduced resaturation slope had no direct impact on functional performance, it may represent an early marker of endothelial dysfunction and increased risk for long-term complications.[8]

Although there was no significant correlation between invasive mechanical ventilation and NIRS parameters, hospital length of stay showed a significant association. This factor has been widely linked to peripheral and diaphragmatic muscle loss and higher mortality rates.[10] Even patients with preserved submaximal exercise responses have shown altered vascular reactivity,[10] emphasizing the relevance of these findings as potential clinical predictors. Despite the lack of randomized clinical trials explaining why endothelial dysfunction as detected by NIRS and VOT does not always translate to reduced function, this condition may still signal an increased risk of organ dysfunction and mortality.

It is of note that the patients evaluated in the present study were not part of the first wave of the COVID-19 pandemic (from 2020 to early 2021), when vaccination was limited and clinical management protocols were still evolving. Our patients likely benefited from improved care, wider vaccine coverage, refined therapeutic strategies, and greater experience from multidisciplinary teams.[3] Finally, the limitations of the present study include loss to follow-up as a result of outdated contact information, relocation, death, or transportation issues, all of which reduced the final

sample size. In addition, external factors such as ambient light, poor sensor fixation, and involuntary movements may have compromised the quality of the NIRS signal.

AUTHOR CONTRIBUTIONS

LIPS: literature review, data collection, study design, data analysis, and manuscript preparation. MCP and BSV: manuscript preparation and critical revision of the manuscript for important intellectual content. RCM and LSRR: study design, data analysis, manuscript preparation, and critical revision of the manuscript for important intellectual content.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Yaqub MA, Wieringa FP, van der Steen AFW, Heger M. Non-invasive monitoring of microvascular oxygenation and reactive hyperemia using hybrid, near-infrared diffuse optical spectroscopy for critical care. J Vis Exp. 2024;(207): e66062. https://doi.org/10.3791/66062
2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4. https://doi.org/10.1016/S0140-6736(20)30628-0
3. Jimeno-Almazán A, Pallarés JG, Buendía-Romero Á, Martínez-Cava A, Franco-López F, Sánchez-Alcaraz Martínez BJ, et al. Post-COVID-19 syndrome and the potential benefits of exercise. Int J Environ Res Public Health. 2021;18(10):5329. https://doi.org/10.3390/ijerph18105329
4. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol. 2020;20(7):389-91. https://doi.org/10.1038/s41577-020-0343-0
5. Mesquida J, Espasa A, Hermida C, Saludes P, Gimeno A, Betbese AJ. Peripheral microcirculatory alterations are associated with the severity of acute respiratory distress syndrome in COVID-19 patients admitted to intermediate respiratory and intensive care units. Crit Care. 2021;25(1):367. https://doi.org/10.1186/s13054-021-03803-2
6. Beć KB, Grabska J, Huck CW. Near-infrared spectroscopy in bio-applications. Molecules. 2020;25(12):2948. https://doi.org/10.3390/molecules25122948
7. Iwama AM, Andrade GN, Shima P, Tanni SE, Godoy I, Dourado VZ. The six-minute walk test and body weight-walk distance product in healthy Brazilian subjects. Braz J Med Biol Res. 2009;42:1080-5. https://doi.org/10.1590/S0100-879X2009005000032
8. Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021;17(1):46-64. https://doi.org/10.1038/s41581-020-00357-4
9. Cruz DA, Gava GC, Nascimento LO, Alves DR, Cardoso AC, Avelar NP. Impacts of invasive mechanical ventilation on patients from COVID-19: integrative review [Article in Portuguese]. Res Soc Dev. 2021;10(11):e380101119656. https://doi.org/10.33448/rsd-v10i11.19656
10. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, Cooper C, et al. A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. Age Ageing. 2011;40(4):423-9. https://doi.org/10.1093/ageing/afr051

Cannabidiol oil—an uncommon cause of exogenous lipoid pneumonia

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TO THE EDITOR:

Lipoid pneumonia is an uncommon condition that results from aspirating or inhaling fatlike material of animal, vegetable, or mineral origin. Lipoid pneumonia can be classified as endogenous or exogenous. CT is the imaging technique of choice for evaluating patients with suspected lipoid pneumonia.[1-3]

Here, we present the case of a 40-year-old woman who sought emergency care for abdominal pain and underwent abdominal CT examination, which showed opacities in the lung bases and prompted her referral to a pulmonologist. The patient had been diagnosed with multiple sclerosis at the age of 18. She had no significant respiratory symptom, reporting no cough, expectoration, dyspnea, or fever. Physical examination and laboratory test findings were unremarkable. Chest CT showed heterogeneous consolidation in the right lung with areas of interspersed fat density (careful measurement of density at different sites of consolidation showed negative densities, ranging from −12 to −88 Hounsfield units [HU]), consistent with lipoid pneumonia (Figure 1). History taking revealed that the patient had been using cannabidiol oil (10 drops taken orally twice a day) for approximately 2.5 years. She reported using no other oily or fatty substances. In addition, she reported choking when drinking liquids, as well as accumulation of mucoid secretions in the oropharynx. The final diagnosis was exogenous lipoid pneumonia (ELP).

ELP is caused by inhalation or aspiration of lipid-containing products such as foods and oil-based medications such as laxatives. Traditional oil-based medications are used in order to treat various diseases in children and are often associated with respiratory diseases. In adults, most cases of ELP result from the use of oil-based laxatives for the treatment of constipation or from nasal instillation of oily products for the treatment of chronic rhinopharyngeal diseases. Other, less common, causes of ELP have been reported.[1,2] Clinically, patients are usually asymptomatic, the only manifestations of ELP being an abnormal chest X-ray and nonspecific symptoms such as cough, tachypnea, and fever, similar to those of bacterial pneumonia. The diagnosis of ELP is based on a history of mineral oil aspiration, radiological findings consistent with ELP—in particular, foci of fat attenuation within areas of consolidation on CT—and/or the presence of lipids in BAL fluid or lung biopsy specimens. It might be difficult to diagnose ELP because a history of oil ingestion is often overlooked. The exposure is often identified retrospectively (i.e., after the diagnosis is suspected), when a directed history is taken from the patient or their parents.[1-3]

The most common CT findings are airspace consolidations, ground-glass opacities, a crazy-paving pattern, interlobular septal thickening, airspace nodules, and mass-like lesions. However, none of these findings is a specific radiological feature of ELP. The most characteristic finding in patients with ELP is consolidation with areas of fat attenuation (i.e., negative attenuation values). However, the measured attenuation values may be higher than those of pure oil, given that the oil is spread within the affected parenchyma and mixed with components of pulmonary fibrosis and/or inflammatory exudates. Care must be taken when measuring these values in order to prevent a false-positive interpretation. These measures should be taken in the most hypodense part of the consolidation areas, free of any aerated parenchyma on the periphery or areas of air bronchogram, because of interferences caused by partial volume averaging of partly aerated lungs. Air and soft tissue, when averaged together, can mimic the characteristic attenuation values of fat. Low densities within consolidations may be due to areas of necrosis or fat. In areas of necrosis, although density measurements are low, they are usually positive. In areas with fat, density measurements are negative. Negative densities in lung lesions can be seen in nodules, masses, or consolidations. The differential diagnosis of nodules or masses containing fat is broad, unlike that of fat-containing consolidations, which, to our knowledge, have only been described in cases of lipoid pneumonia.[1-4] This is corroborated by several studies suggesting that negative density values between −150 HU and −30 HU within areas of consolidation are diagnostic of lipoid pneumonia, especially when associated with a history of exposure to oil.[2,5-7] Demonstration of macrophages containing fat vacuoles is necessary only when CT does not show negative densities interspersed with consolidations.

