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HIGHLIGHT

Identifying malignant mesothelioma by a pathological survey

Asthma in the Brazilian Unified Health Care System: an epidemiological analysis from 2008 to 2021

Management of pediatric pleural empyema: a national survey of pediatric surgeons in Brazil

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

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

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

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

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

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

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

COVIS PHARMA

Material exclusivo de uso do representante comercial
para promoção junto a profissionais de saúde habilitados
a prescrever e/ou dispensar medicamentos.
MP 05.2020 - Junho 2020.

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Choice of inhaler device and its disposal have a significant impact on the environment

José Eduardo Delfini Cançado[1], Omar S Usmani[2]

The delivery of therapeutic vapors and aerosols through inhalation has been used for thousands of years in various cultures. The inhalation of Datura stramonium, a leafy flowering plant (*Hyoscyamus niger*), whose therapeutic properties are attributed to tropane alkaloids, including atropine, for treatment of asthma, comes from circa 2000 BC with early traditional Ayurvedic medicine.[1] The most prominent ancient form of respiratory drug delivery was the smoking of opium for recreational and therapeutic purposes including analgesia, and treatment of diarrhea and of severe cough, with one of the earliest known references dating back to 1100 BC in China.[2] It is clearly recognized that, in comparison with oral or parenteral formulations, the inhaled route allows the therapeutic drug to be directly delivered topically to the airways leading to quicker local efficacy within the lungs, using lower therapeutic doses, and minimizing their systemic effects.[3]

In many respects, the introduction of the pressurized metered dose inhaler (pMDI) in 1956 marked the beginning of the modern pharmaceutical aerosol industry, when Riker Laboratories Inc. (becoming 3M Drug Delivery Systems) introduced the pMDI. The pMDI was the first truly portable and convenient inhaler that delivered drugs to the lungs effectively, and quickly gained widespread acceptance.[4] When originally developed, pMDIs utilized chlorofluorocarbon (CFC) propellants, but they have an effect on depleting the stratospheric ozone layer. So, in the 1990s, the Montreal Protocol led to the phasing out of ozone-damaging CFCs in inhalers. The replacement propellants were hydrofluorocarbons (HFCs). Unlike CFCs, HFCs are not ozone-depleting substances, but they are recognized as greenhouse gases that have a high global warming potential (GWP). The current HFCs in pMDIs are hydrofluoroalkane (HFA)-134a and HFA-227ea, which are 1,000-3,000 times more potent than carbon dioxide and can persist in the atmosphere for 14 years, contributing to worsening climate change. The carbon footprint from 1 pMDI (200 doses) is estimated to be equivalent to a 290-km automobile ride. Figure 1 shows the carbon footprint of different medications and inhaler devices.[5]

According to the IQVIA database (Durham, NC, USA), in the preceding 12 months until June of 2019, there were over 480 million pMDI packs prescribed, equating to 2,400 doses taken every second across the world.[6] In Brazil, the number of pMDI short-acting β_2 agonist (SABA) units sold has been increasing, from 24,849,295 units in 2019 to 31,156,295 units in 2023; a growth of 25.4%.[7] With regard to the existing propellants, there is now development for transitioning to newer propellants, such as HFA-152a that has a lower GWP, and pharmaceutical companies have committed to launch newer pMDIs with this propellant by 2025-6.

Dry powder inhaler (DPI) devices do not contain greenhouse gas propellants and have a lower GWP when compared with pMDIs (Figure 1). However, DPIs are dependent on the inspiratory effort of the patient to effectively activate the dry powder to be inhaled into the lungs, and it has been shown that many patients with asthma and COPD have suboptimal inspiratory effort. Indeed, poor inspiratory effort is recognized in the young, in the elderly, and in patients with an acute exacerbation of asthma or COPD, when DPIs may not be effective. Globally, DPIs represent only 3% of the doses of SABAs, which are the mainstay of reliever medication.[6] Of critical importance, DPIs are not free from having an impact on planetary health due to their plastic content. Indeed, in the whole lifecycle assessment of pMDIs and DPIs, DPIs have a greater adverse effect on marine ecology through their plastic content. Since there is a global policy to curtail the effect of plastics on the environment, we must be careful in our choice of inhalers. The costs of DPIs are greater than those of pMDIs in Brazil. Soft mist inhalers are small portable devices, which are an additional class of inhalers that produce aerosols of breathable diameter from aqueous formulations. They are more environmentally friendly (Figure 1), but are currently more expensive than pMDIs and DPIs.[8]

Another important consideration is the recycling of inhalers. Of the estimated 35 million inhalers prescribed in the UK every year, only about 0.5% is recycled appropriately. Thus, millions of inhalers end up in landfills every year, where DPIs do not only significantly contribute to plastic waste, but also pMDIs release residual HFCs into the atmosphere over time.[9]

In clinical practice, the choice of drug and its dosage, treatment strategy, and inhalation device are crucial to control and prevent asthma and COPD exacerbations. Healthcare professionals, patient organizations, and the pharmaceutical industry should take the lead in health policies to provide environmentally healthier alternatives. Indeed, the greenest inhaler is the one that the patient can use (inhaler technique), will use (inhaler adherence), and has been taught how to use it properly (inhaler mastery) in order to mitigate these planet-warming greenhouse gas emissions. Ideally, prescribing physicians should educate their patients to discard used inhalation devices at pharmacies. If disposed of in regular waste, they can contaminate soil, water, and the atmosphere. However, effective recycling

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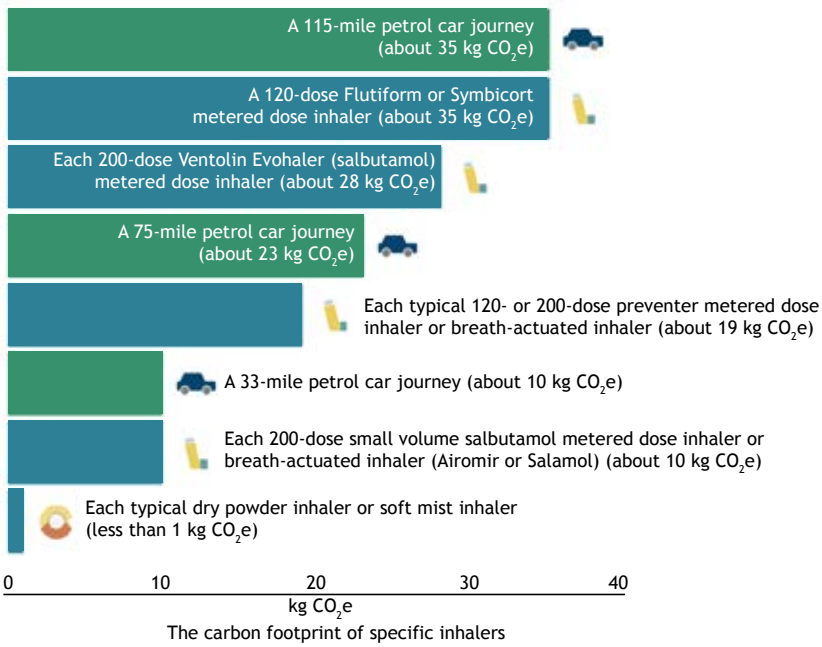

Figure 1. The carbon footprint of medicines and inhaler devices. Based on the National Institute for Health and Care.[5]

requires investment and policies at the governmental level to support pharmacies with appropriate equipment and clear pathways of disassembling the various parts of inhalers and their safe disposal at factories. Decree No. 10,388,[10] published by the President of the Republic of Brazil on June 5th, 2020, regulated the reverse logistics system for expired or unused household medications for human use, both industrially manufactured and compounded, as well as their packaging. These should be disposed of at pharmacies, where they will later be collected and sent for environmentally safe disposal. In this regard, the Brazilian Thoracic Society is conducting a campaign with the aim of educating doctors, other healthcare professionals, and patients about the importance of correct inhalation treatment for prevalent diseases such as asthma and COPD, as well as proper disposal of inhalation devices at pharmacies.

It is time to put the brakes on greenhouse gas emissions and global warming. Choose the better inhaler device for each patient and teach them about the correct disposal. Let's do it now!

