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HIGHLIGHT

Respiratory Syncytial Virus in Older Adults: Brazil 2022-2023

Baseline characteristics of patients from the Brazilian Severe Asthma Registry: the REBRAG study

Smoke Exposure and Health: A Multicenter Primary Care Study in Brazil

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Contents

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Contents

Electronic smoking devices. We cannot let our young people go down this path of addiction and disease

Luiz Fernando Ferreira Pereira[1,2], Maria Enedina Claudino Aquino Scuarcialupi[3,4], Maria Vera Cruz de Oliveira Castellano[5], Carlos Leonardo Carvalho Pessôa[6], Ramiro Dourado[7,8,9]; Comissão de tabagismo da SBPT 2025-26

Worldwide, there are more than 1.25 billion smokers, of whom 80% live in low-income countries, and the majority want to quit smoking. In recent decades, the tobacco industry has invested in new forms of smokeless nicotine consumption, notably moist sachet and snus and, especially, electronic smoking devices (ESDs), also known as electronic cigarettes, vapes, pods, and e-cigs.

Public policies to control smoking in Brazil, including the free treatment program coordinated by the National Ministry of Health and the National Cancer Institute, have made the country a model of reducing cigarette smoking, which fell from more than 34% in the 1980s to less than 10% in 2023.[1]

In contrast to cigarette smoking, which has shown a slow, progressive reduction in several regions of the world, the use of ESDs is growing at an alarming rate, partly due to curiosity, technological appeal, ease of acquisition, and massive dissemination on social media. In some countries, more than 25% of young people have used an ESD in the last 30 days.[2] In Brazil, there are an estimated 3 million ESD users, with a recent increase in current (daily or occasional) use among people 18–24 years of age, which reached 6.6% in 2023.[2-4]

In the media, especially on social media, false or exaggerated statements are often spread, some of which distort the conclusions of scientific articles, in favor of vapes, such as the following: they only release water vapor; they release less nicotine than do cigarettes; they do not pollute the environment; they have fewer harmful health effects in comparison with cigarettes; and they help people quit smoking.

In recent years, the tobacco industry has vehemently argued that authorizing the manufacture and sale of standardized, certified ESDs, with a maximum of 20 mg/ml of nicotine, would guarantee the use of quality products, reduce black-market activity, and increase tax revenues from the sale of tobacco derivatives.

All of these arguments in favor of ESD use are fallacious.

Validated studies with strong scientific evidence, as well as national and international recommendations, including those of the World Health Organization, prove exactly the opposite.[5-8] The main arguments against the use of ESD are as follows:

- ESDs not only release water vapor; their white, odorless vapor contains propylene glycol, glycerol, metals, particulates, carcinogens, and a growing number of substances, many with potential health risks.[9]
- In addition to making it easier to inhale the vapor, the latest generation of ESDs are less irritating to the throat, release a greater quantity of particulates and nicotine (salts that are better absorbed by the lungs) than do regular cigarettes, and can be augmented with more than 16,000 flavorings, which incentivize the initiation and maintenance of their use, especially among younger people.[8,10]
- The use of vapes causes nicotine dependence and other health problems such as coughing, dyspnea, oral/dental changes, cardiovascular risks, risk of cancer, respiratory diseases, and intense withdrawal symptoms after reducing or stopping use, due to the high daily consumption of high concentrations of nicotine.[5,6,8] In addition, vaping can cause health problems due to battery explosions or intoxication due to ingestion of liquid from the reservoirs.
- ESDs can also cause a febrile lung disease, associated with gastrointestinal manifestations with a high risk of severity and death, known as e-cigarette or vaping product use-associated lung injury (EVALI), especially when loaded with marijuana derivatives, vitamin E, or both.[11]
- In Brazil, one out of every three regular cigarettes consumed is obtained from the black market.[12] Tax revenue from the manufacture and sale of tobacco generates less than one tenth of the amount the country spends on treating diseases, pays for early retirements, and loses from deaths due to smoking. [13] Regulating vapes will not solve the problem of the black market, which would continue to sell ESD with a high concentration of nicotine and might increase the consumption of certified products (Table 1).
- Although the illegal sales of regular cigarettes and vapes remain high in Brazil, governmental

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◄ Voltar ao sumário

Table 1. Practical comparisons between regular cigarettes and e-cigarettes.

Aspect	Regular cigarettes	E-cigarettes[a] ESDs
Black market	33%[12]	100%
Released substances	7,500 (250 that are harmful to health)	From tens to hundreds[b] (Dozens that are harmful to health)
Nicotine concentration	1 regular cigarette: ≤ 1 mg	1 ESD capsule ≤ 50 mg/mL[c]
Amount of nicotine consumed	1 pack/day or 600 cigarettes/month 15 puffs/cigarette or 300 puffs/day 20 cigarettes/day = 20 mg 600 mg of nicotine/month	1 ESD 13 mL, 50 mg/mL, 10,000 puffs/unit Tens to hundreds of puffs/day 333 puffs/day = 21.6 mg 650 mg of nicotine/month

ESDs: electronic smoking devices. [a] Many generations and hundreds of nonstandardized brands make it difficult to assess the substances that are released and the harmful effects. 4th-generation ESDs release more particulates, metals, and nicotine than do regular cigarettes. The nicotine salts in 4th-generation cartridges (pods) are better absorbed by the lungs, and > 16,000 flavorings are available. [b] Teharini et al.[9] detected > 2,000 substances. [c] Elfbar, one of the most widely sold disposable ESDs in several countries, has a reservoir of up to 50 mL, releases ≤ 50 mg of nicotine/mL and ≤ 40,000 puffs – www.wolfshopbrasil.com

agencies charged with health oversight, consumer protection, and tax auditing have ramped up their activities, which include inspections, educational actions, fines, and seizures of property.

- A young person who starts vaping triples their risk of starting to smoke regular cigarettes and increases their risk of starting to use other drugs.[14]
- Smoking cessation treatment is effective and is based on behavioral support combined with nicotine replacement therapy (patches, gum, lozenges, or any combination of those), varenicline (temporarily unavailable in Brazil), or bupropion. Although controversy persists regarding the role of ESDs in smoking cessation, a review of the literature demonstrated that they are superior to nicotine patches, although with a success rate much lower than that obtained in structured programs. [15] However, that small gain is offset by the fact that more than half of individuals who quit smoking do not stop vaping, remaining dependent on nicotine, and many revert to smoking regular cigarettes alone. [16,17] To make matters worse, many patients who do not quit smoking continue to use ESDs, becoming dual users, with increased risks to their health.

In 2024, the *Agência Nacional de Vigilância Sanitária* (ANVISA, Brazilian Health Regulatory Agency), after extensive review and discussion, ratified Collegiate Board Resolution no. 855 (4/23/2024), which imposed a nationwide ban on the manufacture, import, storage, distribution, marketing, and advertising of vapes, as well as on their use in closed public spaces.[18]

Historically, the greatest concern of the tobacco industry has never been the health of its users; quite the opposite, its main objective has always been to create ever more nicotine addicts, who will, as we know, use its products for decades.

For the aforementioned reasons, the Brazilian Thoracic Association, together with other national and international associations, ratifies its position against allowing the manufacture, commercialization, and promotion of vapes, as well as vaping in enclosed spaces, and believes that a massive educational campaign, aimed at young people, is essential and urgent, to try to reverse the growing use of these devices in Brazil.[19,20]

The use of ESDs is not a step forward; it is a step backward in the ongoing quest for a tobacco- and nicotine-free world.

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Post-tuberculosis and postinfected bronchiectasis: data from global registries

Grace Oscullo[1,2], Miguel-Angel Martinez-García[1,2], Rosella Centis[3], Lia D'Ambrosio[4], Jose Daniel Gómez-Olivas[1,2], Giovanni Battista Migliori[3]

Evidence on the relationship between bronchiectasis and post-tuberculosis lung disease (PTLD) is scant, and the global prevalence of post-tuberculosis bronchiectasis has yet to be investigated.

Bronchiectasis is characterized by an increased bronchial lumen diameter relative to that of the accompanying vessel. A diagnosis of bronchiectasis is made on the basis of clinical symptoms (especially productive cough, often with a purulent component) consistent with radiological findings.[1,2] There is usually a vicious circle of inflammation and chronic infection by pathogenic microorganisms, explaining symptom progression, radiological findings, and disease prognosis.[3] Bronchiectasis has more than one hundred different causes, both pulmonary and extrapulmonary. In the 20th century, bronchiectasis was an "orphan" disease and was therefore not usually included in the differential diagnosis of chronic inflammatory diseases of the airway. However, since the beginning of the 21st century, large research groups worldwide have been collecting data on patients with bronchiectasis through national and international registries. There are currently 16 countries collecting complete individual datasets. In terms of number of patients, three registries stand out: the first, a national registry in China, with more than 16,000 patients since 2020; the second, a federal registry in the United States, with more than 8,000 patients since 2007; and the third, an international registry, the European Multicenter Bronchiectasis Audit and Research Collaboration registry, which includes 27 countries and more than 19,000 patients.[4]

PTLD has recently attracted considerable interest, given that approximately 50% of the human suffering attributed to tuberculosis occurs after successful completion of tuberculosis treatment.[5-7] Patients continue to suffer from tuberculosis sequelae leading to a range of respiratory symptoms (including bronchiectasis) and nonrespiratory symptoms,[8-10] accompanied by lung function decline,[11] reduced quality of life, reduced exercise tolerance, and other complications, including a mortality rate that is five times higher than that for the general population.[8,10,11]

Little is known about how tuberculosis causes PTLD and bronchiectasis or how other infections can cause these two chronic respiratory conditions. The aforementioned registries allow us to gain a better understanding of the most common etiologies of bronchiectasis. The objective of the present study was to describe the prevalence of post-tuberculosis and postinfective bronchiectasis in different countries in the world and discuss the characteristics of both.

Data from the existing bronchiectasis registries were obtained by personally contacting the coordinator of each registry or by reviewing the most updated published information. Data on post-tuberculosis bronchiectasis in different countries and registries were stratified into three groups on the basis of their proportions: low prevalence (< 10%), intermediate prevalence (10-15%), and high prevalence (> 15%). Proportions were compared by means of the chi-square test. A value of $p \leq 0.05$ was considered significant.

The combined data from all available registries are summarized in Table 1. Of 58,474 patients, 11.8% (range, 1.8-35.5%) had post-tuberculosis bronchiectasis and 27.3% (range, 19-43.2%) had postinfective bronchiectasis.

Our data confirm that although idiopathic forms are the most prevalent,[5] two forms of bronchiectasis are extremely common in almost all countries: post-tuberculosis bronchiectasis and postinfective bronchiectasis.[6,7] Furthermore, although postinfective bronchiectasis remains fairly stable in terms of proportion (approximately 20-40%) and is undoubtedly the most common form of bronchiectasis, post-tuberculosis bronchiectasis shows greater heterogeneity, ranging from 1.8% in Australia to 35.5% in India. This may be due to how tuberculosis-related factors have acted over time, such as the extent of decline in tuberculosis incidence and the impact of tuberculosis control interventions, including the impact of tuberculosis infection management. The relationship between the decline in tuberculosis incidence and the proportions of post-tuberculosis bronchiectasis merits further investigation.

In the case of postinfective bronchiectasis, it is more difficult to determine the etiology. Although the etiology of tuberculosis is bacteriologically confirmed, there is no objective evidence indicating that the cause of postinfective bronchiectasis is an infection, given that it is often attributed to childhood infections occurring several decades before. This means that if a patient had measles or whooping cough during childhood and developed bronchiectasis in adulthood, the bronchiectasis is frequently attributed to the childhood infection without an etiological diagnosis to rule out other potential causes. Perhaps the most reliable diagnosis is post-pneumonia bronchiectasis, given that there is objective imaging

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◄ Voltar ao sumário
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Table 1. Total numbers and proportions of post-tuberculosis bronchiectasis and postinfective bronchiectasis in bronchiectasis registries worldwide. In orange, blue, and yellow, countries with a low, intermediate, and high prevalence of post-tuberculosis bronchiectasis, respectively.

Country or continent	Total number of patients	Period covered	Post-tuberculosis bronchiectasis, n (%)	Postinfective bronchiectasis, n (%)	Other causes of bronchiectasis, n (%)
Europe (EMBARC registry)	19,486	2015-present	955 (4.9%)	4,209 (21.6%)	73.5%
Australia	1,201	2016-present	22 (1.8%)	337 (28.1%)	70.1%
USA (BRR)	8,044	2014-present	322 (4%)	--	96%
Canada	289	2024-present	13 (4.5%)	33 (11.4%)	84.1%
Germany	1,989	1989-present	40 (2%)	378 (19%)	79%
Japan	1,597	2018-present	99 (6.2%)	431 (27%)	66.8%
Spain (RIBRON)	2,631	2015-present	355 (13.5%)	106 (40.4%)	32.6%
Turkey	1,035	2019-present	117 (11.3%)	409 (39.5%)	49.2%
China	16,389	2020-present	200 (12.2%)	708 (43.2%)	44.6%
Spain (SHBR)	2,123	2002-2011	390 (18.4%)	64 (30%)	51.6%
Argentina	617	2024-present	120 (19.4%)	160 (25.9%)	54.7%
South Korea	938	2015-present	189 (20.1%)	179 (19.1%)	60.8%
India	2,135	2015-2017	758 (35.5%)	478 (22.4%)	42.1%
TOTAL	58,474	range, 2002-2025	3,560 (11.8%)	7,492 (27.3%)	60.9%

EMBARC: European Multicenter Bronchiectasis Audit and Research Collaboration; BRR: Bronchiectasis and NTM (Nontuberculous Mycobacteria) Research Registry; RIBRON: *Registro Español Informatizado de Bronquiectasias* (Spanish Online Bronchiectasis Registry); and SHBR: Spanish Historical Bronchiectasis Registry.

evidence of the pneumonic process, which is followed by the appearance of bronchiectasis in the same location. The fact that the aforementioned registries currently attribute bronchiectasis to a bacteriologically confirmed or clinically diagnosed case of infection is a limitation that requires attention to improve the quality of diagnosis of postinfective bronchiectasis.

An interesting issue for reflection is that many studies examining the etiology of bronchiectasis include post-tuberculosis bronchiectasis in the group of postinfective bronchiectasis. This is probably not a good idea because although tuberculosis is a form of (mycobacterial) infection, it has important differentiating characteristics.

There are many future challenges regarding the association of post-tuberculosis bronchiectasis and postinfective bronchiectasis with comorbidities,[12] clinical presentation, and new therapeutic possibilities,[13,14] given that the causative agents are of very different nature and could have different responses to treatment and different prognoses.[15] Among the topics deserving further investigation, the role of rehabilitation in improving lung function, exercise capacity, and quality of life, as underscored in a recent study in Brazil,[16] deserves special attention.

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AUTHOR CONTRIBUTIONS

M-AMG and GBM: writing—original draft. GO, RC, LDA, and JDG-O: critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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COPD in Brazil: where there's smoke...

Frederico Leon Arrabal Fernandes[1]

Brazil is a developing country. As such, its low-income population is more vulnerable to environmental exposures and the harms associated with inhaled pollutants, especially cigarette smoke and biomass burning. Several studies have shown that individuals from lower socioeconomic classes have a higher prevalence of smoking and are more frequently exposed to the burning of wood, charcoal, or other biomass components for heating, energy, and cooking.[1,2] This remains a common practice in rural areas and urban outskirts.[1,2]

This environmental vulnerability is compounded by limited access to health care services, especially in rural and remote regions, where primary care infrastructure may be weak and access to complementary tests—particularly spirometry—may be virtually nonexistent. Thus, populations at a higher risk of developing chronic respiratory diseases such as COPD paradoxically have less access to the resources necessary for their diagnosis and treatment. Reducing this inequality requires public policies focused on expanding health care access, strengthening primary health care (PHC), increasing availability of diagnostic tools, and implementing educational initiatives that consider the social, cultural, and environmental realities of these communities.[3]

The multicenter study "Sociodemographic and clinical characteristics of individuals exposed to smoking or biomass smoke and followed at primary health care centers in Brazil: a multicenter study,"[4] published in the present issue of the *Jornal Brasileiro de Pneumologia*, addresses a highly relevant topic for PHC: the profile of individuals exposed to risk factors for respiratory diseases, such as tobacco smoke and biomass smoke. Conducted at four primary health care units in southern and southeastern Brazil, the study evaluated 737 patients aged 35 years or older, including smokers, former smokers, and individuals exposed to biomass.

The results revealed a population predominantly composed of women (56.3%), with a mean age of 57.7 years, low educational level (over half with nine or fewer years of schooling), and belonging to lower socioeconomic classes (C2/D/E). A noteworthy finding was the high prevalence of overweight and obese individuals (71.5%), along with common comorbidities such as hypertension (51.3%), depression (27.4%), and diabetes (24.3%).[4]

Regarding respiratory symptoms, high rates of cough (37.3%), wheezing (33.8%), and sputum production (27.4%) stand out. Although most patients reported only mild dyspnea (75.1% with mMRC 0-1), the majority had a COPD Assessment Test (CAT) score above 10 points, characterizing them as highly symptomatic. Biomass exposure, though less prevalent, was significantly associated with a greater impact of respiratory symptoms on CAT scores.[4]

Statistical analyses showed that male sex and older age were associated with higher levels of dyspnea, whereas higher BMI and lower socioeconomic status were linked to worse CAT scores. Interestingly, no statistically significant association was found between smoking or obesity and the most prevalent comorbidities, raising hypotheses about limitations inherent to cross-sectional study designs and reinforcing the need for longitudinal research.[4]

The article highlights the strategic role of PHC in addressing vulnerable populations and in the early detection of chronic respiratory diseases.[4] The significant presence of symptoms even in early stages and the frequency of comorbidities point to a critical opportunity for preventive actions and health education at the primary care level. It is also important to emphasize the negative effects of biomass exposure, often overlooked in clinical practice and public policies, but with measurable impact on the quality of life of patients.

In summary, this is an important contribution that sheds light on the clinical and sociodemographic profile of a high-risk population often rendered invisible in large respiratory disease studies. The findings underscore the potential of PHC as a strategic space for prevention, screening, and health education and point to the urgent need for integrated public policies that consider the social and environmental contexts of patients.

One particularly striking finding in the study was the high frequency of respiratory symptoms among participants. Cough, wheezing, and sputum production were reported by more than a third of the sample, in stark contrast to the low prevalence of chronic respiratory disease diagnoses, such as COPD, recorded in the PHC units. This discrepancy is notable when compared with other cross-sectional population studies such as the so-called PLATINO study,[5] which estimated a COPD prevalence of 15.8% in Brazil among adults aged 40 or older, but only 6.8% in the current study.[4] The gap suggests a worrisome underdiagnosis of COPD in PHC, possibly linked to the low awareness of symptoms or the normalization of respiratory illness in vulnerable populations, perhaps because of the lack of routine spirometry.

It is worth emphasizing that the epidemiological and anthropometric profile of the sample, characterized by having advanced age, being overweight, having a low socioeconomic status, and being highly exposed to risk factors, such as smoking and biomass smoke, is highly consistent with the typical profile of COPD patients;

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and yet, the prevalence of this disease, which is the third leading cause of death globally, was relatively low. These findings reinforce the importance of strengthening PHC to actively screen for respiratory diseases through systematic use of spirometry, professional training, and integration with specialized care networks for proper diagnosis and management.

The discrepancy between the high prevalence of respiratory symptoms and the low rate of chronic respiratory disease diagnoses, such as COPD, exposes a critical gap in the diagnostic approach of PHC. This finding underscores the urgent need to enhance the capacity of PHC teams for active case finding of patients with COPD and other chronic lung conditions. Early detection of these diseases relies not only on clinical recognition of symptoms and risk factors but also on the use of objective diagnostic tools, especially spirometry.

Despite being recommended by both national and international guidelines as a first-line diagnostic tool for COPD, spirometry remains underutilized in Brazilian PHC due to structural barriers, lack of technical training, and weak integration with specialized services. Making spirometry more accessible, widely available, and easier to request is essential to enable timely diagnosis and reduce the underdiagnosis so well documented in this[4] and other studies.

COPD diagnosis remains precarious in the PHC setting, even among populations with well-established risk factors. Much of the problem stems from the disease's insidious onset, with symptoms emerging slowly and progressively, making them harder for patients to recognize. Dyspnea on exertion is often attributed to aging or a sedentary lifestyle, while chronic cough and sputum are considered "normal" among smokers. As a result, many individuals do not seek health care facilities for these symptoms and, even when they do for other reasons, tend not to report them spontaneously.

Patients with known risk factors, such as smokers and former smokers, individuals with a history of pulmonary tuberculosis, those exposed to biomass smoke, or with a childhood history of recurrent respiratory infections, should be systematically and thoroughly assessed, spirometry being proactively offered even in the absence of prominent respiratory complaints. The fact that spirometry is mostly restricted to large centers and tertiary care facilities is a significant barrier to more proactive and preventive approaches.

Relying solely on spontaneous demand is insufficient. The implementation of active screening strategies, along with ongoing health professional training and a robust diagnostic support network, can transform PHC into an effective setting for early COPD interception with direct benefits for morbidity, quality of life, and health care costs.

Active case finding, expanded access to spirometry, professional training, and stronger integration across levels of care must be central to public health strategies for tackling COPD. Promoting early diagnosis is not merely a technical goal, it is a matter of social justice, particularly for vulnerable populations who silently face risk factors and develop disabling, yet preventable, symptoms.

We live within a perverse logic: those who are the most susceptible are also those who are the most neglected, which leads to chronic underdiagnosis of COPD especially in its early stages, precisely when interventions could change the trajectory of the disease. Therefore, PHC teams must adopt a proactive stance in investigating respiratory symptoms, identifying risk factors, and adopting clear strategies for timely screening. The popular saying "where there's smoke, there's fire" aptly applies to COPD: in the presence of any significant exposure to tobacco, biomass, or other risk factors, one must consider the possibility of lung disease even when patients do not spontaneously report symptoms.

CONFLICTS OF INTEREST

None declared.

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The staging evolution dilemma: TNM-9 sharpens anatomical precision, but is biology still offstage?

Gustavo Faibischew Prado[1,2,3], Fernanda Kaori Fujiki[3,4], João Marcelo Lopes Toscano de Brito[3]

The 9th edition of the TNM classification for lung cancer (TNM-9),[1] effective as of 2025, represents a further step toward enhanced prognostic accuracy and anatomically guided stratification of thoracic malignancies. Developed from extensive international databases, its primary innovations include the subdivision of N2 disease into N2a (single-level ipsilateral mediastinal nodal involvement) and N2b (multiple levels), as well as the distinction between extrathoracic metastases confined to a single organ system (M1c1) versus those involving multiple systems (M1c2). While these updates represent conceptual advances and improve statistical performance metrics, their direct clinical impact remains a subject of debate.[2–4] The N2 subclassification provides more granular prognostic stratification: patients with N2a disease generally exhibit better overall survival than those with N2b. However, this difference may not always reach statistical significance across all cohorts, and preoperative prediction remains a challenge.[2,5]

In the study by Ferreira et al. (2025), featured in this issue of the *Jornal Brasileiro de Pneumologia*, the authors retrospectively applied TNM-9 to a cohort of 914 lung cancer patients previously staged according to the 8th edition. The reclassification led to notable stage shifts: 34 patients were downstaged, primarily from IIIB to IIIA, while 8 were upstaged from IIIA to IIIB. When evaluating the new N2a/N2b subclassification using EBUS-obtained samples, no statistically significant differences in overall survival (OS) were found between the two subgroups. This finding reflects limitations previously reported in surgical series, which highlight the difficulty of preoperatively predicting the true extent of mediastinal nodal involvement.[6]

Although the discriminative gap between stages IIIA and IIIB has narrowed—reflected in increasingly similar 5-year survival rates—the reclassification has introduced greater intra-stage homogeneity in certain scenarios. For instance, cases downstaged to IIB (e.g., T1N2aM0) exhibited outcomes consistent with others in that stage. Conversely, patients upstaged to IIIB (e.g., T3N2bM0) demonstrated better-than-expected survival, highlighting the persistent heterogeneity despite these adjustments.[1] It is important to acknowledge that such changes may complicate the interpretation of historical data and affect eligibility criteria for clinical trials, thereby introducing new methodological challenges.

A key innovation with demonstrated prognostic impact in the study by Ferreira et al. lies in the subclassification of M1c metastases: patients with multi-organ involvement (M1c2) had significantly worse OS compared to those with metastases confined to a single organ system (M1c1), even within stage IVB. This observation supports recent studies and underscores the potential need to establish a new IVC stage for this subgroup, an aspect not currently addressed in the existing staging framework.[4,6]

The therapeutic implications of topographic refinement must also be taken into account. Patients with N2a disease, and some with N2b, particularly those with limited tumor burden, may be eligible for surgery following neoadjuvant chemoimmunotherapy. In contrast, those with bulky mediastinal disease are more likely to benefit from definitive chemoradiation followed by systemic therapies.[7,8] However, in the absence of high-quality invasive staging, such as EBUS with systematic multistation sampling, this distinction may not be feasible, particularly in resource-limited settings.

It is important to note that landmark trials, such as CheckMate 816, AEGEAN, KEYNOTE 671, CHECKMATE 77T, IMpower010, KEYNOTE 091, and PACIFIC, have demonstrated significant improvements in event-free and overall survival when immune checkpoint inhibitors are incorporated into the treatment of patients with resectable and unresectable stage II and III disease, as compared to historical results.[9–15] These novel strategies have the potential to reshape the survival landscape for patients whose clinical stages often overlap. However, access to these therapies varies considerably across institutions and countries, with socioeconomic disparities potentially confounding the generation and comparison of real-world survival data. As a result, datasets used to validate and refine stage groupings may reflect not only biological and anatomical factors but also be influenced by 'systemic' sociodemographic inequities. This introduces an additional layer of complexity to the interpretation of stage-based survival curves and raises the question of whether, in the era of precision medicine, anatomical staging alone can continue to serve as the core element for prognosis and therapeutic decision-making.

Despite these advances, TNM-9 still does not incorporate molecular, biological, or functional biomarkers, which are becoming ever more important for risk stratification and therapeutic decision-making. Predictive somatic alterations such as EGFR mutations and ALK rearrangements not only

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correlate with distinct prognoses but also guide the use of targeted therapies across all disease stages.[16,17] Novel emerging tools, such as circulating tumor DNA (ctDNA) and pathologic response following neoadjuvant chemoimmunotherapy provide additional layers of prognostic—and potentially predictive—information, especially in the perioperative setting.[18,19] Moreover, molecular profiling may enhance the staging of multifocal lesions by distinguishing synchronous primary tumors from metastases with poor prognosis, thereby enabling more individualized treatment approaches.[19]

As the field advances toward a more integrated and biologically informed approach to oncology, TNM-9 appears to serve as a necessary, yet interim and transitional framework. While it surpasses its predecessor in anatomical granularity, it falls short of capturing the full spectrum of individualized risks and treatment opportunities.

Future staging systems should integrate topographic, molecular, and clinical-functional dimensions not only to improve survival prediction but also to guide increasingly personalized therapeutic decision-making.

Such evolution will also demand updates to medical education and residency curricula, as the growing complexity of staging and therapeutics requires not only clinical acumen but also genomic literacy.

In an era where staging can no longer be a static anatomical snapshot but must instead evolve into a dynamic map of therapeutic possibilities, TNM-9 offers a sharper lens, but still a narrow one.

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Lymph node with central hypodensity

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

A 62-year-old male patient underwent a chest CT for staging bronchial carcinoma. The CT showed a mediastinal lymph node of normal dimensions, with central hypodensity (Figure 1).

Central hypodensity in lymph nodes may be a normal finding or correspond to a series of pathological conditions. The main parameter to be considered in terms of imaging, in addition to dimensions, is the tomographic measurement of central density. This measurement may be low, although positive, or present negative densities, generally between −30 and −150 HU, which represents the presence of fat.

Low positive densities generally indicate the presence of necrosis, both related to neoplastic processes (especially metastases) and infectious processes (tuberculosis, for example). Other less common causes are lymph node infarctions, trauma, and vasculitis.

The presence of macroscopic fat in the hilar region of lymph nodes is, in most cases, a normal finding. However, a lesser-known aspect that deserves to be highlighted is the fact that some abnormal conditions can also present with fat inside the lymph node.

This fat deposit can occur as a direct consequence of obesity, diabetes, thyroid disease, or treatment for neoplastic diseases. Generally, adipose tissue replaces the normal parenchyma, keeping the nodal volume unchanged. In some cases, the lymph nodes may reach unusual dimensions.[1]

Metastatic lymph nodes due to liposarcoma may have malignant fat cells within them. The presence of macroscopic fat expanding the lymph node may also be seen in lymphoproliferative diseases, especially in chronic lymphocytic leukemia secondary to treatment. In these cases, adipocytes in the affected lymph nodes may expand as the lymphatic tissue atrophies during treatment. Adipocytes tend to fill the void left by the atrophic process. This is important because biopsy or excision of these lymph nodes with abundant fat is usually unnecessary.[2-4]

Another interesting aspect is that the finding of lymph node adiposity on screening mammograms may serve as a useful imaging biomarker for steatotic liver disease associated with metabolic dysfunction in women at high risk for developing steatohepatitis. Early intervention in this condition may limit progression to fibrosis and end-stage liver disease.[4]

Our patient presented a lymph node of normal dimensions, with fatty content inside, surrounded by a denser halo with homogeneous thickness, fulfilling the imaging criteria of a normal lymph node.

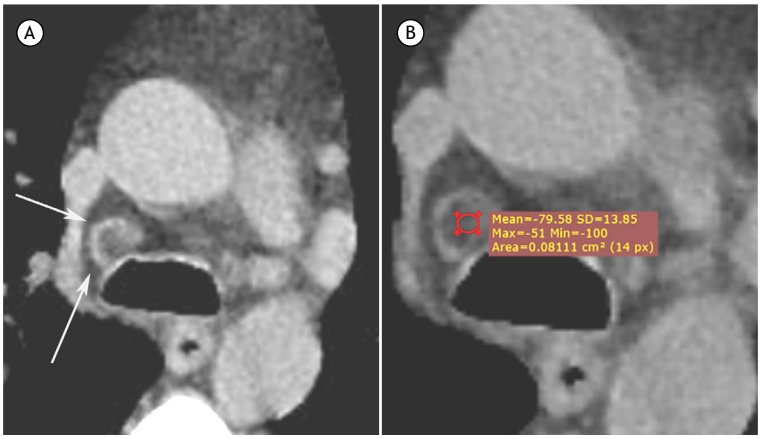

Figure 1. Detail of an axial CT scan of the chest, showing a mediastinal lymph node of normal dimensions (arrows), with a hypodense center (mean density = −80 HU) and a halo with greater, homogeneously thick density on the periphery.

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◄ Voltar ao sumário

Looking back to move forward: insights from retrospective cohort studies

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PRACTICAL SCENARIO

Investigators were interested in estimating the incidence of noninvasive ventilation (NIV) failure in adult patients with acute respiratory failure and identifying the risk factors for failure. They performed a retrospective cohort study and examined the electronic medical records of 2,258 patients admitted to a 31-bed ICU in Brazil over one year and included 114 patients with acute respiratory failure who had received NIV support as the first line of treatment.[1] They reported that the incidence of NIV failure was 41% and that predictors of NIV failure were male sex, infection as the primary cause of acute respiratory failure, and severity of illness at ICU admission. They also found that NIV failure was a risk factor for ICU mortality among those patients.

WHAT ARE COHORT STUDIES?

Cohort studies are defined as observational studies in which participants at risk of developing one or more outcomes of interest are followed over time with the objective of describing the incidence of those outcomes and estimating their association with one or more exposures or predictors. At the beginning of follow-up, participants are free of the outcome(s) of interest. Exposures/predictors of interest are measured at baseline and periodically during follow-up, and patients are followed over time until the end of the study or in the occurrence of the outcome(s) or loss to follow-up.[2]

Cohort studies are prospective when investigators plan the study and define the variables of interest before enrolling patients and follow them over time. Participants are assessed periodically for the occurrence of the outcome. The minimum duration of follow-up and periodicity of measurements depend on the type of outcome and on known or suspected latency between the exposure and the occurrence of the outcome. A cohort study is retrospective when follow-up of participants and outcomes have already occurred when the investigators start the study (Figure 1). Therefore, the study population has already been defined, measurements of the exposure and outcome have already been made by other professionals, and follow-up time has already taken place.

Prospective cohorts allow the investigator to measure variables of interest more accurately and completely, but they can be time consuming, expensive, and inappropriate when immediate results are warranted, given that investigators may need to follow patients over long periods of time. Retrospective studies take advantage of existing data, such as patient medical records, collected in the past for other purposes, thus shortening the duration of the study and decreasing measurement and personnel costs.

ADVANTAGES AND DISADVANTAGES OF RETROSPECTIVE COHORTS

The main advantages of retrospective cohort studies are that they allow investigators to estimate the incidence rate of an outcome in an at-risk population and provide potential causes of outcomes of interest. Since the exposure is present before the outcome occurs, potential causation can be suspected, but not asserted, due to the risk that other unsuspected and/or unmeasured exposures may be the real risk factor for the occurrence of the outcome.

Other advantages of retrospective cohorts include reduced cost and time when compared with prospective cohorts and clinical trials by providing a list of suspected risk factors for the outcomes of interest. In our practical scenario, the study was completed in two months, with minimal funding, whereas, if a prospective cohort had been chosen, the investigators would have needed to spend an entire year screening patients in the ICU daily to include the 114 patients and to be present in the ICU daily to collect demographic, ventilatory, and outcome data.

The main disadvantages of retrospective cohort studies include the limited control that investigators have over the accuracy and completeness of the measurements, availability of important covariates that may also be associated with or predict the outcome, and biases, including selection bias, related to the population included in the study, and measurement bias, related to the fact that measurements were made before the investigators designed the study. For example, in our practical scenario, data related to the presence of relevant comorbidities such as COPD may have been missing or been inaccurate on the electronic medical records, which could have impacted the results. Thus, it is important to identify these issues when designing retrospective cohort studies.

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◄ Voltar ao sumário
ISSN 1806-3756

KEY MESSAGES

1. Retrospective cohorts allow investigators to estimate the incidence of outcome(s) of interest in an at-risk population with reduced time and costs
2. Follow-up, measurement of the exposures, predictors, confounders, effect modifiers, and outcomes happened in the past, before the investigators have begun the study, and thus data is collected retrospectively
3. The main disadvantage of retrospective cohorts is the risk of inaccurate and incomplete data

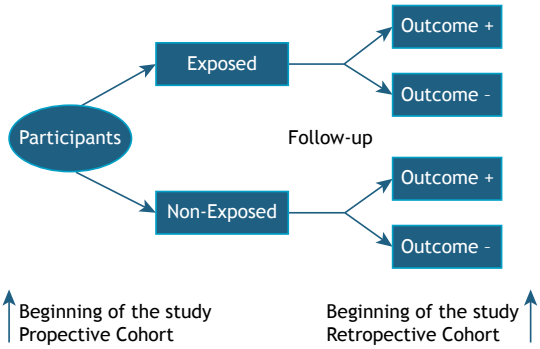

Figure 1. Structure of cohort studies.

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Peculiarities of spirometry in pediatrics

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We face several challenges when evaluating lung function in pediatric patients with respiratory symptoms. On the one hand, their chest wall muscle strength is not enough to maintain low lung volumes (at residual volume), and this is further limited by the fact that lung elastic recoil is increased in children,[1] thus hindering the forced expiratory maneuver of spirometry; on the other hand, communication and interaction with pediatric patients are essential in order to achieve results that meet the current quality standards for spirometry.[2,3]

In order to perform spirometry on a child, we must consider that the laboratory environment should not cause any distractions or overstimulate the child; the calmness and patience of the personnel are essential: better results are achieved if the child perceives the test as a game or becomes familiar with the equipment.[1,3]

Multiple devices have developed animations that invite patients to perform a forced expiratory maneuver and encourage them to complete it; however, certain technical factors should be taken into consideration when choosing the best equipment for preschool children. The dead space of the equipment should be minimized (< 2 ml/kg of weight) because it can influence the results. In cooperative children, performing some maneuvers at tidal volume before a forced expiratory maneuver can lead to better results.[1]

In younger children, reduced respiratory muscle strength and increased lung elastic recoil limit exhalation time. Therefore, $FEV_{0.5}$ and $FEV_{0.75}$ have been used in order to assess obstruction in children in the 3- to 5-year age bracket who cannot achieve FEV_1, with varying degrees of success (between 39% and 70% for $FEV_{0.5}$ and between 9% and 44% for $FEV_{0.75}$), supporting the usefulness of the forced expiratory maneuver in preschool children.[1,4]

In children in whom FEV_1 and FVC are acceptable, the FEV_1/FVC ratio will determine airflow obstruction on the basis of a z score of < -1.645, based on an equation that is appropriate for the study population. Obstruction should be graded on the basis of the FEV_1 z score. If an FVC is adequately performed and FVC is decreased, it should ideally be correlated with lung volumes in order to diagnose a restrictive pattern (FVC ≤ -1.645), a mixed pattern (FEV_1/FVC and FVC ≤ -1.645), or a preserved ratio impaired spirometry pattern (if only FEV_1 is affected; Figure 1).[5]

Evaluating spirometry after administration of a bronchodilator is particularly important in children, whose results can sometimes be within normal limits or be achieved through a less than perfect technique. A significant change as established in the latest European Respiratory Society/American Thoracic Society technical standard (a 10% change in percent predicted FEV_1 or FVC) can guide the therapeutic approach to be used in preschool children with respiratory symptoms.[5]

In conclusion, spirometry is feasible even in preschool children. With the appropriate personnel and by adapting simple laboratory conditions and equipment, reliable results can be obtained for the diagnosis and follow-up of children with respiratory symptoms.

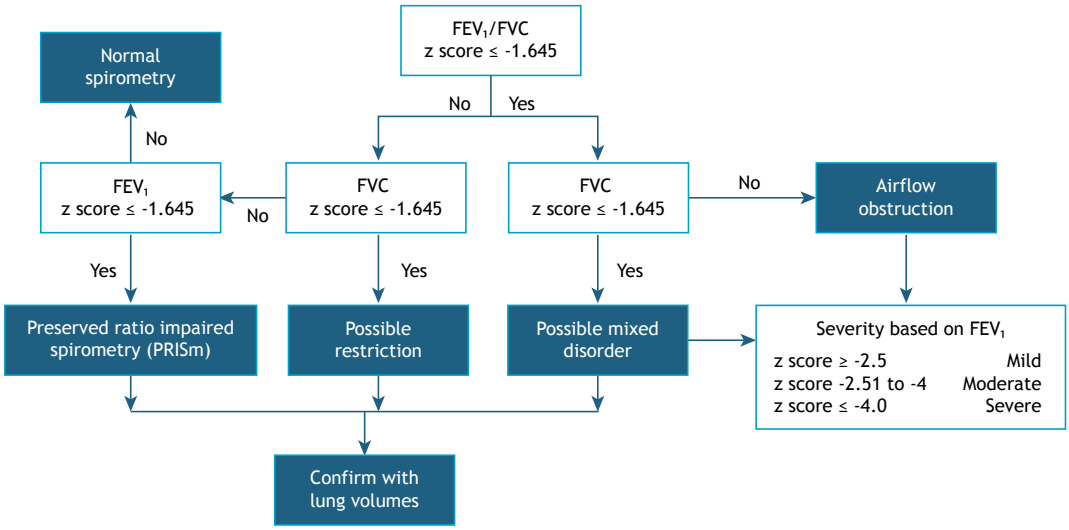

Figure 1. Interpretation of spirometry in pediatric patients.