Historically, cannabis has been globally recognized for its therapeutic effects, leading to a substantial increase in studies on tetrahydrocannabinol, cannabidiol, and the endocannabinoid system. In Brazil, the use of cannabis products (especially cannabidiol) for medicinal purposes has increased in recent years. Cannabidiol has been used for epilepsy, especially in refractory forms, with a high level of evidence. There is moderate evidence for the use of cannabidiol in patients with Parkinson's disease, Alzheimer's disease, or autism. Other indications, such as chronic pain, sleep disorders, depression, anxiety, attention-deficit/hyperactivity disorder, and anorexia, have less robust evidence, or preliminary studies and clinical reports predominate.[8,9]

After an extensive review of the English-language literature, we found only one reported case of ELP

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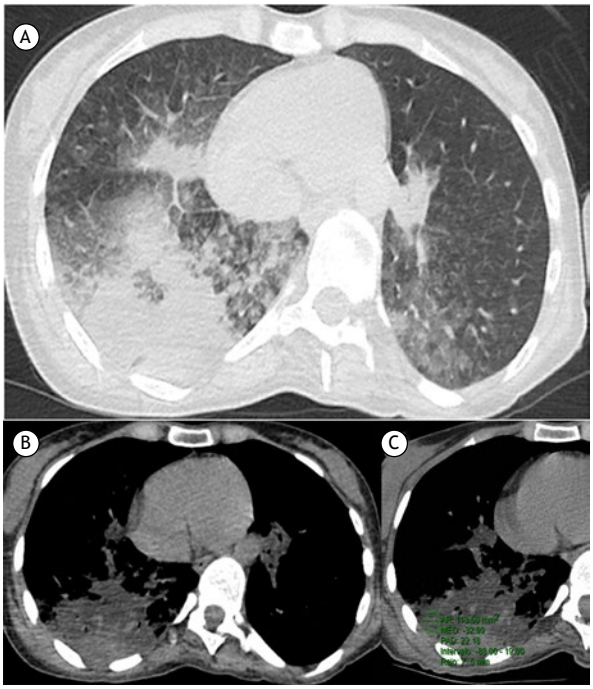

Figure 1. CT scan of the chest at the level of the lower lobe (with lung window settings in A and mediastinal window settings in B and C), showing heterogeneous airspace consolidation with superimposed areas of low attenuation (ranging from −88 to −19 Hounsfield units) in the posterior region of the right lower lobe. This finding is diagnostic of exogenous lipoid pneumonia.

caused by cannabidiol.[10] This was a 4-year-old girl who had epilepsy and seizures, and who presented with respiratory symptoms and alveolar opacities on chest X-ray. BAL was consistent with lipoid pneumonia, which was attributed to the use of cannabidiol for the treatment of epilepsy. The authors of the study stated that, to their knowledge, that was the first description of ELP in the context of chronic aspiration of cannabis oil.[10] Our case differs from that presented by Hanzal et al.[10] because it involved an adult patient, with the diagnosis being made on the basis of CT criteria.

In conclusion, clinicians should be aware that recent increases in the medicinal use of cannabidiol will lead to increases in the number of people with ELP.

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Marchiori E, Zanetti G, Mano CM, Hochhegger B. Exogenous lipoid pneumonia. Clinical and radiological manifestations. Respir Med. 2011;105(5):659-666. https://doi.org/10.1016/j.rmed.2010.12.001
2. Betancourt SL, Martinez-Jimenez S, Rossi SE, Truong MT, Carrillo J, Erasmus JJ. Lipoid pneumonia: spectrum of clinical and radiologic manifestations. AJR Am J Roentgenol. 2010;194(1):103-9. https://doi.org/10.2214/AJR.09.3040
3. Marchiori E, Zanetti G, Mano CM, Irion KL, Daltro PA, Hochhegger B. Lipoid pneumonia in 53 patients following aspiration of mineral oil. Comparison of HRCT findings in adults and children. J Comput Assist Tomogr. 2010;34(1):9-12. https://doi.org/10.1097/RCT.0b013e3181a9ec9f
4. Laurent F, Philippe JC, Vergier B, Granger-Veron B, Darpeix B, Vergeret J, et al. Exogenous lipoid pneumonia: HRCT, MR, and pathologic findings. Eur Radiol. 1999;9(6):1190-6. https://doi.org/10.1007/s003300050815
5. Agarwal R. Low-attenuation consolidation - the most characteristic finding in lipoid pneumonia. Eur J Intern Med. 2006;17(4):307. https://doi.org/10.1016/j.ejim.2005.12.008
6. Sood N, Murin S. Lipoid Pneumonia: Fat Chance of Making the Diagnosis? Chest 2021;160(2):407-408. https://doi.org/10.1016/j.chest.2021.03.054
7. García Latorre R, Rodríguez Díaz R, Barrios Barreto D, Ayala Carbonero A, García Gómez-Muriel MI, Gorospe Sarasúa L. Exogenous Lipoid Pneumonia in Laryngectomy Patients: Radiological Findings. Arch Bronconeumol. 2015;51(7):e36-9. https://doi.org/10.1016/j.arbres.2014.09.002
8. Scattone H, Gauer LE, Pezzini JV, Tófoli LF. Patterns of cannabis use for medical reasons in Brazil: An exploratory latent class analysis study. Int J Drug Policy. 2025;143:104906. https://doi.org/10.1016/j.drugpo.2025.104906
9. Santos Pinto CDB, Esher A, Oliveira CVS, Osorio-de-Castro CGS. Expansion of the medical cannabis market in Brazil and regulatory challenges. Cad Saude Publica. 2024;40(11):e00088624. https://doi.org/10.1590/0102-311xen088624
10. Hanzal N, Mhapankar GS, Sell E, de Nanassy J, Radhakrishnan D. Lipoid Pneumonia Following Chronic Aspiration of Cannabis Oil Used for the Treatment of Seizures. Chest. 2025;167(5):e149-e154. https://doi.org/10.1016/j.chest.2024.10.041

COPD: comparative study of vaccinated and unvaccinated patients for pneumococcal disease

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TO THE EDITOR:

COPD is a heterogeneous disease and one of the top three causes of death worldwide.[1] COPD patients may experience exacerbations, which are common and associated with decline in lung function, increased use of health resources, hospitalizations, and mortality.[2] Pharmacological interventions help reduce exacerbation frequency, but smoking cessation and vaccination are also crucial.[1,3,4]

Pneumococcal vaccines were developed to stimulate protective antibodies against *Streptococcus pneumoniae* strains associated with pneumococcal disease.[5] Conjugate vaccines increase immunogenicity given that polysaccharide antigens are chemically attached to a highly immunogenic inactive protein, inducing a dependent B and T response and an immune memory response.[5,6]

There are few studies comparing pneumococcal vaccines in the population of patients with COPD. For that reason, this study aimed to evaluate whether immunization with pneumococcal vaccine(s) in patients with COPD would interfere in the frequency and severity of acute events related to this disease.