AUTHOR CONTRIBUTIONS

Both authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

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Mesothelioma diagnosis—still a challenge

Ubiratan de Paula Santos[1]

Even though malignant mesothelioma (MM) was first identified and named in 1931,[1] and its link to asbestos exposure has been established since 1960,[1,2] MM diagnosis and, as a result, its registry closer to reality and its treatment are still a challenge. In this current issue of the *Jornal Brasileiro de Pneumologia*, an interesting paper discusses the obstacles that hospitals in the State of São Paulo, Brazil, face in identifying MM and suggests recommendations to reduce uncertainty or diagnostic error.[3]

Although the objective of that study, as described by the authors,[3] was to create a pathology board of experts and review the diagnosis of possible cases and/or occult cases of MM retrieved from the Hospital-Based Cancer Registry database in the State of São Paulo, it also addresses the diagnostic accuracy of MM seen in the hospitals of that State. Their motivation seeks an answer to the low number of mesothelioma diagnoses considering the amount of asbestos that is consumed in Brazil, one of the highest worldwide. From the 1970s to the early 2000s, asbestos consumption was above 1 kg *per capita*,[4] and it is estimated that Brazil consumed around six million tons of asbestos between 1961 and 2012.[5] The low number of MM cases that are diagnosed stands in contrast to the findings of several studies that reveal an association between the amount of asbestos consumed in countries or regions and the incidence of mesothelioma.[5,6]

Underreporting may result from lack of assessment of individuals exposed to asbestos, failure to address the history of occupational or environmental exposure, limitations in imaging analyses, insufficient biopsy material, and difficulties in pathological diagnosis. It is recognized that the histopathological diagnosis of mesothelioma is not straightforward: it is usually complex, requiring the combination of experienced pathologist/pathology service, and, in order to confirm more difficult cases, it is always appropriate for a chest radiologist, an oncologist, and a pulmonologist with expertise in occupational respiratory diseases to be part of the medical staff. Nonetheless, this reality is uncommon in the services that treat, diagnose, and register the majority of cases.

That study, unprecedented in Brazil,[3] revealed the need to review 27% of cases (130 out of 482), which presented topography and/or morphology aspects that were compatible with MM, but with insufficient pathological criteria for diagnosis. Of those 130, 73 biopsy specimens that had topography and/or morphology compatible with MM, but lacked sufficient pathological criteria for a diagnosis, were made available, from 11 of the 25 solicited hospitals, for the expert panel examination. The analyses confirmed 9 cases with MM (12.3% of the 73 cases reviewed), 58 cases (79.5%) had an MM diagnosis excluded, 2 of which had previously been established as MM, and others (n = 6; 8.2%) were found to be inconclusive. In addition to the complexity of the topic since the diagnosis of mesothelioma, in many situations, does not allow for certainty, the study revealed important limitations that make the diagnosis and registration of mesothelioma in Brazil flawed.

That study[3] showed that, in some of the hospitals evaluated, there is a lack of pathology services with expertise in the subject, in addition to presenting evidence of inadequate procedures for the storage of biopsy materials, both in terms of time, which, in accordance with the standardization in the State of São Paulo, should be stored for 5 years, and in terms of quantity and quality of materials to allow adequate reanalysis. It is remarkable that 14 of the 25 hospitals selected to provide materials for the study neither cooperated nor provided any materials.

That article[3] highlights the need to establish regulations for hospitals that care for patients where the diagnostic hypothesis of mesothelioma is imposed, in addition to the use of appropriate histopathological criteria for diagnosis, which requires adequate tissue sampling and the use of a panel with immunohistochemistry markers.[7,8] The relatively high number of inconclusive cases (8%) in the sample evaluated suggests the need to persist in refining biomarkers in order to improve the accuracy of MM diagnosis, as well as the creation of a panel of experts comprising pathologists, pulmonologists with experience in occupational and environmental areas, oncologists, and radiologists to confirm the diagnosis of more complex cases. The importance of an accurate and timely diagnosis impacts the treatment that affects patient survival, the possibility for the patient to claim (or not) their rights with public insurance bodies, and the advancement of understanding the epidemiology of mesothelioma in Brazil.[9,10]

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Anomalous systemic arterial supply to normal lung

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A 47-year-old woman presented with acute respiratory infection. She underwent a chest CT that showed an anomalous vessel originating from the aorta and supplying the left lower lobe (Figure 1). Venous drainage and the regional bronchial tree were normal. The final diagnosis was anomalous systemic arterial supply to normal lung.

Systemic arterial supply to normal basal segments of the lung with no sequestration is a rare congenital anomaly, characterized by the presence of an anomalous systemic artery feeding an area of normal lung parenchyma. This change was previously classified as a subtype of pulmonary sequestration. However, it differs from classic bronchopulmonary sequestration because the involved lung tissue maintains a normal connection with the bronchial tree. Furthermore, the absence of the interlobar artery distal to the superior segmental artery is an important differential from the classic bronchopulmonary sequestration. Venous return occurs through the inferior pulmonary vein to the left atrium. There is no direct communication between the anomalous arterial vessels and the veins of the basal segments. The basal segments of the left lower lobe are most commonly involved. Clinical manifestations of this anomaly are diverse. The majority of adult patients are asymptomatic, and the alteration is incidentally found in imaging tests performed for other purposes. Symptomatic adults generally present with hemoptysis or dyspnea, whereas the most common clinical manifestation in pediatric patients is heart murmur.[1,2]

The examinations of choice for diagnosis is contrast-enhanced CT that shows the anomalous artery, which generally originates from the descending aorta, but it can also arise from the proximal abdominal aorta or the celiac trunk, heading toward the basal segments of the lower lobes, especially the left one. CT can also provide information about the normal morphology of the bronchial tree and lung parenchyma. Venous drainage is also normal. Another finding is the absence of the interlobar artery distal to the superior segmental artery. These tomographic findings make it possible to differentiate it from the classic bronchopulmonary sequestration. Treatment depends on the age at diagnosis and the existence of other associated pulmonary anomalies. In adults, the anomalous connection is usually treated with lobectomy or surgical ligation of the anomalous artery. Surgery is indicated, because the condition presents potential risks, such as hemoptysis due to pulmonary hypertension, heart failure due to left-to-left shunt, and infection. In the majority of reported cases, lobectomy or segmentectomy was performed. Our patient, because she was asymptomatic, refused surgery and was advised to undergo annual periodic control.[1,2]

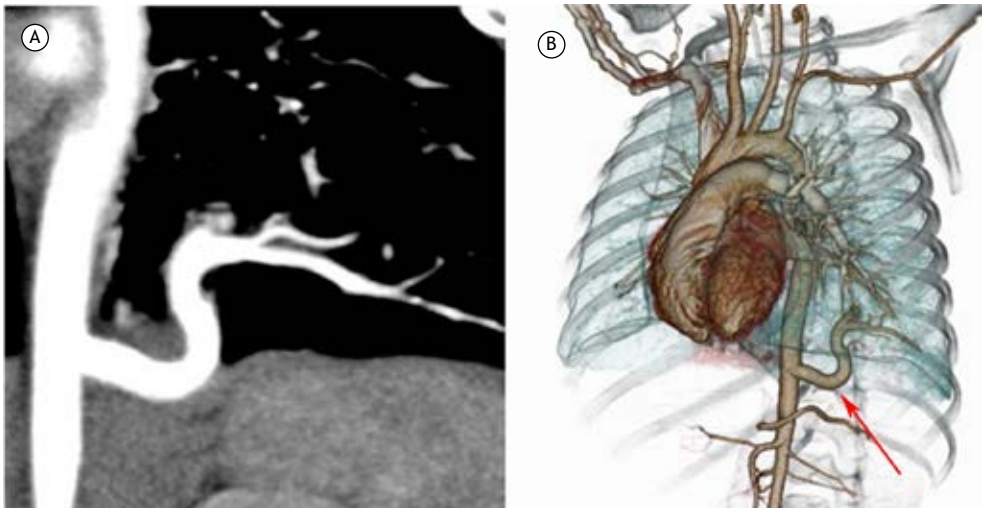

Figure 1. Anomalous systemic arterial supply to normal lung. In A, CT angiography shows an anomalous vessel originating directly from the aorta and heading to the left lower lobe. In B, three-dimensional reconstruction shows the anomalous artery (red arrow) and normal venous drainage of the left lung. In addition, the regional bronchial tree (not shown) was normal.

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What is a manual of procedures and why do we need one?

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PRACTICAL SCENARIO

At the beginning of this millennium, the PLATINO multi-country cross-sectional study was planned by a group of researchers to measure the burden of COPD among adults from major cities in Latin America (São Paulo, Mexico City, Montevideo, Caracas, and Santiago).[1] The investigators measured the prevalence of COPD and its risk factors using a standardized paper questionnaire and standardized pulmonary function methodology. The authors reported that the prevalence of COPD was higher than expected and ranged from 7.8% (95% CI, 5.9-9.7) in Mexico City to 19.7% (95% CI, 17.2-22.2) in Montevideo, Uruguay.[2] To yield accurate results, investigators collected data across study sites using the same methodological standards by writing and implementing a manual of procedures (MOP).[1]

WHAT IS A MOP?