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◄ Voltar ao sumário
ISSN 1806-3756

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

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

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Best clinical practice for imaging in cystic fibrosis referral centers in Brazil: a Delphi consensus panel approach

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INTRODUCTION

Cystic fibrosis (CF) is a genetic disease characterized by morbidity and mortality related to progressive lung disease. Evidence of structural lung disease occurring early in life provides the opportunity to tailor therapies.[1] Although the progression of lung disease is routinely assessed by pulmonary function tests,[1] chest imaging may be more sensitive for the detection of structural lung damage.[2] The use of cross-sectional imaging modalities such as CT and MRI may contribute to the development of patient-tailored therapy.[2] However, for most clinicians, it is unclear precisely when, and how, to use chest X-ray (CXR), CT, and MRI. Standard procedures concerning lung imaging are still highly heterogeneous across CF centers.[3] To address this issue, a Delphi panel of experts in Brazil discussed recommendations for the timing and choice of lung imaging techniques in the assessment of stable or exacerbated CF-related lung disease.

METHODS

We used the Delphi method to determine and quantify group consensus.[4] The working group consisted of pulmonologists, CF clinicians, and radiologists, representing broad experience in CF and image interpretation. The survey was initially organized around key statements facing CF clinicians in the use of imaging, when to obtain them, and how to act upon the results of the testing. The statements were developed on the basis of previous studies.[2,3] The appropriateness of statements was analyzed with a Likert scale ranging from 0 (completely disagree) to 10 (completely agree). In round 1, the participants were provided with the opportunity to add comments in support of their opinions or to suggest alternate wording for clarity. In round 2, expert participants rated the statements from online questionnaire 2—in this round, there is no need to justify the disagreements. Facilitators analyzed the agreement among panelists—for each statement, agreement was considered to have been achieved if at least 80% of panelists rated the statement as "agree" or "completely agree". In round 3, the results of the Delphi panel are discussed in an online meeting to evaluate the statements in depth, identifying those for which the level of disagreement was greatest and those that were the most relevant for clinical practice.

RESULTS AND CONCLUSIONS

Twenty-two recommendations are presented below, including recommendations for diagnosis, follow-up, exacerbations, and radiation dose. Chart 1 shows the main recommendation statements that may be used to inform decisions regarding best clinical practices in CF imaging.

Statement 1: In infants diagnosed with CF via newborn screening, low-dose CT can be used as a sensitive tool to detect early disease and monitor disease progression in symptomatic and asymptomatic patients alike. In clinical practice, it could estimate individual response to standards of care in order to estimate the appropriateness of the treatment the patient is given.

Statement 2: Current best clinical imaging practice at various CF centers is performing CT biennially (i.e., once every 2 years), with a radiation dose determined by adhering to the as low as reasonably achievable (ALARA) principle, the use of which results in a reasonably low risk related to the cumulative dose (a total of nine CTs from 1 to 17 years of age).

Statement 3: CT can detect lung disease progression better than can standard pulmonary function testing parameters (e.g., FEV_1), in cooperative and uncooperative patients, irrespective of disease severity.

Statement 4: CT provides relevant information possibly capable of modifying disease trajectory, patient management, and follow-up, in uncooperative and cooperative patients.

Statement 5: Despite the fact that treatment with a CF transmembrane conductance regulator (CFTR) modulator results in improvements on imaging (reductions

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in mucous plugging and peribronchial thickening, etc.), no deviation from the usual imaging follow-up scheme should be advised in patients undergoing such treatment.

Statement 6: Although MRI of the chest can be considered a surrogate marker for disease severity and treatment response during the short-term follow-up of cooperative patients with CF who are symptomatic or in decline, its use in clinical practice is hampered by its higher cost in comparison with CT; the need for state-of-the-art MRI systems; the occasional need for moderate sedation or general anesthesia in uncooperative children; nonuniformity of MRI protocols; and substantial image variability/capability among MRI manufacturers.

Statement 7: Routine use of CT for short-term follow-up during pulmonary exacerbation is not recommended, because of the risk of a high cumulative radiation dose. Clinicians should consider the risk/benefit ratio related to the radiation dose when prescribing CT during pulmonary exacerbation, which should be performed at a low dose or ultra-low dose.

Statement 8: Despite the fact that many specialist centers are using CXR as the imaging technique of choice in infants and preschool children, a CT scan has higher sensitivity for detecting early abnormalities in symptomatic and asymptomatic patients with CF, regardless of age.

Statement 9: CT can detect acute structural lung abnormalities (e.g., increase of bronchial wall thickening and mucus plugging) during and after pulmonary exacerbation, in cooperative and uncooperative patients.

Statement 10: Although low-dose CT is feasible in cooperative and uncooperative patients, its limitations should be considered, especially in uncooperative patients.

Statement 11: During severe pulmonary exacerbation, CXR can be used. However cases that are more severe might require additional imaging examinations. Alternatives to CXR include low-dose CT (preferable) and lung ultrasound, if available.

Statement 12: In chest MRI, the risk related to moderate sedation or anesthesia needs to be considered in uncooperative patients.

Statement 13: The CT radiation dose should be ALARA without affecting the diagnostic quality of the image. Radiology departments should be encouraged to register the dose-length product in the report for each examination to ensure low-/ultra-low-dose CT and control the cumulative dose.

Statement 14: The cancer risk related to the cumulative radiation dose from CT is reasonably low in children undergoing biennial low-dose CT. Harmonization of CT protocols among CF centers should be promoted to comply with the ALARA principle, given that the lifespan of people with CF is increasing.

Statement 15: With a biennial, low-dose CT scheme, the risk related to the cumulative dose (total of nine CTs from 1 to 17 years of age) has been deemed reasonably low.

Statement 16: Further dose reductions could be achieved by introducing a patient-tailored CT imaging follow-up scheme that would stratify the patients with CF according to their risk factors for disease progression, including chronic bacterial infection, pulmonary exacerbation rate, pancreatic insufficiency, nutritional state, age at diagnosis, therapy adherence,

Chart 1. Main recommendation statements that may be employed to inform decisions and determine best clinical practices in imaging for patients with cystic fibrosis.

Statement: Current best clinical imaging practice at various CF centers is performing CT biennially (i.e., once every 2 years), with a radiation dose determined by adhering to the ALARA principle, the use of which results in a reasonably low risk related to the cumulative dose (a total of nine CTs from 1 to 17 years of age).
Statement: CT provides relevant information possibly capable of modifying disease trajectory, patient management, and follow-up, in uncooperative and cooperative patients.
Statement: Although MRI of the chest can be considered a surrogate marker for disease severity and treatment response during the short-term follow-up of cooperative patients with CF who are symptomatic or in decline, its use in clinical practice is hampered by its higher cost in comparison with CT; the need for state-of-the-art MRI systems; the occasional need for moderate sedation or general anesthesia in uncooperative children; nonuniformity of MRI protocols; and substantial image variability/capability among MRI manufacturers.
Statement: Despite many specialist centers are using chest X-ray as the imaging technique of choice in infants and preschool children, a CT scan has higher sensitivity for detecting early abnormalities in symptomatic and asymptomatic patients with CF, regardless of age.
Statement: Although low-dose CT is feasible in cooperative and uncooperative patients, its limitations should be considered, especially in uncooperative patients.
Statement: During severe pulmonary exacerbation, CXR can be used. However cases that are more severe might require additional imaging examinations. Alternatives to CXR include low-dose CT (preferable) and lung ultrasound, if available.
Statement: The CT radiation dose should be ALARA without affecting the diagnostic quality of the image. Radiology departments should be encouraged to register the dose-length product in the report for each examination to ensure low-/ultra-low-dose CT and control the cumulative dose.
Statement: For quality control, the dose reports of the CT examinations should be provided by all centers, to track and manage the radiation dose received by patients with CF.

CF: cystic fibrosis; ALARA: as low as reasonably achievable; and CXR: chest X-ray.

and use of CFTR modulators. In patients with CF who are more stable, longer CT scan intervals could allow a reduction of the cumulative dose.

Statement 17: For quality control, the dose reports of the CT examinations should be provided by all centers, to track and manage the radiation dose received by patients with CF.

Statement 18: In people with CF, it is recommended that CT severity scores (e.g., Bhalla, Brody, and Oikonomou) or scores that include the severity of bronchiectasis, bronchial wall thickening, consolidation, and atelectasis be used. The use of software could help reduce the time required for image interpretation and interobserver variability in the assessment.

Statement 19: To reduce radiation exposure, when needed in cooperative children with CF, end-expiratory images should be obtained at a low radiation dose. However, the indication for end-expiratory CT should be carefully considered (i.e., screening or first diagnostic examination) according to the ALARA principle.

Statement 20: The use of appropriate CT scoring systems increases the sensitivity of the examination for tracking changes in symptomatic and asymptomatic early lung disease. Therefore, their use is recommended in order to standardize interpretation of CT data according to CF center expertise and capacity.

Statement 21: In uncooperative children with CF, the recommended CT protocol consists of a free-breathing unenhanced CT without sedation. It should be emphasized that this protocol is very useful for detecting acute pulmonary infection and exacerbation, although it could be of limited utility for assessing some specific initial anatomic abnormalities such as bronchial thickening.

Statement 22: There is no international consensus on CT protocols for patients with CF. Volumetric CT acquisition is recommended, preferably in scanners with 16 or more slices, because of the shorter acquisition time using low tube voltages and currents tailored to the weight or age of the patient, as is the use of reconstruction software that reduces image noise from low-dose CT images.

In conclusion, although CT continues to be a cornerstone in the management and monitoring of CF because of its sensitivity for detecting early disease and tracking progression, its biennial use following the ALARA principle ensures that radiation exposure is kept to a minimum.[5] The superiority of CT over standard pulmonary function tests in detecting lung disease progression and its ability to provide critical information for modifying patient management, underscores its importance.[6] Despite advancements in CFTR modulator therapy, the established imaging follow-up protocols should remain unchanged. Although MRI offers a nonradiative alternative with potential benefits, its higher costs, the need for advanced equipment, and other practical limitations restrict its widespread clinical use.

AUTHOR CONTRIBUTIONS

LAP, AFR, ES, LFVM, VG, SSJ, and ISM contributed to the Delphi panel discussions. LAP, ES, and ISM contributed to writing, reviewing, and editing the manuscript.

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CONFLICTS OF INTEREST

None declared.

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Real-world outcomes of mepolizumab in severe eosinophilic asthma: a retrospective cohort study

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Study carried out at the Centro Hospitalar Tondela-Viseu, Viseu, Portugal.

ABSTRACT

Objective: To evaluate the efficacy and safety of mepolizumab in patients with severe eosinophilic asthma (SEA) in a real-world clinical setting. **Methods:** This retrospective, observational cohort study included data from 45 SEA patients who initiated mepolizumab treatment, with 41 completing a 12-month follow-up. Demographic, clinical, and laboratory data—including exacerbation rates, forced expiratory volume in one second (FEV_1), Asthma Control Test (ACT) and CARAT scores, and blood eosinophil counts—were extracted from patient medical records. Paired statistical tests were used to compare pre- and post-treatment outcomes, with significance set at $p < 0.05$. **Results:** Mepolizumab therapy was associated with an 81% reduction in annual exacerbation rates (from 2.68 to 0.51 events; $p < 0.001$) and a 21.6% improvement in FEV_1 (from 1.71 L to 2.08 L; $p < 0.001$). ACT scores increased significantly from 11.91 to 21.29 ($p < 0.001$), with 73.2% of patients achieving well-controlled asthma (ACT ≥ 20). CARAT scores also showed significant improvement, reflecting better control of both asthma and rhinitis symptoms. Blood eosinophil counts decreased by 64% (from 525.9 to 189.4 cells/μL; $p < 0.001$). Overall, the treatment was well tolerated, with only one discontinuation due to a mild headache. **Conclusion:** In this real-world cohort, mepolizumab significantly reduced exacerbation frequency, improved lung function and symptom control, and lowered eosinophil levels over 12 months. These findings support its use as an effective and safe therapeutic option for managing severe eosinophilic asthma.

Keywords: Mepolizumab, Eosinophilic asthma, Severe asthma.

INTRODUCTION

Severe eosinophilic asthma (SEA) is a high-burden, treatment-resistant phenotype characterized by chronic eosinophilic inflammation, frequent exacerbations, and impaired quality of life, despite optimized inhaled and systemic corticosteroid therapy. In clinical practice, real-world data have become increasingly valuable in complementing randomized controlled trials (RCTs), offering insights into the effectiveness, safety, and tolerability of treatments across broader and more diverse patient populations. For both clinicians and patients, real-world evidence supports therapeutic decision-making in routine care settings, where disease presentation, comorbidities, and treatment adherence may differ significantly from those observed in controlled trials.

Mepolizumab, a humanized monoclonal antibody targeting interleukin-5 (IL-5), represents a transformative advancement in the treatment of SEA. By selectively inhibiting IL-5, mepolizumab reduces eosinophilic activity—a key driver of inflammation in this asthma phenotype. Pivotal clinical trials, including the DREAM and MENSA studies, have demonstrated significant reductions in exacerbation rates, improvements in lung function, and enhanced asthma control with mepolizumab therapy. These findings have been further supported by real-world evidence from studies such as REDES and REALITI-A, which highlight the effectiveness and safety of mepolizumab in diverse patient populations.[1]

Despite these advances, real-world data on the impact of mepolizumab in specific populations remain limited. This retrospective, observational study evaluated the efficacy and safety of mepolizumab therapy in patients with SEA over a 12-month period, focusing on clinical outcomes such as exacerbation rates, lung function, symptom control, and blood eosinophil levels. Additionally, the study contextualizes these findings within the broader body of evidence from clinical trials and real-world studies, aiming to provide a more comprehensive understanding of mepolizumab's role in the management of SEA.

METHODS

This retrospective, observational cohort study was conducted in patients with SEA treated with mepolizumab. Eligible patients were identified from clinical records at a single center and included individuals aged 18 years or older who had initiated mepolizumab therapy at least 12 months prior to data collection. A documented diagnosis of SEA was required, based on established clinical criteria, including recurrent exacerbations and

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evidence of eosinophilic inflammation (blood eosinophil counts ≥ 150 cells/μL), in accordance with the Global Initiative for Asthma (GINA) guidelines.[10] Patients with significant comorbid conditions that could influence SEA outcomes, such as uncontrolled sleep apnea or severe rhinitis, were noted but not excluded.

Data were retrospectively collected from electronic medical records, covering the period from January 2016 to August 2024. Extracted variables included demographic characteristics, clinical history, blood eosinophil counts, exacerbation history, lung function parameters, and Asthma Control Test (ACT) scores. Exacerbations were defined as episodes requiring systemic corticosteroids for at least three days or resulting in an emergency department visit or hospitalization. To minimize errors, the completeness and accuracy of the data were verified through cross-referencing with pharmacy records and consultation notes.

Patients received 100 mg of mepolizumab subcutaneously every four weeks, in accordance with standard clinical practice. Mepolizumab initiation was based on poor response to standard asthma therapies or persistently elevated blood eosinophil counts. Treatment adherence was monitored through regular follow-up appointments and pharmacy refill records. Concurrent asthma therapies, including inhaled corticosteroids and bronchodilators, were maintained without modification during the study period to ensure consistency in background treatment.

The primary outcome was the annualized rate of clinically significant exacerbations before and after mepolizumab initiation. Secondary outcomes included changes in lung function (measured by FEV_1), symptom control (assessed using ACT and CARAT scores), and blood eosinophil counts. Safety outcomes, such as the incidence and severity of adverse events, were also recorded. Mild adverse events were defined as transient symptoms that did not require treatment modification, while severe adverse events necessitated treatment discontinuation or additional medical intervention. Additionally, correlations between eosinophil reduction and symptom improvement were explored.

Descriptive statistics were used to summarize baseline characteristics, including means, standard deviations, and proportions. Changes in clinical outcomes before and after treatment were analyzed using paired t-tests or Wilcoxon signed-rank tests for continuous variables, and McNemar's test for categorical variables, depending on data distribution. Sensitivity analyses were conducted to account for variability in data collection and to confirm the robustness of the results. Statistical significance was set at $p < 0.05$. In order to address potential biases, subgroup analyses were performed based on age, baseline eosinophil counts, and comorbidities. All analyses were carried out using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients when required. As a retrospective analysis, patient confidentiality was strictly maintained, and no identifiable information was included in the final dataset.

RESULTS

Overall baseline characteristics of the study population

A total of 45 patients with severe eosinophilic asthma (SEA) initiated treatment with mepolizumab during the study period. Of these, 41 completed the full 12-month follow-up. Four patients (8.9%) discontinued treatment prior to completion: three due to persistent symptoms despite therapy, and one due to an adverse effect (headache). It is worth noting that none of the patients who discontinued treatment achieved well-controlled asthma (ACT ≥ 20), nor did they show significant reductions in blood eosinophil counts or improvements in lung function. These findings underscore the importance of early therapeutic response assessments to guide decisions regarding treatment continuation.

Table 1 presents a comprehensive overview of the baseline demographic and clinical characteristics of the study participants. The analyzed variables

Table 1. Demographic and clinical characteristics of the study population.

Variable	
Age in years, m (SD)	62.71 (9.95)
Sex	
Male, n (%)	14 (34.15)
Female, n (%)	27 (65.85)
Body mass index, mean (SD)	
Normal weight, n (%)	17 (41.46)
Overweight, n (%)	20 (48.78)
Obese, n (%)	4 (9.76)
Atopy, n (%)	
Yes	20 (48.78)
No	21 (51.22)
IgE (IU/mL); m (SD)	252.5 (303.77)
Anxiety/Depression, n (%)	
Yes	8 (19.51)
No	33 (80.49)
Sleep apnea, n (%)	
Yes	13 (31.71)
No	28 (68.29)
Rhinitis, n (%)	
Yes	30 (73.17)
No	11 (26.83)
Nasal polyps, n (%)	
Yes	20 (48.78)
No	21 (51.22)
Gastroesophageal reflux, n (%)	
Yes	4 (9.76)
No	37 (90.24)

included age, sex distribution, body mass index (BMI) categories, prevalence of atopy, comorbid conditions, and blood eosinophil counts. Results were presented as means with standard deviations (SD) for continuous variables and as frequencies (n) with percentages (%) for categorical variables. Notably, the study cohort exhibited substantial disease burden and clinical complexity. The group consisted of 41 individuals, predominantly female (65.9%), with a mean (SD) age of 62.7 (9.9) years. Nearly half (48.8%) of the participants were overweight, and 9.8% were classified as obese. Atopy and nasal polyposis were both prevalent, each affecting 48.8% of the cohort.

The mean (SD) baseline blood eosinophil count of 525.94 (200.3) cells/μL highlights the eosinophilic nature of this patient population. Comorbidities were common, with anxiety or depression affecting 19.5% of patients and sleep apnea diagnosed in 31.7%. Rhinitis was particularly prevalent, present in 73.2% of the participants. These findings underscore the need for tailored interventions to address the multifaceted challenges associated with SEA.

Exacerbations

Mepolizumab treatment resulted in a significant reduction in asthma exacerbations. In Figure 1, it can be noted that the mean (SD) number of episodes decreased from 2.68 (1.12) in the 12 months prior to treatment to 0.51 (0.84) post-treatment, representing an 81% reduction ($p < 0.001$).

Lung function

Significant improvements in lung function were observed following treatment with mepolizumab. The mean (SD) FEV_1 increased from 1.71 (0.54) liters at baseline to 2.08 (0.62) liters post-treatment, with a mean absolute increase of 0.37 L ($p < 0.001$), corresponding to a 21.6% relative improvement (Figure 2). This outcome is consistent with findings from the MENSA study and may be partially attributed to the long-standing duration of asthma in our cohort. The average age of 62.7 years suggests the presence of potentially reversible airflow limitation, likely due to improved inflammatory control.

Symptom control

The ACT scores improved significantly, increasing from a mean (SD) of 11.91 (4.76) at baseline to 21.29 (4.79) at follow-up ($p < 0.001$), as shown in Figure 3. Notably, 73.2% of patients achieved scores ≥ 20, indicating well-controlled asthma, and an equal proportion met the minimal clinically important difference (MCID), with an increase of ≥3 points. At baseline, only 2.4% of patients had an ACT score ≥20, compared to 73.2% after 12 months of mepolizumab therapy. This pronounced categorical shift reflects the substantial clinical impact of mepolizumab treatment on symptom control, consistent with the significant improvement in mean ACT scores.

CARAT scores also improved significantly following treatment. At follow-up, 65.9% of patients achieved a clinically meaningful improvement, defined as an increase of ≥8 points, thus meeting the MCID.

Specifically, the CARAT subdomain scores for asthma and rhinitis demonstrated meaningful improvements. Asthma-related CARAT scores increased from a mean of 6.24 at baseline to 16.21 at 12 months, while rhinitis-related scores rose from 4.60 to 8.30 over the same period (Figure 4). These findings demonstrate

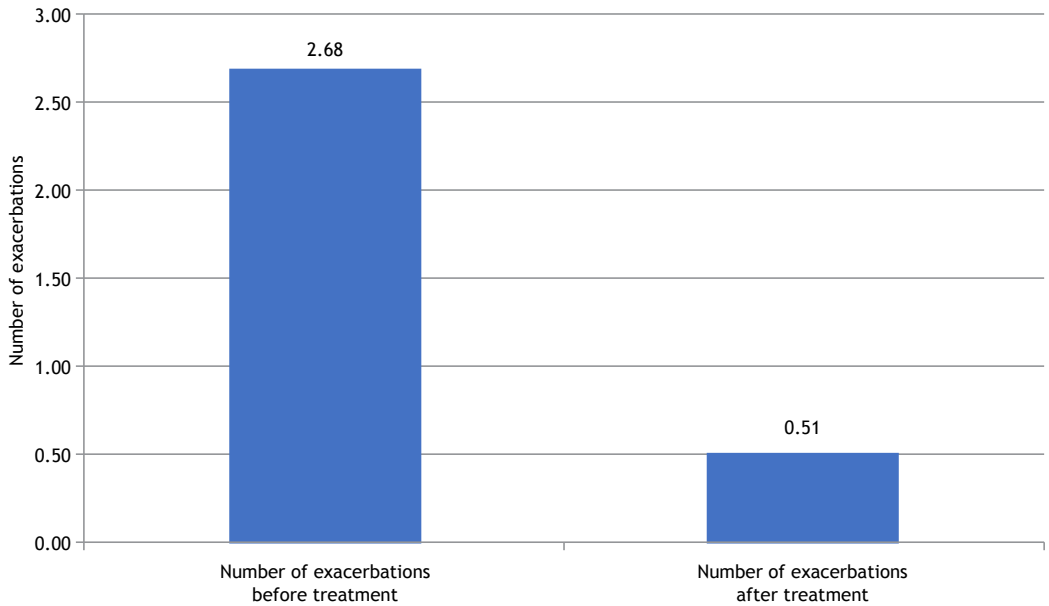

Figure 1. Annual Exacerbation Rates Before and After 12 Months of Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma (SEA). The mean exacerbation rate decreased significantly from 2.68 (SD = 1.12) to 0.51 (SD = 0.84), representing an 81% reduction ($p < 0.001$), thus highlighting the substantial impact of mepolizumab in reducing disease severity and improving patient outcomes.

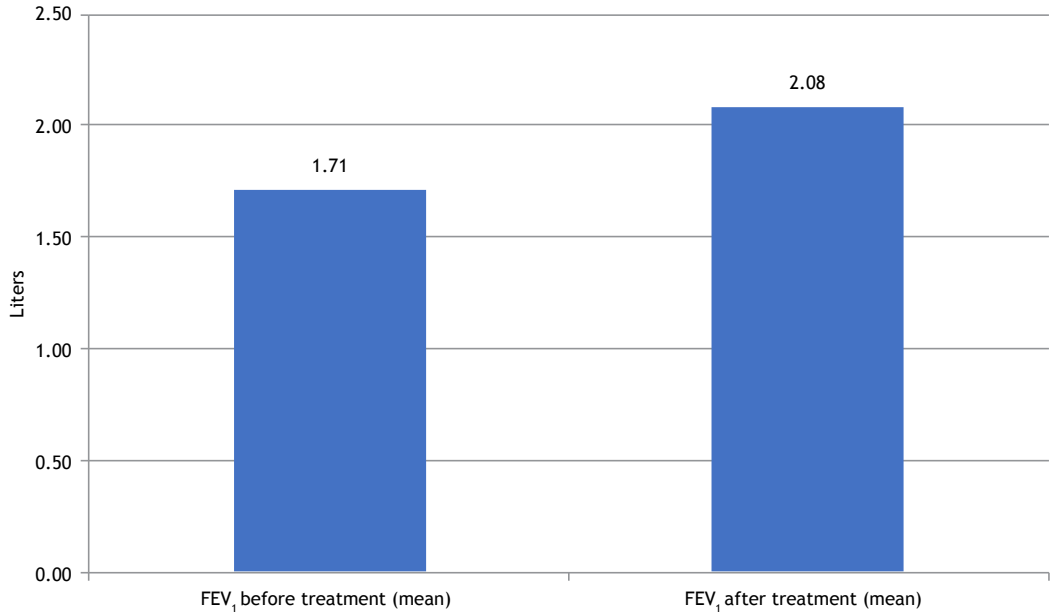

Figure 2. Lung Function Before and After 12 Months of Mepolizumab Treatment. This figure indicates the change in forced expiratory volume in one second (FEV_1) among patients with severe eosinophilic asthma (SEA). The mean FEV_1 increased significantly from 1.71 L (SD = 0.54) at baseline to 2.08 L (SD = 0.62) post-treatment, reflecting a 21.6% improvement ($p < 0.001$). These results underscore the efficacy of mepolizumab in enhancing lung function and reducing airway inflammation.

the dual benefit of mepolizumab in controlling both asthma and upper airway symptoms, which are often interrelated in patients with SEA.

Subgroup analysis based on CRSwNP and atopy status

To explore whether the clinical responses varied across phenotypic subgroups, we conducted an exploratory analysis comparing patients with and without chronic rhinosinusitis with nasal polyps (CRSwNP), as well as those classified as atopic versus non-atopic based on clinical phenotype. Patients with CRSwNP (n = 20) demonstrated numerically greater improvements in asthma control and symptom burden than those without nasal polyps, with mean ACT score increases of +11.2 vs. +8.0 and CARAT score improvements of +11.1 vs. +7.4, respectively. The reduction in the annualized exacerbation rate was also slightly greater in the CRSwNP group (−2.47 vs. −2.29). Conversely, patients with an atopic phenotype (n = 20) experienced greater reductions in exacerbations (−3.00 vs. −2.33) but showed smaller improvements in ACT (+1.0 vs. +10.8) and CARAT (+4.0 vs. +10.6) scores compared to non-atopic individuals. Given the limited sample size, these findings are descriptive and should be interpreted as hypothesis-generating.

Blood eosinophil counts

The mean (SD) blood eosinophil count at baseline was 525.94 (200.3) cells/μL, which decreased to 189.38 (122.1) cells/μL after 12 months of treatment ($p < 0.001$), representing a 64% reduction (Figure 5). At baseline, 12.2% of patients had eosinophil counts between 150–300 cells/μL, while 87.8% had counts above 300 cells/μL, reflecting the predominantly eosinophilic phenotype of the study cohort.

Safety

Mepolizumab demonstrated a favorable safety profile, with only one patient reporting a mild headache that led to a switch in therapy. Transient adverse events including musculoskeletal complaints reported by only two patients, were consistent with those documented in the REDES and REALITI-A studies. Importantly, no serious adverse events were reported, and the high treatment persistence rate (97.6%) reflects the high tolerability and acceptability of mepolizumab in real-world settings.

DISCUSSION

The findings of this study demonstrate the robust efficacy and favorable safety profile of mepolizumab in the management of severe eosinophilic asthma (SEA). The observed improvements in exacerbation rates, lung function, symptom control, and blood eosinophil counts are consistent with results from pivotal clinical trials, including DREAM and MENSA,[5,7] as well as real-world studies such as REDES and REALITI-A. These consistencies reinforce the reliability of mepolizumab across diverse patient populations and clinical settings.

The clinical benefits observed in our study align with findings from both randomized controlled trials and real-world investigations. Notably, the 81% reduction in the annualized exacerbation rate slightly exceeds

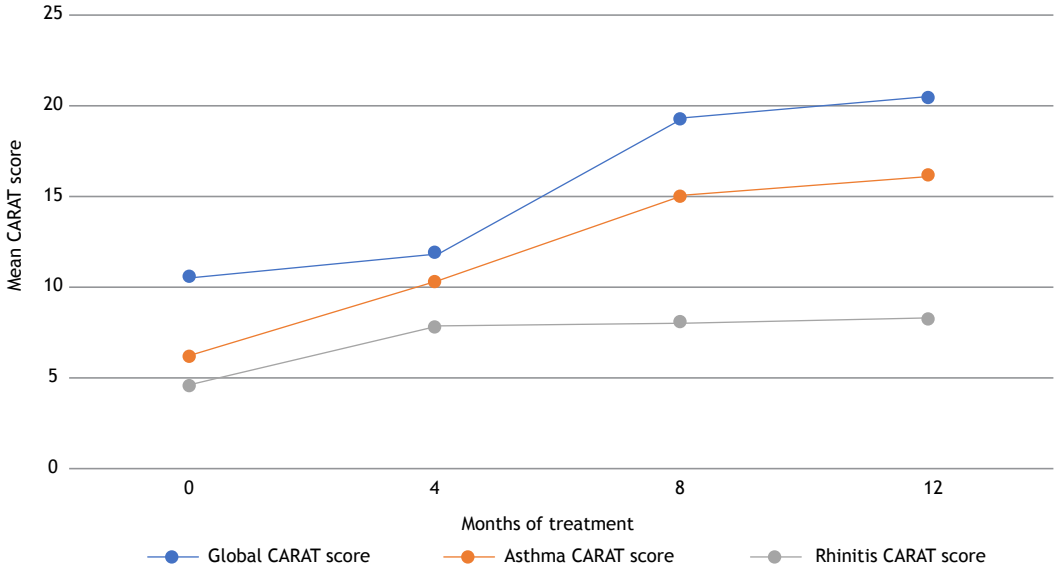

Figure 3. CARAT Scores Over 12 Months of Mepolizumab Treatment. This figure illustrates the progression of CARAT (Control of Allergic Rhinitis and Asthma Test) scores in patients with severe eosinophilic asthma (SEA) at baseline and after 4, 8, and 12 months of mepolizumab therapy. The mean total CARAT score improved significantly from 10.60 (SD = 4.35) at baseline to 20.54 (SD = 6.45) at 12 months ($p < 0.001$), indicating better control of asthma and allergic rhinitis symptoms. Subdomain scores for asthma and rhinitis also showed notable improvements over time. These results demonstrate the dual benefit of mepolizumab in managing both asthma and upper airway symptoms.

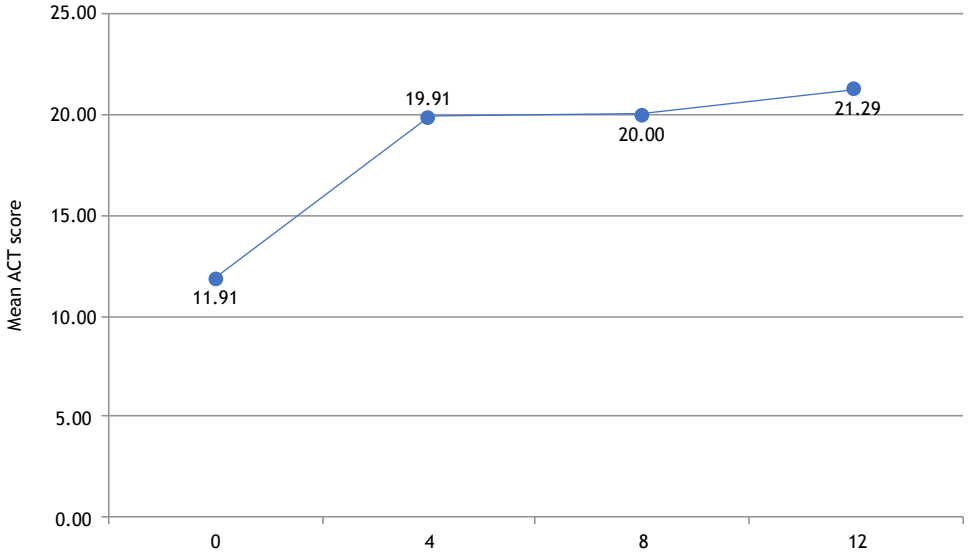

Figure 4. ACT Scores Over 12 Months of Mepolizumab Treatment. This figure depicts the progression of ACT (Asthma Control Test) scores in patients with severe eosinophilic asthma (SEA) at baseline and after 4, 8, and 12 months. The mean ACT score increased significantly from 11.91 (SD = 3.45) at baseline to 21.29 (SD = 3.87) at 12 months ($p < 0.001$), exceeding the minimal clinically important difference (MCID) of 3 points. The percentage of patients achieving well-controlled asthma (ACT ≥ 20) rose from 7.3% at baseline to 73.2% at 12 months, highlighting the substantial impact of mepolizumab on asthma symptom control.

the 77.5% reduction reported in the REDES study and is greater than the 69.6% observed in REALITI-A. Similarly, our cohort showed a mean FEV_1 increase of 0.37 L, compared to gains of approximately 0.22 L and 0.21 L in REDES and REALITI-A, respectively. Improvements in symptom control were also more pronounced, with a mean ACT score increase of 9.38 points and 73.2% of patients achieving well-controlled asthma (ACT ≥20) after 12 months—higher than the rates reported in previous real-world cohorts. Although the 64% reduction in eosinophil counts was lower than the 82.4% observed in REDES, this may reflect baseline differences in eosinophil levels and a higher prevalence of comorbidities in our cohort.

The finding that 73.2% of patients achieved well-controlled asthma (ACT ≥ 20) after 12 months

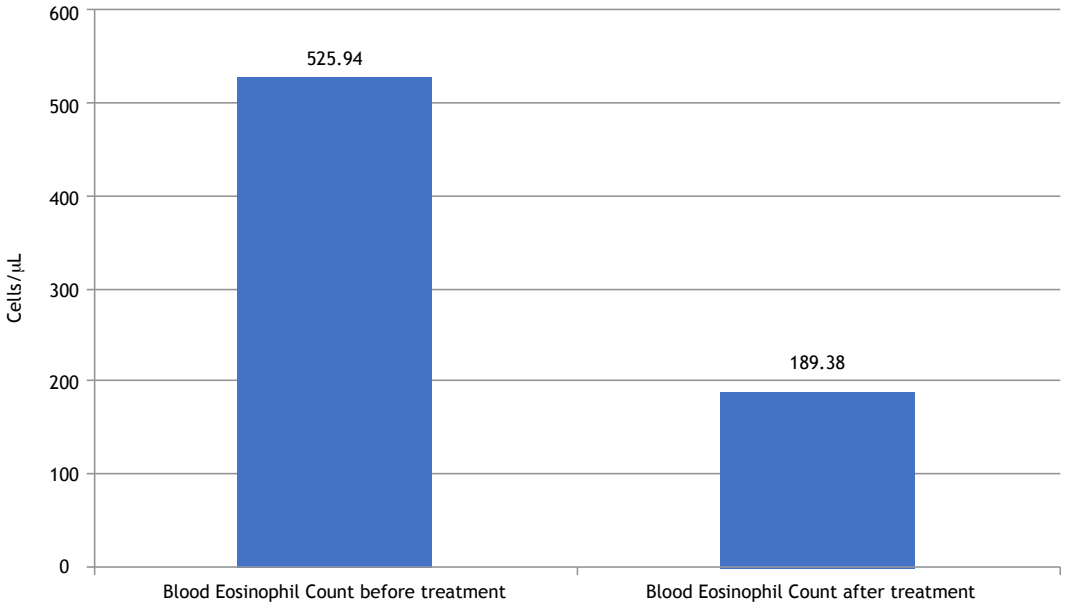

Figure 5. Blood Eosinophil Counts Before and After Mepolizumab Therapy. This figure indicates a significant reduction blood eosinophil counts in patients with severe eosinophilic asthma (SEA) post-treatment. The mean eosinophil count decreased from 525.9 cells/µL (SD = 200.3) at baseline to 189.4 cells/µL (SD = 75.2) post-treatment, representing a 64% reduction ($p < 0.001$). This decline underscores the anti-inflammatory efficacy of mepolizumab in targeting eosinophilic inflammation.

reflects a robust clinical benefit, consistent with the observed improvements in exacerbation rates and lung function. Interestingly, none of the patients who discontinued therapy early demonstrated clinically meaningful improvements across these outcomes, suggesting that an early lack of response may be predictive of long-term non-responsiveness. This observation supports recent evidence advocating for a reassessment of biologic therapy efficacy within the first 4–6 months of treatment.

While consistent with previous studies, the eosinophil reduction observed in this cohort was slightly lower than the 82.4% reported in the REDES study. Potential contributing factors include differences in baseline eosinophil levels and the presence of comorbidities—particularly the high prevalence of rhinitis and sleep apnea in our cohort. Further research is warranted to investigate how these comorbidities may influence treatment outcomes.

This study's focus on a cohort with a high burden of comorbidities—including rhinitis (73.2%) and sleep apnea (31.7%)—provides valuable insights into the effectiveness of mepolizumab in managing SEA within complex patient populations. The findings demonstrate the dual benefit of mepolizumab in addressing both lower and upper airway inflammation, which are frequently interconnected in SEA. Moreover, the significant improvement in ACT scores, with 73.2% of patients achieving well-controlled asthma (ACT ≥ 20) post-treatment, reinforces its potential to substantially improve patient quality of life.

The notable reductions in blood eosinophil counts and exacerbations reaffirm the role of IL-5 inhibition in mitigating eosinophilic inflammation. This mechanistic efficacy likely underpins the improvements in both lung function and symptom control observed in this cohort. Furthermore, the concurrent improvements in CARAT scores for both asthma- and rhinitis-related symptoms suggest that mepolizumab effectively targets systemic eosinophilic inflammation, extending its benefits beyond asthma control alone.

The observed absolute FEV_1 gain of 370 mL over 12 months of treatment was greater than that reported in other real-world studies, such as REDES and REALITI-A, where mean improvements ranged from approximately 190 to 220 mL. One possible explanation for this more pronounced response is the longer disease duration in our cohort (mean of 22.8 years). It is conceivable that patients with longstanding asthma may have accumulated a greater eosinophilic burden and degree of airway remodeling, potentially making them more responsive to IL-5 blockade. These findings raise the hypothesis that disease chronicity may influence the magnitude of functional improvement with targeted biologic therapy, although further prospective studies are needed to confirm this association.

When considering the broader landscape of biologic therapies for severe eosinophilic asthma (SEA), mepolizumab demonstrates comparable efficacy to other IL-5-targeting agents, such as benralizumab, and biologics addressing type-2 inflammation, such as dupilumab. While mepolizumab effectively reduces eosinophil counts and exacerbation rates, real-world studies highlight its particular benefit in patients with complex comorbidities, including rhinitis and nasal polyps, where dual airway inflammation is prevalent.

By inducing apoptosis of eosinophils through IL-5 receptor engagement, benralizumab may achieve faster eosinophil depletion, but it lacks extensive real-world data in diverse SEA populations. Dupilumab, which targets IL-4 and IL-13, broadens the therapeutic scope, offering significant benefits to patients with overlapping atopic conditions. The therapeutic choice should consider phenotypic differences, comorbidities, and patient preferences, such as administration frequency and delivery method. Current evidence underscores the robust efficacy of mepolizumab in SEA management; however, comparative real-world studies are necessary to further refine its positioning among biologics and optimize treatment algorithms.