In this historical cohort, patients from two centers in the city of Florianópolis, Brazil, were recruited. To be eligible for the study, patients must have been 40 years of age or older; have had a confirmed diagnosis of cigarette-smoking-related COPD: have presented with a postbronchodilator FEV_1/FVC ratio < 0.70; have had at least a 10 pack-year history of smoking; have been vaccinated for influenza for two consecutive years, and have been on regular treatment for COPD.

This study was approved by the Human Research Ethics Committee of the institution (CAAE 13620419.6.0000.0110). We included patients who gave written informed consent and underwent the following scheme of pneumococcal vaccination:

Group PPV-23: patients vaccinated only with 23-valent pneumococcal polysaccharide vaccine (PPV-23), having been applied in a period equal to or less than 5 years prior to the inclusion in the study.

Group PPV-23+PCV-13: patients vaccinated with both pneumococcal vaccines: 13-valent pneumococcal conjugate vaccine (PCV-13) and PPV-23, regardless of sequence, and the last vaccine having been applied in a period equal to or less than 5 years prior to the inclusion in the study.

Control group: patients who have never received pneumococcal vaccine.

We excluded patients with asthma and/or chronic suppurative lung diseases, those with clinical conditions that could reduce vaccine response, such as immunosuppression, as well as those who were not under regular medical follow-up.

All participants received annual influenza vaccines during the period of the study. The study period was two years after pneumococcal vaccination(s) or in the two years prior to inclusion in the study (influenza control group).

Medical records of the patients were analyzed, considering the medical visits performed between February of 2014 and March of 2021. At the time of the consultation, the COPD Assessment Test questionnaire and the modified dyspnea scale of the Medical Research Council were performed. Confirmation of vaccination was mandatory.

The main outcome was experiencing any exacerbation of COPD. Secondary outcomes were experiencing any hospitalization (ward or ICU), health care utilization (hospitalization or emergency care, for any cause), classification of COPD according to GOLD, and adverse events to the vaccines of the study (pneumococcal and influenza).

Results were summarized as absolute and relative frequencies, means, and standard deviations. The associations were evaluated using the chi-square test at a significance level of 5%. During the study period, 205 patients were considered eligible, and 122 were included (41 in the PPV-23 group, 41 in the PPV-23+PCV-13 group, and 40 in the control group).

The mean age was 70.5 years, with a predominance of men (61.5%). The mean age of the first or only pneumococcal vaccination was 67.7 years, ranging from 46 to 86 years. The mean smoking history was 53.4 pack-years, and the majority of those patients (82.8%) were former smokers.

There was no significant difference between the groups regarding the frequency of exacerbations during the study period. In the PPV-23 group, 63.4% of the patients had at least one exacerbation. In the

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Table 1. Characteristics of the COPD patients included in the study and outcomes (N = 122).[a]

Variable	Group			Total	p
	PPV-23 (n = 41)	PPV-23 + PCV-13 (n = 41)	Control (n = 40)		
Male sex	24 (58.5)	23 (56.0)	28 (70.0)	75 (61.5)	0.39
Age, years	68.90 ± 9.1	74.51 ± 8.6	68.13 ± 9.6		0.34
Age at first pneumococcal vaccine, years	65.5 ± 8.8	67.6 ± 9.3	------		0.32
Comorbidities					0.04
Yes	37 (90.0)	39 (95.1)	31 (77.5)	15 (12.3)	
No	4 (10.0)	2 (4.9	9 (22.5)	107 (87.7)	
GOLD Grade					0.01
1 Early	1 (2.5)	1 (2.5)	7 (17.5)	9 (7.4)	
2 Moderate	16 (39.0)	20 (48.5)	22 (55)	58 (47.5)	
3 Severe	20 (48.5)	13 (32)	9 (22.5)	42 (34.5)	
4 Very Severe	4 (10)	7 (17)	2 (5)	13 (10.6)	
GOLD Class					0.37
A	12 (29.5)	9 (22)	11 (27.5)	32 (26.2)	
B	14 (34.0)	9 (22.0)	7 (17.5)	30 (24.6)	
E	15 (36.5)	23 (56.0)	22 (55.0)	60 (49.2)	
Ward hospitalization					0.01
No	38 (92.7)	39 (95.1)	30 (75.0)	13 (10.6)	
Yes	3 (7.3)	2 (4.9)	10 (25.0)	15 (12.3)	
ICU hospitalization					0.35
No	41 (100)	39 (95.1)	38 (95.0)	118 (96.7)	
Yes	0 (0.0)	2 (4.9)	2 (5.0)	4 (3.3)	
Any hospitalization					0.046
No	38 (92.7)	37 (90.2)	30 (75.0)	105 (86)	
Yes	3 (7.3)	4 (9.8)	10 (25.0)	17 (14)	
Health care utilization					0.26
No	13 (31.7)	7 (17)	12 (30)	32 (26.2)	
Yes	28 (68.3)	34 (83)	28 (70)	90 (73.8)	
Exacerbation					0.23
No	15 (36.6)	8 (19.5)	12 (30.0)	35 (28.7)	
Yes	26 (63.4)	33 (80.5)	28 (70.0)	87 (71.3)	
Adverse effects					0.17
No	32 (78.0)	38 (92.7)	34 (85.0)	104 (85.2)	
Yes	9 (22.0)	3 (7.3)	6 (15.0)	18 (14.8)	

PPV-23: 23-valent pneumococcal polysaccharide vaccine; and PCV-13: 13-valent pneumococcal conjugate vaccine. Values expressed as n (%) and mean ± SD.

PPV-23+PCV-13 and control groups this frequency was, respectively, 80.5% and 70.0% (p = 0.226). In relation to hospitalizations in a ward, the control group experienced a higher frequency of hospitalizations (at least one hospitalization): 25%; PPV-23 group: 7.3%; and PPV-23+PCV-13 group: 4.9% (p = 0.011). In relation to any hospitalization (either in a ward or ICU), this difference was also significant: 25.0% in the control group, 7.3% in the PPV-23 group, and 9.8% in the PPV-23+PCV-13 group (p = 0.046). The use of health services, either due to exacerbation of COPD or decompensation of other comorbidities, did not differ significantly among the groups (Table 1).

One previous study evaluated PCV-13 vaccination and its impact on COPD exacerbations.[7] There was no significant difference in relation to the rate of exacerbations, but the absence of PCV-13 vaccination almost tripled the risk of hospitalizations.

Ignatova et al. demonstrated that the administration of PPV-23 or PCV-13 reduced by four times the chance of a COPD exacerbation in the first year of that study, when compared with the non-immunized group, and reduced hospitalizations,[8] but PPV-23 had a progressive reduced efficacy after the first year of immunization.