Although the research process begins with an idea derived from an observation, the next steps include writing a research question, a protocol, and a detailed manual of procedures to guarantee accurate data collection process, as well as a comprehensive data analysis plan to provide reliable answers to important research questions that impact population health. At each step of the research protocol, inconsistencies in data collection procedures can lead to excess variation and/or error, jeopardizing the validity and reliability of the results. Therefore, the MOP is necessary to document and standardize all research procedures. The research process evolves from the initial research protocol into a fully detailed operations manual, describing every procedure stated in the protocol, and encompasses study organization, policies, participant recruitment and enrollment, randomization, blinding procedures, variable measurements, quality control, data management practices, and the statistical plan (Table 1).

All types of research study designs need a MOP, but MOPs are especially relevant for randomized clinical trials and cohort studies, because the types of procedures

Table 1. Outline of a manual of procedures (MOP).

Procedure	Example
Introduction	Overview of study goals and rationale
Study protocol	In many cases, the study protocol is the first document included in the MOP
Organization	Description of the team of investigators and research study units in multicentric studies
Recruitment and enrollment procedures	Procedures to identify and recruit potentially eligible patients and check for inclusion and exclusion criteria; informed consent
Randomization & blinding	Procedure used to randomize patients using a website
Ethical considerations	Protection of participant confidentiality and privacy Compliance with ethical guidelines and regulations
Clinic visits	Which variables are to be measured at baseline and at specific time-points during follow-up and how they will be measured
Intervention/exposure/predictors & comparison group	Detailed description of the intervention and the control groups (for unblinded studies)
Study variables	Detailed instructions on how the primary outcome variable and other important variables will be measured, including adverse events that will be measured
Quality control	Responsibilities, training of data collection team, and equipment calibration and maintenance
Data management	How data will be collected and stored; confidentiality; plan for backups
Data analysis	A detailed data analysis plan
Emergency procedures	Protocols for managing medical emergencies during study visits
Communication plan	Procedures for communication among study staff, investigators, and participants Contact information for key study personnel
Appendices	Questionnaires, forms

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used in these studies are complex and need to be well standardized, but descriptive studies are not exceptions.[1] In the case of the PLATINO study, despite cultural, social, and economic disparities among Latin-American cities, the use of a MOP, which included standardized instructions on how to perform a spirometry test, enabled the execution of high-quality research, addressing crucial research questions and establishing the prevalence and severity of COPD in major cities of Latin America.

WHAT GOES IN A MOP?

All study procedures should be included in the MOP. In the PLATINO study, for example, there was a section dedicated to training and certification of study staff to perform spirometry. In addition, there was detailed description on how to perform an acceptable spirometry test and the accepted variability for selected maneuvers. Even simpler procedures, such as the technique to measure anthropometric variables were detailed, as well as the sampling procedure. As individuals were recruited from Portuguese and Spanish speaking cities, the questionnaires were validated for both languages. The MOP meticulously describes procedures, anticipates data variability, addresses recruitment and follow-up errors, and delineates strategies to minimize bias and maximize quality control, assuring validity and generalizability to the target population.

TIPS TO WRITE A MOP

- Describe in depth all the procedures used in the study, like a recipe.
- Be systematic and anticipate all possible misunderstandings; be accurate.
- Ask for feedback from the study team to check for any errors.
- Implement strategies to minimize errors and plan for possible solutions.
- Remember, all investigators and study staff will consult the MOP and are expected to follow the instructions.

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The role of the pulmonary function laboratory to assist in disease management: pulmonary hypertension

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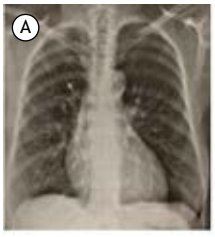
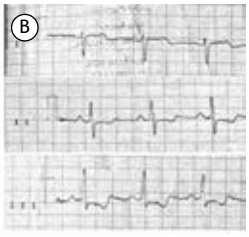
INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease associated with high mortality due to right ventricular dysfunction. During PAH diagnostic workup, pulmonary function tests (PFTs) are essential to exclude relevant parenchymal lung disease. PFTs additionally provide information on PAH severity and prognosis.

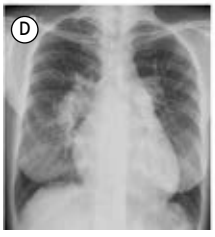
OVERVIEW

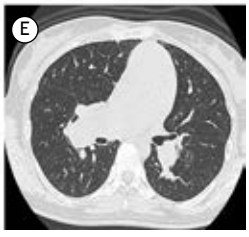
A 22-year-old woman reported a five-year history of progressive dyspnea, functional class II. After a detailed diagnostic workup, an idiopathic PAH (IPAH) diagnosis was made, and bosentan was started. Baseline PFT revealed an obstructive ventilatory pattern with normal lung volumes and a decreased DL_{CO} (Panel 1A-C). She had never smoked and had no previous asthma diagnosis. During follow-up, the patient was treated with add-on triple therapy and was listed for lung transplantation. Eleven years after the onset of the disease, enlarged pulmonary arteries were evident by chest imaging. PFT showed a decrease in FVC, FEV_1, and FEV_1/FVC, with signs of air trapping and reduced DL_{CO} and K_{CO} (Panel 1D-F). In patients with PAH, a decreased DL_{CO} is expected; however, without lung volume abnormalities. Additionally, DL_{CO} is a marker of disease severity,[1-3] and a DL_{CO} < 45% is related to aging, smoking history, lower exercise capacity, and worse survival on PAH.[3] K_{CO} adds information to PFT interpretation, and low levels associated with normal V_A are suggestive of pulmonary vascular disease or intrapulmonary right-to-left shunting, signaling inefficient gas exchange.[4] Both restrictive and obstructive PFT patterns have been described in PAH patients. It has been demonstrated that the worsening of lung function is related to PAH severity.[1-3] Notably, obstructive disturbance among PAH patients is more frequently found in congenital heart disease and connective tissue disease.[3] A recent study has demonstrated that patients with IPAH without lung disease have a better five-year-survival compared with those with mild lung disease (70% vs. 22%, respectively; $p < 0.0001$). However, the mechanisms underlying lung function disturbances in PAH remain unclear. The hypotheses of airflow obstruction are speculative, as an inflammatory response could have similar effects on vascular and airway smooth musculature, causing a proliferation in small airway wall thickening. Another possible explanation includes "competition for space" between hypertrophied vessels and distal airways within the interstitial space.[1,2] Recently, Rahaghi et al. analyzed PFT at baseline and at the time of lung transplantation in PAH and found a reduction in FEV_1, FVC, and FEV_1/FVC over time. There was no evidence of parenchymal or airway disorder in the pathology. Airflow obstruction correlated best with an expanded thoracic blood volume and increased pulmonary artery diameter despite unchanged pulmonary hemodynamics. In this context, airway compression secondary to pulmonary





C	Spirometry, Lung Volumes and DLco (baseline-IPAH diagnosis)		
FVC,L (pred)	3.10 (88%)	TLC,L (pred)	4.29 (82)
FEV_1,L (pred)	2.09 (67%)	RV, L (pred)	1.19 (118)
FEV_1/FVC	0.67	RV/TLC	0.28
$MEF_{25-75\%}$ (pred)	28%	DLco,ml/min/mmHg (pred)	20.5 (76%)





F	Spirometry,Lung Volumes and DLco (11 years after diagnosis- before lung transplantation)		
FVC,L (pred)	2.36(70%)	TLC,L (%pred)	4.70 (90)
FEV1,L (pred)	1.50(51%)	RV,L (%pred)	2.17 (173)
FEV1/FVC	0.63	RV/TLC	0.46
$MEF_{25-75\%}$ (pred)	26%	DLco,ml/min/mmHg (pred)	16 (57%)
		Kco,ml/min/mmHg/L (pred)	3.91 (70%)
		V_A/TLC	0.89