The limitations of this study effectively highlight key concerns regarding its design and methodology. Its retrospective nature introduces biases, including reliance on medical records, the lack of randomization, and the absence of a control group, all of which affect generalizability and the ability to draw causal inferences. The single-center design further limits external validity, and the relatively small sample size reduces the power to detect rare adverse events or provide comprehensive safety data over extended periods.

The lack of detailed information on socioeconomic factors, adherence to concurrent therapies, and other potential confounders poses a significant challenge in fully understanding the range of variables influencing outcomes. Future prospective studies could address these limitations by enabling comprehensive data collection from the outset, incorporating randomization to minimize bias, and including control groups to strengthen causal inferences. Such an approach would also facilitate multicenter collaboration, enhancing sample diversity and statistical power, ultimately yielding more reliable and generalizable findings.

Further research should aim to address these limitations through prospective, multicenter studies with larger sample sizes. Long-term studies evaluating outcomes beyond 12 months may provide valuable insights into the durability of mepolizumab's benefits and its impact on healthcare resource utilization. Additionally, head-to-head comparisons with other biologics targeting distinct inflammatory pathways could help refine treatment algorithms for SEA. Investigating the role of mepolizumab in specific subpopulations—such as individuals with obesity or those requiring maintenance oral corticosteroids—could further support the development of personalized treatment strategies.

In this real-world cohort, mepolizumab was associated with substantial reductions in exacerbations, marked improvements in lung function and symptom control, and a trend toward remission in selected patients—reinforcing its value in everyday clinical practice. Its favorable safety profile and high treatment persistence rates further support its suitability for long-term use, particularly in patients with significant comorbidities. These findings reinforce mepolizumab's role as a cornerstone therapy in SEA management and highlight the need for ongoing research to optimize its use in across various clinical settings.

AUTHOR CONTRIBUTIONS

Writing, review, and imaging: P.F.; Supervision and review: M.S., J.P.S., T.B., and R.F.; Formal analysis and review: A.R.; Conceptualization and software: A.L.

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ORIGINAL ARTICLE

Baseline characteristics of patients from the Brazilian Severe Asthma Registry: the REBRAG study

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Study carried out at the Brazilian Registry of Severe Asthma.

ABSTRACT

Objective: To describe the impact of severe asthma in a real-life cohort in Brazil, reporting on baseline clinical characteristics, access to treatment, and clinical remission under treatment with biologics. **Methods:** Severe asthma patients > 6 years of age were recruited from 23 centers in Brazil. Data on clinical characteristics, lung function, biomarkers, prescribed therapies, and clinical remission under treatment were collected at the baseline visit. **Results:** A total of 417 patients were recruited. Of the 162 adult patients, 71% had a history of hospitalization, with 31% having experienced more than two severe exacerbations in the last 12 months and 6% having experienced cardiopulmonary arrest. Allergic and eosinophilic phenotypes were the most common phenotypes in all age groups, with the T2-low phenotype being observed in 10% of the pediatric patients and in 20% of the adult patients. Only 10% of the adult patients and 1% of the pediatric patients were receiving maintenance oral corticosteroids, whereas 41% of the adult patients were under treatment with biologics, with clinical remission being achieved in 20%. **Conclusions:** Severe asthma in Brazil still results in a high disease burden, with less than half of the patients receiving treatment with biologics and clinical remission being achieved in a subgroup of patients treated with biologics for more than 12 months. Achieving disease control remains a major clinical and health care challenge, requiring further actions from specialists and health care providers, as well as additional studies.

Keywords: Asthma; Phenotype; Biological products.

INTRODUCTION

Severe asthma is defined as asthma requiring treatment with high doses of inhaled corticosteroids (ICS) and a second controller medication, as well as optimal inhaler technique, optimal treatment adherence, and effective control of comorbidities; patients with severe asthma constitute 3-4% of the total asthma population.[1,2] Patients with severe asthma experience the highest rates of morbidity, an increased risk of hospitalization, and loss of lung function, placing a substantial financial burden on health care systems.[3-7] In developing countries, the impact of severe asthma is even more challenging, which is due to the difficulty in establishing an accurate diagnosis, receiving specialist follow-up, and gaining access to high-cost therapies.[8]

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Although there have been studies conducted at referral centers and providing local evidence on severe asthma in small patient samples, studies involving a robust number of participants and prospective follow-up are essential for understanding the impact of severe asthma, patient phenotypes, treatment responses (particularly to biologics), the ability to achieve remission with new targeted therapies, and long-term prognosis. As is the case with the International Severe Asthma Registry (ISAR),[9] real-world data from different countries, including Brazil, are important to addressing regional questions regarding phenotypic profiles, access to treatments, and responses to high-cost therapies. In this context, the *Registro Brasileiro de Asma Grave* (REBRAG, Brazilian Severe Asthma Registry), established in 2021, stands out as a multicenter cohort of pediatric and adult patients with severe asthma, with an annual collection of real-world clinical data. The present study was the first by the REBRAG group, and the objective of the study was to describe the characteristics of severe asthma patients at baseline (including demographic data, comorbidities, level of disease control, level of disease impact, and phenotypic profile) and the therapies used, reporting on the proportion of patients who achieved clinical remission with those therapies.

METHODS

Study design

The REBRAG study was a nationwide, multicenter, prospective cohort registry study. Real-world patient data were collected via electronic medical record review at 23 severe asthma centers in Brazil. The baseline visit was the entry visit, and the same parameters were collected annually. In the present study, we present the results for the 2021-2023 period.

Patients

The inclusion criteria were as follows: 1) ≥ 6 years of age; 2) having a history of symptoms suggestive of asthma; 3) meeting the GINA criteria for severe asthma; 4) having a history of asthma symptoms; 5) having a confirmed diagnosis of asthma based on the presence of reversible expiratory airflow limitation with the use of albuterol; 6) having used high-dose ICS with at least one long-acting β_2 agonist (LABA) for more than 6 months, with or without oral corticosteroids; and 7) having received optimal management (including good treatment adherence, correct inhaler technique, and management of treatable comorbidities) for at least 6 months of follow-up at our referral center. Patients with other chronic pulmonary diseases, cognitive impairment, neurological disorders, or immunodeficiencies were excluded.

Ethics

The present study was approved by the research ethics committees of all REBRAG centers, and all participating patients and/or their legal guardians gave written informed consent.

Data collection, tests, and procedures

Data were entered into an encrypted web-based online registry system with integrated plausibility checks within the database and a random sample of records regularly monitored at each participating center. The collected data included the following: demographic data and medical history (including symptoms, medications, and comorbidities); Asthma Control Test (ACT) or Childhood ACT scores; Asthma Quality of Life Questionnaire or Pediatric Asthma Quality of Life Questionnaire scores; use of rescue medication; exacerbations in the past 12 months; pulmonary function (FEV_1, FVC, and PEF); and biomarkers (complete blood count, total IgE, aeroallergen sensitization, and fractional exhaled nitric oxide). Clinical phenotyping was considered complete when patients had undergone eosinophil count, determination of total serum IgE levels, and aeroallergen sensitization testing.

Airflow limitation was classified in accordance with the severity of respiratory obstruction. Mild airflow limitation was defined as an FEV_1 ≥ 60% of the predicted value up to the lower limit of normal; moderate airflow limitation was defined as an FEV_1 of 41-59% of the predicted value; and severe airflow limitation was defined as an FEV_1 of ≤ 40% of the predicted value. Reversibility was defined as a ≥ 12% increase in FEV_1 after bronchodilator administration.[10]

Severe asthma phenotypes were classified as allergic asthma, eosinophilic asthma, or T2-low asthma, with cases of overlapping allergic and eosinophilic asthma also being considered. The criteria for diagnosing the phenotypes were as follows: allergic asthma—at least one positive skin prick test or blood test for aeroallergens; eosinophilic asthma—blood eosinophils ≥ 150 cells/mm^3; and T2-low asthma—absence of aeroallergen sensitization and blood eosinophils of < 150 cells/mm^3.[1]

Clinical remission was evaluated in patients in GINA treatment step 5 and was defined as no exacerbations or use of oral corticosteroids in the past 12 months and an ACT or Childhood ACT score > 20 on the day of the baseline visit, for at least 12 months after initiation of treatment with a biologic agent or triple therapy.[11]

Statistical analysis

Descriptive statistics were created for the sociodemographic and clinical characteristics of the patients, being presented as mean and standard deviation; median and interquartile range; or proportions. Numerical variables were presented as mean and standard deviation or median and interquartile range, depending on the distribution of the variables. Categorical variables included frequency tables with counts and percentages. A 95% confidence interval was used when applicable. All tests were two-tailed, and the level of significance was set at 5%. All statistical analyses were performed with RStudio, version 4.4.2 (RStudio, Inc., Boston, MA, USA).

RESULTS

A total of 417 patients were included in the present study. Of those, 146 (35%) were in the pediatric age group (< 18 years of age), 162 (38.9%) were in the 18- to 59-year age bracket, and the remaining 26.1% were ≥ 60 years of age. Approximately two thirds of the children were male, unlike the adult group, where women predominated. Slightly more than half of the participants were White. No participant < 18 years of age was a smoker, and the proportion of former smokers was higher with increasing age. Table 1 presents the characteristics of the study participants. With regard to the level of education, 50% had had 9 years of schooling, 5% were illiterate, and 96% used the public health care system exclusively.

Of the 417 patients evaluated in the present study, 231 (55%) were diagnosed with uncontrolled asthma at the time of the first visit on the basis of their ACT scores (Table 1). Early-onset asthma was identified in 164 (61%) of the 271 patients ≥ 18 years of age. A total of 128 (31%) of the 417 patients included in the study reported more than two severe exacerbations in the past 12 months, with severe exacerbations being more prevalent in children (in 49 [34%] of a total of 146). A history of hospitalization was reported by 298 (71%) of the 417 patients included in the present study. Of those, 103 (25%) were admitted to the ICU.

Regarding lung function, 111 (80%) of the 138 patients < 18 years of age showed no evidence of obstructive ventilatory defect. Of the 225 patients ≥ 18 years of age, 59 (26%) showed no evidence of obstructive ventilatory defect ($p < 0.01$; Figure 1A). Reversibility of airflow limitation was observed in 38/135 patients < 18 years of age (28%), whereas, in patients ≥ 18 years of age, reversibility of airflow limitation was observed in 48/225 (21%; Figure 1B). When we analyzed FEV_1 values that did not normalize after bronchodilator administration, we found that 183/225 (81%) of the adult patients showed no reversibility to normal lung function parameters.

Complete clinical phenotyping was performed in 369 (84%) of the 417 patients in the study sample. Among pediatric patients, allergic asthma was the predominant phenotype, whereas overlapping allergic and eosinophilic phenotypes predominated in adult patients. The T2-low phenotype was identified in 8 (10%) of the 82 pediatric patients tested and in 11 (20%) of the 68 adult patients tested. Figure 2 shows the distribution of phenotypes and blood eosinophil levels.

The most prevalent comorbidity in patients < 18 years of age and in those ≥ 18 years of age was allergic rhinitis, in 139/146 (95%) and 189/271 (70%), respectively. Other prevalent comorbidities in adults were anxiety, gastroesophageal reflux, obesity, and hypertension. In children, atopic dermatitis and anxiety were common comorbidities (Figure 3).

Regarding the therapies used, in the pediatric and adult patients, respectively, 21 and 31% were using triple therapy, and 17 and 40% were using biologics (Figure 4). Of the 23 patients < 18 years of age using biologics, 22 (96%) were using omalizumab and 1 (4%) were using mepolizumab, with a median duration

Table 1. Characteristics of severe asthma patients (n=417) and disease burden at baseline.[a]

	< 18 years of age (n = 146)	18-59 years of age (n = 162)	≥ 60 years of age (n = 109)
Age, years	12 [10-14]	47 [40-54]	67 [62-72]
Sex, male	86 (59)	45 (28)	30 (28)
White	92 (63)	87 (54)	64 (59)
Smoker			
Never smoker	146 (100)	138 (85)	72 (66)
Former smoker	0 (0)	22 (14)	33 (30)
Current smoker	0 (0)	2 (1)	4 (4)
Treatment			
ICS, µg/day*	500 [500-1,000]	600 [500-1,000]	500 [500-500]
Uncontrolled disease	67 (46)	107 (66)	57 (53)
Early-onset asthma, < 18 year of age	146 (100)	112 (72)	52 (50)
Age at onset of asthma, years	1 [0.5-3]	7 [1.91-20]	18 [5-35]
Age at asthma diagnosis, years	4 [2-6]	14 [5-30]	30 [8- 43.5]
> 2 severe exacerbations in < 12 months	49 (34)	51 (31)	28 (26)
Hospitalization			
History of hospitalization	109 (75)	114 (70)	75 (69)
Number of hospitalizations	6.0 [2-13]	10.0 [3-20]	10.0 [4-20]
ICU admissions	42 (29)	39 (24)	22 (20)
> 2 ICU admissions	6 (4.1)	12 (7.4)	8 (7.3)
Orotracheal intubation	14 (9.6)	23 (14)	14 (13)
Cardiopulmonary arrest	5 (3.4)	15 (9.3)	6 (5.5)

ICS: inhaled corticosteroids. [a]Data expressed as n (%) or median [IQR]. *Budesonide-equivalent doses.

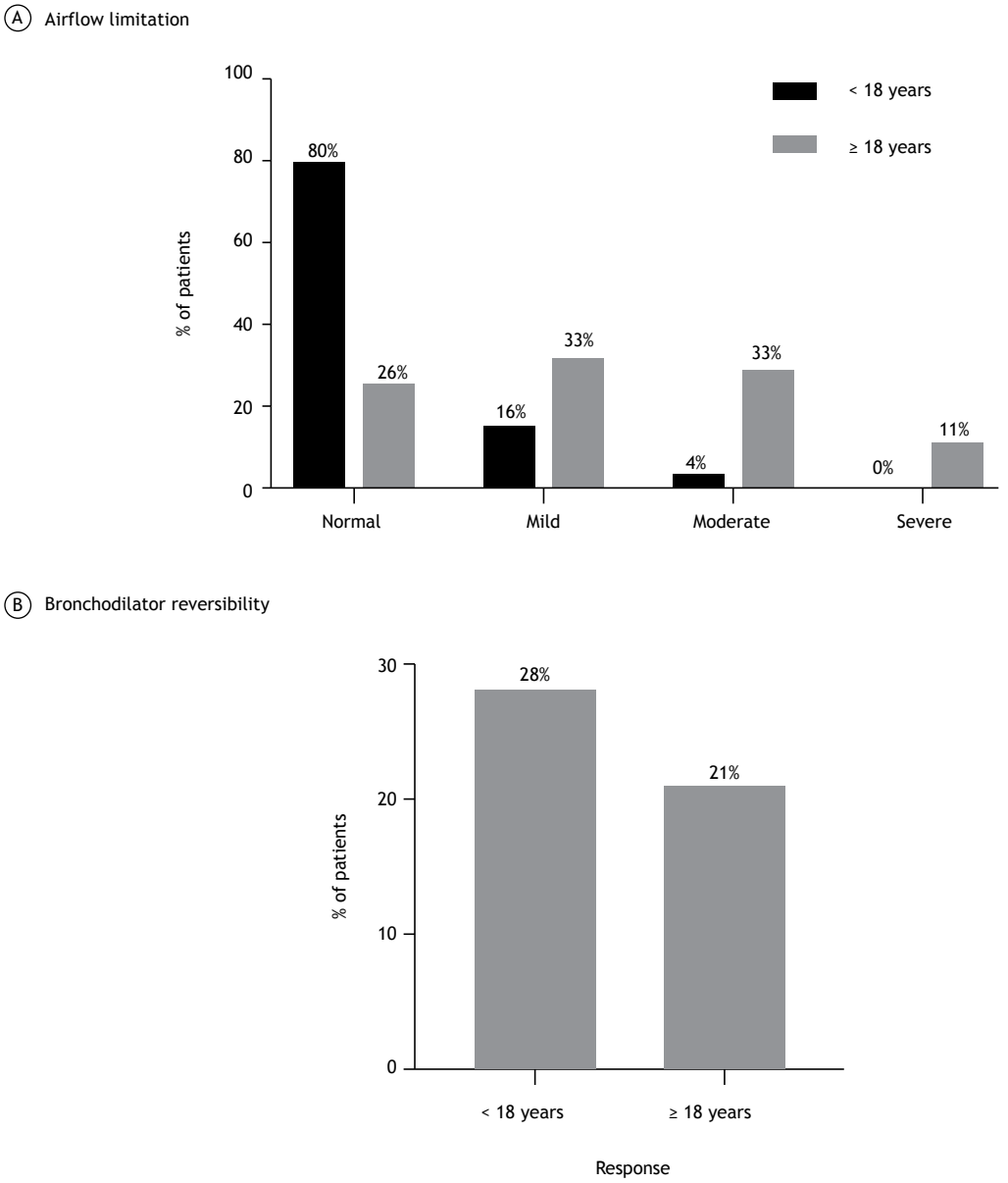

Figure 1. Airflow limitation (in A) and bronchodilator reversibility (in B) in pediatric and adult patients with severe asthma in Brazil, (n = 363).

of use of 21 months (IQR, 14-28 months). Of the 111 patients ≥ 18 years of age using biologics, 75 (68%) were using omalizumab, 28 (25%) mepolizumab, 5 (4%) benralizumab, and 3 (3%) dupilumab, with a median duration of use of 38 months (IQR, 8-89 months). One third of the pediatric patients in our sample were using leukotriene receptor antagonists, and only a few patients were under daily, long-term oral corticosteroid treatment (1% of the pediatric patients and 10% of the adult patients).

Clinical remission was observed in 13 (20%) of the 66 patients ≥ 18 years of age who used biologics. Of the 33 patients ≥ 18 years of age who used a combination of ICS, LABA, and a long-acting muscarinic antagonist, 3 (9%) achieved clinical remission (Figure 5). We were unable to evaluate clinical remission in the patients < 18 years of age because the number of patients available for analysis was low.

DISCUSSION

This was the first analysis of the REBRAG, based on data obtained at the first visit of patients (predominantly from the public health care system) and presenting a real-life overview of severe asthma in Brazil. The population of adult patients with severe asthma is predominantly female, unlike the pediatric

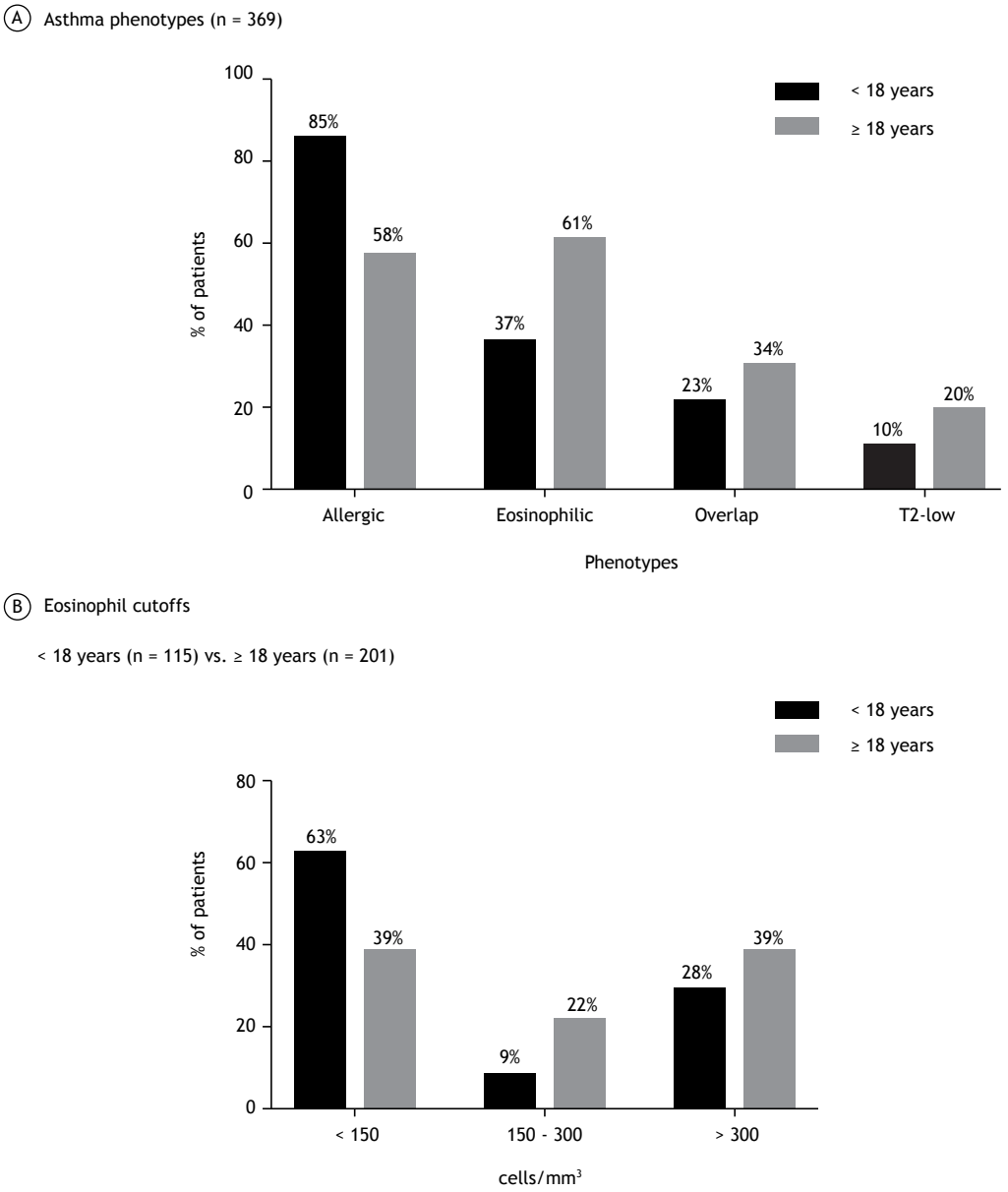

Figure 2. Asthma phenotypes (in A) and eosinophil cutoffs (in B) in pediatric and adult patients with severe asthma in Brazil.

population, which shows increased rates of obesity and physical inactivity. The predominance of adult women with severe asthma reflects national and international reports, as does the high prevalence of obesity and physical inactivity.[5,12] Although severe asthma is more common in males than in females during childhood and adolescence, it becomes more common in females in adulthood, as observed in our study and as reported in previous studies.[5,12]

In the present study, the prevalence of smoking in adult patients was low (1%) in comparison with that of former smokers (14%). According to data from the 2019 Brazilian National Health Survey, the prevalence of smoking among adults in Brazil was approximately 12.6%.[13] Our results show that patients with severe asthma in the country seem to avoid or quit smoking, which becomes a less significant risk factor for these patients. Our results also show that comorbidities are common, being consistent with ISAR data.[14] Many comorbidities have a negative impact on disease management and should therefore always be evaluated in the diagnosis and management of severe asthma. The prevalence of nasal polyposis was low in our sample, possibly reflecting underdiagnosis as a result of limited access to specialized tests in public health care facilities, which accounted for 96% of the records analyzed in the present study.

Despite being followed at referral centers in Brazil, many (66%) of the patients in our study had uncontrolled disease on the day of the first visit. This

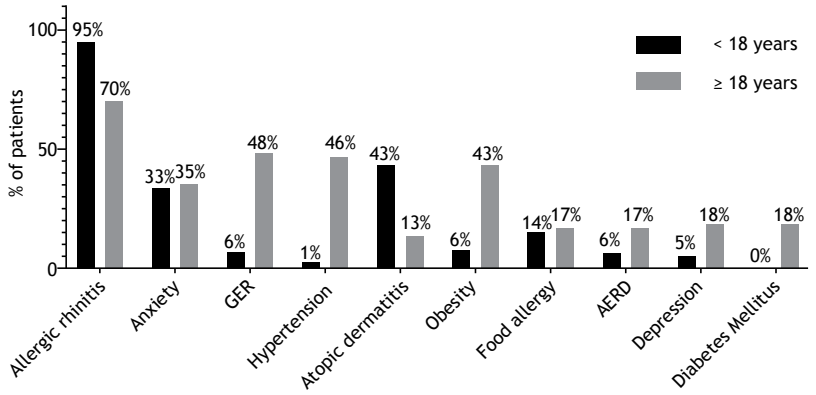

Figure 3. Comorbidities in pediatric and adult patients with severe asthma in Brazil (n = 417). GER: gastroesophageal reflux; and AERD: aspirin-exacerbated respiratory disease.

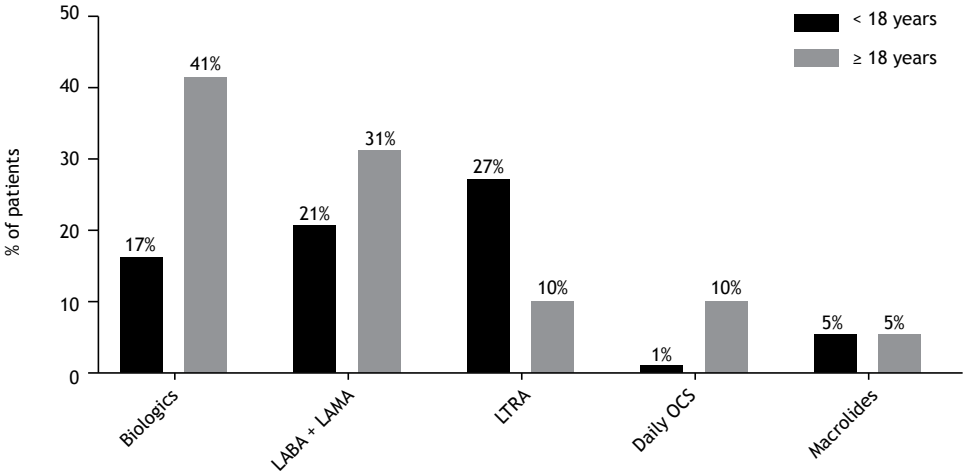

Figure 4. Therapies used in pediatric and adult patients with severe asthma in Brazil (n = 417). ICS: inhaled corticosteroid; LABA: long-acting β_2 agonist; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; and OCS: oral corticosteroid.

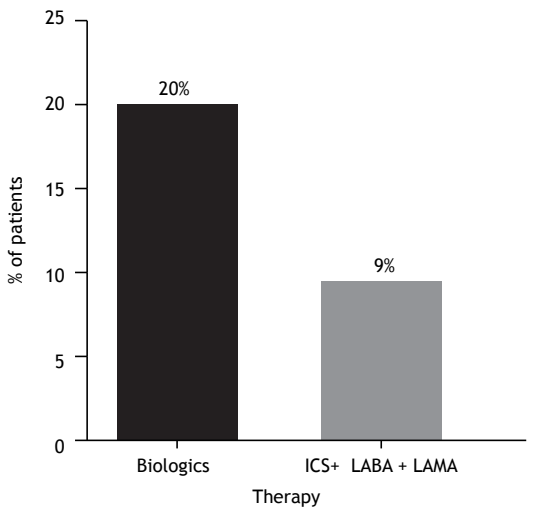

Figure 5. Clinical remission in severe asthma patients (≥ 18 years of age) by type of therapy (n = 99). ICS: inhaled corticosteroid; LABA: long-acting β_2 agonist; and LAMA: long-acting muscarinic antagonist.

is consistent with data from international referral centers,[12] highlighting the need for continuous reassessment of clinical approaches and access to therapies. In Brazil, disease control is achieved in only 12% of patients with asthma, regardless of its severity.[15] Additionally, high rates of severe exacerbations in the past year, hospitalizations, and ICU admissions were observed, as well as many cases of cardiopulmonary arrest, with results similar to those of a study conducted over a decade ago at a referral center in Brazil.[5] These data show that patients with severe asthma still experience high morbidity and an elevated risk of mortality. In this context, data from the Brazilian government show that asthma mortality has increased in recent years.[16]

Most (80%) of the pediatric patients in the present study had normal lung function, unlike the adult patients (26%). Additionally, lung function did not turn to normal values after bronchodilator administration in 81% of the adult patients in the present study. This might reflect the progressive, irreversible loss of lung function experienced by adult patients with

severe asthma, being likely due to airway remodeling. Approximately 55% of the adult patients in the present study had early-onset asthma, being at a higher risk of developing persistent airway obstruction over time. Furthermore, we found that it may take 2 years to establish a diagnosis of asthma in children and 6 years to establish a diagnosis of asthma in adults, highlighting how the journey of patients with severe asthma is compromised right from the onset of their diagnosis. These findings show several factors that increase the risk for poor lung function over time in patients with severe asthma in Brazil. Studies have shown that severe asthma and allergic asthma are both risk factors for progressive, irreversible loss of lung function.[6,17,18] Thus, studies including effective interventions for anti-T2 inflammatory activity early at the onset of the disease are needed to analyze their effect on preventing bronchial remodeling.

The most prevalent phenotype in the present study was allergic asthma (in 66% of the study sample), the T2-low phenotype being the least common (in 19%). Allergic asthma predominated in children and adolescents (in 78%), whereas, in the adult population, the most common phenotype was eosinophilic asthma (in 61%). It is known that childhood-onset asthma is characterized by a more homogeneous phenotype, often associated with an allergic profile. In contrast, eosinophilic asthma is the most common phenotype in adults with severe asthma.[19,20] We found that overlapping allergic and eosinophilic phenotypes are common in severe asthma patients, being observed in 60% of the children and in 61% of the adults in the present study. Patients with overlapping allergic and eosinophilic phenotypes have more than one option for specialists in decision-making regarding the choice of treatment with biologics, although other factors must be taken into consideration, including the presence of comorbidities, relying solely on the presence of biomarkers.

When we analyzed the types of therapies that the patients in the present study were receiving, we found that less than 40% of the patients, regardless of age, were receiving treatment with biologics or triple therapy. In a report by the ISAR study group, 25% of adult patients with severe asthma worldwide were being treated with biologics.[21] These results, along with the fact that many patients still had uncontrolled disease, suggest that patients are being undertreated, either because of misdiagnosis about severe asthma or because of a lack of access to GINA step 5 therapies. On the other hand, the fact that only 10% of the adults and 1% of the children in the present study were receiving long-term oral corticosteroid treatment shows the international trend to recommend this type of treatment as the last treatment option for severe asthma.[1] Despite the most recent recommendations to restrict the use of leukotriene receptor antagonists because of their neuropsychiatric adverse effects, this class of medication is still frequently prescribed, particularly in children (27%).[22]

Another interesting finding of our study concerns clinical remission. We found that 20% of the patients treated with biologics and 9% of those receiving triple therapy achieved clinical remission 12 months after the onset of treatment. Clinical remission has been widely discussed in recent years,[11] particularly with the emergence of biologic agents. Clinical remission achieved with new therapies has become a central goal for many diseases, including severe asthma, opening new pathways for the control of severe and complex diseases. Our initial results in this cross-sectional analysis show that clinical remission with triple therapy or biologics is a reality for many adult patients. Pulmonary function did not differ significantly between patients who achieved clinical remission and those who did not. Previous studies have shown clinical remission rates of 30-46% after 12 months of starting biologics in adult patients with severe asthma.[23-26]

Our study has some limitations, such as its cross-sectional nature, preventing us from presenting results regarding responses to therapies, prognostic risk factors, and lung function changes. Given the long-term follow-up nature of the REBRAG, future analyses have the potential to clarify these issues. Additionally, because our data come from real-life clinical evaluations, missing information poses a particular challenge, being mostly due to a lack of coverage or barriers to accessing certain tests through the public health care system. On the other hand, our study is valuable in that it shows real-life data from referral centers in Brazil, with broad representativeness across regions. Through the recruitment of patients from 23 centers across Brazil, our study shows a real-life profile of patients with severe asthma in the country and offers insights into the overall care of severe asthma patients.

In conclusion, the initial results of the REBRAG study show that patients with severe asthma in Brazil, regardless of age, still experience high morbidity rates, with worsening pulmonary function in adulthood, often without significant reversibility in many patients. Achieving disease control remains a clinical and health care challenge, with the prospect of improvement through enhanced strategies for better access to higher-cost therapies (triple therapy and biologics). Finally, future results from the REBRAG study, with long-term longitudinal follow-up of participants, will potentially provide further insights into how to improve the quality of life and costs of patients with severe asthma in Brazil.

AUTHOR CONTRIBUTIONS

PMP participated in the conception and design of the study; acquisition, analysis, and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. DCCS, FSS, ASM, ASR, AROC, AADCT, LMLBFL, DCB, LFVM, MAL, JGBR, ECFS, KTDF, and AASCF participated in data acquisition and the final review of the manuscript.

MMMP participated in the design of the study; data interpretation; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. All authors approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Evaluation of the accuracy of ChatGPT in answering asthma-related questions

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ABSTRACT

Objective: To evaluate the quality of ChatGPT answers to asthma-related questions, as assessed from the perspectives of asthma specialists and laypersons. **Methods:** Seven asthma-related questions were asked to ChatGPT (version 4) between May 3, 2024 and May 4, 2024. The questions were standardized with no memory of previous conversations to avoid bias. Six pulmonologists with extensive expertise in asthma acted as judges, independently assessing the quality and reproducibility of the answers from the perspectives of asthma specialists and laypersons. A Likert scale ranging from 1 to 4 was used, and the content validity coefficient was calculated to assess the level of agreement among the judges. **Results:** The evaluations showed variability in the quality of the answers provided by ChatGPT. From the perspective of asthma specialists, the scores ranged from 2 to 3, with greater divergence in questions 2, 3, and 5. From the perspective of laypersons, the content validity coefficient exceeded 0.80 for four of the seven questions, with most answers being correct despite a lack of significant depth. **Conclusions:** Although ChatGPT performed well in providing answers to laypersons, the answers that it provided to specialists were less accurate and superficial. Although AI has the potential to provide useful information to the public, it should not replace medical guidance. Critical analysis of AI-generated information remains essential for health care professionals and laypersons alike, especially for complex conditions such as asthma.

Keywords: Asthma; Artificial intelligence; Pulmonologists.

INTRODUCTION

Artificial intelligence (AI) is a broad term referring to the ability of a computer system to simulate human intelligent behavior with a minimum of human intervention.[1] Although the use of the term AI is currently on the rise, the term has been used since the middle of the last century.[2]

ChatGPT, a generative pre-trained transformer developed by OpenAI, is currently one of the most widely used AI tools. ChatGPT is a natural language processing model trained on a variety of text data, being capable of generating human-like responses within seconds.[3] Its accessibility and ease of use have made it a subject of study in various fields of medicine.[4]

Asthma is one of the most common noncommunicable diseases, affecting over 300 million people worldwide. Because asthma is such a common disease, it is not unusual to hear a patient say that they have asthma on the basis of what they read on the internet, which is often superficial and inaccurate.[5] Despite its widespread occurrence, asthma is a disease whose management is complex and involves critical steps, beginning with proper diagnosis and disease staging.[6] This complexity often raises questions even among health care professionals, who frequently rely on internet sources for quick access to relevant information.

Given the timeliness and relevance of this topic, the objective of the present study was to formulate questions addressing various aspects of asthma and pose them to ChatGPT, assessing the quality of the responses from two perspectives: those intended for laypersons and those intended for asthma specialists.

METHODS

Two of the authors of the present study developed twenty-one questions addressing various aspects of asthma and then selected seven that they considered to be the most important and most commonly asked when consulting ChatGPT (Table 1). The two aforementioned authors have extensive experience in asthma management. They formulated the questions using the GINA as a reference. To obtain the most accurate answers, the paid version of ChatGPT (version 4) was used. The questions were asked between May 3, 2024 and May 4, 2024. To ensure the uniformity of the answers provided by ChatGPT, the questions were asked in the same format, with a request for answers to be approximately two pages long, thus guaranteeing

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consistent content. To reflect how the general population uses large language models, specific prompts were avoided. Since ChatGPT can retain information from previous interactions, the option not to save any of the conversations was selected, and the history was deleted after each response in order to minimize potential bias. Each question was asked twice at consecutive times after the previous chat had been cleared in order to assess the reproducibility of the answers.

After data collection, the answers were sent to specialists in pulmonology and asthma, along with a form, for independently assessing the reproducibility and quality of the answers. The experts were instructed to assess the answers on the basis of current guidelines and updates, particularly GINA guidelines.

A total of six experts evaluated the seven answers provided by ChatGPT from two perspectives: ChatGPT answers intended for a layperson; and ChatGPT answers intended for an asthma specialist. Each answer (item) was scored from 1 to 4 on a Likert scale, as follows: 1-totally correct; 2-correct but insufficient; 3-contains information that is correct and information that is incorrect; and 4-totally incorrect. The level of agreement among the six experts was analyzed by calculating the content validity coefficient (CVC)[7] for each item, as follows:

$$CVC = \frac{\left[\left(\frac{\Sigma x}{J}\right)\right]}{Vmx} - p$$

where x represents the mean scores; J represents the total number of judges (or experts, i.e., 6); Vmx represents the highest possible score; and p represents the bias, which was calculated as follows:

$$p = \left(\frac{1}{J}\right)^{J}$$

As a rule, the cutoff point for acceptable item validity is 0.80 in content validity studies of scales measuring psychological phenomena. However, this is not applicable to all contexts, and we did not want to impose a fixed cutoff point in the present context. The program GraphPad Prism, version 8.0 (GraphPad Software, Inc., San Diego, CA, USA) was used in order to create Figures 1 and 2.

RESULTS

Regarding the reproducibility of the answers provided by ChatGPT when questions were asked repeatedly, the expert panel in the present study considered that more than 85% of the answers were consistent. Those who considered that some of the questions lacked reproducibility attributed it to variability or misclassification of certain topics.

The results of the assessments are shown in Figure 1 (from the perspective of asthma specialists) and Figure 2 (from the perspective of laypersons). None of the experts assigned a score of 4 to any of the answers that they analyzed. From the perspective of asthma specialists, the most prevalent scores were 2 (correct but insufficient) and 3 (contains information that is correct and information that is incorrect) across all questions, with question 3 receiving the highest proportion of low scores (100% scored 3). From the perspective of laypersons, a score of 1 (totally correct) was the most common, accounting for 55% of all possible answers. Question 1 had the highest number of responses that received a score of 1 (five of six).

Table 1. Asthma-related questions asked to ChatGPT.

Number	Question
1	What is asthma?
2	How to diagnose asthma?
3	How is asthma severity classified?
4	How is asthma control classified?
5	What is the pharmacological treatment for asthma?
6	Is there a cure for asthma?
7	What are the risk factors for asthmatic patients experiencing poor outcomes in the future?

Table 2 shows the level of agreement among the six experts regarding the suitability of the answers provided by ChatGPT from the perspectives of asthma specialists and laypersons. From the perspective of asthma specialists, CVC values were satisfactory for questions 6 and 7, and reasonable for questions 1 and 4. For questions 2, 3, and 5, however, the experts disagreed with regard to the suitability of the answers provided by ChatGPT. For answers analyzed from the perspective of laypersons, there was greater agreement among the experts in comparison with those assessed from the perspective of asthma specialists, with CVC values exceeding 0.8 for four items: 1, 2, 6, and 7. Lower CVC values were observed for items 3, 4, and 5.

DISCUSSION

The widespread availability of information on the internet has resulted in a growing reliance on knowledge sources without adequate critical analysis, even among health care professionals. This trend presents significant challenges, particularly when clinical management is complex, as is the case with asthma.