Cochrane's last systematic review of 2017 about pneumococcal vaccines in COPD patients have shown that vaccination significantly reduced the probability of an exacerbation of COPD (OR = 0.60; 95% CI: 0.39-0.93).[9]

One aspect to be noted from the present study is its design as a historical cohort, which made it possible to analyze a group of patients not immunized with pneumococcal vaccine(s). If it had a prospective design, ethical considerations should be discussed. Despite its limitations, such as exclusion of immunosuppressed patients, the missing data about comparative analysis

of inhaled therapies in the groups, and the absence of etiological causes of respiratory infections related to the exacerbations, this study indicates that the groups did not differ significantly in relation to COPD exacerbations, but there was a significant difference in relation to hospitalizations. This study strengthens that this preventive measure (pneumococcal vaccination) is important in preventing a severe event in COPD, such as exacerbations leading to hospitalizations.

AUTHOR CONTRIBUTIONS

ASCK: literature review and data collection. RMS: statistical analysis. Both authors wrote, reviewed, and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of COPD 2025 Report. Bethesda: GOLD; 2025.
2. Ritchie AI, Wedzicha JA. Definition, Causes, Pathogenesis, and Consequences of Chronic Obstructive Pulmonary Disease Exacerbations. Clin Chest Med. 2020;41(3):421-438. https://doi.org/10.1016/j.ccm.2020.06.007
3. Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. Chest. 2015;147(4):894-942. https://doi.org/10.1378/chest.14-1676
4. Montes de Oca M. Smoking Cessation/Vaccinations. Clin Chest Med. 2020;41(3):495-512. https://doi.org/10.1016/j.ccm.2020.06.013
5. van Werkhoven CH, Huijts SM. Vaccines to Prevent Pneumococcal Community-Acquired Pneumonia. Clin Chest Med. 2018;39(4):733-52. https://doi.org/10.1016/j.ccm.2018.07.007
6. Josefsberg JO, Buckland B. Vaccine process technology. Biotechnol Bioeng. 2012;109(6):1443-60. https://doi.org/10.1002/bit.24493
7. Figueira-Goncalves JM, Bethencourt-Martin N, Perez-Mendez LI, Diaz-Perez D, Guzman-Saenz C, Vina-Manrique P, et al. Impact of 13-valent pneumococcal conjugate polysaccharide vaccination in exacerbations rate of COPD patients with moderate to severe obstruction. Rev Esp Quimioter. 2017;30(4):269-275.
8. Ignatova GL, Avdeev SN, Antonov VN. Comparative effectiveness of pneumococcal vaccination with PPV23 and PCV13 in COPD patients over a 5-year follow-up cohort study. Sci Rep. 2021;11(1):15948. https://doi.org/10.1038/s41598-021-95129-w
9. Walters JA, Tang JN, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. The Cochrane Database Syst Rev. 2017;1:CD001390. https://doi.org/10.1002/14651858.CD001390.pub4

Is PESI a reliable tool for predicting early mortality in acute pulmonary embolism? Real-life evidence from a single-center study

Tugce Karamustafalioglu[1], Sibel Nayci[1], Yuksel Balci[2], Eylem Sercan Ozgur[1]

TO THE EDITOR,

Recent publications on pulmonary thromboembolism (PTE) have reported signs of right ventricular dysfunction (RVD) on echocardiography or computed tomography (CT) in approximately 34% of patients classified as low risk according to the Pulmonary Embolism Severity Index (PESI).[1] However, these patients are not represented in the early mortality risk assessment tables of current guidelines.[2,3] We defined this subgroup as the so-called "missing group" and aimed to evaluate their clinical characteristics and 30-day mortality outcomes, given the uncertainty surrounding their risk classification.

Between 2018 and 2023, patients diagnosed with PTE at our Pulmonology Clinic were screened to identify individuals meeting the criteria for the "missing group". We analyzed data from patients with low-risk PESI and RVD, representing a rare and underexplored subgroup.

In the present study, patients with <86 points on the PESI (i.e., Class I or II, defined as low risk) were assessed for radiologic and echocardiographic signs of RVD.[4] On chest CT, the following findings were considered markers of RVD: pulmonary artery/aorta diameter ratio ≥1, pulmonary artery diameter ≥3 cm, presence of contrast material in the inferior vena cava (IVC), and right ventricular/left ventricular diameter ratio ≥1.[3] Echocardiographic markers included RV dilation (RV/LV ratio >1), RV hypokinesia, interventricular septal flattening, elevated systolic pulmonary artery pressure, and a dilated IVC with diminished respiratory collapse.[3]

The anatomical extent and location of thrombi were quantified using the Pulmonary Arterial Obstruction Index (PAOI), as modified by Qanadli et al.,[5] which considers segmental involvement of the pulmonary arterial tree and assigns points accordingly.

Twenty-two of the 672 PTE patients (3.2%) met the inclusion criteria for the missing group (Table 1). Their mean age was 44 ± 10 years, and 4 were female (18.2%). A total of 18 patients (81.8%) had no comorbidities. The 30-day mortality rate in this subgroup was 9% (2 patients). One of the deceased was a 29-year-old female (PESI 0, sPESI 0; the simplified Pulmonary Embolism Severity Index [sPESI] is a six-variable scoring system—age >80 years, history of cancer, chronic cardiopulmonary disease, heart rate ≥110 bpm, systolic blood pressure ≤100 mmHg, and oxygen saturation <90%—in which scores ≥1 indicate a higher risk of early mortality), and the other was a 47-year-old male (PESI 10, sPESI 1); both presented with chest pain. One patient had a history of massive pulmonary embolism 11 years earlier, whereas the other had no comorbidities. Their vital signs showed only mild tachycardia (105 and 102 bpm) and slightly reduced oxygen saturation (92% and 91%, respectively). Both had RVD on chest CT and elevated troponin levels. One patient died in hospital, and the other died 11 days post-discharge. These findings highlight a potential gap in risk stratification for patients who appear low risk based on PESI/sPESI but still experience adverse outcomes.

The PESI is a scoring system developed using parameters such as demographic characteristics, comorbidities, and vital signs. It is applied to distinguish intermediate- from low-risk groups in the early mortality risk assessment table. Despite its important role, the PESI has some limitations. For example, patients receive points only when oxygen saturation falls below 90%. However, in younger patients, values of 91–92% should also be considered low and warrant closer monitoring.[6] One of our deceased patients had an oxygen saturation of 91%. Because this value was above the cutoff, the patient's PESI was classified as low, yet death occurred 3 days after the diagnosis. In addition, a history of previous PTE is not among the PESI parameters. The other deceased patient had a history of massive PTE 11 years earlier, but because this factor is not considered in the scoring system, the patient's PESI was also low. Nevertheless, this patient died within 30 days.

For patients diagnosed with PTE and classified as intermediate risk in the early mortality risk assessment table, the 30-day mortality rate ranges from 5% to 15%.[3] In our missing group, a 9% mortality rate was observed, which is notable despite the limited sample size. This finding suggests that careful reassessment of early mortality risk stratification tools is warranted.

This study has two limitations that should be addressed in future research. First, its retrospective design. Second, although the sample size was modest, it was sufficient to provide preliminary insights. The strength of this work lies in its focus on a rarely characterized subgroup within the PTE population. Larger, prospective studies are needed to confirm and expand upon these findings.