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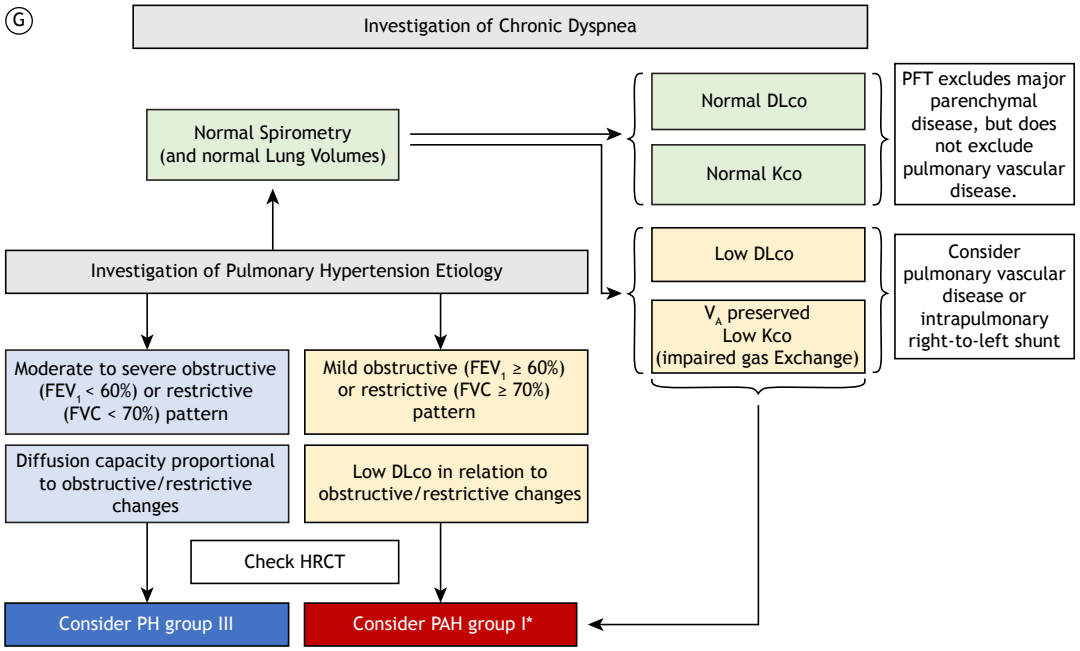

Panel 1. Female, 22 years of age, functional class II at baseline, diagnosed with idiopathic pulmonary arterial hypertension. Echocardiogram showed dilatation of the right chambers and increased systolic pulmonary pressure (sPAP = 50 mmHg), confirmed by right heart catheterization. In A, a chest X-ray was normal (a slight increase of left mediastinum). In B, an electrocardiogram (I, II, and III derivations) revealed right heart chambers overload. In C, baseline pulmonary function test (PFT) revealing mild obstructive ventilatory pattern, normal lung volumes, and a slightly decreased DL_{CO}. Follow-up after 11 years, one year before lung transplantation, functional class III, echocardiogram with sPAP = 116 mmHg: in D, a chest X-ray showing increased pulmonary trunk and right interlobar artery; in E, a chest CT scan showing aneurismatic pulmonary trunk and central pulmonary arteries, with centrilobular nodules in parenchyma; and in F, PFT results showing moderate obstructive ventilatory pattern with air trapping and decreased DL_{CO} and K_{CO}. In G, a flow chart showing the PFT approach for investigation of chronic dyspnea and pulmonary hypertension: consider interpretation according to normal or altered spirometry (arrows). *Similar findings for patients with chronic thromboembolic pulmonary hypertension without comorbidities. $MEF_{25\%-75\%}$: mid-expiratory flow; V_A: alveolar volume; PH: pulmonary hypertension; and PAH: pulmonary arterial hypertension.

arteries dilatation may be a potential mechanism of peripheral airway obstruction in PAH.[4] Regarding DL_{CO}, the reduction could be explained by increased alveolar-capillary membrane thickness related to endothelial cell proliferation and reduced perfused pulmonary capillary bed. However, the loss of alveolar-capillary membrane diffusing capacity and lung capillary blood volume could also explain a reduced DL_{CO} in PAH.[1,2,5]

CLINICAL MESSAGE

PFTs provide valuable information to monitor disease severity and prognosis in PAH. There is a continued interest in understanding the pathophysiology of lung function disturbances in PAH, aiming to improve PAH phenotyping and the potential impact on new targeted treatment approaches. An approach for PFT interpretation in the scope of chronic dyspnea and the investigation of PH etiology is described (Panel 1G).

AUTHOR CONTRIBUTIONS

EVMF: elaboration, writing, and review. JSL: elaboration and writing. RKFO: review. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Atypical bacterial respiratory infections in children

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INTRODUCTION AND EPIDEMIOLOGY

Mycoplasma pneumoniae and *Chlamydia pneumoniae* commonly cause mild infections of the respiratory system. *M. pneumoniae* infections are most common in young adults and school-aged children, but they can affect anyone. The number of *M. pneumoniae* infections varies over time, with peaks of disease every 3 to 7 years. *M. pneumoniae* infections can happen any time of the year. However, they may be more common in summer and early fall. The most common manifestation of *M. pneumoniae* infection is tracheobronchitis (chest cold). Common symptoms of a chest cold include sore throat, tiredness, fever, and slowly worsening persistent cough. *C. pneumoniae* infection can cause sore throat and ear or sinus infection. *C. pneumoniae* can also cause lower respiratory tract infections such as bronchitis. Sometimes these bacteria can cause more serious lung infections that require care in a hospital. Pneumonias caused by atypical pathogens are common etiologies and make diagnosis challenging due to their nonspecific radiological and clinical presentation. Atypical germs have been responsible for up to 23% of pneumonias in children. Clinical manifestations of atypical respiratory infections may be subacute, characterized by constitutional symptoms, with the possibility of overlapping with typical signs of conventional bacterial infections (e.g., *Streptococcus pneumoniae*). This article aims to discuss the diagnostic criteria, management, prognosis, and preventive measures related to atypical respiratory infections in children (Chart 1).[1,2]

DIAGNOSIS

The diagnosis of atypical respiratory infections in children primarily relies on clinical history, age, and response to initial empirical treatment. An insidious onset, coupled with other symptoms such as headache, malaise, nonproductive cough, and low-grade fever, often suggests infections by atypical bacteria. However, despite multiple clinical presentations described in the literature, signs, symptoms, and radiological findings lack sufficient precision to differentiate atypical agents from other etiologies.[1,3]

Regarding laboratory evaluation, testing for *M. pneumoniae* or *C. pneumoniae* is indicated only in severely ill hospitalized children. Nasopharyngeal samples can be obtained, with tracheal aspirates being an option in intubated patients. When confirmation of *M. pneumoniae* or *C. pneumoniae* infection is necessary, PCR-based assays are preferable. PCR-based assays have high sensitivity and specificity, but should be correlated with clinical findings as they do not differentiate acute from previous recent infection. Culture may be an alternative for etiological identification but is rarely used due to the delay in obtaining results. Serological testing has commercially available kits but lacks specificity.[4]

For the confirmation of *M. pneumoniae* or *C. pneumoniae* infection, it is necessary to detect the microorganism or a specific antibody response, along with a compatible clinical syndrome. Confirmation can be achieved through convalescent serology or clinical improvement with specific therapy. Laboratory tests are indicated only if they impact patient management, especially in severe cases or if antimicrobial therapy does not cover atypical germs. In hospitalized patients with community-acquired pneumonia, especially those immunocompromised or presenting with risk factors or extrapulmonary manifestations, testing for *M. pneumoniae* and *C. pneumoniae* may be recommended. In summary, PCR assays in respiratory samples are preferred, but serology is a reasonable alternative if PCR is not available.[5] *C. pneumoniae* can also cause chronic infection. Some experts suggest that chronic *C. pneumoniae* infection might contribute to chronic conditions, such as difficult-to-treat or severe asthma.

RECOMMENDED MANAGEMENT

The initial empirical treatment of pneumonia should be initiated considering the patient's age and clinical presentation, as the pathogen is usually unknown at the time of initial diagnosis.[3] Furthermore, for children older than 3-5 years of age with inadequate response to usual treatment for typical pneumonia agents, particularly if there is bilateral pulmonary infiltrate, along with wheezing, testing for atypical agents may be considered, and empirical treatment against these agents may be added.[6]

In cases of suspected or confirmed infection with *C. pneumoniae* or *M. pneumoniae*, the first choice for oral treatment is azithromycin for 5 days. Azithromycin is the preferred option for these agents due to its high efficacy, prolonged half life, and low incidence of adverse effects. Other options include clarithromycin and levofloxacin. If parenteral treatment is necessary, the first option is intravenous macrolides, levofloxacin also being an option.[6]

C. pneumoniae is resistant to trimethoprim, sulfonamides, aminoglycosides, and glycopeptides. Penicillins have shown in vitro activity against *Chlamydia*

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Chart 1. Atypical respiratory infections.

Etiologic Agent	Respiratory Manifestations	Clinical Presentations	Diagnosis	Treatment
Mycoplasma pneumoniae	**Pneumonia** Acute Bronchitis Upper Respiratory Tract Infection Asthma Exacerbation	Insidious onset Constitutional symptoms Non-productive cough Low-grade fever	Detailed medical history PCR test or serology Chest X-ray	broad-spectrum macrolides Azithromycin orally for 5 days Alternatives: Clarithromycin, Erythromycin Parenteral treatment, if necessary, with Azithromycin, Erythromycin, or Levofloxacin (> 6 months of age)
Chlamydia pneumoniae	**Pneumonia** Rhinitis Sinusitis Pharyngitis Laryngitis Acute Bronchitis	Children > 3-5 years old No response to usual treatment Perihilar and bilateral pulmonary infiltrate with wheezing	Detailed medical history PCR test or serology Chest X-ray	

spp., but are not recommended.[1] Resistance to macrolides emerged in *M. pneumoniae* and has been increasing since the 2000s. Current data suggest that the overall global prevalence of macrolide resistance in *M. pneumoniae* may be around 28%.[4] However, there is significant geographical variation.