Despite being a common condition, asthma requires a multidimensional approach for effective management. The latest GINA report, published in 2024, outlines two potential therapeutic pathways organized into steps, emphasizing the complexity of treatment.[8] Despite the fact that most pulmonologists are well-equipped to manage disease effectively, many patients are treated by primary care physicians. This is due to the high prevalence of asthma. Primary care physicians often lack specialized and comprehensive training in asthma care, and this can impact the quality of care provided to patients.

Reddel et al.[9] evaluated the degree of heterogeneity in the diagnosis and management of asthma and COPD in a cohort of more than 11,000 patients. The

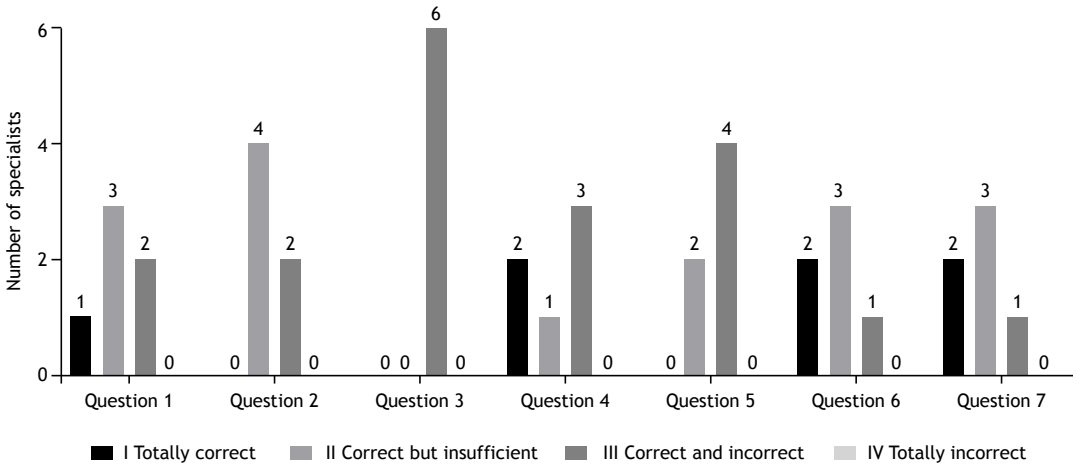

Figure 1. Expert opinion on the quality of ChatGPT answers from the perspective of asthma specialists.

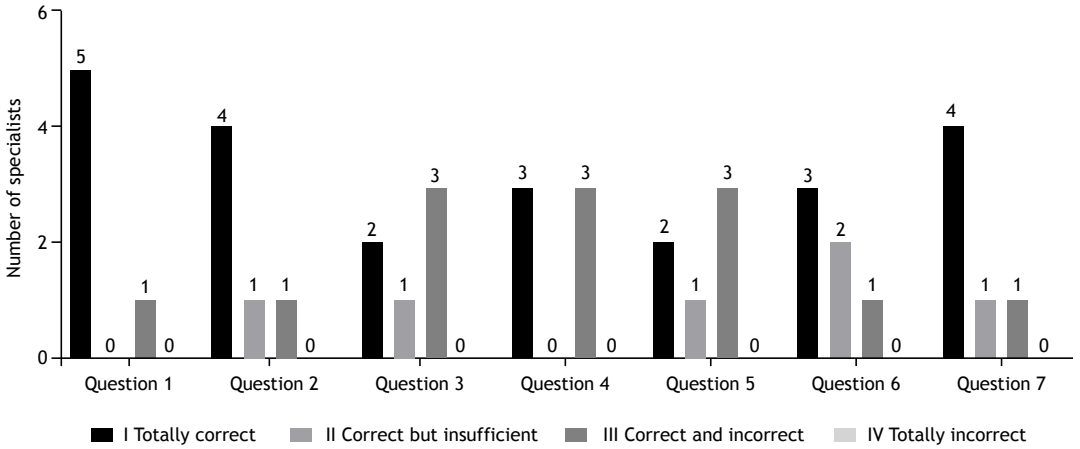

Figure 2. Expert opinion on the quality of ChatGPT answers from the perspective of laypersons.

Table 2. Agreement among judges regarding the suitability of ChatGPT answers from the perspectives of asthma specialists and laypersons.

Question	CVC	
	Specialist	Layperson
1	0.71	0.92
2	0.67	0.88
3	0.50	0.71
4	0.71	0.75
5	0.58	0.71
6	0.79	0.83
7	0.79	0.88

CVC: content validity coefficient.

findings revealed significant variability in diagnosis and treatment, with evidence of under or overtreatment in relation to disease severity. Notably, approximately 50% of those patients were managed in primary care, a proportion that is likely similar to or even lower than that observed in Brazil. Although there is a lack of specific data on this topic, it is plausible that primary care physicians are increasingly relying on AI tools to manage complex conditions such as asthma.

Our analysis revealed that although ChatGPT frequently provided correct information, it also made errors or offered insufficient responses for the required level of expertise. Although ChatGPT did not achieve a CVC with consistently positive concordance values, it can still be useful if the information that it provides is critically evaluated.

The present study also focused on evaluating content generated by ChatGPT from the perspective of a layperson, given the growing trend of self-diagnosis and the increasing search for health information online. Before the widespread use of AI, Google was the primary source for such inquiries, being informally referred to as "Dr. Google." Today, given the easy access to AI-powered tools, it is inevitable that patients will turn to such platforms for information. In a study involving 607 participants, approximately 80% expressed willingness to use ChatGPT for self-diagnosis.[10] This finding underscores the importance of assessing the accuracy of the content that ChatGPT provides to laypersons. The present study shows that, from the perspective of a layperson, the responses were mostly correct but often insufficient, suggesting

the potential of ChatGPT to inform the public. However, it is crucial to emphasize that ChatGPT should not be used as a substitute for a medical diagnosis.

Several studies have evaluated the role of ChatGPT in medical specialties such as urology and oncology, yielding results similar to ours.[11,12] Yeo et al.[11] assessed the quality of ChatGPT responses using brief prompts, with evaluations carried out by two specialists. They found that although most responses were partially correct, they often lacked completeness and included accurate and inaccurate information. These findings are consistent with those of our study. Notably, the accuracy of the responses varied by topic, such as general concepts, diagnosis, and treatment, with higher accuracy observed in specific areas. This was also evident in our analysis. Ayers et al.[13] investigated whether ChatGPT could provide responses comparable in quality and empathy to those of physicians. Interestingly, 80% of patients preferred the responses generated by ChatGPT, suggesting good accuracy and a patient-friendly approach to addressing their questions.

In a recent study conducted in Denmark, the authors analyzed 26 asthma-related questions.[14] The results showed that ChatGPT could provide adequate responses, albeit with some inconsistencies. However, because the aforementioned study was a brief report, it lacked methodological details, such as the version of the software used and the dates when the queries were made. Additionally, there was no evaluation of the responses from the perspective of the lay public.

In our study, we observed a significant inconsistency in the responses provided by ChatGPT, particularly regarding the classification of asthma severity (question 3). According to the American Thoracic Society/European Respiratory Society task force[15] and several international guidelines, asthma severity should currently be classified retrospectively, on basis of the level of treatment required to achieve disease control and prevent exacerbations. In other words, severity is determined by the dose of inhaled corticosteroids needed to manage symptoms rather than by the mere presence or intensity of those symptoms. However, ChatGPT incorrectly described the classification as follows: "The classification of asthma severity is generally divided into four categories: mild intermittent, mild persistent, moderate persistent, and severe persistent. This categorization helps determine the appropriate treatment regimen and is based on the frequency and intensity of symptoms, nighttime awakenings, the use of short-acting beta-agonists for quick relief, and the impact on normal activities." For example, GINA defines severe asthma as asthma that remains uncontrolled despite high doses of inhaled corticosteroids combined with long-acting bronchodilators, or that requires chronic use of oral corticosteroids. In contrast, mild asthma is characterized by symptom control achieved with low doses of inhaled corticosteroids, such as budesonide at a maximum daily dose of 400 µg. Those definitions are different from those provided by ChatGPT.

There was a high level of consistency in the evaluations made by specialists regarding certain responses. For example, question 6 ("Is there a cure for asthma?") received widespread agreement among reviewers. The response provided by ChatGPT was as follows: "There is currently no cure for asthma. However, the condition can be effectively managed through a combination of treatments and strategies, allowing many individuals with asthma to lead normal and active lives." This is consistent with current medical understanding and was deemed accurate and appropriate by most of the asthma specialists in the present study.

The present study has some limitations. One major limitation is the use of short prompts. Although more specific prompts generally produce higher-quality responses, we chose to use concise commands to replicate everyday usage scenarios. However, this decision may have compromised the quality of the generated content to some extent. Additionally, the evaluation of the content was subjective, given that it involved different specialists conducting the assessments. To reduce this bias, we calculated the CVC and included a substantial number of reviewers, thus strengthening our analysis. Another significant limitation is related to the evaluation of layperson-oriented content by specialists. To assess public understanding more accurately, a different methodology would be necessary, although it would not align with the current study design. The objective of our evaluation was to have experts review the content based on what they consider essential for patients to understand about the disease. Finally, since ChatGPT is a constantly evolving model, the responses provided at a later time may vary.

In conclusion, ChatGPT has the potential to generate informative responses for general audiences, with satisfactory agreement among reviewers in certain areas. However, when evaluated by specialists—particularly regarding more complex clinical concepts—the responses were often interpreted with greater variability and deemed less accurate. Given the known risk of AI-generated "hallucinations," which are plausible but incorrect or misleading pieces of information, it is crucial to emphasize that language models such as ChatGPT should not be used as the sole source of health information. This caution is especially important for managing diseases such as asthma, which require individualized and nuanced care. To promote the safe and effective use of AI tools in clinical practice and health education, we recommend the following: use AI-generated information as a complementary tool rather than a replacement for professional medical advice; health care professionals should guide and supervise the use of these tools, especially when patients or caregivers are involved; developing frameworks for validating and curating AI-generated content may help ensure alignment with current clinical guidelines and reduce the spread of misinformation; and educational strategies should include digital health literacy to empower users to critically evaluate the reliability of AI responses.

Ultimately, although ChatGPT can serve as a starting point for health-related inquiries, human oversight remains essential to maintain the quality and safety of medical information.

AUTHOR CONTRIBUTIONS

BPC, LSBC, and JBM: designed the study. BPC, VCSL, and CGF: asked ChatGPT the study questions and wrote the manuscript. FSLF, SMF, RGF, ACVAC, LSBC, and JBM: assessed the answers provided by ChatGPT. BPC: performed the statistical analysis. All authors reviewed and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Sociodemographic and clinical characteristics of individuals exposed to smoking or biomass smoke and followed at primary health care centers in Brazil: a multicenter study

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ABSTRACT

Objective: To describe the sociodemographic and clinical characteristics of individuals exposed to smoking or biomass smoke and followed at primary health care (PHC) centers across three states in Brazil. **Methods:** This was a cross-sectional multicenter study including patients followed at any of four PHC centers in Brazil. Patients ≥ 35 years of age who were smokers or former smokers, or were exposed to biomass smoke were included, the exception being those with physical/mental disabilities and those who were pregnant. Face-to-face assessments included a questionnaire assessing clinical and sociodemographic characteristics, as well as the COPD Assessment Test (CAT) and the modified Medical Research Council (mMRC) dyspnea scale. **Results:** Of a total of 737 patients, 56.3% were female and 64.2% were White, with a mean age of 57.7 ± 11.8 years. Most (54.4%) had < 9 years of schooling, 50.2% had low socioeconomic status, and 71.5% were overweight/obese. Smokers accounted for 43.4% of the study sample, whereas 15.0% had no direct exposure to cigarette smoke. Common symptoms included cough, in 37.3%; wheezing, in 33.8%; and phlegm, in 27.4%. Most (75.1%) of the study participants had mMRC dyspnea scale scores of 0 or 1. CAT scores were 0-10, in 40.2%; 11-20, in 44.6%; 21-30, in 14.1%; and 31-40, in 1.1%. Binary logistic regression showed that sex and age significantly impacted mMRC dyspnea scale predictions, whereas BMI and socioeconomic status influenced CAT predictions. Common comorbidities included hypertension, in 51.3%; depression, in 27.4%; and diabetes, in 24.3%. No association was found between hypertension and obesity or smoking, or between diabetes and obesity or smoking. **Conclusions:** PHC patients with risk factors such as smoking and exposure to biomass smoke have a high comorbidity burden, with over half experiencing mild to moderate quality-of-life impacts. This study emphasizes the need for targeted preventive measures in PHC settings.

Keywords: Smoking; Risk factors; Biomass; Primary health care.

INTRODUCTION

Health care in the Brazilian Unified Health Care System is organized into three levels: primary care, secondary care, and tertiary care.[1] Primary health care (PHC) relies on low-density technology and is provided through PHC centers and family health care centers.

PHC is the main entry point to the Brazilian Health Care Network. Most PHC centers address chronic conditions, with 21 of the 28 most common conditions (82%) being chronic. Only 5.7% of all PHC visits focus on prevention and health maintenance, highlighting a predominant emphasis on acute conditions or exacerbated chronic diseases.[2]

Cardiovascular diseases, arterial conditions, certain cancers, and respiratory diseases such as COPD share common risk factors, mainly smoking and exposure to air pollutants such as biomass smoke and occupational dust.[3-4] Many result from long-term smoking, and, if organ damage occurs, disease progression may continue despite smoking cessation. This is particularly true for COPD, in which inflammation remains progressive once initiated.[5]

Assessing the profile of PHC patients is crucial for early interventions to prevent or slow disease progression, alleviate symptoms, and improve quality of life.[6] Identifying patients with risk factors such as smoking and biomass exposure enables early diagnosis, benefiting the health care system and patients. The objective of the present study was to describe the sociodemographic and clinical characteristics of individuals exposed to smoking

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or biomass smoke and followed at PHC centers across three states in Brazil.

METHODS

The present study was approved by the Research Ethics Committee of the *Universidade Federal de São Paulo* (CAAE 81033317.8.1001.5505; Ruling no. 3,618,999) and was registered at ClinicalTrials.gov under NCT03018808.

The study was conducted at four PHC centers without specialists in respiratory medicine. Patients ≥ 35 years of age attending PHC centers for spontaneous or scheduled routine visits in the cities of Porto Alegre, Londrina, Araraquara, and Botucatu, Brazil, were invited to participate in the study.

Inclusion criteria

The inclusion criteria were as follows: being ≥ 35 years of age; being a current or former smoker (having smoked ≥ 100 cigarettes in their lifetime); and having been exposed to biomass smoke (having been exposed to biomass smoke for ≥ 100 h in their lifetime).

Exclusion criteria

The exclusion criteria were as follows: having mental or physical impairments; having a heart rate ≥ 120 bpm; currently receiving treatment for tuberculosis; concurrently participating in a clinical trial; being pregnant; and having any contraindication to spirometry.

Assessment

Eligible patients who gave written informed consent completed a standardized questionnaire adapted from the *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO, Latin American Project for the Investigation of Obstructive Lung Disease) study,[7] the COPD Assessment Test (CAT),[8] and the modified Medical Research Council (mMRC) dyspnea scale.[9] Briefly, the data collection included the following: sociodemographic characteristics; respiratory symptoms in the past 12 months; a history of atopy; self-reported disease diagnosis; smoking status; environmental exposures; socioeconomic status, in accordance with the Brazilian Institute of Geography and Statistics criteria[10]; and BMI, calculated by collecting data on patient weight and height. A patient was considered to have a prior diagnosis of COPD if they reported having been diagnosed with chronic bronchitis, emphysema and/or COPD by a physician and if they were ≥ 35 years of age at the time of diagnosis.

Statistical analysis

Descriptive and inferential analyses were conducted with the IBM SPSS Statistics software package, version 22 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test evaluated the distribution of the data. Numerical variables were described as means and standard deviations, and categorical variables were expressed as absolute numbers and proportions. All statistical inference tests were performed with bootstrap sampling (1,000 replicates), allowing the use of parametric tests. This is a robust and reliable method to provide valid confidence intervals when normal distribution of residuals is not observed and/or the sample is small.[11] The level of significance was set at $p < 0.05$ (two-tailed) for all tests.

Numerical variables were compared by means of one-way ANOVA (for three or more groups) and the unpaired t-test (for two groups), and categorical variables were analyzed by means of Pearson's chi-square test or Fisher's exact test, as appropriate. To minimize the risk of type II errors, effect sizes were calculated using Hedges' *g* for comparisons made with ANOVA and the unpaired t-test. The effect size was interpreted as weak (< 0.39), moderate (0.40-0.69), strong (0.70-0.99), or perfect (= 1). For comparisons made with Pearson's chi-square test, the effect size was calculated by Cramér's V, being interpreted as weak (> 0.05), moderate (> 0.10), strong (> 0.15), or very strong (> 0.25).[12]

A binary logistic regression analysis (enter method) was performed to investigate the extent to which the occurrence of dyspnea, as assessed by the mMRC dyspnea scale, and the impact of respiratory symptoms on daily life, as assessed by the CAT, could be predicted by sociodemographic characteristics (including sex, age, BMI, the Charlson Comorbidity Index, socioeconomic status [class A, B, C, or D/E], and smoking history).

RESULTS

A total of 737 patients were included in the present study. Of those, 56.3% were female, and approximately two thirds were White. The mean age of the study participants was 57.7 ± 11.8 years. Most had < 9 years of schooling; belonged to socioeconomic class C1, C2, or D/E; and were predominantly overweight or obese (Table 1).

According to the mMRC dyspnea scale, 33.4% of the study participants had dyspnea on exertion only (a score of 0); whereas 41.7%, 13.7%, 8.3%, and 3.0%, respectively, had a score of 1, 2, 3, and 4. With regard to the impact of respiratory symptoms on patient health status, as assessed by the CAT, 40.2% experienced no impact (a score of 0-10), whereas 44.6%, 14.1%, and 1.1%, respectively, experienced moderate (a score of 11-20), severe (a score of 21-30), and very severe (a score of 31-40) impacts.

The binary logistic regression model for predicting the occurrence of dyspnea was statistically significant ($\chi^2(8) = 28.570$; $p < 0.001$; Nagelkerke's $R^2 = 0.067$), correctly predicting 73.2% of cases (98.9% of cases correctly classified for those with an mMRC dyspnea scale score of 0 or 1 and 1.9% for those with an mMRC dyspnea scale score ≥ 2). Of all predictors analyzed, only sex and age had a significant impact

Table 1. Sociodemographic characteristics of individuals exposed to smoking or biomass smoked and followed at any of four primary health care centers in Brazil.[a]

Variable	N = 737
Sex	
Male	322 (43.7)
Female	415 (56.3)
Skin color	
White	473 (64.2)
Non-White	264 (35.8)
Age, years	57.7 ± 11.8
Weight, kg	76.1 ± 16.0
Height, m	1.64 ± 0.1
BMI, kg/m^2	28.2 ± 5.5
Nutritional status	
Underweight	10 (1.4)
Normal	200 (27.1)
Overweight	282 (38.3)
Obese	245 (33.2)
Level of education	
Illiterate/< 9 years of schooling	197 (26.7)
= 9 years of schooling/incomplete high school education	361 (49.0)
Complete high school education	149 (20.2)
Higher education	30 (4.1)
Socioeconomic status[b]	
Class A	9 (1.2)
Class B1/B2	97 (13.2)
Class C1/C2	468 (63.5)
Class D/E	163 (22.1)
People living in the same household	
1	104 (14.1)
2	240 (32.6)
3	196 (26.6)
≥ 4	196 (26.6)

[a]Data are presented as n (%) or mean ± SD. [b]In accordance with the Brazilian Institute of Geography and Statistics criteria,[10] as follows: socioeconomic class A, 45-100 points; socioeconomic class B1, 38-44 points; socioeconomic class B2, 29-37 points; socioeconomic class C1, 23-28 points; socioeconomic class C2, 17-22 points; and socioeconomic class D/E, 0-16 points.

on mMRC dyspnea scale predictions. Men were 1.94 times more likely to have an mMRC dyspnea scale score ≥ 2 than were women, and for each additional year of age, the likelihood of an mMRC dyspnea scale score ≥ 2 increased by 1.03 (Table 2).

Regarding the CAT, the model was also statistically significant ($\chi^2(8) = 46.619$; $p < 0.001$; Nagelkerke's $R^2 = 0.102$), with the predictors correctly classifying 68.9% of cases (23.9% of cases correctly classified for those with a CAT score of < 10 and 93.4% for those with a CAT score ≥ 10). Only BMI and socioeconomic status had a significant influence on predicting the impact of respiratory symptoms on health status. For each one-unit increase in the BMI, the likelihood of impact on health status increased by 1.05 times. Regarding socioeconomic status, patients belonging to socioeconomic class A were 0.20 times less likely to experience an impact on health status than were those belonging to socioeconomic class D/E; patients belonging to socioeconomic class B were 0.18 times less likely to experience an impact on health status than were those belonging to socioeconomic class D/E; and patients belonging to socioeconomic class C were 0.61 times less likely to experience an impact on health status than were those belonging to socioeconomic class D/E (Table 3).

The diseases that were most commonly reported by the study participants were hypertension, in 51.3%; depression, in 27.4%; diabetes mellitus, in 24.3%; rhinitis, in 20.8%; asthma, in 16.8%; COPD, in 6.8%; and tuberculosis, in 3.8%. There was no association between having a diagnosis of hypertension and obesity ($\chi^2(1) = 0.499$; $p = 0.480$; Cramér's V = 0.026) or smoking status ($\chi^2(2) = 0.845$; $p = 0.655$; Cramér's V = 0.034). Similarly, no association was found between having a diagnosis of diabetes mellitus and obesity ($\chi^2(1) = 0.266$; $p = 0.606$; Cramér's V = 0.019) or smoking status ($\chi^2(2) = 0.085$; $p = 0.958$; Cramér's V = 0.011). The comparison between patients with and without a prior diagnosis of COPD showed that the proportion of men was significantly higher than that of women in the COPD group. Additionally, patients with COPD had a significantly higher smoking history. No significant differences were observed for the remaining variables (Table 4).

Patients reported experiencing the following respiratory symptoms over the past 12 months: cough, in 37.3%; phlegm, in 27.4%; dyspnea, in 25.0%; wheezing, in 33.8%; and both wheezing and dyspnea, in 15.1%. Table 5 describes smoking status and exposure to biomass smoke. Approximately 15% of the patients had no direct contact with cigarette smoke, whereas 42% were exposed to secondhand smoke and 10% were exposed to biomass smoke. A high prevalence of smoking history was observed, both in terms of pack-years and the number of years smoked. The comparison between patients classified as exposed to biomass smoke and those classified as not exposed to biomass smoke showed that the former had significantly higher CAT scores than did the latter. No significant differences were observed for the other variables (Table 6).

A comparison of clinical characteristics among patients revealed that former smokers were significantly younger and had significantly lower BMI than never smokers and current smokers. CAT scores were significantly lower in never smokers than in former smokers. No differences were observed among the groups regarding mMRC dyspnea scale scores (supplementary material, Table S1).

DISCUSSION

Most of the patients exposed to smoking or biomass smoke and followed at PHC centers across four cities in Brazil were female; were White; had low

Table 2. Influence of sociodemographic variables in the logistic regression model for predicting the occurrence of dyspnea, as assessed by the modified Medical Research Council dyspnea scale, in individuals exposed to smoking or biomass smoke and followed at any of four primary health care centers in Brazil.

	Wald	df	p	Exp(B)	95% CI for Exp(B)	
					Lower	Upper
Sex, male	10.469	1	< 0.001	1.935	0.245	1.140
Age, years	10.903	1	0.003	1.028	0.011	0.048
BMI, kg/m^2	4.030	1	0.057	1.034	0.002	0.073
Pack-years	0.414	1	0.492	0.998	−0.008	0.004
Charlson Comorbidity Index	1.252	1	0.263	0.284	−0.143	0.037
Socioeconomic status						
Class A	0.514	1	0.473	0.236	−20.437	0.874
Class B	0.203	1	0.652	0.686	−0.850	0.492
Class C	1.868	1	0.172	0.184	−0.716	0.113
Constant	22.089	1	< 0.001	0.027	−5.387	−2.149

df: degrees of freedom.

Table 3. Influence of sociodemographic variables in the logistic regression model for predicting the impact of respiratory symptoms on activities of daily living, as assessed by the COPD Assessment Test, in individuals exposed to smoking or biomass smoke and followed at any of four primary health care centers in Brazil.

	Wald	df	p	Exp(B)	95% CI for Exp(B)	
					Lower	Upper
Sex, male	3.247	1	0.070	1.387	−0.044	0.706
Age, years	0.003	1	0.943	1.000	−0.015	0.017
BMI, kg/m^2	6.574	1	0.009	1.045	0.009	0.082
Pack-years	0.026	1	0.906	1.000	−0.004	0.009
Charlson Comorbidity Index	0.236	1	0.622	0.981	−0.102	0.073
Socioeconomic status						
Class A	4.328	1	0.017	0.201	−21.942	−0.061
Class B	28.633	1	< 0.001	0.179	−2.397	−1.126
Class C	4.541	1	0.032	0.610	−0.973	−0.043
Constant	0.117	1	0.732	0.784	−1.643	1.032

df: degrees of freedom.

Table 4. Comparison of sociodemographic and clinical variables between individuals with and without a prior diagnosis of COPD followed at any of four primary health care centers in Brazil.[a]

	Prior diagnosis of COPD*		p	Effect Size
	No (n = 653)	Yes (n = 50)		
Sex				
Male	280 (42.9)	31 (62.0)	0.011	0.10
Female	373 (57.1)	19 (38.0)		
Age, years	57.9 ± 11.7	57.7 ± 12.7	0.926	0.01
BMI, kg/m^2	28.2 ± 5.5	29.2 ± 6.0	0.248	0.19
Pack-years	35.2 ± 32.7	47.1 ± 34.3	0.039	0.36
mMRC dyspnea scale score	1.1 ± 1.0	1.0 ± 0.9	0.528	0.09
CAT score	12.9 ± 7.7	12.3 ± 6.7	0.521	0.09
Socioeconomic status				
Class A	9 (1.4%)	0 (0.0%)	0.896	0.03
Class B	87 (13.3%)	7 (14.0%)		
Class C	414 (63.4%)	31 (62.0%)		
Class D/E	143 (21.9%)	12 (24.0%)		

mMRC: modified Medical Research Council; and CAT: COPD Assessment Test. [a]Data are presented as n (%) or mean ± SD. *Of the 737 individuals in the sample, 34 responded "I don't know" or "I don't remember" to the question of whether a physician had ever diagnosed them with COPD or chronic bronchitis and were therefore excluded from the analysis.

socioeconomic status; were overweight or obese; and had a low level of education.

We found that 56% of the patients participating in the present study were female. Data from 81 randomized

Table 5. Environmental exposure and smoking status in individuals followed at any of four primary health care centers in Brazil.[a]

Variable	N = 737
Smoking status	
Former smoker	306 (41.5)
Current smoker	320 (43.4)
Never smoker	111 (15.1)
Smoking history, pack-years	35.7 ± 32.7
Smoking duration, years	31.8 ± 14.1
Received smoking cessation advice	287 (38.9)
Secondhand smoke exposure	
Yes	313 (42.5)
No	424 (57.5)
Exposure to biomass smoke	
Yes	74 (10.0)
No	654 (88.6)
Don't know/Don't remember	9 (1.2)

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

Table 6. Comparison of sociodemographic and clinical variables between individuals with and without environmental exposure to biomass smoke and followed at any of four primary health care centers in Brazil.[a]

	Exposure to biomass smoke*		p	Effect size
	No (n = 654)	Yes (n = 74)		
Sex				
Male	287 (43.9)	32 (43.2)	> 0.999	0.004
Female	367 (56.1)	42 (56.8)		
Age, years	57.7 ± 11.7	58.1 ± 12.3	0.798	0.03
BMI, kg/m^2	28.1 ± 5.6	29.1 ± 5.3	0.131	0.18
Pack-years	34.9 ± 28.3	44.9 ± 59.7	0.260	0.31
mMRC dyspnea scale score	1.0 ± 1.0	1.2 ± 1.2	0.102	0.20
CAT score	12.7 ± 7.4	15.0 ± 8.4	0.032	0.29
Socioeconomic status				
Class A	8 (1.2)	1 (1.4)	0.556	0.05
Class B	85 (13.0)	11 (14.9)		
Class C	412 (63.0)	50 (67.6)		
Class D/E	149 (22.8)	12 (16.2)		

mMRC: modified Medical Research Council; and CAT: COPD Assessment Test. [a]Data are presented as n (%) or mean ± SD. *Of the 737 individuals in the sample, 9 responded "I don't know" or "I don't remember" to the question of whether they had been exposed to biomass smoke and were therefore excluded from the analysis.

PHC clinical trials from the Netherlands, the USA, the UK, and Spain also revealed a predominance of women, with rates between 55% and 60%.[13] Studies conducted in the city of Goiânia, in central-western Brazil, reported a prevalence of women ranging from 39% to 71%.[14] The frequency of medical visits has been reported to be 1.90 to 2.43 times higher in women than in men.[15] Reasons for this disparity are not clear but may include the perception that men seeking health care are demonstrating weakness, fear, or insecurity, which contrasts with the idealized notion of male invulnerability. Additionally, work schedules often conflict with health care service hours, posing a barrier for men.[16] The fact that women tend to assess their own health status as being worse might explain their higher demand for health services. In addition, a double burden of work and household chores, particularly among low-income women, combined with psychological and emotional exhaustion, likely further increase their health care needs.[17]

Our sample predominantly came from peripheral PHC centers, with 85.6% of patients being classified as belonging to low socioeconomic classes and one quarter being illiterate or having had < 9 years of schooling, findings that are in accordance with those of the 2013 and 2019 Brazilian National Health Surveys. This vulnerable population remains heavily reliant on PHC.[18] Brazil displays significant disparities in social class, level of education, and access to health care, and PHC plays an essential role in promoting equity among those populations. There is a direct relationship between education levels and health care utilization. The PLATINO study found that 54.3% of patients in the city of São Paulo, Brazil, had had ≤ 4

years of schooling,[19] and the 2019 Brazilian National Household Sample Survey found that 51.2% of the Brazilian population > 25 years of age had had < 9 years of schooling.[18]

In a study published in 2023,[19] low-income populations in 20 cities in Brazil were reported to have better access to PHC facilities than did high-income populations accessing private services; this is largely due to a wide distribution of PHC centers and prioritization of underserved areas in the Brazilian national PHC network. However, Black populations still face more barriers in accessing PHC than do White populations.[20]

In our study, 71.5% of the patients were classified as being overweight or obese on the basis of their BMI, a finding that underscores an urgent need for care strategies for patients with excess weight. In a meta-analysis published in 2022, excess weight in adults in Brazil was reported to have increased from 33.5% in the 1974-1990 period (95% CI, 25.0-42.6) to 52.5% in the 2011-2020 period (95% CI, 47.6-57.3).[21] However, according to the Health Information System for PHC in Brazil, obesity accounts for < 3% of all conditions evaluated in over 105 million consultations.[22] The 2019 Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases showed a high prevalence of overweight and obesity in Brazilian state capitals, ranging from 49.1% in the city of Vitória to 60.9% in the city of Manaus.[23] Obesity has been reported to be most prevalent in non-White women with low education levels and men in the 40- to 59-year age bracket with average incomes.[24] Similar trends have been reported in PHC settings in the city of São José dos Pinhais, Brazil, where 67.3% have been classified as being overweight or obese.[25] Overweight and obese patients tend to utilize health care services more frequently because of a higher prevalence of comorbidities such as hypertension and diabetes mellitus.[26] In the PLATINO study, overweight and obesity rates ranged from 54.5% in São Paulo, Brazil, to 68.5% in Santiago, Chile.[19]

Although our sample had a high prevalence of current smokers (43.4%), it is important to note that smoking was a criterion for inclusion in the study. Smoking cessation programs are highly cost-effective, extending survival by 10-15 years and reducing the risk of chronic noncommunicable diseases associated with tobacco.[27] Even brief advice to quit smoking, without pharmacological intervention, improves cessation rates and positively impacts lung function and quality of life.[28] Although official smoking cessation programs provide guidance and medications at no cost in Brazil, fewer than 5% of smokers receive this treatment.[29] In our sample, 42.5% of the patients were found to be exposed to secondhand smoke. According to the WHO, 33% of men, 35% of women, and 40% of children worldwide are exposed to secondhand smoke.[30] Data from the 2013 and 2019 Brazilian National Health Surveys show a reduction in secondhand smoke exposure at home (by 1.6%) and in the workplace (by 5%), with higher exposure among patients with lower education levels.[31]

We found that 75% of the patients in the present study had an mMRC dyspnea scale score of 0-1, and 80% had a CAT score of 0-20, indicating low to moderate levels of dyspnea and disease impact. Although several studies have assessed COPD symptoms in PHC settings, few have evaluated dyspnea using the mMRC dyspnea scale or disease impact using the CAT. Studies conducted in the UK, Greece, and Spain reported similar findings, with approximately 50% of patients showing mild dyspnea (a median MRC scale score of ≤ 2).[32-34] Although our logistic regression model including sociodemographic variables showed high accuracy in classifying patients without dyspnea (98.9%), its performance in correctly identifying those with dyspnea was extremely low (1.9%). This suggests that variables other than sociodemographic variables play a more relevant role in predicting dyspnea among patients with risk factors such as smoking and exposure to biomass smoke in PHC settings and should be considered in future analyses. In contrast, our model for predicting CAT scores performed better in terms of correctly identifying patients in whom respiratory symptoms had an impact on activities of daily living (93.4%), with only BMI and socioeconomic status having a significant influence. It is expected that patients from higher socioeconomic classes have greater access to health care; on the other hand, the impact of increased BMI on activities of daily living may be due to excess weight itself and obesity-related diseases.

One third of our sample reported at least one respiratory symptom, with cough being the most common (37.3%), followed by wheezing (33.8%). Respiratory symptoms are common in smokers because of airway inflammation and persistent airflow limitation.[35] In the city of São Paulo, the PLATINO study found that 54.8% of individuals reported at least one respiratory symptom, with wheezing and dyspnea being the most common (34.9%).[7] In a study conducted in central-western Brazil, symptom burden was found to be high in patients with risk factors for COPD, with symptoms including dyspnea (58.4%), sputum production (39.4%), and chronic cough (35%).[36] Current smokers were significantly more likely to experience severe dyspnea, productive cough, and exertional dyspnea than were former smokers or never smokers.[36] Patients exposed to biomass smoke had higher CAT scores than did those without exposure to biomass smoke, indicating a greater impact on their quality of life.[36] Similarly, Mexican women exposed to biomass smoke have been reported to have more respiratory symptoms,[37] a finding corroborated by a study conducted in China and reporting that COPD patients exposed to biomass smoke alone had higher CAT scores than did those exposed to tobacco alone or occupational hazards alone (17.5 ± 6.3 vs. 15.3 ± 6.3 vs. 15.2 ± 6.3; $p < 0.05$).[38]

In addition to respiratory symptoms, comorbidities were common in our sample. Hypertension affected one in two patients, whereas one in four reported depression or diabetes mellitus. Shared risk factors such as physical inactivity and smoking, as well as systemic inflammation and oxidative stress, contribute to these comorbidities. Although our sample did not show an association of hypertension and diabetes mellitus with smoking and obesity, it is well known that systemic inflammation contributes to the development of insulin resistance and the onset of diabetes mellitus.[39] Smokers are twice as likely to develop diabetes mellitus as are nonsmokers, the risk increasing with greater smoking intensity.[40] The acute effects of smoking on blood pressure include transient sympathetic activation; however, the chronic mechanisms remain unclear.

The present study was conducted in four PHC centers across different regions of Brazil, specifically targeting patients with risk factors such as smoking and exposure to biomass smoke, showing a high prevalence of respiratory symptoms, hypertension, and diabetes mellitus. These findings underscore the importance of evaluating risk factors for prevalent diseases so as to allow early diagnosis and intervention.

The present study has some limitations. Although it was originally designed to include data from other regions of Brazil, this was not possible, because of the COVID-19 pandemic. Although several PHC centers in other states were contacted, they could not initiate data collection. Because the study was conducted in four PHC centers located either in southeastern Brazil or in southern Brazil, it could not fully capture the diversity of PHC users across the country. The high smoking prevalence observed in the present study cannot be considered representative of the regions, because smoking was one of the inclusion criteria. The fact that there was a large number of patients with lower socioeconomic status and lower education levels may limit the generalizability of the findings to other populations. Finally, the information collected was self-reported through questionnaires. Although this is needed in order to investigate the frequency and severity of symptoms, it may be subject to biases.

The evaluation of patients with risk factors such as smoking and exposure to biomass smoke in PHC settings revealed a predominance of women with low socioeconomic status and low education levels, as well as a high prevalence of respiratory symptoms, hypertension, and diabetes mellitus. These findings are crucial for understanding and developing public health policies focusing on risk factors, allowing early diagnosis and timely interventions.

AUTHOR CONTRIBUTIONS

JOB and JRJ: design and planning of the study; interpretation of findings; and writing and revision of preliminary drafts and the final version of the manuscript. FFA, CAN, LGF, SET, GFS, and OAN: interpretation of findings; writing and revision of preliminary drafts; and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Inhaler identification: evaluating a potential screening method for adherence in chronic respiratory disease management

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ABSTRACT

Objectives: This study explores the relationship between inhaler visual identification, naming, and adherence outcomes, and evaluates the potential of combining these factors into a screening tool for identifying poor adherence. **Methods:** This observational, prospective study included adult patients with COPD, asthma, or asthma+COPD who had been on chronic inhalation therapy for at least the past year. Data were collected through patient interviews and medical records. Adherence was assessed using the Test of Adherence to Inhalers (TAI) questionnaire and prescription records, calculated as the Proportion of Days Covered (PDC). The patients completed a questionnaire to evaluate their ability to visually identify and name their inhalers. **Results:** Among the 196 participants, significant differences in adherence levels were observed across the COPD, asthma, and asthma+COPD groups, with COPD patients demonstrating higher adherence rates (p=0.001). Concordance between TAI and PDC was highest in the COPD group (75.0%), compared to the asthma (51.3%) and asthma+COPD (55.5%) groups. Correct naming of inhalers was not significantly correlated with adherence. However, correct inhaler visual identification was associated with better adherence. Incorrect visual identification showed low sensitivity (15.9%) but high specificity (92.6%) for detecting poorly adherent patients. **Conclusions:** The ability to visually identify inhalers was associated with better adherence, while the ability to name inhalers was not. Although incorrect visual identification has limited utility as a screening tool, it may still serve as a rapid and practical method for identifying poorly adherent patients in clinical practice.

Keywords: COPD, asthma, inhalers, therapeutic adherence, visual perception.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and asthma are prevalent respiratory conditions that significantly impact patients' quality of life and healthcare systems worldwide.[1,2] Adherence to inhaler therapy is a critical component in effectively managing these disorders. Poor adherence can lead to suboptimal disease control, increased healthcare utilization, reduced quality of life, and higher mortality rates in these patients.[3–11]

Assessing adherence during medical consultations is crucial but often challenging and time-consuming. Indirect methods such as patient self-reporting, prescription records, and electronic monitoring are commonly used.[12] Self-reporting is frequently employed in clinical practice but tends to overestimate adherence due to its subjective nature.[13] Prescription records are generally less biased but may be more time-consuming for clinicians to analyze. Electronic monitoring, while promising, is not yet widely accessible. Consequently, there is a need for a quick and practical initial screening tool to identify patients who may benefit from more comprehensive adherence assessments.