Although the Qanadli index was calculated for all patients who underwent chest CT, it did not correlate

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Table 1. Classification of 22 patients based on right ventricular overload findings.

	n	ECHO or CT		Troponin	Qanadli Index Average
		ECHO	CT		
If the PESI were high, these patients would be in the "intermediate-high" risk group (n = 13)	9	+	+	+	63.8%
	1	+	-	+	27.5%
	3*	-	+	+	25%
If the PESI were high, these patients would be in the "intermediate-low" risk group (n = 9)	1	-	-	+	17.5%
	6*	+	+	-	41.6%
	0	-	+	-	
	2	+	-	-	26.2%

*The deceased patients belonged to these groups. CT findings = RV/LV ≥1 and/or PA diameter ≥3 cm and/or PA/AO diameter ratio ≥1 and/or presence of contrast agent in the IVC. Abbreviations: PESI, Pulmonary Embolism Severity Index; CT, computed tomography; ECHO, echocardiography; RV, right ventricle; LV, left ventricle; PA, pulmonary artery; AO, aorta; IVC, inferior vena cava.

directly with early mortality in our cohort. The two patients who died had only moderate obstruction scores, suggesting that clot burden alone may not be sufficient for risk assessment. Our results emphasize the importance of integrating anatomical assessment with biomarkers and RVD evaluation to improve prognostication.

Only a small proportion of patients diagnosed with PTE present with both RVD and a low PESI. Although current guidelines mention this condition either in the text or in table footnotes, it is not included in the most widely used and practical early mortality risk assessment tables. This omission may contribute to under-recognition in clinical practice. Our findings raise the question of whether the PESI alone is sufficient to guide management in all cases.

In light of these concerns, our findings underscore the need for an updated and more comprehensive risk stratification tool. Such a system should integrate elements from other validated instruments, such as the Hestia score—which incorporates recurrence risk and social considerations—and include clinical history, particularly prior venous thromboembolism episodes. This approach may more effectively identify high-risk patients who might otherwise be overlooked by traditional metrics.

Thank you for the opportunity to share our perspective.

AUTHOR CONTRIBUTIONS

TK: study conceptualization, data collection, writing of the manuscript. SN: study supervision, critical review, methodology. YB: statistical analysis, results interpretation. ESO: study design, final approval of the manuscript.

CONFLICTS OF INTEREST

The authors have no potential conflicts of interest to disclose.

REFERENCES

1. Barco S, Mahmoudpour SH, Planquette B, Sanchez O, Konstantinides SV, Meyer G. Prognostic value of right ventricular dysfunction or elevated cardiac biomarkers in patients with low-risk pulmonary embolism: a systematic review and meta-analysis. Eur Heart J. 2019;40(11):902–910. https://doi.org/10.1093/eurheartj/ehy873.
2. Amado VM, Fernandes CJCDS, Salibe-Filho W, Gazzana MB, Rocha AT, Yoo HHB, et al. Brazilian guidelines for the pharmacological treatment of pulmonary embolism. Official document of the Brazilian Thoracic Association based on the GRADE methodology. J Bras Pneumol. 2025;51(2):e20240314. https://doi.org/10.36416/1806-3756/e20240314.
3. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41(4):543–603. https://doi.org/10.1093/eurheartj/ehz405.
4. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med. 2005;172(8):1041–6. https://doi.org/10.1164/rccm.200506-862OC.
5. Qanadli SD, El Hajjam M, Vieillard-Baron A, Joseph T, Mesurolle B, Oliva VL, et al. New CT index to quantify arterial obstruction in pulmonary embolism: comparison with angiographic index and echocardiography. AJR Am J Roentgenol. 2001;176(6):1415–20. https://doi.org/10.2214/ajr.176.6.1761415.
6. Graham HR, King C, Duke T, Ahmed S, Baqui AH, Colbourn T, et al. Hypoxaemia and risk of death among children: rethinking oxygen saturation, risk-stratification, and the role of pulse oximetry in primary care. Lancet Glob Health. 2024;12(8):e1359–e1364. https://doi.org/10.1016/s2214-109x(24)00209-2.

Tracheobronchial metastasis from atypical carcinoid

Alan Jhunior Solis[1], Jimmy Icaza-Vera[1], Javier Flandes[1]

A 78-year-old male with no relevant medical history was diagnosed with atypical carcinoid in 2012 and underwent left upper lobectomy with curative intent. Three years later, the patient presented with a single local recurrence, and a left pneumonectomy was performed. Twelve years after the initial diagnosis, a CT scan was performed because of dyspnea, revealing multiple round lesions in the tracheobronchial tree (Figures 1A and 1B). Bronchoscopy showed several polypoid lesions (Figures 1C and 1D), and cryobiopsies were performed. Pathological examination showed well-differentiated neuroendocrine cells, and immunohistochemistry showed a Ki-67 proliferation index of 50%, as well as positivity for CD56, synaptophysin, and chromogranin A, the final diagnosis being atypical carcinoid (Figures 1E and 1F). During a second bronchoscopy, laser and electrocautery resection of the tracheobronchial lesions was performed.

The most common site of carcinoid tumors is the gastrointestinal tract, followed by the tracheobronchial tree.[1] Diagnosis requires a biopsy with histological confirmation, and atypical carcinoids are less common than typical carcinoids, the recurrence rate for the former being higher than that for the latter.[1,2] Atypical carcinoid usually presents as a peripheral lung lesion or a solitary endobronchial lesion.[1] We found only two case reports of multiple tracheobronchial lesions, with tracheobronchial spread occurring seven and eight years after surgical treatment, respectively.[1,2] In the case reported here, tracheobronchial spread occurred nine years after the second surgical procedure and 12 years after the first.

INFORMED CONSENT

Written informed consent was obtained from the patient for the publication of his clinical data and the use of diagnostic images.

AUTHOR CONTRIBUTIONS

AJS, JI-V, and JF: conceptualization, methodology, formal analysis, validation, research, and writing—review and editing. AJS and JI-V: data curation, software, and writing—original draft. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