PREVENTION AND PROGNOSIS

C. pneumoniae and *M. pneumoniae* are transmitted through person-to-person contact or via fomites. Thus, frequent handwashing, use of personal protective masks, and avoidance of contacts with symptomatic individuals are recommended for prevention. For patients hospitalized for atypical germ pneumonia or pneumonia of unknown origin, standard precautions are indicated.

In summary, pneumonia caused by atypical pathogens is typically mild and has long-lasting symptoms. Patients frequently recover during treatment without complications. In some children infected with *C. pneumoniae*, there may be prolonged cough, with an average duration of 25-30 days. The vast majority of children treated for pneumonia due to *M. pneumoniae* or *C. pneumoniae* have an excellent prognosis and fully recover.[1]

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AUTHOR CONTRIBUTIONS

PBB, LFX, ECH and MFGMF contributed to searching and writing. ICSF and LAP contributed to writing, reviewing, and editing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Identifying malignant mesothelioma by a pathological survey using the São Paulo state hospital cancer registry, Brazil

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Study carried out under the auspices of the "*Projeto interdisciplinar sobre a exposição ocupacional ao asbesto e seus efeitos sobre a saúde no Brasil.*"

ABSTRACT

Objective: To review the pathological diagnosis of possible cases and/or hidden cases of malignant mesothelioma (MM) between 2000 and 2012 using the Hospital-Based Cancer Registry database in the state of São Paulo, Brazil. **Methods:** Possible cases were retrieved by assessing the database. Inclusion criteria were being older than 30 years of age and having ICD-O-3 topography and morphology codes related to MM. A board of expert pathologists reviewed the pathology reports and requested paraffin blocks in cases that demanded revision. After staining with calretinin, D2-40, WT-1 (as positive MM markers) and Ber-EP4 and MOC31 (as negative MM markers), cases were divided and studied independently by a pair of pathologists to confirm or discard the diagnosis of MM. **Results:** Our sample comprised 482 cases from 25 hospitals, and 130 needed further histological revision. We received 73 paraffin blocks with adequate material. After board analysis, there were 9 cases with a definitive diagnosis of MM, improving the diagnostic rate in 12%. Two cases of previously diagnosed MM were discarded by review. **Conclusions:** Our results confirm that part of MM underdiagnosis and underreporting in Brazil is due to incomplete or mistaken pathological diagnosis.

Keywords: Mesothelioma, malignant/pathology; Mesothelioma, malignant/diagnosis; Immunohistochemistry; Registries.

INTRODUCTION

Malignant mesothelioma (MM) is the commonest primary cancer of the pleura,[1] but it also occurs in other mesothelial tissues such as the peritoneum, pericardium, and tunica vaginalis. It is a rare cancer, strongly linked to occupational and environmental asbestos exposure with a long latency period. MM has an attributable fraction (AF) to asbestos of approximately 90% in men, while it is lower in women.[2] The lower AF in women possibly represents our failure to identify non-occupational exposures in history taking.[3] It is the fingerprint of asbestos consumption in a given society. Due to its rarity and strong link with asbestos, specific registries were implemented in industrialized countries to improve surveillance, to investigate, and to analyze disease distribution, diagnosis, and compensation.[4] Between 1993 and 2015, the Italian MM registry (designated ReNaM) compiled 27,356 MM cases, from which 93% were pleural, 6.5% were peritoneal, and the remaining 0.5% was pericardial or in the tunica vaginalis.[5]

In addition to Italy, other countries have established national registries for MM: Australia, France, Germany, the UK, and New Zealand are examples. Recognized as another sound experience, Australia registered 14,271 MM cases between 2000 and 2020: 11,633 (81.5%) and 2,638 (18.5%) were in men and in women, respectively. Restricting cases to those diagnosed between 2010 and 2020, 93.7% of those were pleural, 5.5% were peritoneal, 0.2% occurred in the tunica vaginalis, 0.1%

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was in mediastinum, 0.1% was pericardial, and 0.5% occurred elsewhere (overlapped or unknown sites).[6]

In Brazil, by linking five health information systems between 1996 and 2017, 2,405 MM-related deaths (as the underlying or the contributing cause of death) were retrieved, of which 74.7% were pleural or unspecified and 17.3% were peritoneal.[7] Since the 1960s, approximately 9 million tons of chrysotile and small amounts of anthophyllite were produced and about 7 million tons of asbestos were consumed in Brazil.[8] The production and consumption of asbestos-containing products were mostly concentrated in the southeastern region of the country, particularly in the state of São Paulo.[9]

The underdiagnosis of MM and the underreporting of the deaths of these patients is global.[10] In Brazil, the small number of records of asbestos-related diseases in vital statistics, its work-relatedness, and the few studies addressing the subject limit the understanding of the burden of those diseases. A compilation of records between 2008 and 2014 from hospital admissions, hospital cancer registries, and compulsory disease registry added one third of MM-related deaths to those registered in the Brazilian mortality database.[11] Based on death certificates between 1996 and 2010, 976 MM records were found, with a male-to-female ratio of 1.4:1, while the number of deaths increased from 44 in 1996 to 85 in 2010.[12] Considering the period between 2000 and 2012, a study reported that MM was the underlying cause of death in 929 cases and that the mortality rate in the state of São Paulo was increasing.[9] Both studies pointed out potential underdiagnosis and/or underreporting, given the small number of deaths and the massive asbestos consumption during the period. To foster suspicion, investigation, and diagnosis of pleural MM, a Brazilian guideline has recently been published.[13]

The pathological diagnosis of MM remains challenging and may contribute to underreporting. Diffuse mesotheliomas involving the pleura, pericardium, and peritoneum are heterogeneous tumors, including three main histological subtypes: epithelioid (60-80%), sarcomatoid—including desmoplastic—(< 10%), and biphasic subtypes (10-15%).[14] However, in most cases, these subtypes can mimic other secondary neoplasms, especially adenocarcinomas, mainly when examining limited specimens, such as effusion specimens and small tissue biopsies. To distinguish mesothelioma from other tumors, metastases, or primary malignancies, an immunohistochemistry panel comprising pancytokeratin (multiple keratins, such as AE1/AE3) plus a minimum of two positive and two negative mesothelial markers are recommended.[14,15] Some markers have more specificity whereas others have more sensitivity, but none of the antibodies used for the diagnosis of MM are 100% sensitive or specific. It is recommended that the panel should have sensitivity or specificity greater than 80%, and the interpretation of immunostaining should consider the localization of the marker (membrane, nucleus, cytoplasm) and the proportion of positive cells, of which more than 10% has been suggested for cytoplasmic membranous markers.[16] In addition, negativity for the mentioned mesothelial antibodies does not exclude the diagnosis of pleural MM since 30% of these cases present a "null" phenotype.[17] When facing complex cases, pathologists should seek for an expert second opinion and refer to national mesothelioma panels,[16] which do not exist in Brazil.

Given the pathological diagnostic challenges associated with MM and variations in expertise among pathologists, coupled with differences in access to diagnostic tools, our hypothesis was that MM may be underdiagnosed within hospitals participating in the Hospital-Based Cancer Registry (HBCR) in the state of São Paulo. As of June of 2021, the HBCR network in the São Paulo state comprises 77 hospitals, providing coverage across all regions of the state.[18] Between the years 2000 and 2022, the database recorded a total of 1,159,914 cancer cases.[18]

The objective of this study was to create a pathology board of specialists and review the diagnosis of possible cases and/or hidden cases of MM retrieved from the HCBR database in the São Paulo state between 2000 and 2012 by picking on selected topographies and presenting inconsistencies in the original pathology reports. This study is part of the Interdisciplinary Project on Occupational Exposure to Asbestos and its Health Effects in Brazil that aims at investigating the burden of asbestos-related diseases by using Brazilian health information systems.

METHODS

Case search and selection

We identified the potential cases by assessing the HBCR database. State public hospitals were the majority of the facilities in the period between 2000 and 2012. The inclusion criteria were as follows: subjects older than 30 years of age; topographic codes according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3): mediastinum, pleura, pericardium, and peritoneum; and ICD-O-3 morphology codes that could be differential diagnoses for MM (Table 1).[19] For instance, an undifferentiated carcinoma (morphology) of the pleura (topography) was considered a potential case to be reviewed by the pathology board.