Various determinants that influence adherence, either increasing or decreasing its likelihood, have already been identified in patients with COPD and/or asthma.[14–16] Nevertheless, there is limited evidence regarding the impact of correctly identifying and naming inhalers on adherence to chronic inhalation therapy.

The aim of this study, which was conducted within the Pulmonology Department of our hospital, was to explore the relationship between inhaler visual identification and naming and adherence outcomes, as well as to evaluate the potential of combining these factors as a screening tool for detecting poor adherence.

This study investigated adherence to chronic inhalation therapy among patients with COPD, asthma, and asthma+COPD by combining self-reporting and objective adherence measures to provide a comprehensive analysis of adherence patterns and their predictors.

Through this approach, we aim to deepen the understanding of adherence behaviors in chronic respiratory conditions and propose a rapid, practical tool for assessing adherence in clinical settings. Ultimately, our goal is to contribute to improved disease management and better patient outcomes.

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Conflicts of interest: None declared.

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METHODS

Study Design and Participants

This analytical, observational, cross-sectional prospective study was conducted in the Pulmonology Department of our hospital. Adult patients who attended consultations or were hospitalized there between January 2022 and July 2023 were considered for inclusion. Eligible patients were required to have a diagnosis of chronic obstructive pulmonary disease (COPD), asthma, or asthma+COPD, as determined by the attending physician, and to have been undergoing chronic inhalation therapy for at least the past year. Individuals with visual or cognitive impairments that could interfere with their ability to adequately complete the questionnaires were excluded.

Data Collection

Data were collected through patient interviews and medical record reviews. The diagnosis of COPD, asthma, or asthma+COPD was confirmed by the attending pulmonologist. Relevant clinical and demographic information, including details on chronic inhalation therapy and its duration, was recorded. Adherence to chronic inhalation therapy was assessed using two distinct methods: patient self-report via the Test of Adherence to Inhalers (TAI) questionnaire, and prescription records, by calculating the Proportion of Days Covered (PDC). Visual identification and naming of the patient's inhaler(s) were evaluated using a questionnaire developed by the authors for this purpose (see Supplementary Material). Correct naming was defined as the patient's ability to provide either the commercial name or the pharmaceutical components of their inhaler(s).

Chronic Inhalation Therapy Adherence

As previously mentioned, adherence to chronic inhalation therapy was assessed using two methods, patient self-report and review of prescription records, as detailed below:

- Patient Self-Report: The TAI questionnaire was developed to assess adherence to inhaler use among patients with respiratory conditions such as asthma and COPD. It is designed to identify patterns of non-adherence and their underlying causes, thereby facilitating targeted interventions to improve medication use. The TAI consists of two parts: a 10-item patient self-report questionnaire (TAI-10) and a 12-item healthcare professional (HCP) assessment. Each item on the TAI-10 is scored from 1 to 5, with higher scores indicating better adherence. The total score ranges from 10 to 50 and categorizes adherence into three levels: good adherence (50), intermediate adherence (46-49), and poor adherence (≤ 45).[17] In this study, we used the 10-item TAI questionnaire, which has been validated for the Portuguese population.

- Prescription Records Review: Adherence was also assessed using the PDC, calculated based on prescription refill data. The PDC estimates the proportion of time a patient has had access to their medication, providing an objective measure of medication availability. Unlike self-reported tools such as the TAI, the PDC is less susceptible to recall bias or social desirability. Although it assumes that dispensed medication is actually taken—an acknowledged limitation—the PDC is generally considered a more specific and objective measure of adherence and is often used as a reference standard in studies on chronic medication use. The PDC was calculated using the following formula:

$$PDC = \left(\frac{Number\ of\ days\ covered\ by\ medication}{Number\ of\ days\ under\ observation} \right) x\ 100$$

In this study, the observation period was one year (365 days), and medication coverage was determined using prescription refill data from the national prescription platform PEM (*Prescrição Eletrónica de Medicamentos*). A PDC of 80% or higher was considered indicative of good adherence.[18,19]

Questionnaire

The patients were asked to complete a questionnaire to assess their ability to visually identify and name their inhaler(s) (see Supplementary Material). They were shown a set of images depicting all inhalation devices available on the Portuguese national market and asked to select the image(s) corresponding to their prescribed inhaler(s). The physician recorded the selected images. Next, the patients were asked to name either the commercial designation or the pharmaceutical components of their inhaler(s). Finally, the physician recorded whether the patient correctly or incorrectly identified and named their inhaler(s).

Statistical Analysis

Data were analyzed using Stata Statistical Software (StataCorp. 2023. Stata Statistical Software: Release 17. College Station, TX, USA: StataCorp LLC). Categorical variables were presented as frequencies and percentages, while normally distributed continuous variables were expressed as mean ± standard deviation (SD). The chi-square test was used to compare categorical variables. For continuous variables, an independent-samples t-test was applied when the data followed normal distribution, and Mann-Whitney U tests were used for skewed distributions. Pearson's correlation was used to assess the relationship between TAI scores and PDC. Concordance between the two adherence measures was also calculated. To align the three-level TAI classification with the binary PDC categorization, TAI scores indicating "intermediate adherence" were grouped with "good adherence", forming a single "good adherence" category. This approach enabled direct comparison between the tools and is consistent with a previous study that considers intermediate TAI scores to reflect acceptable adherence levels.[17]

A fractional logit model analysis was conducted to identify predictors of adherence to chronic inhalation therapy. Although a fractional probit model yielded similar results, it demonstrated a poorer fit to the data. Fractional logit models are appropriate for dependent variables expressed as proportions or bounded between 0 and 1. Therefore, the TAI score was transformed to fit this model using the following formula:

$$\frac{TAI - 10}{50 - 10}$$

No transformation was necessary for the PDC. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

This study was approved by our hospital's Ethics Committee (Reference No. 215-CA-2-7). Informed consent was obtained from all participants prior to their inclusion.

RESULTS

A total of 196 participants were included. The general characteristics of the study sample and their adherence to chronic inhalation therapy are presented in Table 1.

Regarding the TAI score, a mean difference of 1.62 ± 0.67 was observed between patients with COPD and those with asthma+COPD (p=0.017). As for the PDC, the mean difference between patients with COPD and those with asthma was 11.95 ± 3.62 (p=0.001), and 14.62 ± 5.46 between patients with COPD and those with asthma+COPD (p=0.008).

A mild, positive linear correlation was found between TAI scores and PDC (r=0.37; p=0.000).

The overall concordance between adherence categorization by the TAI score and PDC was 64.3%. Specifically, for COPD, asthma, and asthma+COPD, the concordance rates were 75.0%, 51.3%, and 55.5%, respectively.

Adherence to chronic inhalation therapy based on inhaler visual identification and naming is shown in Table 2.

Tables 3 and 4 present the fractional logit model coefficients of adherence to chronic inhalation therapy, as measured by the PDC and TAI, respectively.

The sensitivity, specificity, and area under the receiver operating characteristic (AUROC) curve for incorrect inhaler visual identification in detecting poorly adherent patients were calculated based on adherence classifications from the PDC and TAI scores. The results are shown in Table 5.

DISCUSSION

According to our findings, patients with COPD demonstrated significantly better adherence to inhaled therapy compared to those with asthma or asthma+COPD. Moreover, visual identification of inhalers was more strongly associated with adherence than correct naming and may serve as a useful tool for identifying patients with poor adherence.

The higher adherence rate among COPD patients compared to those with asthma is consistent with findings reported in previous studies.[3,20,21] This may be partly age-related, as COPD patients in our study were significantly older than asthma patients (mean age: 72.1 vs 58.5 years). Older individuals may adhere more consistently to medication use due to increased health awareness, more frequent contact with healthcare providers, or fear of disease progression. Although age alone was not statistically significant in predicting adherence in the PDC model (p=0.188), it approached significance in the TAI model (p=0.096). When the individual variables age and pathology were replaced with an interaction term, the analysis revealed that older patients with COPD tend to exhibit better adherence than their younger counterparts—a relationship that warrants further investigation. While disease severity likely influences adherence, our study did not address this factor, highlighting yet another area for future research. The significant differences observed in adherence across the diagnostic groups underscore the need for tailored interventions to improve inhaler use and therapeutic compliance.

The concordance between adherence categorization by the TAI score and PDC was significantly higher in COPD patients (75.0%) than in those with asthma (51.3%) or asthma+COPD (55.5%). Additionally, poor adherence was more frequently identified using the PDC than the TAI score across all groups. These results suggest that asthma patients may overestimate their adherence to inhaled therapy to a greater extent than COPD patients when completing self-report questionnaires. The authors propose that at least two factors may help explain this discrepancy: 1) asthma patients tend to have lower adherence rates overall, which could lead to a wider gap between self-reported and objectively measured adherence; and 2) asthma is inherently a variable disease, with fluctuations in both severity and symptomatology that may lead to irregular inhaler use and influence patients' perception of their adherence based on current symptom control. As a result, self-report questionnaires like TAI may yield more reliable adherence estimates in COPD patients than in those with asthma.

This study examined the relationship between patients' ability to visually identify their inhaler(s) and adherence outcomes. Our findings indicate that correct visual identification is associated with better adherence, as measured by both the PDC and the TAI questionnaire. These results underscore the importance of patient education in adherence management. Ensuring that patients can visually recognize and correctly use their inhaler(s) should be a key component of strategies aimed at improving adherence.

Conversely, the ability to recall the commercial name or pharmaceutical components of an inhaler was not

Table 1. General characteristics and characterization of adherence to chronic inhalation therapy in the study sample.

Characteristics	COPD (n = 104)	Asthma (n = 74)	Asthma + COPD (n = 18)	All (n = 196)	p-value
Age (years)	72.1 ± 9.3	58.5 ± 17.7	63.4 ± 4.6	66.2 ± 14.6	0.000
Sex, n (%)					0.000
> Female	26 (25.0%)	62 (83.8%)	8 (44.4%)	96 (49.0%)	
> Male	78 (75.0%)	12 (16.2%)	10 (55.6%)	100 (51.0%)	
Smoking status, n (%)					0.001
> Current	16 (15.4%)	6 (8.1%)	8 (44.4%)	30 (15.3%)	
> Former or never	88 (84.6%)	68 (91.9%)	10 (55.6%)	166 (84.7%)	
Exacerbations in the past year*, n (%)					0.789
> Yes	36 (34.6%)	22 (29.7%)	6 (33.3%)	64 (32.7%)	
> No	68 (65.4%)	52 (70.3%)	12 (66.7%)	132 (67.3%)	
Hospitalization in the past year**, n (%)					0.100
> Yes	38 (36.5%)	16 (21.6%)	6 (33.3%)	60 (30.6%)	
> No	66 (63.5%)	58 (78.4%)	12 (66.7%)	136 (69.4%)	
Number of inhalers, n (%)					0.555
> 1	68 (65.4%)	54 (73.0%)	12 (66.7%)	134 (68.4%)	
> 2	36 (34.6%)	20 (27.0%)	6 (33.3%)	62 (31.6%)	
Inhaler type***, n (%)					
> DPI	65 (62.5%)	55 (74.3%)	17 (94.4%)	137 (69.9%)	0.039
> pMDI	9 (8.7%)	12 (16.2%)	5 (27.8%)	26 (13.3%)	0.119
> pMDI with VHC	21 (20.2%)	9 (12.2%)	0 (0.0%)	30 (15.3%)	0.076
> SMI	41 (39.4%)	21 (28.4%)	3 (16.7%)	65 (33.2%)	0.039
TAI (score)	48.9 ± 2.6	48.1 ± 4.2	47.2 ± 2.7	48.4 ± 3.3	0.089
Adherence by TAI, n (%)					0.069
> Good	70 (67.3%)	42 (56.8%)	6 (33.3%)	118 (60.2%)	
> Intermediate	26 (25.0%)	22 (29.7%)	8 (44.5%)	56 (28.6%)	
> Poor	8 (7.7%)	10 (13.5%)	4 (22.2%)	22 (11.2%)	
PDC (score)	82.2 ± 21.5	70.3 ± 25.3	67.6 ± 20.8	76.4 ± 23.7	0.001
Adherence by PDC, n (%)					0.001
> Good	70 (67.3%)	32 (43.2%)	6 (33.3%)	108 (55.1%)	
> Poor	34 (32.7%)	42 (56.8%)	12 (66.7%)	88 (44.9%)	
Inhaler visual identification, n (%)					0.073
> Correct	90 (86.5%)	70 (94.6%)	14 (77.8%)	174 (88.8%)	
> Incorrect	14 (13.5%)	4 (5.4%)	4 (22.2%)	22 (11.2%)	
Inhaler naming, n (%)					0.002
> Correct	32 (30.8%)	42 (56.8%)	8 (44.4%)	82 (41.8%)	
> Incorrect	72 (69.2%)	32 (43.2%)	10 (55.6%)	114 (58.2%)	

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; n, number; PDC, proportion of days covered; pMDI, pressurized metered-dose inhaler; SMI, soft mist inhaler; TAI, test of adherence to inhalers; VHC, valved holding chamber. *Due to their respiratory condition, without the need for hospitalization. **Due to their respiratory condition. ***Note that 62 (31.6%) participants had 2 inhalers.

Table 2. Characterization of adherence to chronic inhalation therapy according to inhaler visual identification and inhaler naming.

Adherence methods	Inhaler Visual Identification		p-value	Inhaler Naming		p-value
	Correct (n = 174)	Incorrect (n = 22)		Correct (n = 82)	Incorrect (n = 114)	
TAI (score)	48.6 ± 3.3	46.8 ± 3.4	0.017	48.2 ± 4.4	48.6 ± 2.2	0.398
Adherence by TAI, n (%)			0.000			0.009
> Good	110 (63.2%)	8 (36.4%)		56 (68.3%)	62 (54.4%)	
> Intermediate	50 (28.7%)	6 (27.2%)		14 (17.1%)	42 (36.8%)	
> Poor	14 (8.1%)	8 (36.4%)		12 (14.6%)	10 (8.8%)	
PDC (score)	78.1 ± 22.6	62.9 ± 28.0	0.004	78.5 ± 23.9	74.9 ± 23.6	0.293
Adherence by PDC, n (%)			0.061			0.161
> Good	100 (57.5%)	8 (36.4%)		50 (61.0%)	58 (50.9%)	
> Poor	74 (42.5%)	14 (63.6%)		32 (39.0%)	56 (49.1%)	

n: number; PDC: proportion of days covered; TAI: test of adherence to inhalers.

Table 3. Predictors of adherence to chronic inhalation therapy when measured based on PDC according to the results of the fractional logit model.

Determinant	Forest Plot (-2 -1 0 1 2)	Coefficient (Std. Error)	z-value	p-value
Older age (≥ 65)		.3482674 (.2645803)	1.32	0.188
Sex (male)		.0021043 (.2409677)	0.01	0.993
Smoking		-.2712544 .2421464	-1.12	0.263
Pathology (Reference: Asthma)				
> COPD		.4942129 (.2966214)	1.67	0.096
> Asthma+COPD		.0160121 (.3202303)	0.05	0.960
Inhaler visual identification		.6300489 (.2703577)	2.33	0.020
Inhaler naming		-.0040883 (.2277411)	-0.02	0.986
Multiple inhalers		.7967108 (.3536215)	2.25	0.024
Exacerbations*		-.2570593 (.1916981)	-1.34	0.180
Hospitalizations**		.2965935 (.2265943)	1.31	0.191
Inhaler type:				
> pMDI		-.4136654 (.5035871)	-0.82	0.411
> pMDI with VHC		-.3607462 (.4723194)	-0.76	0.445
> DPI		.2827291 (.476611)	0.59	0.553
> SMI		.4727223 (.3822675)	1.24	0.216
Constant		-.193884 (.5833687)	-0.33	0.740

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; PDC, proportion of days covered; pMDI, pressurized metered-dose inhaler; SMI, soft mist inhaler; Std, Standard; VHC, valved holding chamber. * Without the need for hospitalization. **Due to their respiratory condition.

associated with better adherence when measured by the PDC and was even linked to poorer adherence when assessed using the TAI score. This may be partially explained by the picture superiority effect (PSE)—a cognitive phenomenon in which images are more easily recognized and remembered than names or labels.[22–24] This finding may be particularly relevant for patients managing multiple medications, as visual cues can help reduce confusion and promote correct inhaler use. Therefore, recalling an inhaler's name does not appear to be a reliable indicator of adherence and may not be a useful focus in adherence-improvement strategies.

The use of two inhalers, compared to a single inhaler, was associated with better adherence, regardless of whether it was measured using the TAI questionnaire or the PDC—an unexpected finding that contrasts with previous research.[25–29] However, this result should be interpreted with caution considering the study's design and population characteristics. Evaluating the association between the number of inhalers and adherence was not a predefined objective. Additionally, previous studies focus primarily on patients with COPD, who tend to be more adherent, whereas our sample included a mixed population of patients with asthma, COPD, and asthma+COPD. Prior research also frequently compared single-inhaler triple therapy with multiple-inhaler triple therapy, while in our study, single-inhaler therapies could contain one, two, or three components. Furthermore, most asthma patients—who typically exhibit lower adherence—used a single inhaler (73.0%). A more detailed analysis showed that 66.7% of asthma patients using a single inhaler had poor adherence based on the PDC, compared to only 30.0% of those using two inhalers.

Although the use of multiple inhalers appeared to be associated with better adherence in our study, another crucial factor to consider is inhaler technique. Previous studies have shown that using multiple inhalers is strongly associated with a higher risk of critical

Table 4. Predictors of adherence to chronic inhalation therapy when measured based on TAI according to the results of the fractional logit model.

Determinant	Forest Plot (-4 -2 0 2 4 6)	Coefficient (Std. Error)	z-value	p-value
Older age (≥ 65)		-.6564047 (.3945885)	-1.66	0.096
Sex (male)		.3700067 (.3611608)	1.02	0.306
Smoking		-1.436869 (.3632019)	-3.96	0.000
Pathology (Reference: Asthma)				
> COPD		.3490573 (.4392229)	0.79	0.427
> Asthma+COPD		.1058628 (.4036983)	0.26	0.793
Inhaler visual identification		.7310443 (.3349092)	2.18	0.029
Inhaler naming		-.8541548 (.2669214)	-3.20	0.001
Multiple inhalers		1.639927 (.4396881)	3.73	0.000
Exacerbations*		-.5519098 (.2504454)	-2.20	0.028
Hospitalizations**		.1299456 (.5632743)	0.23	0.818
Inhaler type:				
> pMDI		-1.81924 (.73418)	-2.48	0.013
> pMDI with VHC		-.3884083 (.6841373)	-0.57	0.570
> DPI		-1.279668 (.5610579)	-2.28	0.023
> SMI		-.5880969 (.3978188)	-1.48	0.139
Constant		4.524437 (.8408395)	5.38	0.000

COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler; SMI, soft mist inhaler; TAI, test of adherence to inhalers; VHC, valved holding chamber. * Without the need for hospitalization. ** Due to their respiratory condition.

Table 5. Sensitivity, specificity, and AUROC of incorrect inhaler visual identification for detecting poorly adherent patients.

Adherence Assessment Method	Sensitivity	Specificity	AUROC
Proportion of Days Covered (PDC)	15.9%	92.6%	0.54
Test of Adherence to Inhalers (TAI) Score	17.9%	93.2%	0.56

AUROC, area under the receiver operating characteristic; PDC, proportion of days covered; TAI, test of adherence to inhalers.

errors in inhaler technique, which can compromise clinical outcomes by reducing therapeutic efficacy.[30,31] Therefore, we advocate for therapy simplification and recommend avoiding the use of multiple devices whenever possible, in accordance with current GOLD and GINA guidelines.[1,2]

Four additional determinants were found to be associated with adherence; however, they were only relevant when adherence was measured using the TAI, not the PDC. As such, the following findings should be interpreted with caution. The occurrence of exacerbations in the previous year (not requiring hospitalization) was associated with poorer adherence, consistent with findings from other studies.[25,32] Smoking was also linked to lower adherence, although the literature on this association is mixed—some studies support our findings,[30,33] while others have reported a positive association between smoking and adherence.[15] In addition, the use of a dry powder inhaler (DPI) or a pressurized metered-dose inhaler (pMDI) without a valved holding chamber (VHC) was associated with poorer adherence. This may be partially explained by challenges patients face in coordinating actuation with inhalation (for pMDIs) or generating

sufficient inspiratory flow (for DPIs), which can lead to frustration or a perceived lack of efficacy.

According to the analyzed data, correct visual identification of the inhaler does not definitively classify a patient as adherent or non-adherent; however, it is associated with a greater likelihood of adherence. In such cases, clinicians should use additional methods to further assess adherence.

Using incorrect visual identification of inhalers to detect poorly adherent patients demonstrated low sensitivity but high specificity (93.2% with the TAI and 92.6% with the PDC). These results suggest that, overall, this method is not effective as a general screening tool. However, when a patient incorrectly identifies their inhaler(s), it serves as a reliable indicator of poor adherence.

Therefore, given its rapid and practical application, the authors believe that the image set proposed in this study—**which** encompasses all inhalation devices available on the national market—could serve as a valuable tool in clinical practice, particularly for identifying patients with poor adherence. It should also be considered as part of a broader adherence assessment strategy.

The main limitations of this study include its single-center design, the cross-sectional nature of some data, and the partial reliance on self-reported information. Furthermore, the image set used reflects inhalation devices available in our national market, which may not be representative of those found in other countries. Key strengths of the study include its prospective design, the incorporation of a visual identification component—**an aspect not** previously explored in other studies—and the use of multiple adherence assessment methods, providing a comprehensive evaluation from both subjective and objective perspectives.

In conclusion, asthma patients appear to overestimate their adherence more than COPD patients when completing self-report questionnaires. The ability to visually identify inhalers was associated with better adherence, whereas the ability to recall the commercial name or pharmaceutical components was not. Although incorrect visual identification has limited value as a general screening tool, it can still reliably identify poorly adherent patients, providing a quick and practical strategy for use in clinical practice.

Future studies should explore broader assessment methods and aim to develop a tool that combines visual identification with other adherence metrics. Such a tool should be designed for rapid use during medical consultations to facilitate the early detection of poor adherence.

AUTHOR CONTRIBUTIONS

DSG and JC: study design; JC: study supervision; DSG: data collection; DSG and CS: statistical analysis of the data. DSG: writing the original draft; DSG, CS, and JC: manuscript review and editing. All authors contributed to the interpretation of the results and read and approved the final manuscript.

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Results of radiotherapy for thymoma: retrospective cohort and propensity score matching analysis

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ABSTRACT

Objective: Thymic tumors are a rare group of anterior mediastinal tumors. Surgery is the primary treatment. Adjuvant treatment is used in select cases. The purpose of this study was to evaluate the outcomes of patients with thymic tumors, submitted or not to radiotherapy, and identify risk factors that could impact the outcomes to better support patient selection for RT. **Methods:** This is a single institution retrospective cohort study. Patients with histologically proven thymoma or thymic carcinoma treated from July of 2009 to November of 2020 were included. Analysis was based on the use of radiation therapy (RT). Overall survival and disease-free survival were assessed from the date of diagnosis. To minimize selection bias, propensity score matching (PSM) regression using Kernel matching was used, estimated on the population for average treatment effect. **Results:** Overall, 101 patients were analyzed, with mean age at diagnosis of 54.6 years (range 25-84 years). Unfavorable histology and more advanced stages predominated in the cohort. Nevertheless, most (69.3%) were treated with radical intent. RT was delivered in 52.9% of these patients. Five-year OS, local progression and distant progression free survivals were 81.0%, 95.0% and 88.1%, respectively for the radical intent cohort. PSM showed that RT reduced the chances of death by 6.3% (matched sample size was 60, p = 0.02). **Conclusions:** In this retrospective cohort, RT had a positive impact in OS after PSM analysis. Prospective data regarding the role of RT in this disease is needed to validate these findings.

Keywords: Thymoma; Thymus neoplasms; Radiotherapy.

INTRODUCTION

Thymoma is a rare malignant tumor located in the anterior mediastinum. Because most cases are asymptomatic, they are often diagnosed in advanced stages.[1]

Currently, the standard treatment for initial cases of thymoma involves surgical intervention without any adjuvant therapy. However, for advanced tumors, radiotherapy (RT) can be employed as a postsurgical treatment, leading to improved outcomes, including overall survival.[2]

The classification of thymoma is based on several staging systems, TNM,[3], WHO,[4] and Masaoka-Koga,[5] TNM being the most up to date. being the most up to date. Factors associated with poorer prognosis include older age, incomplete resection, a WHO B2/B3, and higher stage.[6]

Given the limited data available in the literature regarding the use and goals of RT in thymoma treatment, there is a significant knowledge gap. Most current data come from large, retrospective cohorts and large databases. Although RT has been shown to improve overall survival in stage III patients,[7-9] it has shown no evident benefit in earlier stages.[10-12] However, there is evidence of benefit in local control with RT for metastatic and recurrent thymoma.[13]

The objectives of the present study were to evaluate the outcomes of patients with thymic tumors undergoing or not undergoing RT and identify risk factors for poor outcomes, thus improving patient selection for RT and providing personalized treatment options.

METHODS

This was a single-center retrospective cohort study assessing patients diagnosed with either thymoma or thymic carcinoma and treated between July of 2009 and November of 2020. All patients receiving any type of treatment within the aforementioned time period were assessed, with no other exclusion criteria.

Demographic variables were assessed, including age, sex, Masaoka-Koga staging,[14] TNM staging,[15] and WHO histological classification.[16] Treatment procedures such as surgery, surgical margin status, chemotherapy (including drugs and regimens), and RT (including

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radiation doses and fractionation schedules) were also assessed.

Statistical analysis included frequency and descriptive statistics. Patients treated with curative intent were divided into two groups: those who received RT and those who did not. Between-group comparisons were performed by means of Fisher's exact test. Overall survival and disease-free survival were calculated from the date of diagnosis. Survival was assessed by the Kaplan-Meier method, and the log-rank test was used for univariate analysis. Patients treated with palliative intent were excluded from the univariate analysis and all subsequent analyses. To assess the impact of RT with reduced selection bias, propensity score matching was used with kernel matching for average treatment effect. The Stata statistical software package, version 18 (StataCorp LLC, College Station, TX, USA) was used for all analyses, and the level of significance was set at 5% ($p \leq 0.05$).

The present study was approved by the local research ethics committee in April of 2021 and was conducted in accordance with Brazilian law and the Declaration of Helsinki.

RESULTS

One hundred and one patients were included in the present study. Most (53.5%) were male. The mean age at diagnosis was 54.6 years (range, 25-84 years). Most of the participating patients had WHO histological type B2 tumors or higher and advanced stage disease. Approximately 70% were treated with curative intent and underwent surgery. Demographic and treatment characteristics can be seen in Table 1.

The median follow-up was 47.1 months. There were 24 deaths in the period. The mean overall survival was 94.4 months, and the median overall survival was not reached. The median local progression-free survival (LPFS) and distant progression-free survival (DPFS) were not reached. Five-year overall survival, LPFS, and DPFS rates were 81.0%, 95.0%, and 88.1%, respectively. Local control at 5 years was 95.0% (96/101) for the entire cohort and 95.7% (67/70) for the patients treated with curative intent. Local control at 5 years for the patients undergoing surgery was 94.3% (68/71), and all of those who underwent adjuvant RT achieved local control at 5 years. The rate of patients undergoing RT was 96.4% (53/55), and that of those undergoing RT alone was 89.5% (17/19). Kaplan-Meier curves for overall survival related to treatment intent can be seen in Figures 1 and 2, whereas those for LPFS can be seen in Figure 3.

RT and chemotherapy regimens varied. Regarding RT, the mean radiation dose was 54 Gy (range, 48-61.2 Gy). Most treatments were delivered with conformal technique (53/93.0%). The target included residual gross disease, including the previous surgical bed. No elective lymph node drainage was included. Regarding chemotherapy, the most common regimen was anthracycline-based chemotherapy (in 18.8%), followed by platinum-based chemotherapy (in 16.8%). The median number of cycles of chemotherapy was 4 (range, 1-6) for the entire cohort and 4 (range, 2-6) as adjuvant/neoadjuvant treatment for the patients treated with curative intent. No grade III or higher non-hematological toxicities were reported.

The radical intent group was analyzed separately in order to assess the impact of RT. The impact of radiotherapy was analyzed by comparing the groups treated with curative intent, submitted or not to irradiation. The differences between these groups can be seen in Table 2. Patients undergoing RT had more aggressive histology (B2-C; $p = 0.015$) and residual disease or positive surgical margins ($p = 0.001$). In the univariate analysis, a more favorable histological type, negative margins, and chemotherapy were significantly associated with better overall survival. Histology also correlated with LPFS. The Masaoka-Koga and TNM stages, as well as histology, were associated with better DPFS (Table 3). Multivariate analysis showed no significant independent variable for DPFS or overall survival. Kaplan-Meier curves for overall survival, LPFS, and DPFS for the curative intent group can be seen in Figures 1, 2, and 3, respectively.

Propensity score matching analyses were performed to assess the impact of RT on overall survival. There were too few events among the remaining outcomes to be included in the analysis. The independent variables selected were age, sex, Masaoka-Koga stage, WHO subtype, TNM stage, and margin status. Propensity score matching showed that RT reduced the chance of death by 6.3% (matched sample size, 60; 95% CI, −0.119 to 0.105; $p = 0.02$). The standardized mean differences were age (0.41), sex (0.032), Masaoka-Koga stage (0.75), WHO subtype (0.76), TNM stage (0.51), and margin status (0.008), including that the better balanced variables below 0.1 were gender and margin status

DISCUSSION

In our retrospective study, we sought to explore the role of RT in the treatment of patients with thymoma. Patients were assessed for benefit from RT during curative treatment. A significant proportion (69.3%) underwent radical treatment, with 72 patients (71.3%) undergoing surgery classified as curative intent. These findings suggest that a considerable number of cases were diagnosed at initial stages. Amongst the study limitations, we must address the limited sample due to the disease's rarity, the retrospective nature of this study, and the fact that this is a single center report. Although the frequency of events in the study population was low, the impact of RT should be addressed in prospective studies, given that the influence of unmeasured confounding is always present in nonrandomized studies.

The use of RT in stages I and II remains a topic of debate, particularly in cases in which R0 resection with clear margins has been achieved. Given the

Table 1. Demographic characteristics and type of treatment.

Variable	All patients N = 101		Radical treatment n = 70 (69.3%)		Palliative treatment n = 31 (30.7%)	
	Number (n)	(%)	Number (n)	(%)	Number (n)	(%)
Age, years						
Mean (range)	54.6 (25-84)		54.6 (25-77)		58.6 (34-84)	
Sex						
Male	54	53.5	37	52.9	17	54.8
Female	47	46.5	33	47.1	14	45.2
WHO classification						
A	9	8.9	9	12.9	-	-
AB	20	19.8	18	25.7	2	6.5
B1	13	12.9	11	15.7	2	6.5
B2	18	17.8	14	20.0	4	12.9
B3	21	20.8	13	18.6	8	25.8
C	20	19.8	5	7.2	15	48.4
Masaoka-Koga stage						
I	18	17.8	18	25.7	-	-
IIA	24	23.8	24	34.3	-	-
IIB	14	13.9	11	15.7	3	9.7
III	23	22.8	16	22.8	7	22.5
IVA	3	3.08	-	-	3	9.7
IVB	19	18.8	1	1.4	18	58.1
T stage						
Tx	1	1.0	1	1.4	-	-
T1a	33	32.7	33	4.7	-	-
T1b	9	8.9	9	12.8	-	-
T2	16	15.8	12	17.1	4	12.9
T3	17	16.8	13	18.6	4	12.9
T4	25	24.8	2	2.8	23	74.2
N stage						
Nx	14	13.9	10	14.3	4	12.9
N0	71	70.3	59	84.3	12	38.7
N1	7	6.9	1	1.4	6	19.4
N2	9	8.9	-	-	9	29.0
M stage						
M0	85	84.2	60	100	15	48.4
M1a	7	6.9	-	-	7	22.6
M1b	9	9.0	-	-	9	29.0
Treatment						
Surgery						
No	29	28.7	-	-	29	93.5
Yes	72	71.3	70	100	2	6.5
Radiotherapy						
No	44	43.6	33	47.1	11	35.5
Yes	57	56.4	37	52.9	20	64.5
Chemotherapy						
No	64	63.4	63	90.0	1	0.3
Yes, platinum-based	17	16.8	3	4.3	14	45.1
Yes, anthracycline-based	19	18.8	4	5.7	15	48.3
Yes, gemcitabine-based	1	1.0	-	-	1	0.3

rarity of thymoma, studies investigating the role of RT are predominantly retrospective and limited to single institutions. Retrospective studies have shown conflicting results, including potential benefits for stage II patients,[17] even in the negative margin setting.[18] In our sample, RT was given primarily after surgery with positive margins, which after all did not impact survival. Retrospective data[19] have shown that

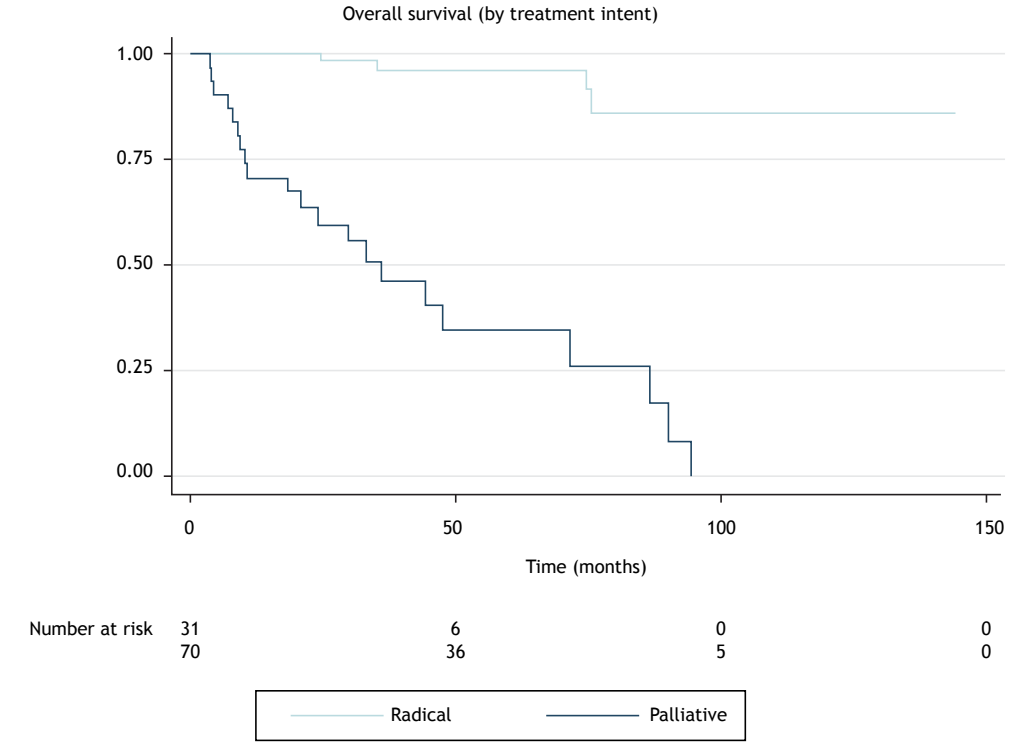

Figure 1. Overall survival for the sample as a whole, by treatment intent. Notes: Median survival not reached for the sample as a whole cohort or the group of patients treated with curative intent. Median survival for the group of patients treated with palliative intent was 35.9 months ($p > 0.001$).

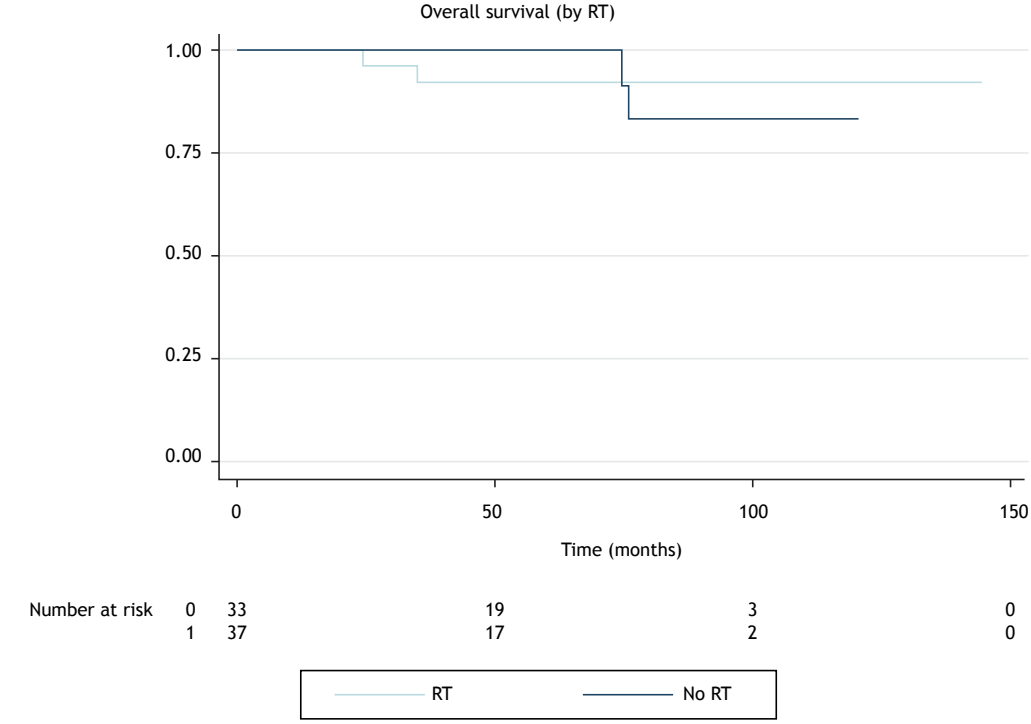

Figure 2. Overall survival for the group of patients treated with curative intent and undergoing or not undergoing radiotherapy (RT). Note: No median survival reached ($p = 0.06$).

adjuvant RT for positive margin patients may render similar results to negative margin surgery, even with macroscopic disease after surgery. Our results support that finding. Nevertheless, approximately one third

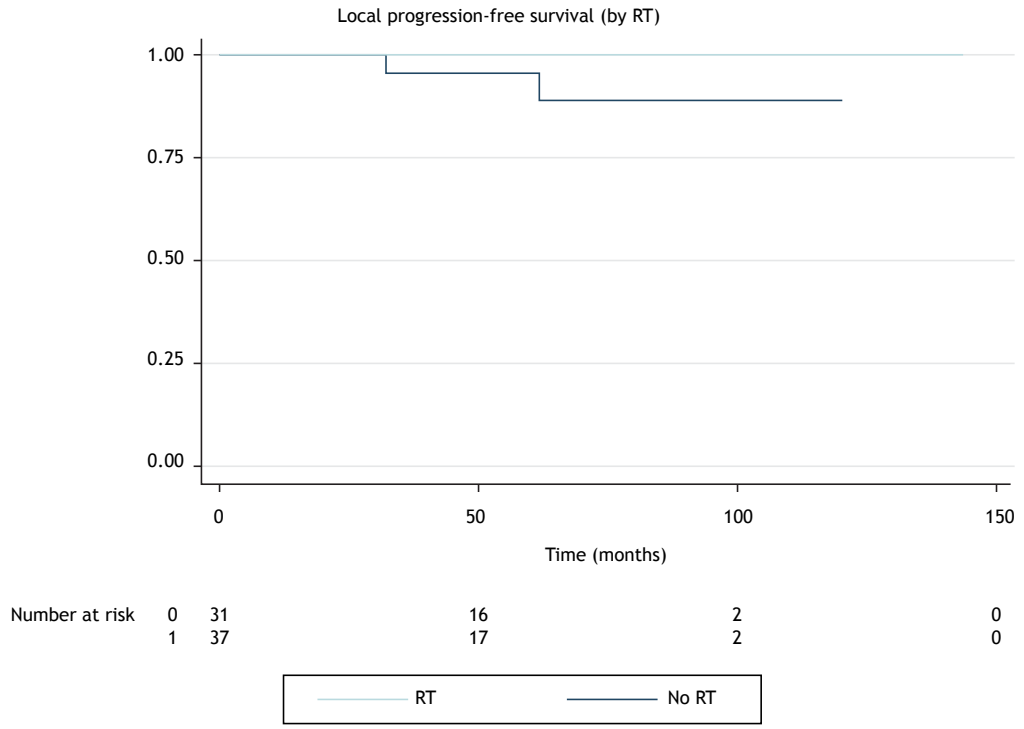

Figure 3. Local progression-free survival for the group of patients treated with curative intent and undergoing or not undergoing radiotherapy (RT). Note: No median survival reached (p = 0.14).