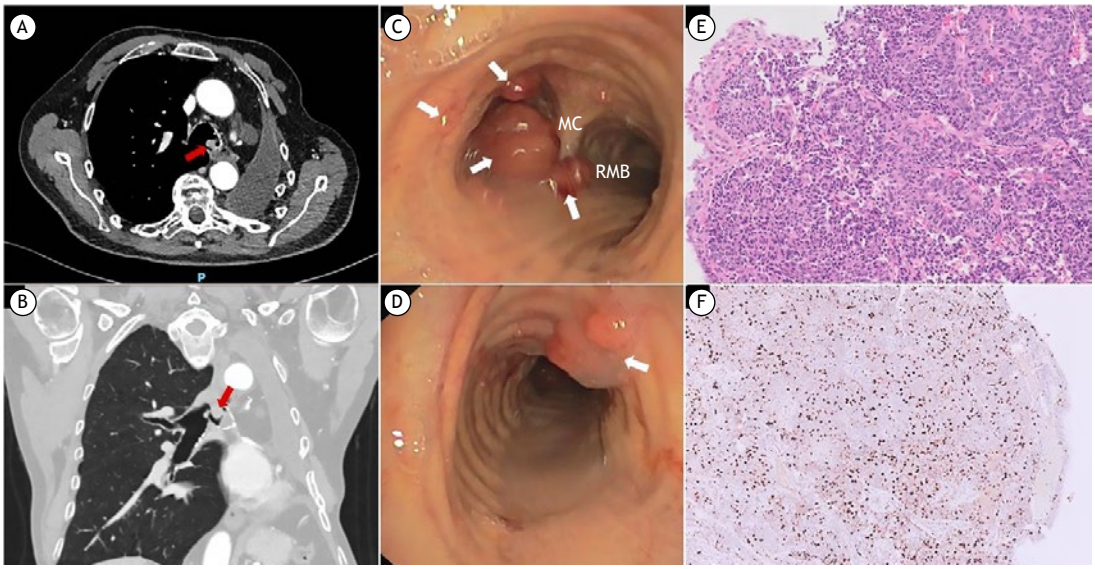

Figure 1. In A, axial CT scan showing a nodular endobronchial lesion with soft tissue density (red arrow). In B, frontal CT scan showing the same nodular lesion (diameter, 19 mm; red arrow). In C and D, flexible bronchoscopy showing polypoid lesions at the entrance of the left main bronchus, main carina, and trachea (white arrows). In E, pathological examination showing well-differentiated neuroendocrine cells forming nests and trabeculae (H&E; magnification, ×10). In F, immunohistochemistry showing a Ki-67 proliferation index of 50%. MC: main carina; and RMB: right main bronchus.

REFERENCES

1. Surani S, Tan J, Ahumada A, Surani SS, Sudhakaran S, Varon J. Delayed Recurrence of Atypical Pulmonary Carcinoid Cluster: A Rare Occurrence. Case Rep Pulmonol. 2014;2014:620814. https://doi.org/10.1155/2014/620814
2. Amemiya R, Takada I, Yazaki Y, Ono S, Kou K, Morishita Y, et al. Atypical carcinoid with multiple central airway metastases: A case report. Respir Med Case Rep. 2021;34:101550. https://doi.org/10.1016/j.rmcr.2021.101550

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Gas dissection from the thorax to the abdomen

Marina Manica Tamiozzo[1], Letícia Dalmolin[1], Mariana Manica Tamiozzo[2]

An 80-year-old woman with systemic arterial hypertension was admitted to the emergency department after a transient loss of consciousness. On arrival, she presented with hypoxemia and decreased sensorium, requiring orotracheal intubation. Chest computed tomography (CT) revealed a large bilateral pneumothorax, pneumoperitoneum, and retroperitoneal air (Figure 1). A chest tube was placed. An initial suspicion of hollow viscus perforation was ruled out after exploratory laparotomy showed no visceral injury. The combination of imaging findings and clinical context strongly suggested barotrauma secondary to excessive positive-pressure ventilation. This likely resulted in alveolar rupture due to elevated intrathoracic pressure, with air dissecting along bronchovascular sheaths—a phenomenon known as the Macklin effect. From the lungs, air extended into the mediastinum and, in rare cases, progressed as gas dissection through mediastinal vessels into the retroperitoneal space and peritoneal cavity, leading to pneumoperitoneum without visceral perforation. The patient subsequently developed an ischemic stroke and died following clinical deterioration.

Pulmonary barotrauma is uncommon but potentially life-threatening, resulting from sudden increases in intrathoracic pressure. Common complications, such as hypoxemia and subcutaneous emphysema, are typically managed conservatively. However, gas dissection into the retroperitoneum and peritoneum, though rare, represents a serious and diagnostically challenging condition. Early recognition through CT is essential for timely and appropriate management.[1–2]

AUTHOR CONTRIBUTIONS

Mariana Manica Tamiozzo contributed directly to the reporting of the computed tomography findings presented in this article. Mariana Manica Tamiozzo, Letícia Dalmolin, and Marina Manica Tamiozzo were equally involved in the conceptualization, writing, reviewing, drafting, editing, and supervision of the manuscript. Written consent for publication was obtained from the patient.

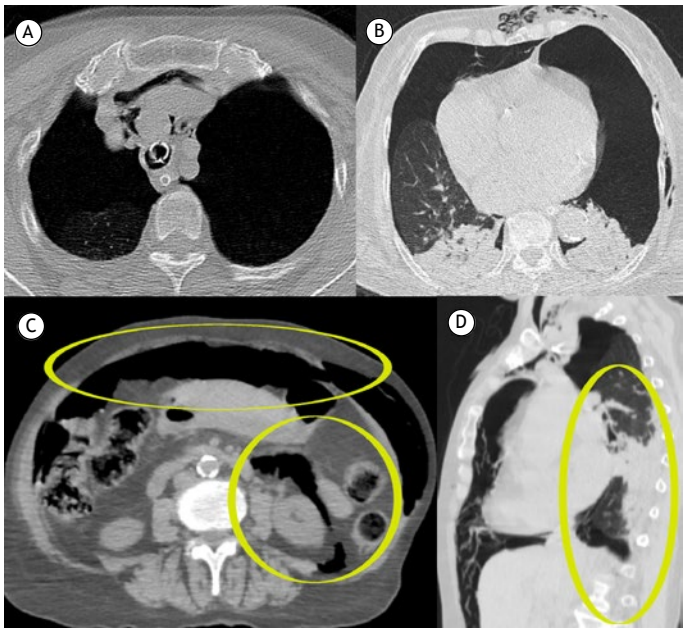

Figure 1. Pneumomediastinum (A) and large bilateral pneumothorax and emphysema on chest CT (B). Pneumoperitoneum and retroperitoneum on abdominal CT scan ellipses (C), and gas dissection of the thorax and infradiaphragmatic gas on sagittal CT slice (D).

REFERENCES

1. Po TL, Bai HF, Lin CH, Lin CC. Pneumomediastinum and tension pneumoperitoneum following bronchioloalveolar lavage in a mechanically ventilated patient. Respir Med Case Rep. 2021;32:101341. https://doi.org/10.1016/j.rmcr.2021.101341.
2. Pavrey R, Makwana N, Das N. A rare co-occurrence of spontaneous pneumomediastinum, pneumothorax, and pneumoperitoneum: Macklin effect. World J Emerg Med. 2024;15(3):246–248. https://doi.org/10.5847/wjem.j.1920-8642.2024.044.

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Treatment of sarcoidosis—an opinion

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Sarcoidosis is a systemic granulomatous disease of unknown etiology, being characterized by the formation of noncaseating granulomas in multiple organs. The clinical presentation of sarcoidosis is highly variable, and in most cases the disease follows a benign course, with high rates of spontaneous resolution. This variability has hindered the development of robust clinical trials to define optimal therapeutic strategies, leading to treatment decisions that are largely based on expert opinion.[1]

In certain subsets of patients, particularly those who are asymptomatic or have minimal organ involvement, a "watchful waiting" approach without immediate treatment may be appropriate. Conversely, chronic and insidious forms of sarcoidosis tend to follow a protracted course and may carry a worse prognosis, necessitating therapeutic intervention.[1,2]

First-line treatment typically involves corticosteroids. However, because of the potential for significant side effects with long-term corticosteroid use, corticosteroid-sparing agents such as methotrexate are considered for use as second-line therapies.[1] Corticosteroids exert most of their clinical effects within the initial months of treatment, with limited additional benefit thereafter and a progressively higher risk of adverse effects. Methotrexate, on the other hand, reaches its maximal therapeutic effect only after several months of use and is associated with fewer side effects. This pharmacological profile raises the question of whether these characteristics could be leveraged to optimize therapeutic response.