Of the 75 hospitals that composed the registry network in 2012, 55 reported 864 cases within the selected topographies/morphologies. We arbitrarily selected hospitals that reported at least ten registries with the abovementioned criteria, comprising 716 cases. No attempt was made to contact the remaining 30 hospital units.

In sequence, the pathological reports of the selected cases were requested and were reviewed by the pathology board, composed of eight pathologists with expertise in pulmonary and/or oncological pathology.

Each report was classified according to the necessity of revision or not. Cases were confirmed as mesothelioma or non-mesothelioma if immunohistochemistry test

Table 1. International Classification of Diseases for Oncology, 3rd edition (ICD-O-3)-based topography and morphology codes to identify possible undiagnosed malignant mesothelioma cases.

ICD-O-3	Topography code
C38.1	Anterior mediastinum
C38.2	Posterior mediastinum
C38.3	Mediastinum, part unspecified
C38.4	Pleura
C38.8	Overlapping lesion of heart, mediastinum and pleura*
C48.0	Retroperitoneum
C48.1	Specified parts of peritoneum
C48.2	Peritoneum, unspecified
C48.8	Overlapping lesion of retroperitoneum and peritoneum*
ICD-O-3	Morphology code
M8000/1	Neoplasm, uncertain whether benign or malignant
M8000/3	Neoplasm, malignant
M8010/2	Carcinoma in situ, NOS
M8010/3	Carcinoma, NOS
M8012/3	Large cell carcinoma, NOS
M8020/3	Carcinoma, undifferentiated, NOS
M8031/3	Giant cell carcinoma
M8033/3	Pseudosarcomatous carcinoma
M8050/3	Papillary carcinoma, NOS
M8070/3	Squamous cell carcinoma, NOS
M8140/3	Adenocarcinoma, NOS
M8211/3	Tubular adenocarcinoma
M8230/3	Solid carcinoma, NOS
M8244/3	Composite carcinoid
M8260/3	Papillary adenocarcinoma, NOS
M8313/3	Clear cell adenocarcinofibroma
M8800/3	Sarcoma, NOS
M8804/3	Epithelioid sarcoma
M8980/3	Carcinosarcoma, NOS
M9050/3	Mesothelioma, malignant or NOS
M9051/3	Fibrous mesothelioma, malignant or NOS
M9052/3	Epithelioid mesothelioma, malignant or NOS
M9053/3	Mesothelioma, biphasic, malignant or NOS

NOS: not otherwise specified.

results present in the reports had an adequate panel of markers. In all other cases, we requested the corresponding paraffin blocks from each institution to perform the pathological review. In none of the cases we had access to clinical data.

Pathological review

New sections were performed from the paraffin blocks, which were routinely immunostained with five immunohistochemical markers: calretinin, D2-40, and WT-1 (as positive MM markers), as well as Ber-EP4 and MOC31 (as negative MM markers). Briefly, 5-µm thick sections were deparaffinized, and a 0.5% peroxidase in methanol solution was applied for five minutes to inhibit endogenous peroxidase activity. Antigen retrieval was performed with citrate solution for 20 min. Sections were incubated overnight with antibodies, and 3,3 diaminobenzidine (Sigma Chemical Co., St Louis, MO, USA) was used as a chromogen. The sections were counterstained with Harris hematoxylin (Merck, Darmstadt, Germany). All primary and secondary antibodies were applied to negative and positive controls.

The cases were then sorted out among pathologists, divided into four groups of paired pathologists who received a set of slides (those stained with H&E, and those stained with each of the five immunohistochemical markers), and previous pathological reports with the results of any available immunohistochemistry panel. Cases were duly labeled for a blind reading without knowledge of the original institution. Each pair reviewed independently the cases to confirm or discard the diagnosis of MM.

The discordant cases were digitized for review by the pathologist board using a panoramic scanner (Pannoramic SCAN; 3DHISTECH Ltd., Budapest, Hungary). Due to the COVID-19 pandemic, in-person board meetings could not be performed as previously planned. Each pathologist received the scanned images prior to the synchronous virtual meetings. During the meetings, images were conjunctively reviewed, and a consensus diagnosis was reached.

All reviewed cases were classified as confirmed for mesothelioma; mesothelioma discarded; inconclusive for mesothelioma; and inadequate for analysis. For confirmation of mesothelioma diagnosis, at least two mesothelioma markers had to be positive, and Ber-EP4/MOC31 had to be negative. Cases were considered inadequate when there was no sufficient tumor for analysis or if it contained extensive artifacts. Cases were considered inconclusive when the histological aspect was suspected for mesothelioma, but only one MM marker was positive, or one MM/one carcinoma marker was positive.

Ethical approval

This study was approved by the Research Ethics Committee of the *Instituto de Saúde Coletiva*, *Universidade Federal da Bahia*, located in the city of Salvador, Brazil (CAAE no. 36547514.9.0000.5030).

RESULTS

There were 25 public hospitals that had more than 10 registries of confirmed mesothelioma or needing revision in the study period, to which we requested the corresponding pathological reports. Thirteen hospitals had more than 20 cases, and 12 had between 10 and 19 cases diagnosed with MM during the study period. According to the inclusion criteria, 716 cases were selected. Demographic data, topography, and the number of cases diagnosed as MM in the registry database are shown in Tables 2 and 3.

Figure 1 depicts the study flow chart for the selected 716 cases. After contacting each institution, we

received 482 pathology reports from 11 hospitals, all of which from services reporting more than 20 cases and mostly from state referral oncology or university hospitals. The remaining hospitals did not reply, refused to send materials, or had already discarded the blocks. Of the 482 reports, 130 had the diagnosis of MM, and 222 had the diagnosis of MM discarded, since all of the diagnostic criteria were complete in the pathological reports. After analyzing the pathological reports, 130 cases were selected for histological review. After requesting the blocks to the hospitals, we received 77 paraffin blocks, from which 73 had adequate material for analysis. The four discarded blocks were not representative of the tumor or were insufficient to carry out further analyses.

Table 2. Demographic data and topography of the 716 cases with topography related to malignant mesothelioma in 25 public hospitals in the São Paulo State Hospital Cancer Registry.

Variable	Result
Cases, n	716
Sex M/F, n	429/287
Age, years (mean)	60
Topography, n	
Mediastinum	171
Peritoneum	118
Pleura	256
Retroperitoneum	171

Table 3. Demographic data and topography of the 179 cases with the diagnosis of MM. in 25 public hospitals of the São Paulo State Hospital Cancer Registry.

Variable	Result
Cases, n	179
Sex M/F, n	118/61
Age, years (mean)	60
Male	60
Female	59
Topography, n	
Mediastinum	1
Peritoneum	33
Pleura	131
Retroperitoneum	13

After analysis by the board of pathologists, we had as final diagnoses nine cases of confirmed MM, 58 MM diagnosis discarded, and six cases remained inconclusive. Of the nine confirmed mesothelioma cases, there were three *de novo* diagnoses, and six had the MM diagnosis confirmed by the immunohistochemistry panel that had not been performed before. All MM cases were of epithelioid morphology. Two cases of previously diagnosed mesothelioma were discarded by review. Of the inconclusive cases one had a sarcomatous aspect, three showed epithelioid morphology, and two had an anaplastic aspect. Demographic and topographic of the newly diagnosed or confirmed cases of mesothelioma are shown in Tables 4 and 5.