Table 2. Demographic characteristics of the 70 patients treated with curative intent.[a]

Demographics	Radiation therapy		p*
	No n = 33 (47.1%)	Yes n = 37 (52.9%)	
Age, years			
≤ 50	10 (30.3%)	15 (40.5%)	0.372
> 50	23 (69.7%)	22 (59.5%)	
Sex			
Female	17 (51.5%)	16 (43.2%)	0.489
Male	16 (48.5%)	21 (56.8%)	
WHO histology			
A-B1	23 (69.7%)	15 (40.5%)	0.015
B2-C	10 (30.3%)	22 (59.6%)	
Masaoka-Koga stage			
I-II	28 (84.9%)	25 (67.6%)	0.092
III-IV	5 (15.1%)	12 (32.4%)	
TNM stage			
I-II	28 (84.8%)	26 (70.3%)	0.147
III-IV	5 (15.2%)	11 (29.7%)	
Surgical margin			
Negative	22 (78.6%)	11 (34.4%)	0.001
Positive	6 (21.4%)	21 (65.6%)	
Chemotherapy			
No	31 (93.9%)	32 (86.5%)	0.299
Yes	2 (6.1%)	5 (13.5%)	

[a]Data expressed as n (%). *Values of p stand for the correlation of each variable with radiation therapy.

(34%) of patients with negative margins received RT. This was mostly due to other risk factors such as high-grade histology and locally advanced disease, which were also related to the outcomes.

Retrospective studies have shown varying results for adjuvant RT for stage III disease. Studies with sample sizes ranging from 21[20] to 205[21] have shown local control varying from 53%[22] to 84%[23] in 5

Table 3. Univariate analysis of survival outcomes.

Patient characteristic	N	LPFS*		DPFS*		OS*	
		Mean	p	Mean	p	Mean	p
Age							
< 50 years	25	52.2	0.10	50.2	0.49	54.1	0.07
> 50 years	45	51.9		51.4		53.5	
Sex							
Female	33	50.3	0.22	50.4	0.10	50.4	0.09
Male	37	53.6		51.5		56.7	
WHO histology							
A-B1	7	61.2	0.03	60.6	0.02	61.2	0.001
B2-C	18	40.5		38.7		44.8	
Masaoka-Koga stage							
I-II	18	54.3	0.45	52.8	0.02	59.1	0.97
III-IV	20	51.4		50.4		52.0	
TNM stage							
I-II	54	57.3	0.45	55.7	0.02	62.251.2	0.97
III-IV	16	50.6		49.6			
Surgical margin							
Negative	33	54.3	0.11	52.5	0.43	56.3	0.01
Positive	27	35.8		35.8		37.0	
Radiation therapy							
No	33	55.0	0.14	53.7	0.36	58.2	0.06
Yes	37	49.6		48.6		49.7	
Chemotherapy							
No	63	51.8	0.56	51.5	0.07	53.5	0.01
Yes	7	54.6		46.4		55.7	

LPFS: local progression-free survival; DPFS: distant progression-free survival; and OS: overall survival. *In months.

years.[24-30] Our results of 14 Masaoka-Koga stage III patients with a 5-year local control of 71.4% are consistent with the literature.

A prospective phase III trial named RADIORYTHMIC is currently underway.[31] The objective of the trial is to compare postoperative RT with surveillance in Masaoka-Koga stage IIb/III thymoma after completing surgical resection. The trial, which began enrolling patients in January of 2021, is expected to yield results in 2028, with the primary endpoint being recurrence-free survival. This trial could answer in a sounder manner the impact of RT on patients with thymoma.

In more advanced stages, RT plays a major role in unresectable disease. Retrospective data have shown that unresectable thymoma can be properly treated with concurrent chemotherapy and RT in different regimens.[32,33] Those samples varied from 11 to 100 patients and local control was as high as 93.5%,[34] especially when the regimen adopted consisted of RT and chemotherapy. Prospective data from small trials have shown adequate local control,[35-39] although only when RT is present.[40] Those trials showed important response rates, including complete responses, obtainable only with combined therapy. Although our sample of 19 unresected patients was small, local control at 5 years was observed in 89.0% (17/19), a finding that is consistent with the literature.

We reported our findings in a retrospective cohort of thymoma patients treated at a single university hospital. RT had a positive impact on overall survival in the study sample. Our results show that histology, stage, and surgical status are key for adequate patient selection and treatment, with consistent outcomes. Although we acknowledge the limitations of our retrospective study, our findings can contribute to future studies. Further research is needed to validate our findings and guide treatment decisions for this rare and challenging condition.

AUTHOR CONTRIBUTIONS

KMLBL, JPS, CCAR, and GFN: study design. GPM: research ethics committee approval and statistical analysis. KMLBL, JPS, and GPM: data collection. JPS and GPM: writing of the manuscript. GFN, CCAR and PHXNA: manuscript review. HAC: study supervision and manuscript review.

CONFLICTS OF INTEREST

None declared.

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Out with the old – advancements and shortcomings of the updated 9th edition of the Tumor, Node, Metastasis (TNM) classification system for lung cancer

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ABSTRACT

Objectives: The 9th edition of the Tumor, Node, Metastasis (TNM-9) lung cancer classification is set to replace the 8th edition (TNM-8) starting in 2025. Key updates include the splitting of the mediastinal nodal category N2 into single- and multiple-station involvement, as well as the classification of multiple extrathoracic metastatic lesions as involving a single organ system (M1c1) or multiple organ systems (M1c2). This study aimed to assess how the TNM-9 revisions affect the final staging of lung cancer patients and how these changes correlate with overall survival (OS). **Methods:** This retrospective cohort study included patients diagnosed with lung cancer between 2018 and 2021, who were staged according to both TNM-8 and TNM-9 criteria. The staging classifications were analyzed and compared in relation to OS. **Results:** Among a total of 914 patients, 42 were re-staged using TNM-9. Of the 382 patients classified as stage IVB, 55.9% were reclassified as M1c2. Despite an absolute increase in mean OS for patients re-staged from IIB to IIA and from IIIA to IIB, the observed differences were not statistically significant. Median OS differed significantly both within stage IVB and between patients with M1c2 disease and other stage IV subgroups. Multi-organ metastatic disease was an independent predictor of poorer OS, regardless of age, sex, performance status, and oncologic treatment. **Conclusions:** TNM-9 improves prognostic accuracy in lung cancer. Although patients with multiple extrathoracic metastases involving different organ systems are not yet independently staged from IVB, they demonstrated significantly poorer OS compared to other advanced-stage patients.

Keywords: Lung cancer, Metastasis, Lymph nodes, Prognosis, Survival.

INTRODUCTION

Despite significant efforts in both prevention and screening, lung cancer remains the leading cause of cancer-related death worldwide.[1] One major area of advancement in lung cancer management is the optimization of staging systems, which aim to more accurately predict which patients are best suited for specific treatment modalities.

Since 1966, the well-established Tumor, Node, Metastasis (TNM) classification has been used to stage cancer patients based on the anatomic extent of malignancy—both to guide treatment decisions and to serve as a prognostic indicator. Recent updates have been driven by large-scale, prospective research led by the International Association for the Study of Lung Cancer (IASLC).[2] The 9th edition of the TNM staging system (TNM-9), set to become standard practice as of January 2025, is based on comprehensive analyses of international lung cancer databases compiled by the IASLC. As in previous editions, TNM-9 categorizes tumors according to primary tumor characteristics (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M).[3] The proposed changes in TNM-9 include the subdivision of the former mediastinal nodal category (N2) into single-station (N2a) and multiple-station (N2b) involvement, as well as the reclassification of multiple extrathoracic metastatic lesions (M1c) into either single-organ system (M1c1) or multiple-organ system (M1c2) categories.[4] While the N2a/N2b distinction may alter a patient's final stage compared to the 8th edition (TNM-8), the new subcategorization of M1c patients does not yet alter the overall stage—all such cases remain classified as stage IVB.

In this study, we aimed to evaluate how the application of the novel TNM-9 staging criteria affects the final classification of lung cancer patients previously staged using TNM-8, and how these changes may translate into differences in overall survival (OS).

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METHODS

This retrospective cohort study included all patients diagnosed with lung cancer at a tertiary center between January 2018 and December 2021. Data were manually extracted from the electronic health records of patients treated at our institution. Patients with insufficient clinical information were excluded from the final analysis (see Supplementary Figure 1). Additionally, individuals diagnosed and treated at another facility or referred to our center solely for treatment were also excluded. To ensure patient confidentiality, no personally identifiable information was collected.

All patients were staged either clinically or, when applicable, pathologically (after surgery), in accordance with international guidelines. Aside from the data required for complete TNM staging—primary tumor size, lymph node involvement, and presence of metastases—additional variables collected included sex, age at diagnosis, smoking status, baseline Eastern Cooperative Oncology Group Performance Status (ECOG-PS), lung cancer-related symptom status

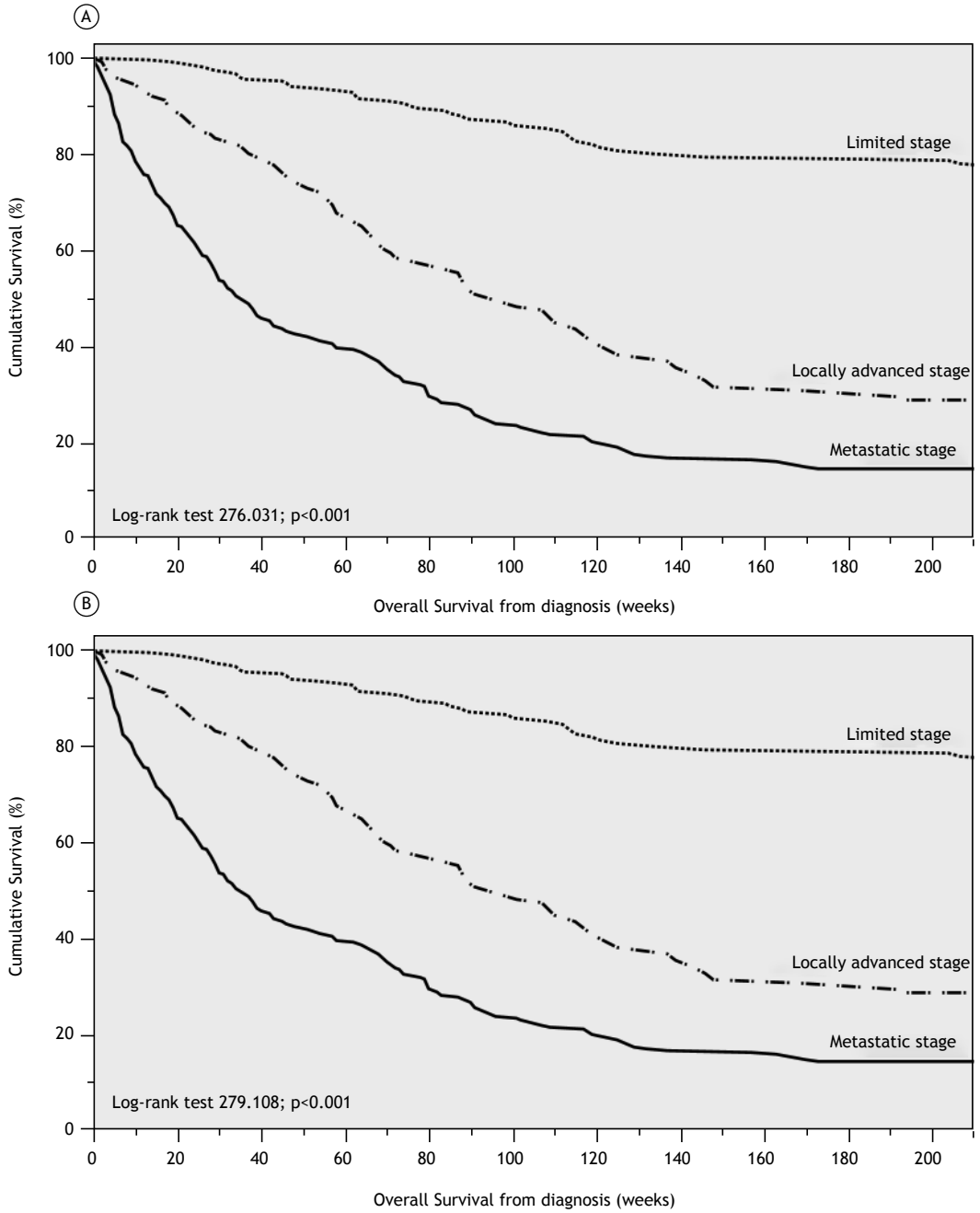

Figure 1. Kaplan-Meier curves showing the cumulative survival of the overall sample stratified by general staging classification (limited, locally advanced, and metastatic stages): TNM-8 (A) and TNM-9 (B).

(symptomatic or asymptomatic), and patient referral setting. Information regarding first-line treatment, clinical status (alive or deceased), and overall survival (OS) was also gathered. Each patient was staged according to both TNM-8 and TNM-9 criteria. In order to stratify lymph node involvement according to the novel TNM-9 system, all histopathological results obtained from endobronchial ultrasound (EBUS) sampling were reviewed. Imaging data—including computed tomography (CT), positron emission tomography–CT (PET-CT), and brain magnetic resonance imaging (MRI)—were reassessed alongside baseline multidisciplinary tumor board reports to reclassify metastatic involvement.

Statistical analysis was performed using SPSS version 28.0 (SPSS Inc., Chicago, IL, USA). The normality of variable distribution was assessed using the Kolmogorov-Smirnov test. Categorical variables were compared using the chi-square test, and the strength of associations was measured using Cramer's V. Survival analyses were conducted using the Kaplan-Meier method (log-rank tests), and multivariate analysis was performed using the Cox proportional hazards model.

This study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the São João Local Healthcare Unit, in Porto, Portugal (CES ULSSJOAO: 21/2024). Due to its retrospective nature, the requirement for individual informed consent was waived by the committee.

RESULTS

A total of 914 patients were diagnosed with lung cancer during the study period. The majority were male (71.7%), and the mean age at diagnosis was 67.72 (± 10.59) years. Most patients exhibited either active or former smoking habits (77.7%) and were symptomatic at the time of diagnosis (59.8%). Patients were primarily referred from outpatient settings, either following consultation with a general practitioner (35.6%) or a hospital-based consultation (32.2%). The median ECOG-PS at diagnosis was 0 (range: 0–4). The most common histological subtype was lung adenocarcinoma (n=570; 62.4%), followed by squamous cell carcinoma (n=167; 18.3%) and small cell lung cancer (n=98; 10.7%). Additional demographic data are presented in Table 1.

Table 1. Baseline characteristics of the study population.

	N = 914
Age (years)	67.8 ± 10.6
Sex (male)	655 (71.7)
Smoking status	
Non-smoker	204 (22.3)
Former smoker	312 (34.1)
Active smoker	398 (43.5)
Referral setting	
Primary healthcare	325 (35.6)
Outpatient clinic	294 (32.2)
Hospital ward	223 (24.4)
Emergency department	72 (7.9)
ECOG Performance Status	
0-1	730 (79.9)
2-4	184 (20.1)
Histological subtype	
Adenocarcinoma	570 (62.4)
Squamous cell carcinoma	167 (18.3)
Small cell lung cancer	98 (10.7)
Carcinoid tumor	33 (3.6)
NSCLC-NOS	29 (3.2)
Large cell carcinoma	17 (1.9)
Oncologic treatment	
Chemotherapy	229 (25.1)
Surgery (VATS)*	202 (22.1)
Chemoradiation therapy	189 (20.7)
Stereotactic body radiation therapy	85 (9.3)
Target therapy	68 (7.4)
Immune checkpoint inhibitor therapy	53 (5.8)
Chemoimmunotherapy	26 (2.8)
Hormone therapy	1 (0.1)
Watchful waiting/Best supportive care	61 (6.7)
Mortality	
Overall mortality	494 (54)
12-month mortality	342 (37.4)

Legend: ECOG, Eastern Cooperative Oncology Group; NSCLC-NOS, Non-small cell lung cancer not otherwise specified; VATS, Video-assisted thoracoscopic surgery. Continuous variables presented as mean ± standard deviation; qualitative variables presented as absolute number (percentage).

The complete TNM staging classifications for the 8th (TNM-8) and 9th (TNM-9) editions are presented in Supplementary Table 1. Based on TNM-8, 270 patients (29.5%) were classified as having limited-stage disease, whereas under TNM-9 criteria, this number increased slightly to 279 (30.5%). This shift is attributable to the downstaging of 9 patients who had previously been classified as having locally advanced disease under TNM-8 (261 patients vs. 252 under TNM-9). As expected, the number of advanced-stage patients remained unchanged between editions (n=383; 41.9%). Overall, this resulted in a significant, strong, and positive correlation between the two staging systems (p=0.003; V=0.983). An in-depth analysis revealed that 34 patients were downstaged and 8 were upstaged when transitioning from TNM-8 to TNM-9. Table 2 details these changes in final clinical staging. Downstaging occurred at three levels: 6 patients from IIB to IIA, 9 from IIIA to IIB, and 19 from IIIB to IIIA. Upstaging, on the other hand, involved 8 patients reclassified from IIIA to IIIB. The TNM-8 N2 subgroup (n=237) was further subdivided in TNM-9 into N2a (n=115; 48.5%) and N2b (n=122; 51.5%). Among the 382 advanced-stage patients, 290 (75.9%) were classified as stage IVB

Table 2. Re-staged lung cancer patients after TNM-9 staging criteria.

	DOWNSTAGED			UPSTAGED	
	IIB to IIA (n = 6)	IIIA to IIB (n = 9)	IIIB to IIIA (n = 19)	IIIA to IIIB (n = 8)	IVB* (n = 290)
Primary tumor size					
T1a	1 (16.7)	1 (11.1)	0 (0)	0 (0)	14 (4.8)
T1b	3 (50.0)	6 (66.7)	0 (0)	0 (0)	22 (7.6)
T1c	1 (16.7)	2 (22.2)	0 (0)	0 (0)	28 (9.7)
T2a	1 (16.7)	0 (0)	0 (0)	6 (75.0)	41 (14.1)
T2b	0 (0)	0 (0)	0 (0)	2 (25.0)	19 (6.6)
T3	0 (0)	0 (0)	19 (100)	0 (0)	58 (20.0)
T4	0 (0)	0 (0)	0 (0)	0 (0)	108 (37.2)
Lymph node staging					
N1	6 (100)	0 (0)	0 (0)	0 (0)	58 (20.0)
N2a	0 (0)	9 (100)	19 (100)	0 (0)	40 (13.8)
N2b	0 (0)	0 (0)	0 (0)	8 (100)	46 (15.9)
N3	0 (0)	0 (0)	0 (0)	0 (0)	146 (50.3)
Metastatic disease					
IVB (M1c1)	0 (0)	0 (0)	0 (0)	0 (0)	128 (44.1)
IVB (M1c2)	0 (0)	0 (0)	0 (0)	0 (0)	162 (55.9)

Legend: TNM-9, Tumor, Node, Metastasis classification for lung cancer (9th edition). Qualitative variables presented as absolute number (percentage). *Not an actual re-staging, but an updated differentiation between multiple metastatic lesions in a single organ system (M1c1) versus in more than one organ system (M1c2).

(M1c) due to multiple metastases. Under the updated TNM-9 criteria, although no change occurred in overall staging due to the current classification structure, 128 patients (44.1%) were categorized as M1c1 (single-organ system involvement), and 162 (55.9%) as M1c2 (multi-organ system involvement). The distribution of primary metastatic sites by TNM-9 M subclassification is provided in Supplementary Table 2.

The median OS (mOS) at diagnosis was 96 weeks (95% CI: 83.99–108.01) and differed significantly by overall stage (limited, locally advanced, and advanced) under both TNM-8 and TNM-9 criteria (Figure 1).

Stratification by N status revealed statistically significant differences in mOS under both staging systems. While patients with N1 and N3 disease showed similar survival patterns, TNM-8 N2 patients had a mOS of 72 weeks (95% CI: 61.62–82.38) after diagnosis. Under TNM-9, this group was subdivided into N2a [mOS 74 weeks (95% CI: 63.32–84.68)] and N2b [mOS 71 weeks (95% CI: 47.97–94.03)]. Among patients staged between IIA and IIIC, survival differed significantly according to stage, regardless of the TNM edition applied. Although the overall mOS across both editions was identical (110 weeks, 95% CI: 93.05–126.95), a notable difference was observed in stage IIIA: TNM-8 stage IIIA patients had a mOS of 143 weeks (95% CI: 114.28–171.72), compared to 119 weeks (95% CI: 95.71–142.29) for TNM-9 stage IIIA patients. No survival differences were observed between TNM-8 and TNM-9 in stages IIIB and IIIC. In patients downstaged under TNM-9, mOS was not reached due to high survival rates at the time of the analysis. However, mean survival times were higher for patients downstaged from IIB to IIA and from IIIA to IIB, though not for those downstaged from IIIB to IIIA (Figure 2). Despite these absolute increases in survival, the differences were not statistically significant.

OS did not differ significantly between stages IVA and IVB under either classification system (p=0.497). However, specific metastatic sites—particularly the liver and adrenal glands—were associated with significantly poorer prognoses. Patients with liver metastases had a mOS of 4 months (95% CI: 0.71–7.29), compared to 9 months (95% CI: 6.81–11.19) in those without liver involvement (p<0.001). Similarly, patients with adrenal metastases had a mOS of 4 months (95% CI: 1.56–6.44) versus 8 months (95% CI: 5.95–10.01) in those without adrenal involvement (p=0.011). When stratified by the M1c classification (Figure 3), M1c2 patients had significantly shorter survival than those with M1c1 disease [25 weeks (95% CI: 18.82–31.18) vs. 68 weeks (95% CI: 44.18–91.82); (p<0.001)], as well as when compared to all other M1 patients combined (i.e., stage IVA and non-M1c2 stage IVB) [mOS of 42 weeks (95% CI: 24.24–59.76); p<0.001]. No other statistically significant differences in OS were observed across metastatic stages. In a multivariate analysis restricted to stage IVB patients (Table 3), including variables such as M1c subclass (M1c1 vs. M1c2), sex, age at diagnosis, smoking status, ECOG-PS, specific metastatic sites (brain, bone, pleura), and treatment modality (systemic therapy vs. best supportive care), the M1c2 status remained an independent predictor of poorer OS [HR 1.43 (95% CI: 1.03–1.97); p=0.031], as did worse baseline ECOG-PS [HR 1.81 (95% CI: 1.26–2.60); p=0.001].

DISCUSSION

The application of the novel TNM-9 lymph node staging criteria resulted in the downstaging of 34

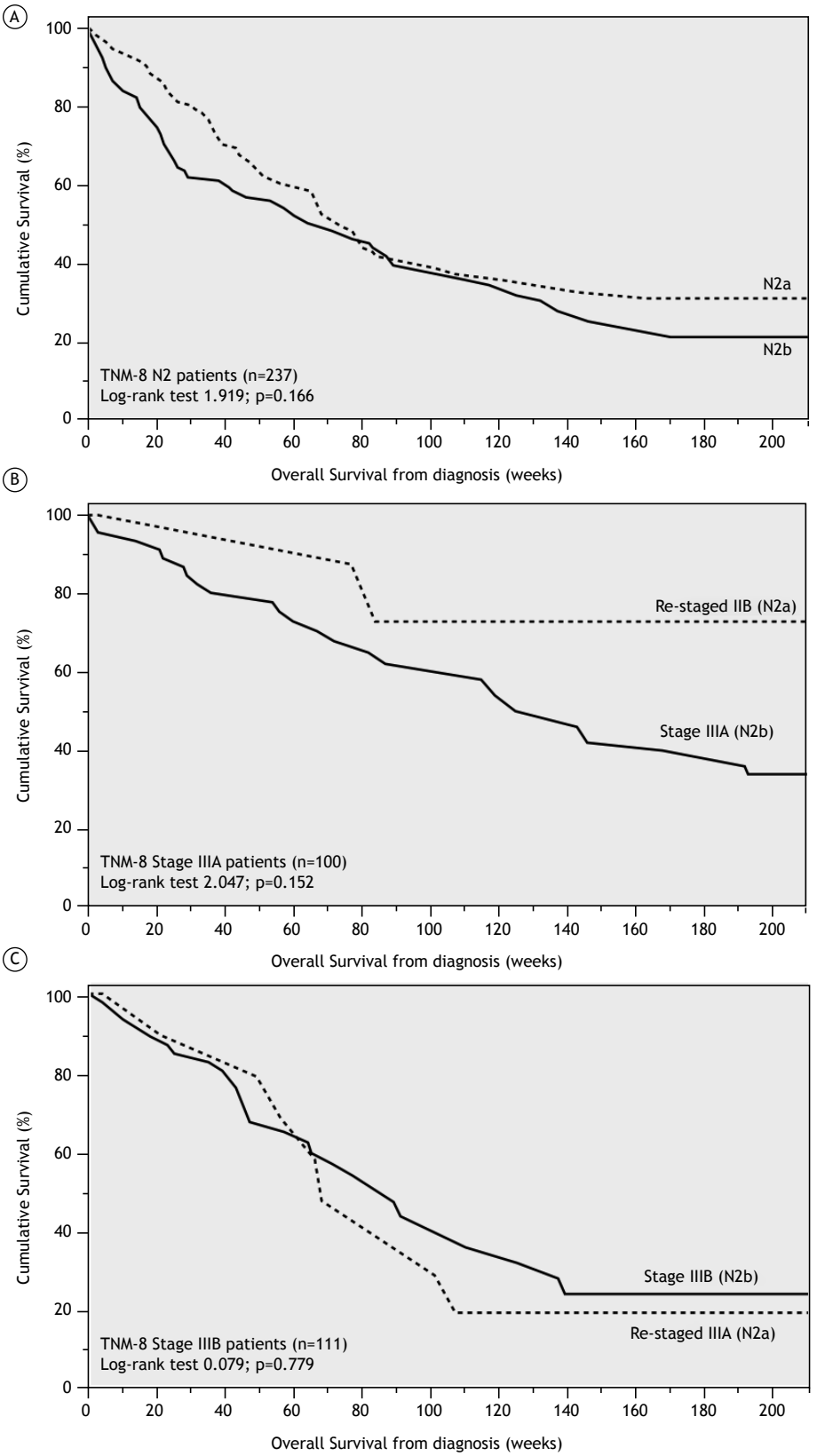

Figure 2. Kaplan-Meier curves showing the cumulative survival based on lymph node involvement after TNM-9 reclassification: overall N2 involvement (A); TNM-8 stage IIIA patients (B); TNM-8 stage IIIB patients (C).

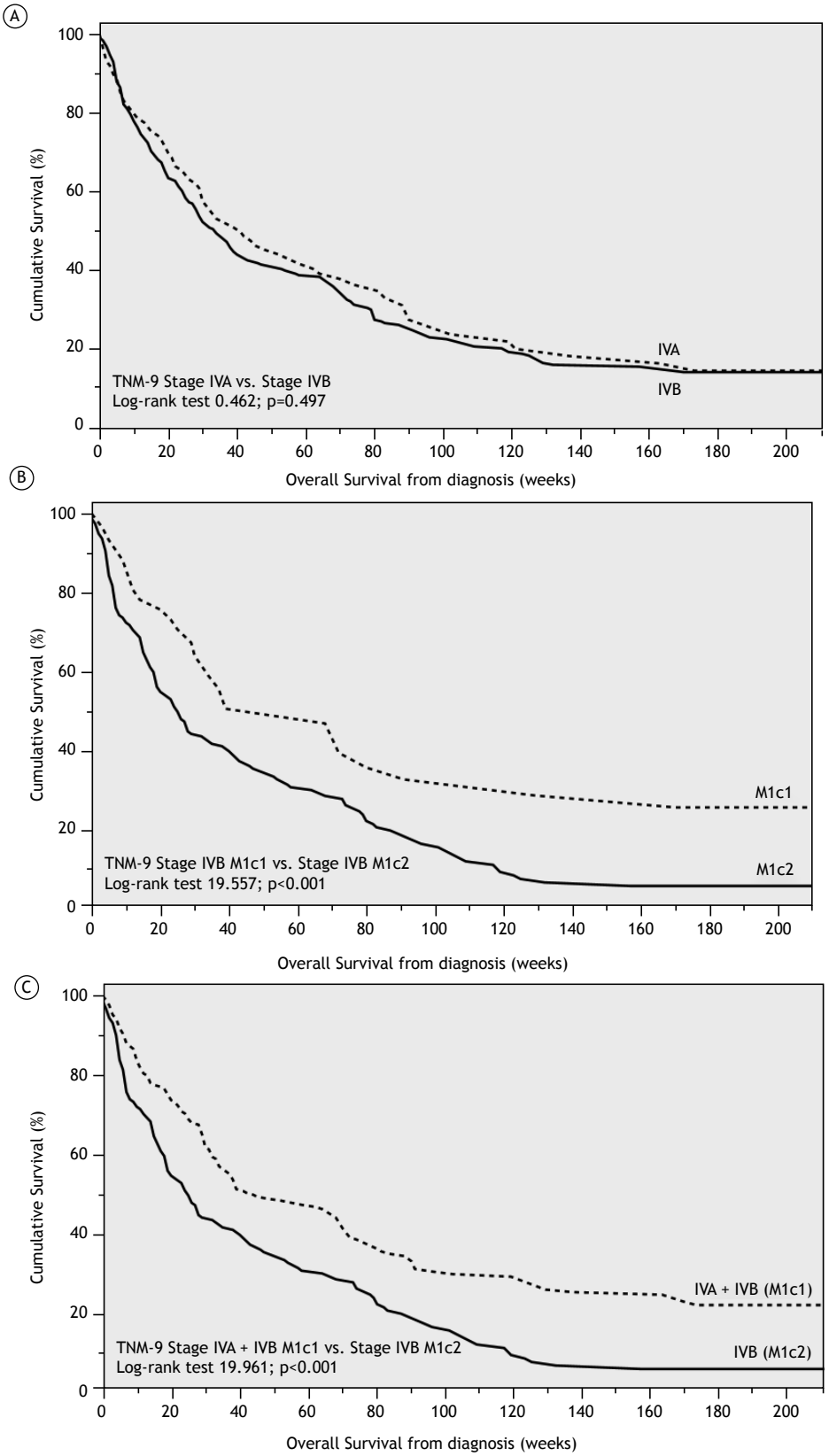

Figure 3. Kaplan-Meier curves showing the cumulative survival of patients with metastatic disease: stage IVA versus IVB (A); stage IVB patients stratified by M1c1 versus. M1c2 (B); M1c2 patients (multiple metastases in >1 organ system) versus all other stage IV patients (C).

Table 3. Adjusted survival analysis of stage IVB lung cancer patients according to the updated TNM-9 classification – univariate and multivariate logistic regression analyses.

	Univariate Analysis		Multivariate Analysis	
	Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Sex (male)	1.18 (0.89-1.58)	0.246	1.29 (0.89-1.85)	0.172
Age at the time of diagnosis	1.02 (1.01-1.04)	<0.001	1.01 (0.99-1.03)	0.071
Smoking (active/former smoker)	1.63 (1.18-2.25)	0.003	1.31 (0.85-2.01)	0.225
ECOG Performance Status (2-4)	2.63 (1.99-3.48)	<0.001	1.81 (1.26-2.60)	0.001
Specific metastatic sites				
Brain metastasis	1.03 (0.78-1.37)	0.818	1.20 (0.85-1.69)	0.291
Pleural metastasis	1.34 (0.96-1.86)	0.085	1.28 (0.88-1.87)	0.202
Bone metastasis	0.87 (0.67-1.13)	0.298	0.99 (0.72-1.38)	0.983
Treatment (Systemic vs. BSC)	0.17 (0.12-0.26)	<0.001	0.35 (0.22-0.58)	<0.001
Multiple metastasis in >1 organ system (M1c2)	1.83 (1.39-2.40)	<0.001	1.43 (1.03-1.97)	0.031

Legend: BSC, Best supportive care; CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, Hazard ratio; TNM-9, Tumor, Node, Metastasis classification for lung cancer (9th edition).

patients—primarily from stage IIIB to IIIA—and the upstaging of 8 patients from IIIA to IIIB. Although downstaged patients showed a trend toward improved OS when compared to those whose stage remained unchanged regardless of the TNM edition, no statistically significant differences in OS were observed following N2 re-stratification. The new TNM-9 subclassification of M1c patients revealed significantly different OS outcomes between single-organ and multi-organ metastatic disease. However, this distinction itself is not yet reflected in final stage grouping, as both M1c1 and M1c2 remain classified as stage IVB.

The rationale behind introducing a new stratification model for nodal disease in TNM-9 stems from previous reports suggesting poorer prognoses associated with either the number of involved lymph nodes[5] or the number of nodal stations affected.[6,7] It is important to note, however, that in the 9th edition database, the prognostic distinction between N2a and N2b was primarily established through imaging techniques (CT, PET-CT) used to determine clinical stage,[8] rather than through invasive procedures such as EBUS. This contrasts with the present study, in which each patients' histopathological record was reviewed and re-staged based on transbronchial needle aspiration (EBUS-TBNA). Lymph node sampling is arguably the most significantly impacted component of staging with the implementation of TNM-9.[9] EBUS remains the most widely adopted method for lymph node staging in lung cancer, and—together with transesophageal endoscopic ultrasound (EUS/EUS-b)—is currently recommended over mediastinoscopy for pathological mediastinal staging.[10,11] Traditionally, EBUS-based staging begins with any N3 station (if present), subsequently proceeding to more proximal lymph node stations (N2, N1). PET-CT and ultrasound features, such as lymph node size, uptake, and vascularity, can help determine which N2 lymph nodes are most likely malignant and should be prioritized for sampling.[12–14] With the introduction of the TNM-9 classification, however, due to the staging implications related to N2a/N2b differentiation, it is now mandatory to sample all ipsilateral mediastinal and subcarinal stations. Moreover, other lymph node stations—including the superior paratracheal (2L and 2R), paraoesophageal,[8] and pulmonary ligament nodes[9]—are expected to become part of routine systematic staging. This expanded approach not only increases overall procedure duration but also raises the cost of lymph node staging. While the principle of sampling N3 stations first and progressing to N2 and N1 remains valid, sampling multiple N2 stations may require changing needles to avoid cross-contamination. In our study, we found no significant difference in OS when stratifying N2 patients with pathological confirmation of single- versus multi-station involvement. Prospective studies will be essential to determine whether the additional effort required for the new nodal stratification ultimately results in meaningful improvements in treatment decision-making and patient outcomes.

In contrast to lymph node staging, the changes introduced by TNM-9 in the assessment of metastatic disease did not alter the overall classification of stage IV patients.[15] Although some authors have suggested that subdividing M1c into M1c1 (multiple extrathoracic metastases within a single organ system) and M1c2 (multiple extrathoracic metastases across multiple organ systems) is relevant for refining prognoses,[4,8] the lack of a distinct final stage classification results in the impact of multi-organ dissemination being diluted within the broader IVB category. Our study indicates a significant difference in clinical outcomes for patients with M1c2 disease, both within the IVB subgroup and compared to all other stage IV patients. This finding is supported by several studies on lung cancer metastasis, which highlight the impact of a higher metastatic burden on overall prognosis.[16,17] Notably, the survival difference between M1c2 and other stage IV patients was greater than that observed between M1a and the rest of the stage IV population, underscoring the importance of identifying this subset for both accurate prognostication and potential treatment stratification. Overall, these findings are consistent with the evolving understanding of oligometastatic disease, a concept first introduced

in 1995.[18] Although no universally accepted definition exists, oligometastatic disease generally refers to a limited number of metastatic lesions in a limited number of organs that may be amenable to curative local therapy.[19] While some debate persists over the false notion that metastatic disease follows bimodal distribution (oligometastatic vs. multi-metastatic) instead of a disease continuum,[20] defining oligometastasis holds clinical relevance in the sense that it may guide the use of different, curative-intent treatment modalities in this specific context.[21,22] Therefore, clearly delineating the prognostic distinction between patients potentially classified as oligometastatic (M1a, M1b, and M1c1) and those unlikely to benefit from more radical treatment approaches (M1c2) becomes increasingly important in the era of patient-tailored medicine.[23] Although the novel TNM-9 classification represents a step forward from TNM-8, it falls short in refining the staging of advanced-stage lung cancer by failing to independently classify M1c2 patients and by not fully addressing the prognostic differences observed in this subgroup.

This study has some limitations. First, it was a retrospective, single-center study, inherently dependent on the quality of available clinical data. Reports of N2 lymph node involvement relied on procedures performed before the implementation of the novel staging recommendations. Reclassification into N2a/N2b was based on histopathological confirmation of multi-nodal disease via EBUS-TBNA; however, these procedures may not have adhered to the revised systematic assessment of all relevant lymph node stations. Additionally, since this is not yet standard practice, TBNA needles were likely not changed between N2 stations, introducing the potential for cross-contamination. Although our dataset is smaller than those used by the IASLC, it represents a substantial real-word sample. This difference may explain the lack of statistical significance observed following N2a/N2b reclassification, as only 42 patients were affected by the updated criteria. Nevertheless, with regard to advanced-stage disease in particular, we believe our data are robust enough to support a discussion about the lack of practical distinction between other stage IVB patients and those reclassified as M1c2—who may be more appropriately staged as IVC. Future prospective studies should focus on assessing the clinical impact of the novel N2 classification and establishing prognostic thresholds for M1c2 patients to determine whether they should be staged separately.

In conclusion, the updated TNM-9 staging guidelines introduce significant changes to both the lymph node involvement and metastatic disease components of the previous edition, enhancing prognostic accuracy for patients with lung cancer. Although M1c2 patients—those with multiple extrathoracic metastases involving multiple organ systems—are not classified separately within stage IV disease, they exhibited significantly poorer OS rates compared to other advanced-stage patients. This finding highlights the need for future discussions on prognostic stratification and treatment strategies within the context of disseminated disease.

AUTHOR CONTRIBUTIONS

Writing – review & editing: PMF, CS, DA, and MGF; Writing – original draft: PMF; Validation: PMF, DA, and MGF; Visualization: RC, CV, JF, CS, CF, DA, HNB, AM, and MGF; Resources: PMF; Project administration: PMF and MGF; Methodology: PMF, CS, DA, and MGF; Conceptualization: PMF, CV, JF, CS, CF, DA, HNB, AM, and MGF; Investigation and Formal analysis: PMF; Data curation: PMF, RC, CV, JF, and CS; Supervision: CS, DA, and MGF.