Recent data from a randomized trial of methotrexate vs. prednisone in pulmonary sarcoidosis demonstrated the noninferiority of methotrexate when compared with corticosteroids as a first-line therapy in pulmonary sarcoidosis.[2] This supports an "off-label" approach that one of us (EPB) has employed for some time now, i.e., using a combination of corticosteroids and methotrexate from the outset in cases of sarcoidosis with signs of severity and/or chronicity. When corticosteroids and methotrexate are initiated simultaneously, the former provide a rapid therapeutic effect in the early phase, whereas the latter begins to exert its efficacy at approximately three months after treatment initiation. By this time, corticosteroids are often associated with more adverse effects than benefits. Therefore, starting both treatments together allows for corticosteroid tapering and discontinuation at approximately three months after treatment initiation without triggering disease relapse, given that methotrexate has reached its full therapeutic potential by then. This combined approach in comparison with conventional monotherapy is an interesting point to be studied. Preliminary impressions suggest a lower incidence of side effects and a similarly effective therapeutic response.[3]

In conclusion, although corticosteroids remain the cornerstone of sarcoidosis treatment, the use of methotrexate as a first-line agent, either alone or in combination, offers a promising strategy to optimize therapeutic outcomes and minimize adverse effects.

AUTHOR CONTRIBUTIONS

EPB: study advisor and supervision. MCB: study conception, literature review, and study development. PS: study collaborator and supervision.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357(21):2153-65. https://doi.org/10.1056/NEJMra071714
2. Kahlmann V, Janssen Bonás M, Moor CC, Grutters JC, Mostard RLM, et al. First-Line Treatment of Pulmonary Sarcoidosis with Prednisone or Methotrexate. N Engl J Med. 2025;393(3):231-242. https://doi.org/10.1056/NEJMoa2501443
3. Nagai S, Yokomatsu T, Tanizawa K, Ikezoe K, Handa T, Ito Y, et al. Treatment with methotrexate and low-dose corticosteroids in sarcoidosis patients with cardiac lesions. Intern Med. 2014;53(5):427-433. https://doi.org/10.2169/internalmedicine.53.0794

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CT characterization of idiopathic inflammatory myopathy-associated interstitial lung disease: frontiers to strengthen diagnostic accuracy

Kadir Burak Akgün[1], Antonio M Esquinas[2]

We read with great interest the article by Oliveira Filho et al. entitled "Clinical, functional, and computed tomographic characterization of idiopathic inflammatory myopathy-associated interstitial lung disease: a retrospective cohort study."[1] The study provides valuable insights into the epidemiological, clinical, and imaging features of this rare condition. Nevertheless, we would like to highlight several methodological and interpretive points that we believe could refine the conclusions.

First, although lung biopsy is often unnecessary in cases with clear clinicoradiological concordance such as nonspecific interstitial pneumonia patterns, nearly half of the patients in the study presented with an indeterminate pattern. In such cases, histopathological confirmation is strongly recommended in order to improve diagnostic accuracy.[2] The absence of biopsy in this large subgroup limits pathological characterization and may affect treatment decisions.

Second, the cohort was predominantly composed of antisynthetase syndrome patients, with other idiopathic inflammatory myopathy (IIM) subtypes being underrepresented. This limits the generalizability of the findings to the wider IIM population. Moreover, no significant association was reported between antibody profiles and functional or respiratory outcomes. This could have provided additional prognostic information.

Third, the time frame for assessing changes in FVC was not specified. In progressive fibrosing interstitial lung disease, a ≥ 10% annual decline is considered clinically meaningful and prognostically relevant. Without standardized intervals and clear thresholds, interpretation of FVC change becomes challenging—especially since FVC is effort-dependent and may decline due to muscular weakness rather than interstitial disease progression.[3] The use of DL_{CO} could have provided a more reliable measure of interstitial involvement.

Fourth, the diagnosis of pulmonary hypertension relied solely on echocardiography and radiological findings. The gold standard, right heart catheterization, was not performed, which may have resulted in underdiagnosis.[4] The discussion statement "We found no cases of pulmonary arterial hypertension" is therefore methodologically uncertain and likely reflects the limitations of noninvasive assessment in patients with fibrotic lung disease.

Fifth, it is unclear how HRCT scans were reviewed. The methods section suggests that they were evaluated by two of the authors of the study, but a consensus approach or interobserver agreement was not mentioned. Such details are important to ensure reproducibility.

Finally, although the authors reported improvement in symptoms such as dyspnea and cough, this appears to have been based on patient self-report without validated scales. Given that treatment was individualized, the relationship between therapy and symptom or functional improvement remains difficult to assess.

We commend the authors for assembling a well-characterized cohort and for providing long-term follow-up data. We hope that our considerations will encourage further research to strengthen diagnostic accuracy, standardize functional assessment, and refine prognostic evaluation in IIM-associated interstitial lung disease.

AUTHOR CONTRIBUTIONS

KBA: literature review and writing of the original draft. AME: conceptualization, project administration, and manuscript review.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Oliveira Filho JRB, Costa AN, Baldi BG, Wanderley M, Sawamura MVY, Kairalla RA. Clinical, functional, and computed tomographic characterization of idiopathic inflammatory myopathy-associated interstitial lung disease: a retrospective cohort study. J Bras Pneumol. 2025;51(4):e20250123. https://dx.doi.org/10.36416/1806-3756/e20250123
2. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188(6):733-48. https://doi.org/10.1164/rccm.201308-1483ST
3. Ponce MC, Sankari A, Sharma S. Pulmonary function tests. In: StatPearls [monograph on the Internet]. Treasure Island (FL): StatPearls Publishing; [updated 2023 Aug 28; cited 2025 Jan 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482339/
4. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1):1801913. https://doi.org/10.1183/13993003.01913-2018

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Authors' Reply

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We thank the authors for their thoughtful correspondence designated "CT characterization of idiopathic inflammatory myopathy-associated interstitial lung disease: frontiers to strengthen diagnostic accuracy," which includes comments regarding our manuscript "Clinical, functional, and computed tomographic characterization of idiopathic inflammatory myopathy-associated interstitial lung disease: a retrospective cohort study," as well as for the opportunity to clarify several methodological points. We herein explain the comments made by the authors point-by-point.