DISCUSSION

In this study, by reviewing the pathology of cases registered at the São Paulo State HBCR between 2000 and 2012 that presented a topography of MM but inadequate pathological workout, we were able

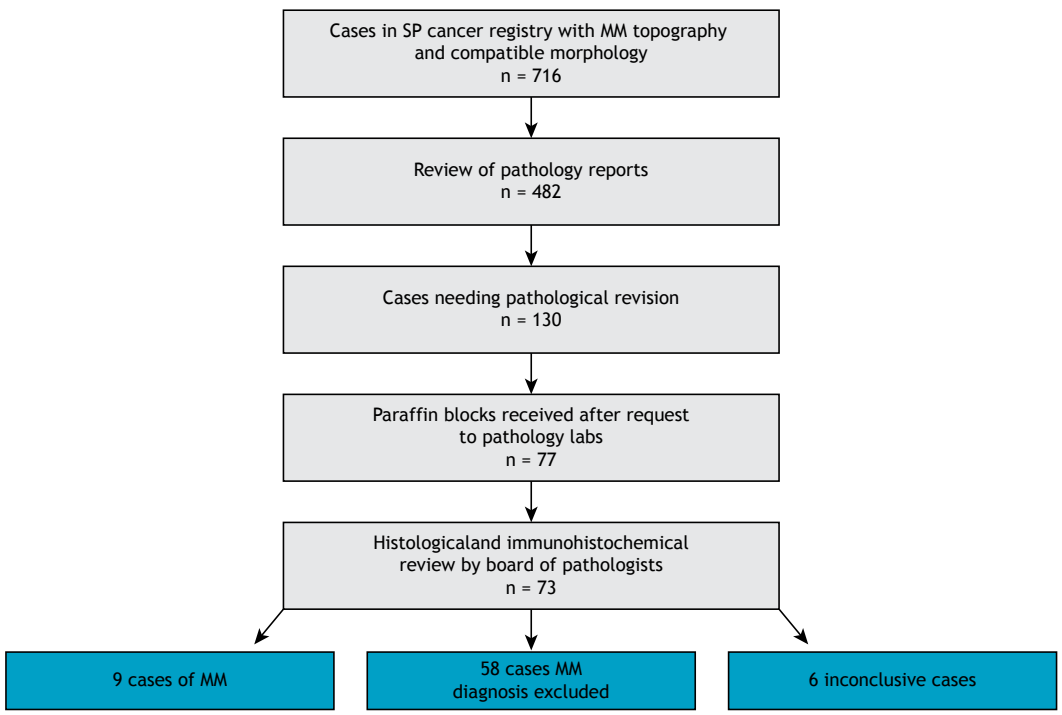

Figure 1. Flow chart showing the different steps of the study. N represents reports and tissue blocks received after request to the corresponding hospitals and pathology laboratories. SP: São Paulo; and MM: malignant mesothelioma.

to increase the MM diagnostic rate in 12%, which is substantial considering the rarity of this malignancy. Our results confirm that part of MM underrecognition and underreporting in Brazil is due to incomplete or mistaken pathological diagnosis. To our knowledge, this is the first study on MM in Brazil with a board of specialized pathologists to review cases that could improve MM diagnosis in the country.

Despite our best efforts in contacting hospitals and pathology services, we were unable to retrieve pathological reports or tissue specimens for revision from 14 of 25 pathology laboratories, 12 of which from smaller hospitals that had at least ten cases during the study period. It is not uncommon that smaller and non-academic hospitals make use of third-party laboratories that may change overtime, have no expert pathologists, or have no complete access to immunohistochemistry panels, increasing the chance of misdiagnosing MM cases. Indeed, most of the cases that we investigated came from larger university hospitals or oncological centers with expert pathologists and adequate panels, which make our findings likely to be underrepresented and underestimated. In addition, São Paulo state laws authorize to discard slides and paraffin blocks after five years.[20] Several steps to overcome this situation should be taken, starting with the creation of a pathology network and financial support for the purchase of antibody panels with the objective of offering expert advice for difficult or suspicious cases. An MM registry, either regional or national, may be a future goal to be pursued, but it demands a complex structure, including integration of the country's health care systems, a dedicated staff, expert consultancy of hygienists, social service workers, and health professionals, as well as specific and long-lasting financing.[21]

Our data confirm the challenges for the pathological diagnosis of MM and the necessity of clinical information for definitive diagnosis. Even with a board of expert pathologists and recommended immunohistochemistry panels, six cases (8%) remained inconclusive based on pathology alone, as were the cases with sarcomatous or anaplastic aspects, which had inconclusive immunohistochemistry test results.[14,15] A multidisciplinary team is indeed necessary to reach a final diagnosis in difficult cases, especially considering the occupational connection of MM and the legal consequences of an MM diagnosis. In Quebec, Canada, less than a quarter of MM cases identified in the Quebec Tumour Registry were compensated as an occupational disease.[22] These prompted investigators to study if there was an overregistration of MM cases. An expert panel composed of one pathologist, one radiologist, and one pulmonologist reviewed available materials from cases diagnosed between 2001 and 2002 in provincial hospitals using guidelines defined for pathological diagnosis and/or clinical and radiological data when pathological specimens were unavailable. After analyzing charts with good quality data, they found that 88% of the cases were correctly diagnosed, and MM was not confirmed in 9-11% of the cases. The authors concluded that the provincial registry was a valid source of information.[22]

In this study, two cases previously regarded as MM were discarded after review by the pathology board. One case of pleural MM was considered a metastasis of an adenocarcinoma, and one that had epithelioid features had no positive markers for mesothelioma or adenocarcinoma. These data reinforce that, in the absence of adequate MM panels, the diagnosis must be done with extreme caution.

Table 4. Final diagnosis of 73 potential cases with topography and morphology for malignant mesothelioma (MM) with available paraffin blocks for revision.

Variable	Result
Cases, n	73
Sex M/F, n	52/21
Age, years (mean)	61
Male	59,5
Female	64
Topography, n	
Mediastinum	15
Peritoneum	9
Pleura	28
Retroperitoneum	21
Final diagnosis	
MM	9
Prior diagnosis of MM discarded	2
Inconclusive for MM	6
Discarded for MM	56

Table 5. Confirmed cases of malignant mesothelioma after final review of the pathology board.

Case	Age	Sex	Topography	Initial diagnosis
1	55	male	Pleura	Epithelioid Mesothelioma
2	61	male	Retroperitoneum	Sarcoma
3	68	male	Pleura	Epithelioid Mesothelioma
4	59	male	Mediastinum	undifferentiated malignant neoplasm, epithelioid pattern favoring mesenchymal lineage
5	66	male	Pleura	Adenocarcinoma
6	70	female	Pleura	Pleomorphic Carcinoma x mesothelioma
7	68	female	Pleura	Metastatic Adenocarcinoma
8	68	male	Pleura	Undifferentiated malignant neoplasm, suggestive of mesothelioma
9	60	male	Pleura	Epithelioid Mesothelioma

A major limitation of this study includes its retrospective design. We had no access to clinical and/or radiological information, which could have contributed to diagnostic conclusions. Of the 11 hospitals that sent pathology reports, only two were non-specialized cancer hospitals or university-related services. Also, the lack of access to pathology specimens from 14 hospitals, whose majority (n = 12) were general non-specialized hospitals, may have contributed to an underestimation of MM hidden cases.

In Brazil, asbestos consumption persisted until 2018, and chrysotile mining and exports are still active. Based on consumption data until 2012, it was expected that MM would reach its peak incidence in Brazil by 2026.[8] Between 1996 and 2017, MM-related mortality was on the rise, faster for men, presenting with a 6% annual mean increase, while it was less than 1% among women.[6] Part of MM underdiagnosis has its origin during pathological diagnosis, and, therefore, pathologists must be alert to identify MM cases, seeking expert advice and working in a multidisciplinary manner, thereby increasing the quality of cancer registries in this country.

AUTHOR CONTRIBUTIONS

FDCB, MD, and TM: study design; data analysis; and drafting, editing, and review of the manuscript. EA: conceptualization; study design; data analysis; funding acquisition; and drafting, editing, and review of the manuscript. CALP, IMO, ENAMC, ECAS, and AJFN: data analysis; and editing and review of the manuscript. DV, CL, and DR: data acquisition and analysis; and editing and review of the manuscript. RL: study design; data acquisition and analysis; and editing and review of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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Lung ultrasound teaching in medical education: a pilot study at a Brazilian medical school

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ABSTRACT

Objective: To evaluate cognitive learning, ability to perform and interpret lung ultrasound exams, and self-perception of learning among medical students after a short pedagogical intervention at a medical school in Brazil. **Methods:** An experimental pilot study was conducted with medical students at different stages of their education (basic cycle, clinical cycle, and medical internship). The participants underwent a cognitive test before and after the intervention, a practical test, a test to recognize lung ultrasound pathologies, and a qualitative evaluation test at the end of the intervention. Statistical analysis was performed using a significance level of $p < 0.05$. **Results:** A total of 42 students were included in the study, with a median age of 23 years and a predominance of males. The mean score of the pre-intervention cognitive test was 2.97 ± 0.87, and that of the post-intervention test was 6.57 ± 1.41, showing significant improvement ($p < 0.001$). The score of the practical test and that of the recognition of pathologies test also showed significant improvement after the intervention. There was no significant difference in execution time between the groups. Students in the clinical cycle had a better self-perception of learning. **Conclusions:** Theoretical teaching and practical training of lung ultrasound in a short pedagogical intervention can improve cognitive performance, practical skills, and interpretation of the exam. The level of learning achievement was higher among more advanced students in medical education. Additionally, the students in the clinical cycle had a better perception of their learning.

Keywords: Ultrasonography; Lung; Students, medical; education, medical.