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Burden of respiratory syncytial virus in older adults in Brazil: insights from national surveillance data for the 2022-2023 period

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ABSTRACT

Objective: Respiratory syncytial virus (RSV) is a major cause of severe respiratory infections in older adults, particularly those with comorbidities. Despite its clinical impact, RSV remains underdiagnosed and underreported. We sought to assess the burden of RSV in older adults (≥ 60 years of age) in Brazil using national surveillance data for the 2022-2023 period. **Methods:** We analyzed RSV cases reported in the *Sistema de Informação de Vigilância Epidemiológica*, identifying them among reported cases of SARS. Cases were examined by demographic characteristics, seasonal trends, and clinical outcomes. RSV cases were compared across defined etiologies. **Results:** Among 355,230 reported cases of SARS in older adults, 201,965 (56.8%) had a defined etiology, and 1,465 (0.7%) were confirmed as RSV cases. Cases peaked in the second quarter of each year, with the highest incidence in the southern and southeastern regions. Despite a low hospitalization rate (2.3 per 100,000 population), severe outcomes were common: 30.4% required ICU admission, and 24.9% resulted in death, with mortality being highest in those ≥ 90 years of age. **Conclusions:** RSV-related hospitalizations in Brazil appear underestimated, with reported cases likely representing the most severe spectrum due to underreporting and diagnostic limitations. Seasonal patterns peaked in April-May, and regional differences highlight a higher incidence in the southern and southeastern regions, likely due to epidemiological factors and diagnostic disparities. Although the recent approval of RSV vaccines offers an opportunity to reduce disease burden, successful implementation requires broader access and inclusion in the Brazilian National Immunization Program. Strengthening surveillance, diagnostic capacity, and reporting processes is critical for better disease assessment and public health planning.

Keywords: Respiratory syncytial virus infections; Severe acute respiratory syndrome; Hospitalization; Epidemiology; Aged; Surveillance.

INTRODUCTION

Respiratory syncytial virus (RSV) is a major cause of respiratory infections in older adults (≥ 60 years of age), particularly those with preexisting health conditions such as cardiopulmonary disease, immunosuppression, and frailty.[1] Individuals with chronic conditions such as COPD, heart failure, and diabetes are at an increased risk of severe outcomes.[2,3] Immunocompromised individuals, including those undergoing solid organ transplantation and receiving immunosuppressive therapy, are also highly susceptible.[4] Older adults may contract RSV through close contact with children in their households or exposure in long-term care facilities and health care settings.[5]

Severe RSV infections in older adults often lead to complications such as pneumonia and exacerbations of underlying conditions, resulting in increased hospitalizations and mortality.[6,7] Studies have shown that RSV is a significant contributor to respiratory hospitalizations in this age group, second only to influenza among viral causes of cardiopulmonary admissions. Despite its impact, RSV remains underdiagnosed and underreported in older adults due to the nonspecific nature of symptoms, limited awareness among health care providers, and challenges in diagnostic testing availability and utilization.[7-10] In many cases, RSV infections may be misattributed to other respiratory pathogens, such as influenza or bacterial infections, further complicating public health assessments.

In developed countries, RSV incidence rates in older adults have been estimated at approximately 600 cases per 100,000 person-years, with hospitalization rates reaching 157 per 100,000 person-years.[7,11,12] In Latin America, systematic reviews have shown that older adults, particularly those > 65 years of age, face a high incidence of severe RSV-related outcomes, including ICU admissions and increased lethality.[13] RSV is also a significant cause of respiratory infections in this population, contributing to hospitalizations for influenza-like illness and pneumonia.[14] Despite these findings, data gaps persist, highlighting the need for further research to guide prevention and management strategies.[15]

In Brazil, RSV vaccines have recently been approved for older adults and pregnant women, representing an important step toward protecting these vulnerable

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populations. Additionally, vaccinating pregnant women and eventually infants may provide indirect protection for older adults by reducing virus circulation within the community. However, because these vaccines have yet to be incorporated into the Brazilian *Programa Nacional de Imunização* (PNI, National Immunization Program), access is still limited for those at an increased risk. Nevertheless, passive immunization with monoclonal antibodies has been incorporated into the PNI for certain high-risk pediatric populations, and additional antibody therapies are currently being developed and are expected to be available in Brazil soon.

The objective of the present study was to provide a comprehensive description of the burden of RSV among older adults (≥ 60 years of age) in Brazil, using data from the *Sistema de Informação de Vigilância Epidemiológica* (SIVEP, Information System for Epidemiological Surveillance) for the 2022-2023 period (i.e., the post-COVID-19 period). Our analysis focused on demographic and seasonal patterns, as well as the proportion of RSV cases among reported cases of SARS and those with confirmed etiology.

METHODS

Data source

The SIVEP was implemented in 2000 as a sentinel surveillance system for flu-like syndromes. During the 2009 influenza A (H1N1) pandemic, the SIVEP was expanded to include SARS cases, the reporting of which became mandatory nationwide.[16] In 2020, the SIVEP was further modified to include COVID-19 cases. All hospitalized SARS cases and related deaths must be reported within 24 h by all registered health care facilities, regardless of hospitalization status.

The definition of flu-like syndrome requires at least two symptoms, such as fever, chills, sore throat, headache, cough, and loss of taste/smell. Severe cases, classified as SARS cases, involve respiratory distress, persistent chest pain, oxygen saturation below 95%, or cyanosis. Hospitalized flu-like cases that do not meet the criteria for SARS must be reported in the Brazilian Unified Health Care System reporting system *e-SUS Notifica* instead. All public and private health care facilities must report SARS cases, and epidemiological surveillance personnel at each facility are responsible for completing reporting forms in accordance with Brazilian National Ministry of Health guidelines.[17,18]

The SIVEP database is publicly available on the Brazilian Unified Health Care System Information Technology Department website, ensuring patient confidentiality as it contains no identifying information. Therefore, in accordance with Brazilian regulations, ethical approval was not required for the present study.

Case definitions

The classification of SARS cases in the dataset was based on the CLASSI_FIN variable, which includes five distinct categories: (1) "SARS by influenza," (2) "SARS by another respiratory virus," (3) "SARS by another specified agent," (4) "SARS unspecified," and (5) "SARS by COVID-19." COVID-19 cases were identified by using the classification "SARS by COVID-19," whereas influenza cases were defined by the classification "SARS by influenza." RSV cases were identified within the "SARS by another respiratory virus" category and required additional confirmation through a positive result in either the rapid antigen test (AN_VSR) or the PCR test (PCR_VSR) variables. Cases classified as "SARS by another respiratory virus" but without a confirmed RSV test result, along with those classified as "SARS by another specified agent," were categorized under "Other defined etiology." Finally, cases classified as "SARS unspecified" were grouped under the category of "Other undefined etiology."

All reported cases were considered to be SARS cases following the surveillance definition. We also analyzed a subdivision of SARS cases with a defined etiology, which included all categories except "Other undefined etiology."

Analysis

Cases were analyzed by sex, age group (60-69, 70-79, 80-89, and ≥ 90 years), hospitalization status (hospitalized vs. non-hospitalized), ICU admission (ICU vs. non-ICU), Brazilian macroregion (central-west, northeastern, northern, southeastern, and southern), year, quarter, and risk factors. The database considered individual conditions such as chronic cardiovascular, hematologic, liver, neurological, pulmonary, and kidney diseases; Down syndrome; asthma; diabetes mellitus; immunodeficiency/immunosuppression; obesity; and other specified conditions. Cases were also classified by treatment in public or private facilities by using the Brazilian National Registry of Health Care Facilities, which compiles data on health care facilities in Brazil and was deterministically linked to the SIVEP for this analysis. Results were presented in frequency tables and graphs to highlight temporal and demographic trends.

Reporting rates were calculated by year, sex, age group, and region by using 2022 Brazilian Institute of Geography and Statistics population estimates and were expressed per 100,000 population. Two RSV case proportions were determined: RSV-positive cases among all SARS reports and RSV-positive cases among SARS cases with a defined etiology. These proportions were further stratified by all analyzed variables. Differences were assessed by chi-square tests.

Data management, analysis, and deterministic linkage were conducted with Stata software, version 17 (StataCorp LLC, College Station, TX, USA).

RESULTS

During the study period, 835,234 SARS cases were reported across all age groups, of which 401,107

(48.0%) had a defined etiology and 44,731 (11.2%) were confirmed as RSV cases. Among older adults (≥ 60 years of age), 355,230 cases accounted for 42.5% of the total number of SARS cases, with 201,965 (56.8%) having a defined etiology and 1,465 (0.7%) being confirmed as RSV cases.

Table 1 shows that COVID-19 accounted for the largest proportion of SARS cases (52.4%), with the highest proportion in the first quarter of 2022 (63.1%) and the lowest in the second quarter of 2023 (25.2%). RSV represented 0.4% of all cases, peaking at 1.5% in the second quarter of 2023 and reaching its lowest proportion of 0.1% in the fourth quarters of both years. Influenza contributed to 2.4% of SARS cases, with notable peaks in the first quarter of 2022 (2.7%) and the second quarter of 2023 (9.3%). Other defined etiologies accounted for 6.3% of cases, with the highest proportion observed in the third quarter of 2023 (9.5%). Cases with undefined etiologies made up 38.5% of the total, varying from 29.2% in the first quarter of 2022 to 60.9% in the third quarter of 2023.

Figure 1 illustrates the seasonal distribution of all reported cases of SARS among older adults, including those with a defined etiology. Throughout the study period, the trend of SARS cases with a defined etiology closely mirrors that of total SARS cases, running almost parallel and indicating that a substantial proportion of reported cases had a confirmed cause. The prominent peak observed in early 2022 corresponds to the end of the third COVID-19 wave in Brazil.

Figure 2 illustrates the seasonal distribution of laboratory-confirmed RSV cases reported among older adults (≥ 60 years of age) across the five regions of Brazil, showing peaks generally occurring around April and May, with some regional variations. The overall number of RSV cases is considerably lower in comparison with the total number of SARS cases shown in Figure 1, highlighting the contribution of various respiratory pathogens to the burden of severe infections in this population. The southeastern region of Brazil consistently reported the highest number of cases, followed by the southern region, whereas the northern region recorded the lowest numbers. These regional differences may be influenced by variations in laboratory capacity and reporting practices.

Table 2 presents the distribution of confirmed RSV cases stratified by various demographic and clinical characteristics. Of the 1,465 reported cases, a higher proportion occurred in 2022 (56.5%) in comparison with 2023 (43.5%). The proportion of cases among total SARS cases and cases with a defined etiology was higher in 2023 than in 2022. Women accounted for a larger share of cases (59.7%) than did men (40.3%). The highest proportion of cases occurred among those in the 70- to 79-year age bracket (33.6%). Rates increased with age. Hospitalization was common, with 96.1% of reported cases requiring hospital admission and 30.4% requiring intensive care. Mortality was 24.9%, increasing with age: 15.7% among individuals in the 60- to 69-year age bracket; 24.6% among those in the 70- to 79-year age bracket; 30.3% among those in the 80- to 89-year age bracket; and 43.6% among those ≥ 90 years of age. Most cases (82.5%) had underlying risk factors. Seasonal distribution shows that the majority of cases occurred in the second quarter of each year, with the highest proportion consistently in this period and the lowest in the fourth quarter. Regarding geographic distribution, the southern and southeastern regions accounted for the highest shares, followed by the central-west and northern regions. The highest rate was observed in the southern region, followed by the central-west and northern regions. RSV cases were nearly evenly distributed between public (46.6%) and private (53.4%) health care facilities. The values of p indicate that most comparisons were statistically significant, with the majority below 0.001 and some above this threshold but still significant at $p < 0.05$. However, age group ($p = 0.085$ for RSV+/SARS) and health care sector distribution ($p = 0.763$ for RSV+/SARS) did not reach statistical significance, whereas

Table 1. Quarterly distribution of SARS cases among older adults (≥ 60 years of age) in Brazil for the 2022-2023 period, by etiology.[a]

Etiology	2022				2023				Total
	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Quarter 1	Quarter 2	Quarter 3	Quarter 4	
COVID-19	81,313 (63.1)	29,884 (51.3)	19,613 (47.4)	24,775 (59.4)	10,948 (44.1)	6,002 (25.2)	4,735 (27.4)	8,938 (46.6)	186,208 (52.4)
RSV	263 (0.2)	468 (0.8)	53 (0.1)	43 (0.1)	146 (0.6)	361 (1.5)	109 (0.6)	22 (0.1)	1,465 (0.4)
Influenza	3,461 (2.7)	725 (1.2)	590 (1.4)	593 (1.4)	436 (1.8)	2,221 (9.3)	276 (1.6)	141 (0.7)	8,443 (2.4)
Other defined	6,130 (4.8)	3,571 (6.1)	2,798 (6.8)	3,193 (7.7)	1,654 (6.7)	1,885 (7.9)	1,641 (9.5)	1,487 (7.8)	22,359 (6.3)
Other undefined	37,600 (29.2)	23,613 (40.5)	18,327 (44.3)	13,122 (31.4)	11,628 (46.9)	13,384 (56.1)	10,509 (60.9)	8,572 (44.7)	136,755 (38.5)
Total	128,767 (100.0)	58,261 (100.0)	41,381 (100.0)	41,726 (100.0)	24,812 (100.0)	23,853 (100.0)	17,270 (100.0)	19,160 (100.0)	355,230 (100.0)

RSV: respiratory syncytial virus. [a]Values expressed as n(%).

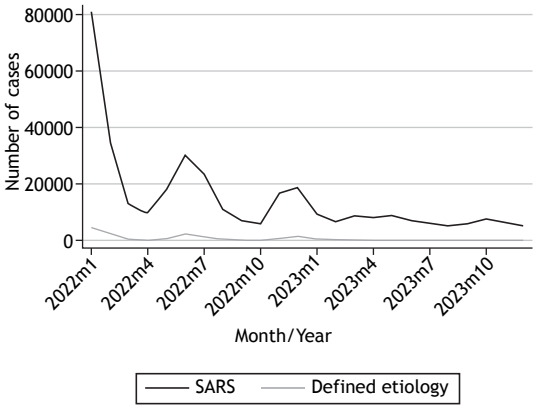

Figure 1. Seasonal distribution of all reported cases of SARS and those with defined etiology among older adults (≥ 60 years of age) in Brazil for the 2022-2023 period.

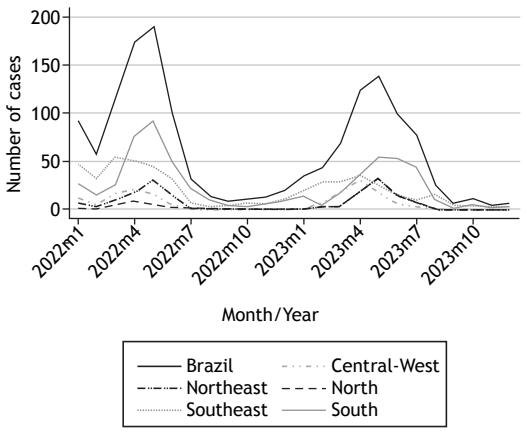

Figure 2. Seasonal distribution of laboratory-confirmed respiratory syncytial virus cases among older adults (≥ 60 years of age) across the five regions of Brazil for the 2022-2023 period.

health care sector distribution ($p = 0.002$ for RSV+/Defined etiology) remained significant at $p < 0.05$.

DISCUSSION

The present study analyzed the burden of RSV in older adults (≥ 60 years of age) in post-COVID-19 Brazil on the basis of national surveillance data for the 2022-2023 period. Our findings show a low hospitalization incidence (2.3 per 100,000 population), a low RSV proportion among SARS cases (0.41%), and high rates of underlying conditions, ICU admissions, and mortality. Nearly one third of hospitalized cases required intensive care, and approximately 25% died. These results highlight the need for targeted prevention and management, considering potential underreporting of milder cases.

During the COVID-19 pandemic, Brazil expanded PCR testing to SARS-CoV-2, with mass testing in some areas and coverage by health insurance plans.[19] However, access to other viral PCR tests varies by resource availability and regional policy.[20,21] Public health care facilities offer these tests free of charge, whereas private facilities may charge for them, limiting access for uninsured individuals and even some insured, depending on the coverage. Although PCR testing for COVID-19 for those who have private health insurance is mandated by the Brazilian National Health Insurance Agency, coverage of other molecular tests depends on individual plan conditions and regulations.

The reporting of SARS cases is compulsory in Brazil, and individuals hospitalized for acute lower respiratory infection are most commonly classified as being SARS cases.[18] Non-hospitalized cases resulting in death and cases of patients treated exclusively in emergency rooms—often for extended periods while awaiting hospital beds—must also be reported to the SIVEP. Patients testing negative or untested should still be reported under SARS criteria. Assessing potential bias toward more severe cases in the SIVEP is crucial. Our findings suggest that such a bias occurred, as shown by our research team in a study that is currently under review and that linked SIVEP records with 2022-2023 Brazilian Unified Health Care System Hospital Information System records. Notably, 85% of ICD-10-coded RSV records in the Hospital Information System had not been reported in the SIVEP, despite the fact that reporting is mandatory. These results indicate significant underreporting in Brazil, with reported cases likely representing the most severe spectrum. This bias likely explains the low hospitalization incidence, low RSV proportion among SARS cases, and high ICU admission and mortality rates observed in our study.

This context suggests that access to diagnostic tests plays a major role in observed differences in RSV incidence. While the incidence rate of RSV hospitalizations in our study was low at 2.3 per 100,000 population—comparable to low-resource settings and significantly lower than the 190-254 per 100,000 population reported in the USA—this disparity may be at least partially influenced by differences in health care access, alongside possible true epidemiological variations.[22,23] The proportion of RSV cases among the total number of SARS cases was also low (0.41%), with a slight increase from 0.31% in 2022 to 0.75% in 2023. A meta-analysis found that among all patients with acute respiratory infection, RSV accounted for 1-10% in adults and 2-14% in patients with chronic diseases or transplant recipients, most of whom were hospitalized.[23] Although testing capacity improved during the COVID-19 pandemic, timely access to specific tests in both public and private health care settings remains a critical factor in surveillance and disease burden assessment.

Underreporting and underascertainment of RSV cases are well-documented challenges in surveillance systems. Studies indicate that RSV hospitalization rates are often underestimated because of limited diagnostic testing and reporting. In a systematic review and modeling study adjusted for diagnostic underascertainment, hospitalization rates among older

Table 2. Distribution and rates of confirmed respiratory syncytial virus cases among older adults (≥ 60 years of age) in Brazil for the 2022-2023 period, by demographic and clinical characteristics.

Category	N	Category/RSV+, %	Rate per 100,000	% RSV+/SARS	% RSV+/Defined etiology
Total	1,465		2.3	0.41	0.67
2022	827	56.5	2.6	0.31	0.5
2023	638	43.5	1.9	0.75	1.71
Female	874	59.7	2.4	0.47	0.85
Male	591	40.3	2.1	0.35	0.59
60-69 years	401	27.4	1.1	0.44	0.84
70-79 years	492	33.6	2.5	0.43	0.78
80-89 years	416	28.4	5.5	0.39	0.65
≥ 90 years	156	10.7	11.3	0.37	0.59
Quarter 1 (q1)	409	27.9		0.27	0.42
Quarter 2 (q2)	829	56.6		1.01	2.00
Quarter 3 (q3)	161	11.1		0.28	0.6
Quarter 4 (q4)	65	4.4		0.11	0.18
q1_2022	263	31.8		0.2	0.31
q2_2022	468	56.6		0.8	1.46
q3_2022	53	6.4		0.13	0.25
q4_2022	43	5.2		0.1	0.17
q1_2023	146	22.9		0.59	1.22
q2_2023	361	56.6		1.51	3.81
q3_2023	109	17.1		0.63	1.76
q4_2023	22	3.4		0.11	0.23
Central-West	156	10.9	3.6	0.58	0.90
Northeast	166	11.3	1.0	0.29	0.58
North	64	4.4	1.8	0.47	0.84
Southeast	491	33.5	1.6	0.27	0.46
South	585	39.9	5.5	0.80	1.43
Hospital	1,408	96.1		0.42	0.73
Non-hospital	39	2.7		0.53	0.92
Unknown	18	1.2		0.18	0.46
ICU	446	30.4		0.42	0.69
Non-ICU	890	60.8		0.46	0.79
Unknown/Non-hospital	129	8.8		0.24	0.52
Dead	364	24.9		0.35	0.54
Alive	1,101	75.1		0.44	0.82
Risk factor +	1,208	82.5		0.45	0.76
Risk factor –	257	17.5		0.30	0.59
Public facility	682	46.6		0.42	0.73
Private facility	783	53.4		0.41	0.62

RSV: respiratory syncytial virus.

adults were shown to be approximately 2.2 times higher than previously reported.[7] This underascertainment may be especially pronounced for RSV in older adults, given that RSV is still widely perceived as a disease that primarily affects children. As a result, clinical suspicion for RSV in elderly patients tends to be low, and diagnostic testing is often not pursued by physicians or geriatricians.[24] While other respiratory infections such as influenza and COVID-19 are also subject to underreporting and data limitations, RSV in older adults is particularly affected by diagnostic neglect, contributing to a more significant severity bias in reported cases. The implications of severity bias in reported cases, particularly in older adults, are further explored later in the discussion. These findings highlight the need to enhance surveillance strategies to capture the true burden of RSV and inform public health interventions.

Despite a decline in reported SARS cases from 2022 to 2023, the proportion of RSV-positive cases among those with a defined etiology increased. This decline likely reflects the absence of a significant COVID-19 wave in 2023, whereas higher numbers in 2022 correspond to the end of the Omicron wave.[25] Notably, the first RSV peak coincided with a peak in

total SARS cases, suggesting RSV contributed modestly to the overall SARS burden.

The seasonal peaks of RSV cases in April and May coincide with autumn in Brazil. This pattern aligns with findings from other regions, where RSV tends to peak earlier than influenza, often in late autumn or early winter.[26,27] In 2022, the first year of the study, the RSV peak was followed by a SARS peak in June, suggesting a slightly earlier RSV season in comparison with other respiratory viruses. However, this pattern was not observed in 2023. Regional variations in peak timing could also be influenced by climate differences, such as rainfall patterns. While RSV seasonality in southern Brazil generally coincides with colder months, in central and northern regions it aligns more closely with the rainy season.[28,29] Although some variation in peak timing was observed across regions, the overall seasonal pattern remains relatively similar. Additionally, differences in health care access, health care-seeking behavior, diagnostic capacity, and reporting practices across regions may further contribute to these variations.

Geographic analysis showed the highest RSV case numbers and incidence rates in the southern and southeastern regions of Brazil, where colder temperatures may increase transmission. These regions also have better health care infrastructure and laboratory capacity, with detection and reporting therefore being better.[30] However, pronounced seasonality suggests that the higher incidence reflects true epidemiological patterns rather than differences in health care access. Lower detection in the northern and northeastern regions may result from underdiagnosis and a genuinely lower incidence.

Clinically, a significant proportion of RSV cases required hospitalization, with nearly one third requiring intensive care and approximately 25% resulting in death. In developed countries, in-hospital case-fatality rates for older adults with RSV range from 1.6% to 7.1%,[7,8,31] although a systematic review reported an in-hospital case-fatality rate of 11.0% in adults with comorbidities.[3] Despite the high comorbidity prevalence in our study, the nearly 25% fatality rate is markedly higher, suggesting disparities in health care access, disease severity, or population characteristics. This discrepancy likely reflects reporting bias, with more severe cases being captured in the surveillance system.

Older adults in the 70- to 79-year age bracket accounted for the largest share of RSV cases, whereas those ≥ 90 years of age had the highest incidence and mortality rates, reflecting their greater vulnerability. This aligns with global findings that advanced age is a key risk factor for severe RSV.[12,22] Women made up a higher proportion of cases, although no clear sex-based difference in RSV incidence is established. This disparity may stem from health care utilization patterns or underlying conditions, warranting further study. Most cases involved individuals with comorbidities, reinforcing the need for targeted interventions in high-risk populations.[23,32]

The recent approval of RSV vaccines for older adults in Brazil marks a key step in reducing disease burden in this high-risk group. These vaccines provide direct protection and may lower transmission when combined with maternal and infant vaccination programs. However, their impact depends on broad accessibility and inclusion in the PNI, which is still pending. Equitable access through public health programs is crucial, especially for vulnerable populations. As seen in other countries, robust surveillance and ongoing epidemiological assessments are essential to guide vaccination policies, optimize coverage, and evaluate real-world effectiveness. Strengthening these efforts will help reduce RSV-related morbidity and mortality in older adults.

This study highlights the burden of RSV among older adults in Brazil, revealing key seasonal, demographic, and regional patterns. Findings reinforce the significant impact of RSV and the urgent need for targeted interventions and improved surveillance. Regional and seasonal variations emphasize tailoring prevention strategies and resource allocation to local epidemiology. Addressing diagnostic gaps and improving reporting processes are critical for accurate disease assessment. Integrating RSV vaccines into national immunization strategies could significantly reduce morbidity and mortality. Continued monitoring and research are essential for evidence-based public health policies that effectively meet the needs of older adults in Brazil.

AUTHOR CONTRIBUTIONS

ALB contributed to conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft, visualization, project administration, and funding acquisition. OTR was responsible for writing—review and editing, and supervision.

CONFLICTS OF INTEREST

The opinions expressed in this paper are those of the authors and do not necessarily represent those of Merck Sharp & Dohme LLC.

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Assessment of body composition as a predictor of disease severity in patients with COVID-19

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ABSTRACT

Objective: This study sought to estimate body composition values by disease severity in patients recovered from COVID-19. **Methods:** This was an observational, analytical, prospective cross-sectional study involving patients recovered from COVID-19 and employing the following assessment methods: bioelectrical impedance analysis, dual-energy X-ray absorptiometry, and air displacement plethysmography. **Results:** A total of 210 volunteers were included. Demographic characteristics, comorbidities, and body composition values highlighted significant differences between men and women across disease severity levels. **Conclusions:** Sex differences influence the severity of COVID-19. Our results provide a cross-sectional analysis of the impact of body composition on COVID-19 patients, showing risk factors and parameters that can contribute to the treatment, health recovery, and quality of life of this population.

Keywords: COVID-19; Body composition; Risk factors; Quality of life.

INTRODUCTION

Patients who have recovered from COVID-19 continue to suffer from sequelae and treatments that impact their quality of life and health restoration.[1] Anthropometric characteristics play a role in the severity of disease in COVID-19 patients. Obesity has been identified as a characteristic feature of the disease,[2] whereas the musculoskeletal system plays a protective role in regulating the immune system.[3] In these two aspects, the influence of body composition on the severity of COVID-19 has yet to be better understood, leaving knowledge gaps regarding prevention and treatment strategies for COVID-19.

COVID-19 is a severe acute respiratory syndrome caused by SARS-CoV-2.[4] It is an infection that affects the immune system through the pulmonary airways,[5] leading to a rapid systemic viral spread affecting the respiratory, cardiovascular, and nervous systems.[6,7] The symptoms of COVID-19 can range from mild to critical,[4] often requiring ICU admission, with high mortality rates[8] and sequelae, including changes in body composition.[9]

Body composition analysis has been shown to be relatively accurate[10] when employed in health assessment and in identifying risk factors in a clinical setting.[11] Fat mass and fat-free mass are well-established markers in the literature.[12] Although the use of various integrated devices involving different methods and procedures presents challenges,[13,14] they were rigorously controlled across all evaluation procedures in the present study.

The primary objective of the present study was to estimate body composition values by disease severity in patients recovered from COVID-19. Secondary objectives included a comparison of body composition assessments, including bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), and air displacement plethysmography (ADP).

METHODS

The present study was approved by the Research Ethics Committee of the *Universidade Estadual de Campinas*, located in the city of Campinas, Brazil (Protocol no. CAAE 36305120.0.0000.5404). This was an observational, analytical, prospective cross-sectional study examining

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the relationship between COVID-19 severity and body composition measurements. The study sample consisted of patients recovered from COVID-19 and selected from various sources, including hospital records, health centers, local authorities, and personal referrals. The time elapsed between SARS-CoV-2 infection (confirmed by RT-PCR) or hospitalization and body composition assessment ranged from 90 days to 12 months. Inclusion criteria were as follows: having a positive laboratory or clinical test for COVID-19; being > 18 years of age; and having no preexisting chronic diseases.

Patients were instructed to wear light clothing, with no metals or objects that could interfere with the assessments. They were also instructed as to what they were allowed to eat before the assessments. Access to the testing environment was restricted to authorized personnel. The testing environment comprised a waiting room, an individual screening room, and adequately equipped assessment rooms. The temperature was maintained at 21°C, being constantly monitored with digital and mercury thermometers, with an atmospheric pressure of 937 hPa.[15] All patients underwent an initial screening, in which physiological markers were measured. Clinical history taking included colds, fever, blood pressure changes, and frailty, as well as questions regarding the decision to withdraw from the study. All participating patients gave written informed consent.

Body composition assessments included the following: body weight (in kg), measured to the nearest 0.1 kg with a digital scale (PL-200; Filizola S.A., São Paulo, Brazil)[16]; height (in cm), measured to the nearest 0.1 cm with a wall-mounted stadiometer (Holtain Ltd, Crosswell, UK)[17]; BIA with a 450 bioimpedance analyzer (Biodynamics Corporation, Seattle, WA, USA)[19,20]; DXA with a Lunar iDXA device (GE Healthcare Technologies, Inc., Chicago, IL, USA)[21]; and ADP with a Bod Pod GS body composition tracking system (COSMED srl, Rome, Italy).[22] Upon completing the assessments, all participating patients had a debriefing interview with the principal investigator and received a participation certificate showing the main results of the study.

Body composition assessment utilized nine variables of interest as independent predictors: BMI; resting metabolic rate (RMR), in kcal/day; body volume (BV), in L; body density (BD); body surface area (BSA), in cm^2; total body fat (TBF), in kg; fat-free mass (FFM), in kg; relative skeletal muscle index (RSMI); and visceral fat mass (VFM), in kg. The dependent variable was disease severity (nonsevere, severe, or critical), in accordance with the 2020 WHO criteria.[23] Study biases were addressed by taking into consideration age, self-reported physical activity level,[24,25] comorbidities, and other factors identified during the initial screening.

Patient data records on the devices included sex, age, body mass, height, self-reported ethnicity, and physical activity level as references for body composition calculations, as well as data cross-referencing between devices. Bioimpedance measures, body imaging measures, and air displacement measures formed both device-specific equations and combined equations.

The results of the assessments were recorded in a Microsoft Excel spreadsheet or Windows Notepad file and then transferred to the IBM SPSS Statistics software package, version 25.0 (IBM Corporation, Armonk, NY, USA). Descriptive analyses verified data dispersion and normality. Categorical variables determined the distribution among groups, and continuous variables were analyzed through comparisons. Measures with statistically significant values ($p < 0.05$) were further analyzed for explanatory analysis between groups.

RESULTS

A total of 210 volunteers were included in the present study. Corrected post hoc tests found an effect size of $f^2 = 0.28$ and a power $1-\beta = 0.80$ ($\alpha = 0.05$), calculated using G*Power software, version 3.1.9.7 (Institute for Experimental Psychology, Dusseldorf, Germany). Of the 210 study participants, 110 (52.4%) were women. Of the 89 patients who had had nonsevere COVID-19, 60 (67.4%) were women. Of the 67 patients who had had critical COVID-19, 44 (65.7%) were men. Of the 54 patients who had had severe COVID-19, 27 (50%) were women and 27 (50%) were men.

Categorical tests found differences in COVID-19 severity only for the sex variable [$X^2(2) = 16.942$; $p < 0.001$]. Among men and women, differences were observed between those with nonsevere disease and those with critical disease (−3.7 vs. 3.6 and 3.7 vs. −3.6, respectively).

Comparative tests between sexes by disease severity level showed significant differences ($p < 0.05$), the exception being VFM. To avoid type II errors, all variables were considered separately by sex. Continuous variables demonstrated normality for both sexes, as assessed by the Shapiro-Wilk test. Among men, significant results were found for body weight, BMI, RMR, BSA, TBF, FFM, and VFM ($p < 0.001$), as well as for RSMI ($p = 0.001$). Among women, significant results were found for body weight ($p = 0.001$), BMI ($p = 0.005$), RMR ($p = 0.010$), BSA ($p = 0.025$), TBF ($p = 0.012$), FFM ($p = 0.006$), and VFM ($p = 0.008$). Dispersion values for men are shown in Table 1. Dispersion values for women are shown in Table 2. The time elapsed between COVID-19 diagnosis and body composition assessment was adjusted to prevent it from acting as a confounding factor. After the adjustment, the Kruskal-Wallis test was performed, and no significant differences were observed.

Anthropometric comparisons distinguished men from women among severity groups. Men had lower RSMI, whereas women had normal RSMI. The mean age was 69.4 ± 4.1 years for men and 69.3 ± 2.9 years for women. In the group of patients with nonsevere

Table 1. Measures of dispersion for male patients recovering from COVID-19, by disease severity.

Parameter	Nonsevere COVID-19		Severe COVID-19		Critical COVID-19		Men		
	N	mean ± SD*/ median (IQR)**	N	mean ± SD*/ median (IQR)**	N	mean ± SD*/ median (IQR)**	Nonsevere vs. severe	Nonsevere vs. critical	Severe vs. critical
Age, years*	29	48.4 ± 12.2	27	53.8 ± 12.6	44	50.3 ± 9.6			
Body weight, kg**	29	81.6 (18.7)	27	82.9 (33.9)	44	94.6 (23.5)	0.872	0.014	0.326
Height, cm*	29	176.2 ± 6.2	27	172.9 ± 8.8	44	174.9 ± 7.5			
PCR-days**	29	246 (309)	27	173 (225)	44	332 (332)			
BMI**	29	26.9 (5.0)	27	28.8 (8.2)	44	31.2 (4.2)	0.085	p < 0.001	0.520
RMR**	29	1,721.4 (286.0)	27	1,692.6 (571.7)	44	1,933.8 (342.3)			
BV**	29	77.2 (19.3)	24	81.1 (37.9)	42	90.4 (27.1)	0.314	0.029	1.000
BD*	29	1.041 ± 0.020	24	1.023 ± 0.018	42	1.025 ± 0.016	0.002	0.001	1.000
TGV**	29	4.1 (0.5)	24	4.1 (0.8)	42	4.0 (0.5)			
BSA**	29	197.4 (22.2)	24	196.7 (48.6)	42	211.3 (29.0)			
TBF**	29	23.1 (10.5)	27	27.1 (18.7)	44	32.4 (10.3)	0.037	< 0.001	0.699
FFM**	29	56.2 (8.1)	27	54.7 (12.4)	44	58.5 (12.2)			
RSMI**	29	8,6 (1,5)	27	8,5 (2,0)	44	9,0 (1,5)			
VFM**	29	2,108.9 (1,494.0)	27	2,917.9 (2,186.7)	44	3,432.9 (1,482.3)	0.030	< 0.001	0.859

PCR-days: time elapsed between SARS-CoV-2 infection (confirmed by RT-PCR) and body composition assessment; RMR: resting metabolic rate; BV: body volume; BD: body density; TGV: total gas volume; BSA: body surface area; TBF: total body fat; FFM: fat-free mass; RSMI: relative skeletal muscle index; and VFM: visceral fat mass. *ANOVA. **Kruskal-Wallis test.

disease, women were younger (42.8 ± 11.8 years vs. 48.4 ± 12.2 years; p = 0.042) and lighter (74.2 ± 21.4 kg vs. 81.6 ± 18.7 kg; p = 0.005), although men were taller (176.2 ± 6.2 cm vs. 161.9 ± 6.9 cm; p < 0.001).

In the group of patients with severe disease, men were taller (172.9 ± 8.8 cm vs. 160.5 ± 6.2 cm; p < 0.001) and had a lower BMI (28.8 ± 8.2 vs. 32.7 ± 7.7; p = 0.025). In the group of patients with critical disease, men were younger (50.3 ± 9.6 years vs. 55.5 ± 10.6 years; p = 0.046), heavier (94.6 ± 23.5 kg vs. 84.1 ± 23.3 kg; p = 0.023), and taller (174.9 ± 7.5 cm vs. 159.9 ± 7.0 cm; p < 0.001). With regard to disease severity in men, differences were observed between those with nonsevere disease and those with severe disease regarding BD (p = 0.002), TBF (p = 0.037), and VFM (p = 0.030), as well as between those with nonsevere disease and those with critical disease regarding body weight (p = 0.014), BMI (p < 0.001), BV (p = 0.029), BD (p = 0.001), TBF (p < 0.001), and VFM (p < 0.001).

With regard to disease severity in women, differences were observed between those with nonsevere disease and those with severe disease regarding body weight (p = 0.003), BMI (p=0.001), RMR (p=0.007), BV (p=0.124), BD (p = 0.001), BSA (p = 0.014), TBF (p = 0.005), FFM (p = 0.013), RSMI (p = 0.005), and VFM (p = 0.003), as well as between those with nonsevere disease and those with critical disease regarding age (p<0.001), body weight (p = 0.023), BMI (p = 0.002), BV (p = 0.014), BD (p < 0.001), TBF (p = 0.009), and VFM (p = 0.009). No differences were found between men or women with severe disease and men or women with critical disease.

DISCUSSION

The present study allowed a precise comparison of body composition between male and female post-COVID-19 patients.[11] The novelty of the present study lies in its integrating different devices and body composition markers, all of which were controlled at the same time of assessment. This allowed us to include a large number of post-COVID-19 patients, ranging from those who were asymptomatic to those who were still recovering in terms of health and quality of life.

Our study revealed a trend across disease severity levels, with the most significant differences found

Table 2. Measures of dispersion for female patients recovering from COVID-19, by disease severity.