1. Lung biopsy in connective tissue disease (CTD)-related interstitial lung disease (ILD) is infrequently performed at our center because, in routine practice, histology usually does not modify management, especially when the diagnosis of a CTD is confirmed, even when there is an indeterminate pattern on CT scans. This approach—also acknowledged among the limitations of our study—reflects contemporary practice in autoimmune ILD.[1,2]
2. We agree with the authors that antisynthetase syndrome is over-represented in our cohort. This bias occurred due to convenience sampling in a referral ILD clinic, and inclusion criteria were restricted to participants with data available for longitudinal analysis in this retrospective design—points we have explicitly recognized as a selection bias limiting generalizability of the findings to the wider idiopathic inflammatory myopathy (IIM)-related ILD group. We did not evaluate the association of antibody profile with clinical and functional outcomes due to missing data regarding these serum exams.
3. We agree with the authors that the absence of DL_{CO} and respiratory muscle strength metrics (e.g., PI_{max}/PE_{max}) may influence interpretation of FVC. We decided not to apply the International Myositis Assessment & Clinical Studies (IMACS) or the current ATS/ERS recommendations that define clinically meaningful (e.g., ≥10%) annual decline, because annual, standardized spirometry results were not consistently available due to the retrospective nature of the study. We therefore reported change between the first and last available tests and recognize the effort-dependence of FVC as a limitation.
4. We agree that right-heart catheterization remains the gold standard for confirming pulmonary hypertension (PH). In our cohort, however, this invasive test was not performed due to the clinical judgment of the health care team, mainly because it was considered unlikely to change management decisions or was limited by the functional status of the patients. This reflects the inherent constraints of a retrospective study and underscores some of its methodological limitations. In line with the 2022 ESC/ERS pulmonary hypertension guideline,[3] our surveillance used recommended screening tools—transthoracic echocardiography and CT measures (e.g., main pulmonary artery diameter/PA:A ratio). Although suspected PH was noted by echocardiography in a subset of patients, we found no features suggesting group-1 PH (pulmonary arterial hypertension; PAH); most suspicions were compatible with PH associated with parenchymal lung disease (group 3).
5. HRCT examinations were reviewed by two thoracic radiologists with expertise in ILD, and, in cases of disagreement, adjudicated by an ILD pulmonologist—thereby ensuring a consensus-based final interpretation.
6. Symptom data necessarily relied on patient reports because of the retrospective chart-review design. Validated scales to assess symptoms were not routinely applied in our center. Dyspnea was graded using the mMRC scale, which was the instrument routinely applied in our service.

We appreciate the colleagues' engagement and believe these clarifications strengthen the interpretation and context of our findings.

REFERENCES

1. Kannappan R, Kumar R, Cichelli K, Brent LH. A Review of Myositis-Associated Interstitial Lung Disease. J Clin Med. 2024;13(14):4055. https://doi.org/10.3390/jcm13144055
2. Johnson SR, Bernstein EJ, Bolster MB, Chung JH, Danoff SK, George MD, et al.. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) Guideline for the Screening and Monitoring of Interstitial Lung Disease in People with Systemic Autoimmune Rheumatic Diseases. Arthritis Care Res (Hoboken). 2024;76(8):1051-1069. https://doi.org/10.1002/acr.25348
3. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618-3731. https://doi.org/10.1093/eurheartj/ehac237 Erratum in: Eur Heart J. 2023;44(15):1312. https://doi.org/10.1093/eurheartj/ehad005

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Accuracy of ChatGPT in answering asthma-related questions

Hinpetch Daungsupawong[1], Viroj Wiwanitkit[2]

The publication on "Evaluation of the accuracy of ChatGPT in answering asthma-related questions"[1] is interesting. That study, which evaluated the quality of ChatGPT's responses to asthma-related questions, is noteworthy because it demonstrates the potential and limitations of large language model (LLM) in interacting with both medical professionals and the general public. However, thorough study exposes statistical limitations, confounding factors, and points that must be reinterpreted in order to broaden the conversation.

Although a Likert scale and content validity coefficient (CVC) were employed to test interrater consistency, the limited number of questions and six raters may not accurately reflect the diversity of real-world situations. Using more powerful statistical methods, such as the intraclass correlation coefficient (ICC), may improve interrater reliability. Furthermore, rather than merely reporting averages or CVC numbers, tests capable of meaningfully comparing subgroups should be used to analyze disparities between physician and patient opinions.

The perceptions of medical professionals and the general population differ significantly. Physicians may anticipate detailed responses that address guidelines and empirical data, whereas the general public may prefer simple, accessible explanations. This means that the "quality" score is based on the rater's expectations rather than the actual correctness of the data. Furthermore, raters' familiarity with the LLM could be a confounder in the perceived quality of the response.

Given that ChatGPT obtained a score of 2-3 from professionals but a high CVC from laypeople, it appears that the model has the capacity to communicate basic asthma knowledge to patients but lacks the depth required for academic or complex patient treatment. According to a new interpretation, ChatGPT's strength rests in its role as a supplementary health communication tool, rather than in clinical decision-making itself.

This study raises further questions, such as whether employing personalized prompts will enable ChatGPT to give better guideline-based responses. How would real patients with chronic asthma rank the quality of their responses compared to laypeople? Could merging expert and patient assessments result in a new criterion for determining an AI's "medical quality"? Would comparing ChatGPT to other LLMs, such as Claude or Gemini, affect the results for the same question?

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AUTHOR CONTRIBUTIONS

HP: conception, drafting, reviewing, and approval of the final version of the manuscript. VW: conception, supervision, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Cerqueira BP, Leite VCDS, França CG, Leitão Filho FS, Faresin SM, Figueiredo RG, et al. Evaluation of the accuracy of ChatGPT in answering asthma-related questions. J Bras Pneumol. 2025;51(3):e20240388. https://doi.org/10.36416/1806-3756/e20240388

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Authors' Reply

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We read with great interest the correspondence regarding our recently published article and would sincerely like to thank the authors for their thoughtful and insightful comments. We greatly appreciate the opportunity to discuss the scope and implications of our work further.

We recognize that, like any exploratory study, our study has inherent limitations, some of which we addressed in the original manuscript. We intentionally limited the number and the wording of questions to keep the article concise and focused on the main asthma-related issues.

Regarding the statistical approach, our team, together with the statistical advisors, selected the content validity coefficient (CVC) to assess agreement among evaluators. We determined that this method was appropriate for the objectives of our study and that it provided a reliable measure of inter-rater agreement.

We also agree that the perceptions of medical professionals and laypeople may differ considerably, and we recognize this as the primary limitation of our study. To incorporate evaluations from the general population, it would have been necessary to conduct pre- and post-tests, requiring a methodology distinct from what was proposed. The objective of our study, however, was to assess the perspectives of physicians experienced in managing asthma patients in both private and public outpatient clinics, focusing on what they consider essential for patients to understand about the disease. While we acknowledge that this approach is subjective and limited, we still regard it as valuable data that adds to the discussion.

The additional questions raised represent promising directions for future research. The decision to avoid highly specific prompts was made to simulate real-life interactions better; however, studies utilizing personalized prompts may produce different outcomes. Involving real patients with chronic asthma and integrating both expert and patient assessments could establish new and meaningful criteria for evaluating AI-generated medical information. Furthermore, comparative analyses of various large language models, including those developed for scientific or medical applications such as OpenEvidence, constitute an important next step in this field.

The authors' valuable contribution is appreciated. Their observations highlight significant avenues for further research, and such scientific dialogue enhances the understanding and development of large language model applications in the medical field.

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Examples: Journal Articles

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

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

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