Parameter	nonsevere COVID-19		severe COVID-19		critical COVID-19		Women		
	N	mean ± SD*/ median (IQR)**	N	mean ± SD*/ median (IQR)**	N	mean ± SD* / median (IQR)**	nonsevere vs. severe	nonsevere vs. critical	severe vs. critical
Age, years*	60	42.8 ± 11.8	27	48.0 ± 10.9	23	55.5 ± 10.6	0.15	< 0.001	0.068
Body weight, kg**	60	74.2 (21.4)	27	86.0 (24.1)	23	84.1 (23.3)	0.003	0.023	1.000
Height, cm*	60	161.9 ± 6.9	27	160.5 ± 6.2	23	159.9 ± 7.0			
PCR-days**	60	198 (161)	27	303 (332)	23	320 (256)			
BMI**	60	27.6 (8.3)	27	32.7 (7.7)	23	33.1 (7.0)	0.001	0.002	1.000
RMR**	60	1,630.7 (188.0)	27	1,746.4 (243.9)	23	1,704.7 (229.6)	0.007	0.083	1.000
BV**	60	67.1 (28.7)	27	78.6 (26.3)	23	84.3 (25.4	0.124	0.014	1.000
BD*	60	1.015 ± 0.020	27	1.000 ± 0.014	23	0.997 ± 0.012	0.001	< 0.001	1.000
TGV**	60	3.1 (0.3)	27	3.1 (0.3)	23	3.2 (0.4)			
BSA**	60	178.0 (20.7)	27	188.5 (20.9)	23	185.3 (25.3)	0.014	0.182	1.000
TBF**	60	31.6 (15.3)	27	39.5 (20.9)	23	38.0 (10.7)	0.005	0.009	1.000
FFM**	60	40.2 (4.9)	27	42.9 (7.6)	23	42.4 (11.5)	0.013	0.432	0.848
RSMI**	60	7,0 (1,0)	27	7,8 (1,6)	23	7,6 (1,8)	0.005	0.264	0.820
VFM**	60	2,484.5 (1,550.3)	27	3,444.1 (2,214.6)	23	3,122.3 (1,461.6)	0.003	0.009	1.000

PCR-days: time elapsed between SARS-CoV-2 infection (confirmed by RT-PCR) and body composition assessment; RMR: resting metabolic rate; BV: body volume; BD: body density; TGV: total gas volume; BSA: body surface area; TBF: total body fat; FFM: fat-free mass; RSMI: relative skeletal muscle index; and VFM: visceral fat mass. *ANOVA. **Kruskal-Wallis test.

between nonsevere and critical cases. Age and male sex were found to be predictors of disease severity.[26] Risk factors such as ethnicity, BMI, and cardiometabolic comorbidities have been analyzed in hospitalized patients.[27] No differences were found regarding ethnicity, whereas sex was a criterion for grouping in most markers. Anthropometry showed greater predictive power for women, including comparative age and better frequency outcomes among the groups. The literature indicates that men may be more vulnerable than women in terms of immunological, hormonal, and genetic health. However, reduced access and lack of personal care are also risk factors.[28] It is known that women in the post-recovery period are more vulnerable to experiencing a lower quality of life.[29]

Height and body weight were used as demographic markers for calculating BMI, being widely employed in health contexts.[26] Interestingly, BMI, originally known as the Quetelet index,[30] has limitations and is often erroneously associated with weight, localized fat deposits, and even social aspects or aspects related to physical activity and age.[31]

When we compared BMI by sex, we found that only the group of patients with severe COVID-19 showed differences. Body weight, which is an important modulator, did not follow this pattern. Height, on the other hand, influenced all three groups of disease severity. When we analyzed the results by disease severity, we found that BMI correlated with most markers, with a greater influence on women.

Among body components, fat mass, represented by VFM, showed a strong association with BMI[26] and BD.[32] In our study, these body components showed a strong relationship among groups for both men and women. Only BMI differed from the main results in men.

FFM had no influence on severity in men and showed inconsistent differences in women. These findings suggest an imbalance in body composition, with obesity (BMI > 30 kg/m^2)[26,32] standing out as one of the main characteristics of COVID-19,[2] increasing the risk of severe disease. It is known that a balanced relationship between adequate levels of adipose tissue and lean mass constitutes an important health protective factor.[33]

Obesity, independently of COVID-19, is an inflammatory disorder that exacerbates health problems, influencing the immune and neuroendocrine

systems.[34] Under the effect of COVID-19, obesity can impair respiratory function through hormonal signaling and the release of proinflammatory adipocytokines from adipose tissue itself.[35] Conversely, musculoskeletal tissue acts as the main endocrine organ, regulating the immune system.[3] Through physical activity, it produces anti-inflammatory myokines capable of reducing the systemic concentration of inflammatory cytokines.[36] This mechanism directly links exercise to muscle mass volume.[37] The relative musculoskeletal index, composed of the sum of appendicular musculature, is an important DXA marker based on body height.[38] Its results correlated with lean components, showing no influence on men and limited influence on women. The values found were low for health in men, and women showed a normal index.

In the present study, age also included patients with immunosenescence. From a longevity perspective, it is known that a decrease in muscle and bone tissue, with a peak in adipose tissue increase, occurs on average between the ages of 65 and 70 years, which suggests a significant risk factor extended to the general population.[39] The decline in immune function accompanies the decrease in lean mass in the physiological process of immunosenescence.[3] The importance of these changes suggests that the musculoskeletal tissue is the main organ in health prevention in response to advancing age. In this physiological process, there is a decrease in immunity to new infections, as well as in the effects of vaccination, along with an increase in chronic systemic inflammation.[40]

Sex differences influence the severity of COVID-19. The use of various assessment tools allowed us to obtain precise values in the distribution of groups. Adiposity indices and FFM can be modulated as health protective factors. Our results support outpatient evaluations for appropriate interventions, including nutritional guidance and structured physical activity programs.

The present study allowed a cross-sectional analysis of the impact of body composition on COVID-19 patients. Specifically, the identified markers may assist in comparing COVID-19 with other comorbidities and physiological parameters.

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AUTHOR CONTRIBUTIONS

PBMC, MAP, MAGOR, CCSG, APS, ES, GGJ, and JDR: study conception, design, and planning; data analysis; and drafting and reviewing of the manuscript. TC, SDS, and DSPB: study conception, design, and planning; data analysis; and reviewing of the manuscript. The UNICOVIDS Study Group: reviewing of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Indocyanine green used in association with a surgical hemostatic agent as a fiducial marker to reduce overflow during robot-assisted thoracic surgery

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TO THE EDITOR:

Unsuccessful localization of pulmonary nodules during video-assisted thoracic surgery is the most common reason for conversion to thoracotomy. Fiducial markers such as hook wires, microcoils, and liquid markers such as methylene blue have been used in order to assist in locating subcentimeter pulmonary nodules during video-assisted thoracic surgery.[1] More recently, robot-assisted thoracic surgery (RATS) has been used as a minimally invasive surgical technique for pulmonary nodule resection. However, the presence of robotic arms over the patient may prevent appropriate C-arm positioning and the use of radiopaque markers.

Indocyanine green (ICG) is a near-infrared fluorescent dye that is used as a liquid fiducial marker with great sensitivity and specificity for direct visualization in the near-infrared spectrum of light.[2] ICG is advantageous over metal markers such as coils, with reports of fewer complications; does not require intraprocedural imaging; and does not dictate the surgical approach.[3] Liquid fiducial markers such as methylene blue, India ink, and radionuclides are comparable to ICG but have limitations such as radiation exposure and lower sensitivity.[1] However, overflow, which is the migration of a liquid fiducial marker beyond the target lesion, has been reported to be more common with ICG than metallic marker migration.[2] This study sought to describe a fiducial marker technique in which ICG is used in association with a surgical hemostatic agent with tissue adhesive properties to reduce overflow.

This was a single-center retrospective study approved by the local institutional review board. A search was conducted in the interventional radiology database of a tertiary care medical center to identify patients who underwent preoperative percutaneous localization of lung lesions between May of 2021 and December of 2023. A total of 18 patients (25 lesions) were included.

Lesions were marked with a 40-slice multidetector CT scanner (SOMATOM Definition AS; Siemens Healthineers, Erlangen, Germany) under general anesthesia. Patients were then sent to an operating room for resection or to a hybrid operating room with a robotic C-arm (Artis zeego; Siemens Healthineers) for cone-beam CT. All localization procedures were performed by an experienced interventional radiologist assisted by a fellow interventional radiologist. All surgical procedures were performed by the local thoracic surgery team, which is experienced in RATS.

A coaxial introducer needle was percutaneously inserted into the target lesion under fluoroscopic guidance. Further cone-beam CT images or CT images were acquired to confirm the position of the needle. A 5 mg/ml solution of ICG was prepared in a 10 ml syringe, with only one drop being placed within one of the chambers (the thrombin chamber) of the double-chamber (2 ml + 2 ml) syringe for the hemostatic agent TISSEEL (Baxter International Inc., Deerfield, IL, USA), thus creating a solution with a concentration of approximately 0.125 mg/ml of ICG. The double-chamber syringe was then attached to the coaxial needle, and up to 0.5 mL was injected through the mandrel. The inner stylet was used in order to push any remaining solution inside the coaxial needle lumen. The system was then removed. RATS was performed, and pulmonary nodules were located by using a near-infrared fluorescence thoracoscope (da Vinci Firefly; Intuitive Surgical, Inc., Sunnyvale, CA, USA). A wedge resection of the nodule was then performed, and accuracy was confirmed by pathological examination.

A total of 18 patients underwent preoperative percutaneous localization of lung lesions between May of 2021 and December of 2023. Of the 18 patients, 12 (66.7%) were women and 6 (33.3%) were men. The mean age of the patients was 66 ± 14.06 years. A total of 25 lesions were analyzed. Of the 18 patients who underwent preoperative percutaneous localization of lung lesions during the study period, 13 (72.2%) underwent localization of one lesion, 3 (16.7%) underwent localization of two lesions, and 2 (11.1%) underwent localization of three lesions.

Pathological examination of the lung lesions showed that 14 of the 18 patients had malignant disease (primary lung cancer, in 12; renal cancer metastasis, in 1; and colon cancer metastasis, in 1) and 4 had benign disease (granuloma, in 2; fibrosis, in 1; and lymphoid hyperplasia, in 1). Mean lesion size was 1.2 ± 0.96 cm (range, 0.3-4.4 cm). Mean lesion-pleura distance was 1.48 ± 1.47 cm (range, 0.1-5 cm).

Of the 18 patients analyzed in the present study, 14 (77.8%) underwent preoperative lesion localization in the hybrid operating room and 4 (22.2%) underwent preoperative lesion localization by CT (Figures 1 and 2). Thirteen patients (81.3%) underwent nodule marking

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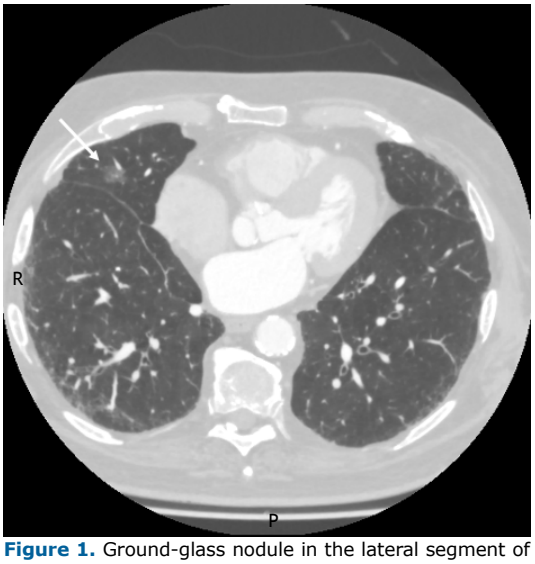

Figure 1. Ground-glass nodule in the lateral segment of the middle lobe, measuring 1.4 cm.

using a 19-gauge coaxial needle (range, 18-22 gauge). Of the patients who experienced complications, 2 developed pneumothorax after nodule marking. This, however, did not change the surgical plan. Complications such as hemoptysis and hemothorax were not observed.

In comparison with other liquid makers, ICG provides superior visualization (when compared with blue dyes), especially in patients with anthracosis.[4] Dyes such as lipiodol may pose a risk of pulmonary or cerebral infarction because of their high viscosity.[4] Furthermore, ICG is one of the least expensive dyes, making it easily available.

According to the manufacturer, a potential risk of using TISSEEL in the lung is embolization; therefore, caution is advised when inserting the coaxial needle, in order to avoid blood vessels. Nevertheless, metal fiducial markers are more commonly associated with complications, including pneumothorax.[3]

The association of ICG with a hemostatic agent with tissue adhesive properties has solved the problem of overflow in our center, although more robust studies are warranted to confirm such benefits. Furthermore, this technique can be used with fiducial markers other than ICG.

In conclusion, the use of ICG in association with a surgical hemostatic agent with tissue adhesive properties for RATS is valuable because it can increase the ability to locate small pulmonary nodules intraoperatively, thus reducing the rates of conversion to thoracotomy, without the inconvenience of positioning a C-arm between the robotic arms.

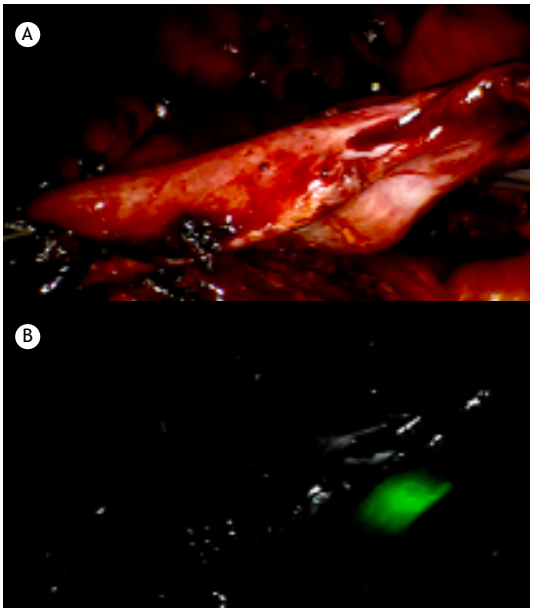

Figure 2. In A, posterior view of the lateral portion of the middle lung lobe, showing a nodule previously marked with indocyanine green before the use of a near-infrared fluorescence thoracoscope. In B, posterior view of the lateral portion of the middle lung lobe, showing the nodule as viewed with the near-infrared fluorescence thoracoscope.

AUTHOR CONTRIBUTIONS

GFM and MFA: conceptualization, data curation, formal analysis, investigation, methodology, and writing—original draft. PMF: conceptualization, formal analysis, investigation, methodology, project administration, writing—original draft, and writing—review and editing. ARN: data curation, formal analysis, investigation, methodology, and writing—original draft. RGG: conceptualization, formal analysis, investigation, methodology, supervision, and writing—review and editing. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Scaling up tuberculosis preventive treatment in Brazil: the ExpandTPT way forward

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TO THE EDITOR:

Tuberculosis elimination will not be possible without scaling up prevention through tuberculosis preventive treatment (TPT).[1,2] Contacts of persons with pulmonary tuberculosis and people living with HIV/AIDS are the two largest eligible populations for TPT. Although the individual absolute risk of progression from infection to disease is higher among people living with HIV/AIDS,[3] most new tuberculosis diagnoses are in contacts, who constitute the largest population in terms of attributable risk, especially in high-burden countries. However, there has been little progress in providing TPT to contacts worldwide,[4] and Brazil is no exception.[5]

Contacts were, therefore, the target audience of the *Rede Brasileira de Pesquisas em Tuberculose* (REDE-TB, Brazilian Tuberculosis Research Network) ExpandTPT project, which was initially funded by the Stop TB Partnership (TB REACH Grant no. 10429) in five Brazilian capitals with a high tuberculosis burden (Manaus, Porto Alegre, Recife, Rio de Janeiro, and São Paulo; phase 1) and then extended to three other cities (João Pessoa, Nova Iguaçu, and Salvador; phase 2) with resources from the Brazilian National *Ministério da Ciência, Tecnologia e Inovação*, *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Grant no. 445684/2023-2).

Phase 1 of the ExpandTPT project was conducted between April of 2023 and July of 2024 and was based on the lessons learned from the ACT4 cluster randomized clinical trial, which identified bottlenecks of the cascade of care for tuberculosis contacts and implemented tailored solutions.[6,7] The ExpandTPT project was conducted in close partnership with the Brazilian National Tuberculosis Program, with participation of civil society advocates (through a community advisory board) and city-level tuberculosis programs. In brief, during technical visits with Brazilian National Tuberculosis Program officials, the ExpandTPT team, and the community advisory board, city tuberculosis program officials discussed the main bottlenecks in primary health care services, as well as customized solutions to improve the cascade of care for tuberculosis contacts. Those visits included meetings with municipal health department officials and managers of the services providing care to tuberculosis contacts. In addition to service reorganization, the main bottlenecks identified were the knowledge and skills required to perform the tuberculin skin test (TST). Therefore, more than 15,000 health professionals and community health workers received online training on the Brazilian national TST guidelines, the training course being provided by the ExpandTPT team and Brazilian National Tuberculosis Program officials. In 327 clinics where there was at least one new person with tuberculosis per month on average, ExpandTPT offered a simplified training course on the TST, the number of clinics offering the TST thus being expanded from 63 to 234 between October of 2023 and July of 2024. In addition, ExpandTPT provided in-service training using a dedicated contact registry book. The delay in training on the TST was due to a shortage of PPD RT23 in Brazil during the first six months of the project.

A strategic component of the ExpandTPT project was the direct participation of a select group of tuberculosis advocates (the community advisory board) in each city. They monitored the training; contributed to its improvement and the planning of actions; developed specific materials for community health workers; participated in monitoring and technical visits; and proposed specific solutions to the city tuberculosis programs.

With the implementation of the actions, the overall number of TPTs prescribed to contacts in those five cities increased by 70% after a sharp drop in the first semester related to the lack of PPD, surpassing the expected values had no intervention occurred (Figure 1). This increase in the number of TPTs was due to an improvement in two steps of the cascade of care for tuberculosis contacts: an increase in the number of contacts identified, indicating the central role of community health workers; and, after TST training, an increase in the proportion of contacts tested (data not shown), showing the impact of the PPD stockout and revealing the fragility of depending on a single consumable, as well as the need to incorporate other technologies for the diagnosis of *Mycobacterium tuberculosis* infection.

The ExpandTPT legacy also includes the following: a partnership among federal, state-level, and city-level programs to improve tuberculosis care in primary health care settings; visibility of civil society advocates and an understanding of the positive impact of their efforts on tuberculosis care; and simplification of recommendations for TST training,[8] as a result of ExpandTPT advocacy activities and on the basis of evidence generated by ExpandTPT,[9] as well as other evidence.

A final ExpandTPT seminar was held in Brasilia on March 13, 2025, when the project partners agreed on the next

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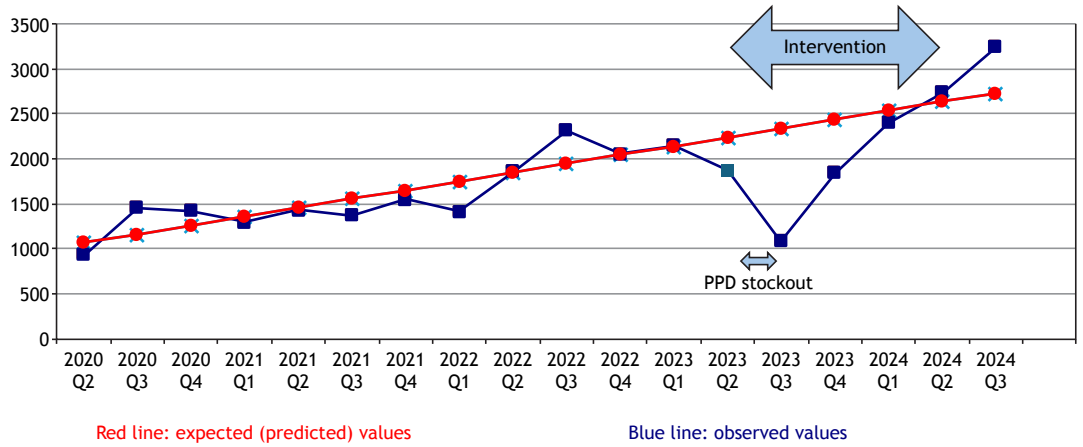

Figure 1. Number of tuberculosis preventive treatments prescribed to contacts reported in five cities in Brazil.

steps. First, investments will be needed in order to leverage TPT in the country. Funding is needed for at least one nurse dedicated to TPT follow-up activities in city-level tuberculosis programs; for indirect costs of personnel time for training activities; and for community-based civil society activities. Resources are also needed for effective implementation of an industrial park that guarantees autonomy in the development and production of strategic consumables for the country. In the short term, we recommend prompt evaluation and incorporation of new technologies for the diagnosis of *M. tuberculosis* infection. Tuberculosis-specific skin tests are more cost-effective than the tests currently used in Brazil and would be an attractive alternative. Other rapid point-of-care blood-based tests are in the pipeline[10] and should be evaluated for incorporation into the Brazilian public health system.

Outcomes revealed how collaboration among city-level tuberculosis programs and their local partners is key to ensure rapid access to chest X-rays to accelerate and improve access to TPT. Expanding the network for tuberculin skin testing also proved to be pivotal in this effort, requiring increasing the number of trained professionals and ensuring that refrigerators are available for adequate PPD storage.

Finally, social determinants were identified in the challenges on reception, testing, and follow-up at the primary health care level, as well as reaching out to contacts, revealing the need for restructuring services in a decentralized, accessible, and reliable logic under the view of service users.[11]

In conclusion, ExpandTPT leveraged TPT scale-up, but there is a need for improvement. The efforts and resources utilized to promote TPT expansion need to be guaranteed to further reach out and treat eligible contacts.

AUTHOR CONTRIBUTIONS

AT wrote the original draft. All authors made contributions to and approved the final version of the manuscript.

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CONFLICTS OF INTEREST

None declared.

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Aerobic capacity after lung resection in patients with COPD

Danielle C C Bedin[1], Roberta P Ramos[2], Elaine Brito Vieira[2], Ivan Ivanaga[2], Sonia M Faresin[1]

TO THE EDITOR:

Cardiopulmonary exercise testing is an important functional tool for the preoperative assessment of operability in lung resection for NSCLC.[1] Among the parameters evaluated, peak VO_2 (VO_{2peak}) has been reported to be a better predictor of postoperative complications and mortality than are resting pulmonary and cardiac function.[2] Despite advances in preoperative assessment, the magnitude of functional changes after lung resection, particularly in patients with COPD, is still matter of debate.[3,4]

We conducted a prospective study to quantify the impact of pulmonary resection on the exercise capacity of patients with COPD scheduled for lung resection surgery at our institution. All participants provided written informed consent, and the study was approved by the medical ethics committee of the institution (Reference no. 89661117.2.0000.5505).

Patients were divided into two groups: those with normal spirometry values (control group) and those with expiratory obstruction on baseline spirometry (COPD group).[5]

The preoperative assessment, which included functional analysis with spirometry, measurement of the DL_{CO}, and cardiopulmonary exercise testing (CPET),[2] was performed before and six months after the surgical procedure. Predicted postoperative FEV_1, DL_{CO}, and VO_{2peak} values were calculated at baseline according to segmental loss. All of the patients underwent lateral thoracotomy. For the analysis, continuous variables are presented as mean and standard deviation or as median and interquartile range, being compared by using the paired Student's t-test, Wilcoxon test, or Mann-Whitney test, as appropriate. Two-way repeated-measures ANOVA was performed to compare functional changes between the two groups. Categorical variables are presented as absolute and relative frequencies and were compared by using Fisher's exact test. The Kolmogorov-Smirnoff test was employed to assess the normality of the distribution of all variables. Values of $p < 0.05$ were considered statistically significant. All analyses were performed with the IBM SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA).

During the study period, 18 patients underwent preoperative assessment: 10 in the COPD group and 8 in the control group. The diagnosis of COPD was defined by the presence of clinical findings consistent with the disease, a history of smoking, and an FEV_1/FVC ratio below the lower limit of reference. Baseline clinical characteristics and pulmonary function test results are shown in Table 1. The complication rates in the postoperative period were similar between the two groups. In the control group, 3 patients presented with respiratory infections, whereas in the COPD group, 3 patients presented with respiratory infections and 1 presented with atrial fibrillation ($p = 0.91$). Similarly, there were no differences between the two groups in terms of the length of ICU stay and hospital stay (Table 1). Because there were no deaths in either group during the study period, all of the patients in our sample underwent evaluation at baseline and postoperatively. It is also noteworthy that the extent of lung resection was comparable between the two groups (Table 1).

There were no significant differences between the preoperative (baseline) and postoperative (month-six) time points, in either group, in terms of the spirometric and DL_{CO} values (Table 1). However, the pattern of change in VO_{2peak} (in absolute values and adjusted for body weight) was significantly different between the two groups, being significantly greater postoperatively in the control group (Table 1). These findings were reinforced by the ANOVA, which demonstrated a distinct behavior of VO_{2peak} between the two groups and time points ($p = 0.011$ and $p = 0.024$, respectively, for the absolute and adjusted values). In addition, the decrease in VO_{2peak} relative to the number of resected segments was greater in the control group than in the COPD group, with a median loss of 60.2 mL/min/segment in the control group and 20.3 mL/min/segment in the COPD group ($p = 0.043$). In the COPD group, predicted VO_{2peak} values underestimated the actual values obtained six months after the surgery, whereas no significant difference was observed in the control group (Table 2).

In our study sample, the patients with COPD presented no significant deterioration of VO_{2peak} after lung resection, whereas the patients with preserved lung function at baseline presented greater declines, not only in absolute values but also in VO_{2peak} per resected segment. In addition, the predicted values of FEV_1 and VO_{2peak} overestimated the functional deterioration in the patients with COPD.

In a study of 12 patients with COPD, Bobbio et al.[6] found a 21% decrease in VO_{2peak} at three months after lung resection. Miyoshi et al. also observed a decrease in VO_{2peak} after lung resection, although without differentiating between patients with COPD and patients

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Table 1. Characteristics of patients in the control and COPD groups before and six months after lung resection.

Variables	Control (n = 8)			COPD (n = 10)		
	preoperative	postoperative	p	preoperative	postoperative	p
Age (years), mean ± SD	66.0 ± 9.0			66.9 ± 9.4		0.84
Male sex, n (%)	6 (75)			6 (60)		0.64
Body mass index (kg/m^2), mean ± SD	24.5 ± 3.2			23.7 ± 3.0		0.63
Smoking status, n %						
Never smoker	0 (0)			0 (0)		
Former smoker	6 (75)			3 (30)		0.057
Current smoker	2 (25)			7 (70)		
Resected segments (n), median [IQR]	4 [2-5]			3 [3-5]		0.90
Hospital stay (days), median [IQR]	6 [5-7]			7 [5-9]		0.90
ICU stay (days), median [IQR]	3 [2-6]			4 [3-5]		0.46
Spirometry parameters, mean ± SD						
FEV_1 (%)	86.1 ± 16.4	80.6 ± 17.7	0.40	65.4 ± 10.1	62.1 ± 14.5	0.46
FEV_1/FVC ratio	0.75 ± 0.03	0.76 ± 0.03	0.33	0.60 ± 0.06	0.60 ± 0.08	0.08
DL_{CO} (%)	73.8 ± 15.9	63.2 ± 14.6	0.13	67.5 ± 22.6	53.6 ± 19.6	0.09
CPET parameters, mean ± SD or median [IQR]						
Work load, watts	94.6 ± 33.3	82.0 ± 31.5	0.005	69.5 ± 23.3	59.9 ± 25.8	0.01
VO_{2peak}, mL/min	1350 ± 438.0	1108.4 ± 320.0	0.004	993.9 ± 240.0	937.0 ± 30.0	0.16
VO_{2peak}, mL/kg/min	20.8 ± 7.1	16.3 ± 5.3	0.007	15.6 ± 3.7	14.5 ± 4.1	0.07
VO_{2peak}, % of predicted	91.5 ± 18.9	77.4 ± 17.9	0.01	74.9 ± 16.6	70.5 ± 19.7	0.15
VO_2 LT, %	55.9 ± 18.3	41.4 ± 7.9	0.14	49.3 ± 10.1	44.1 ± 10.2	0.36
DVO_2/DW	10.3 ± 1.9	9.5 ± 2.7	0.10	8.9 ± 2,3	10.9 ± 1,7	0.02
VE_{peak}, L/min	62.0 ± 19.2	49.8 ± 10.2	0.06	43.8 ± 10.2	48.9 ± 8.4	0.66
VE /MVV_{peak}	0.55 ± 0.16	0.52 ± 0.09	0.74	0.53 ± 0.1	0.6 ± 0.2	0.38
VE/VCO_{2peak}	31.8 ± 4.3	32.4 ± 3.4	0.38	31.4 ± 4.0	31.6 ± 4.3	0.87
$DVE/DVCO_{2peak}$	35.1 ± 5.6	36.6 ± 5.5	0.42	34.0 ± 4.7	34.8 ± 5.6	0.56
Intercept $DVE/DVCO_{2VT}$, L/min	+2.7 ± 2.1	3.0 ± 1.9	0.93	2.9 ± 2.0	4.4 ± 2.4	0.04
Intercept $DVE/DVCO_{2peak}$, L/min	+0.9 ± 2.5	0.5 ± 2.8	0.79	1.5 ± 2.0	2.3 ± 2.9	0.07
Nadir VE/VCO_{2peak}, L/min	34.3 ± 2.7	36.6 ± 3.3	0.08	35.7 ± 4.1	37.8 ± 3.9	0.11
HR_{peak}, bpm	145 ± 16	134 ± 13	0.001	120 ± 17	114 ± 22	0.69
VO_2/HR_{peak}, % of predicted	102.8 ± 26.7	92.4 ± 25.6	0.12	100.8 ± 18.3	103.2 ± 24.6	0.83
DHR/DVO_2, beats/L	62 ± 18	61 ± 12	0.91	56.7 ± 22.1	47.6 ± 16.2	0.40
SpO_2 at rest, %	98 [97-99]	97 [97-98]	0.34	97 [95-97]	96 [94-97]	0.72
Peak SpO_2, %	98 [96-99]	97 [97-99]	0.32	97 [90-98]	92 [88-96]	0.11

VO_{2peak}: peak VO_2; VO_2 LT: VO_2 at the lactate threshold; W: work rate; VE_{peak}: peak VE; MVV: maximal voluntary ventilation: VCO_2: carbon dioxide output; and VT: ventilatory *threshold*.

Table 2. Comparison between the predicted and actual postoperative peak VO_2 values at six months after lung resection.

Variable	Control (n = 8)		p	COPD (n = 10)		p
	Predicted	Actual		Predicted	Actual	
VO_{2peak}, mL/min	1105.0 ± 399.4	1108.4 ± 20.0	0.96	815.1± 233.2	937.0 ± 306.0	0.007
VO_{2peak},% pred	73.6 ± 17.8	77.4 ± 17.9	0.54	60.9 ± 15.8	70.5 ± 19.7	0.003
VO_{2peak},mL/kg/min	16.9 ± 5.9	16.3 ± 5.3	0.68	12.8 ± 3.6	14.5 ± 4.1	0.007

VO_{2peak}: peak VO_2.

with preserved lung function at baseline. In addition, those authors revaluated exercise capacity after a shorter follow-up period. Similarly, Bolliger et al.[1] showed that the VO_{2peak} decreased by three months after the operation but reverted to the preoperative values by six months after, without specifically addressing patients with COPD. That finding aligns with the minor changes in lung function observed in our study at six months after the surgical procedure.

In parallel with the pulmonary function tests, predicted postoperative VO_{2peak} was similar to the actual measurements six months after surgery in the control group but was significantly lower than the actual measurements in the COPD group. These findings

are consistent with those of Brunelli et al.,[8] who noted the imprecision of predicted postoperative VO_2, particularly when the preoperative values are lower.

We find it interesting that, after the VO_{2peak} decrease had been adjusted for the number of resected segments, the functional loss was three times greater in our control group than in our COPD group (60.2 mL/min/segment vs. 20.3 mL/min/segment). Previous studies of patients undergoing segmentectomy, lobectomy, or pneumonectomy have shown that greater lung tissue loss results in greater loss of pulmonary function.[1,9] However, the authors of those studies did not take the baseline ventilatory pattern or the presence of COPD into account.

Our study has limitations that should be acknowledged. It was a single-center study conducted by the same team of thoracic surgeons and pulmonologists in order to ensure uniformity in the preoperative evaluation. The postoperative tests were performed six months after surgery, a time point chosen somewhat arbitrarily on the basis of data in the literature suggesting that lung function stabilizes at three to six months after pulmonary resection.[4,10] Our results show that patients with COPD submitted to lung resection demonstrated distinct functional behavior. However, the limitations imposed by our sample size should be considered before our findings are extrapolated to other populations. In addition, our COPD group included only patients with mild or moderate COPD, which might preclude extrapolation of our results to patients with severe COPD. However, the fact that such patients were not included allowed us to speculate that the lack of room for deterioration after surgery did not explain the small size of the decrease in functional capacity in the COPD group. Furthermore, we did not correlate the functional findings with patient reported outcome measures, which could have reinforced the relevance of our findings.

In our study, the predicted postoperative VO_{2peak} values appeared to overestimate the decrease in aerobic capacity following lung resection in patients with mild or moderate COPD. Our findings suggest that, in patients with COPD, there is a need for a more comprehensive preoperative analysis, with less emphasis on the predicted postoperative CPET values.

AUTHOR CONTRIBUTIONS

DCCB and SMF designed the study, collected the data, analyzed the data, and participated in drafting the manuscript. RPR analyzed the data and participated in drafting the manuscript. EBV and IV collected and analyzed the data.

CONFLICTS OF INTEREST

None declared.

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Pulmonary hyalinizing granulomas

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

A 28-year-old female patient presented with dyspnea, cough, chest pain, and weight loss. She reported having had tuberculosis 20 years prior. Chest CT) showed multiple, partially calcified pulmonary nodules and a cavitated mass (Figures 1A-C). Open lung biopsy revealed inflammatory lesions consisting of mature fibrous tissue, with areas of calcification and ossification infiltrated by small numbers of lymphocytes and plasma cells, consistent with hyalinizing granulomas (Figure 1D). Pulmonary hyalinizing granuloma (PHG) is a rare benign lung disease characterized by fibrosing nodules consisting of central whorled deposits of lamellar-collagen hyaline. The probable etiology of this condition is an exaggerated immune response to the antigenic stimuli of infectious agents, such as tuberculous bacilli and histoplasma organisms, or an autoimmune process. Because the symptoms are absent or mild, most PHG lesions are found incidentally by radiological examination and are not initially diagnosed correctly. Chest radiography and CT show solitary or multiple randomly distributed nodules and/or masses with or without calcification. Although rare, cavitation has been reported. The prognosis is generally excellent, although some patients develop retroperitoneal fibrosis or sclerosing mediastinitis.[1-4] PHG should be considered in the differential diagnosis of pulmonary nodules or masses, even those that are cavitary or contain calcifications.

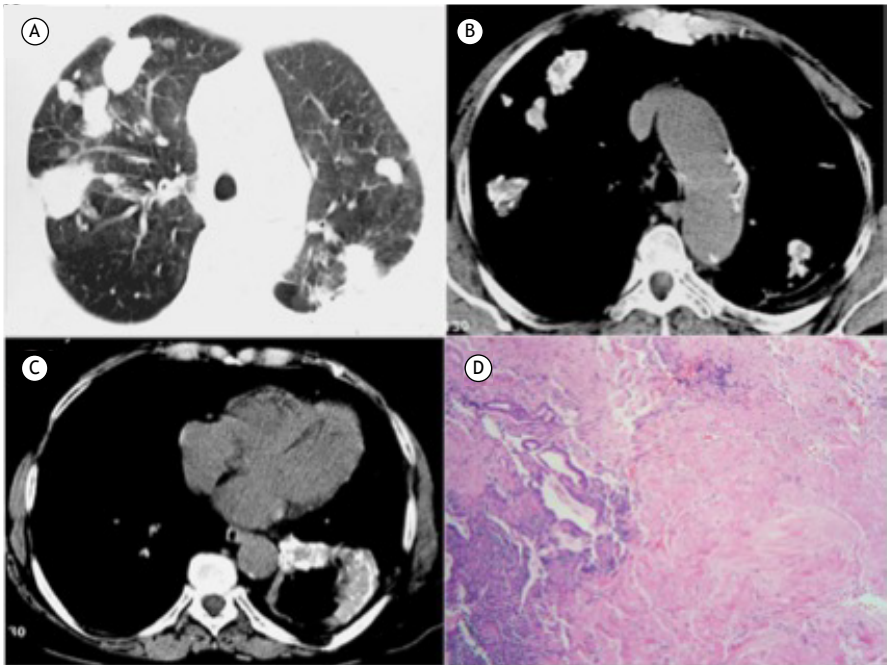

Figure 1. Chest CT images obtained with lung (A) and mediastinal (B and C) window setting showing multiple nodules of various sizes and irregular contours in both lungs, with soft-tissue density and foci of calcification within them. A cavitated mass with thick, irregular, partially calcified walls is also visible in the left lower lobe (C). In D, histological staining confirmed the deposition of hyaline tissue masses composed of hypocellular collagen lamellae, accompanied by sparse lymphocytic infiltrate that compresses and distorts the remaining bronchioles (H&E; original magnification, ×40).

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◄ Voltar ao sumário
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High-grade chondrosarcoma of the sacrum with mediastinal metastases and a tumor thrombus to the inferior vena cava and right atrium

Flávia Angélica Ferreira Francisco[1], João Victor Cavalcanti Mesquita Pinto[1], Edson Marchiori[1]

A 19-year-old female patient complained of shortness of breath and syncope, as well as progressive pain and right leg paresthesia for 6 months. She also developed urinary retention, followed by urinary incontinence, as well as difficulty walking.

CT scans of the chest, abdomen, and lumbosacral spine revealed a mixed lytic and sclerotic infiltrative lesion in the sacrum, with extensive thrombosis in the iliac veins and foci of calcification in between, extending into the inferior vena cava and finally entering the right atrium. Heterogeneous masses with foci of calcification, consistent with metastases, were also present in the right lower mediastinal region and left lower lobe (Figure 1).

Percutaneous biopsy of the sacral lesion revealed a high-grade chondrosarcoma. The patient underwent pelvic radiation therapy and chemotherapy, but the treatment was discontinued because her clinical condition worsened; she died shortly thereafter.

Although intravenous leiomyomatosis is the most common cause of neoplastic thrombi extending through the inferior vena cava and reaching the heart, malignant diseases such as leiomyosarcoma, renal carcinoma, adrenal carcinoma, hepatocellular carcinoma, and Wilms tumor can also exhibit this behavior. However, we found no case of a bone tumor showing this particular behavior.[1-3] The case reported herein is of particular interest to pulmonologists because of its clinical presentation (shortness of breath and syncope), as well as the presence of mediastinal metastases.

AUTHOR CONTRIBUTIONS

FAFF, JVCMP, and EM: conceptualization, data curation, validation, visualization, writing—original draft, and writing—review and editing. EM: supervision. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

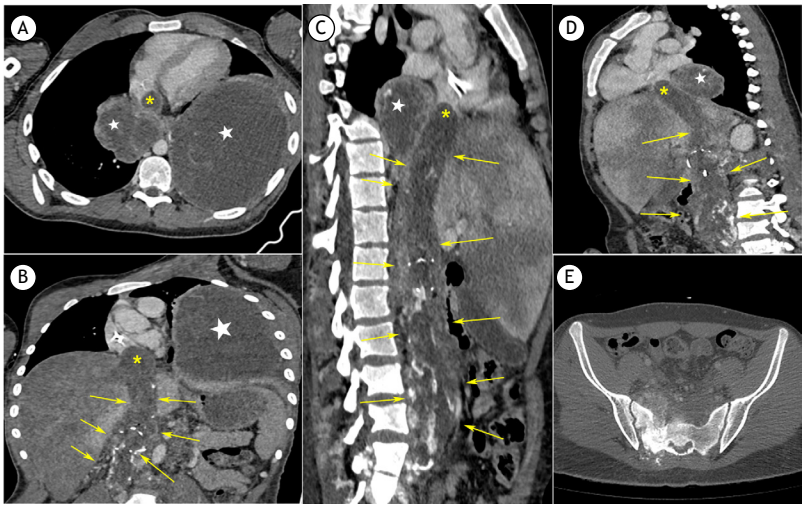

Figure 1. Intravenous contrast-enhanced CT scans of the chest, abdomen, and pelvis, with axial (in A), coronal (in B), and sagittal (in C and D) reconstructions of the thoracoabdominal region, as well as axial CT scan of the pelvis (in E), showing a heterogeneous mass with coarse foci of calcification originating in the pelvic region and extending superiorly through the inferior vena cava (yellow arrows), reaching the right atrium (yellow asterisks). Heterogeneous masses are also present in the right posteroinferior mediastinal region and left lower lobe (in A; white stars), in addition to a mass projecting from the right atrium (yellow asterisks). In E, a mixed lytic and sclerotic lesion is seen on the right side of the sacrum.

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