INTRODUCTION

Point-of-care ultrasound (POCUS) is a tool used by non-imaging specialist physicians to answer clinical questions and aid in medical decision-making. It enhances the accuracy of bedside diagnoses, enables real-time monitoring of critically ill patients, and improves the safety of guided procedures.[1]

Initially established in emergency medicine with the Focused Assessment with Sonography for Trauma (designated FAST) protocol,[2] POCUS has now become an essential component of clinical evaluation and critical patient assessment in ERs and ICUs.[3-5]

As a consequence of the inclusion of POCUS in daily clinical practice, medical education programs have also started incorporating POCUS training into their curricula, especially in the United States.

Even though we do not have a Brazilian consensus on the inclusion of POCUS in medical undergraduate education, with the increasing number of publications on the subject it is becoming clear that integrating POCUS education into medical undergraduate programs can enhance the performance of and understanding of physical examinations by medical students, along with a subjective improvement in their confidence in examinations.[7]

Various models for incorporating ultrasound into the curriculum have been proposed in the literature, with a focus on longitudinal integration from basic disciplines such as anatomy to clinical practice.[6,8] Despite the emphasis on the longitudinal model, brief training sessions covering cognitive, practical, and clinical integration aspects are already capable of positively impacting diagnostic accuracy of students and assisting in decision-making. This highlights the need to encourage the inclusion of training, even if brief, in undergraduate curricula.[9]

Among the numerous challenges in implementing POCUS education in Brazil, the lack of official POCUS training or certification, the limited number of qualified professionals to teach the subject, and the absence of a consensus on basic competencies for some specialties are limiting factors for its widespread use.[9]

The main objective of this study was to evaluate the learning of lung ultrasound and the bedside lung ultrasound in emergency (BLUE) protocol[12] among medical students at different stages of their education

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at the Federal University of Santa Catarina, located in the city of Florianópolis, Brazil. The secondary objectives were to compare the learning capacity in terms of cognitive aspects, practical skills, and the ability to recognize lung ultrasound pathologies among students at different stages of their medical education. Additionally, the study aimed to evaluate the students' perception of the teaching and the learning methods employed.

METHODS

An experimental pilot study was conducted at the Federal University of Santa Catarina involving medical students at different stages of their education. The study received ethical approval of the Research Ethics Committee of the Federal University of Santa Catarina (CAE n. 96912918.7.0000.0121), and informed consent was obtained from the participants.

The study included medical students at the 4th, 5th, 7th, 10th, and 11th semesters with the objective of approaching a sample of the basic cycle (4th and 5th semesters; Group A), the clinical cycle (7th semester; Group B), and the medical internship cycle (10th and 11th semesters; Group C). Students who had already undergone some practical ultrasound training were excluded.

In total, the study included 57 participants: 21 in Group A, 16 in Group B, and 20 in Group C.

The study consisted of a short pedagogical intervention focused on lung ultrasound and the BLUE protocol, in four meetings. The intervention included reading two articles, one lecture, and one session of hands-on training. The article "Relevance of Lung Ultrasound in the Diagnosis of Acute Respiratory Failure (The BLUE Protocol)"[12] and the article "Lung ultrasound in critically ill patients: a new diagnostic tool"[13] were shared with the students. The lecture provided an overview of lung ultrasound principles, indications, techniques, and interpretation of findings, lasting two hours. The hands-on training session lasted 90 minutes, during which students, in groups of 8 to 10, had the opportunity to perform and interpret lung ultrasound exams under the guidance of experienced instructors.

Before and after the intervention, the participants underwent several assessments to evaluate their learning outcomes. These assessments included a cognitive test (Test 1), a practical test (Test 2), a test to recognize lung ultrasound pathologies (Test 3), and a qualitative evaluation test (Test 4).

The cognitive test consisted of 22 questions that assessed the participants' theoretical knowledge of lung ultrasound and the BLUE protocol. Test 1 was performed before (Score 1) and after (Score 2) the intervention. The practical test (Test 2; Score 3) assessed the participants' ability to perform the BLUE protocol on a standardized patient (healthy voluntary live model). Participants were evaluated on their technique, accuracy, and interpretation of findings. The test to recognize lung ultrasound pathologies (Test 3; Score 4) presented to the participants five images of lung ultrasound findings and asked them to identify the corresponding pathology. The qualitative evaluation test (Test 4) aimed to gather feedback from the participants regarding the teaching methods, content, and overall learning experience. It included a qualitative questionnaire using a Likert scale about the perspective of learning (Figure 1).

Statistical analyses were conducted using the IBM SPSS Statistics software package, version 2019 (IBM Corporation, Armonk, NY, USA). To assess the normality of variables, a Kolmogorov-Smirnov test was employed. Descriptive analyses were performed for both categorical and numerical variables. Categorical variables were presented as absolute numbers and frequencies, while numerical variables were reported in terms of means and standard deviations for those with a normal distribution. For numerical variables exhibiting non-normal distribution, medians and interquartile ranges were utilized. To compare Score 1 and Score 2 across the three groups (A, B, C) for Test 1, execution time, and Test 3 variables, the chi-square test was employed for categorical variables. Meanwhile, Student's t-test or ANOVA with Bonferroni correction was used for the comparison of numerical variables in repetitive measures. For Score 3 and Score 4, which displayed non-normal distribution, the Mann-Whitney and Kruskal-Wallis tests were applied for comparisons between two or more groups, respectively.

The sample size calculation was based on a gain of at least 2 points between the initial and final scores, considering that the initial score of 5 is a standard deviation of 2, with a power of 80% and a bilateral confidence interval of 95%, which indicated that each group should have 16 members. The level of statistical significance was considered at $p < 0.05$.

RESULTS

All stages of the study were completed by 73.7% (42 of the initial 57) students: 13 in Group A (61.9%), 14 in Group B (87.5%), and 15 in Group C (75.0)%. The distribution between the different cycles of the medical course was equitable, with a median age of 23 years and a predominance of males, as shown in Table 1.

All test results were converted into a score ranging from 0 to 10. Score 1, which represents the total number of correct answers in Test 1 before the pedagogical intervention, had a general mean of 3.83 ± 1.23. The subgroup means for groups A, B, and C were, respectively, 2.97 ± 0.87, 4.19 ± 1.38, and 4.24 ± 1.03. Score 2, representing the total number of correct answers in Test 1 after the pedagogical intervention, had a general mean of 7.22 ± 1.33. The subgroup means for groups A, B, and C were 6.57 ± 1.41, 6.98 ± 1.49, and 8.00 ± 0.59, respectively.

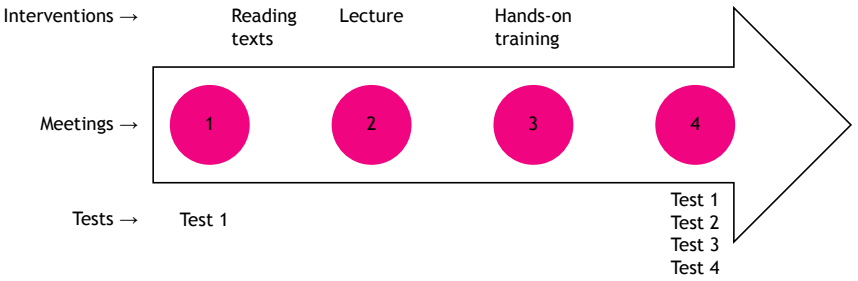

Figure 1. Study design showing the timeline of the study with chronological orientation of the four meetings and moments of application of Tests 1, 2, 3 and 4.

Table 1. Demographic data of participants.

Variable	General	Group A	Group B	Group C
Semester		4 and 5	7	10 and 11
Education level		Basic cycle	Clinical cycle	Medical internship
Participant,n	42	13	14	15
Age, years*	23 (22-24)	21 (20.5-22)	23 (22-25)	24 (23-26)
Sex, male/female, n/n	29/13	9/4	12/2	8/7

*Data presented as median (IQR).

In the comparative analysis of Score 1 (cognitive assessment) among groups with a normal distribution, ANOVA with Bonferroni correction revealed a significant difference in grades between the groups ($p = 0.007$). The same was observed for Score 2 (cognitive assessment after intervention; $p = 0.01$). In the discriminant analysis of variance for Score 1 between each pair of groups, there was a statistical difference between groups A and B ($p = 0.02$) and between groups A and C ($p = 0.01$), but not between groups B and C ($p = 1.00$). The comparison of Score 2 between the three different groups showed a statistical difference only between groups A and C ($p = 0.01$), but not between groups A and B ($p = 1.00$) or between groups B and C ($p = 0.09$), as depicted in Figure 2 and Table 2. The t-test comparing the means of Score 1 and Score 2 showed statistical significance between all of the groups ($p < 0.001$).

For Score 3, which had a non-normal distribution, the Kruskal-Wallis test was used to assess whether there was a difference between the groups. The test revealed a significant difference ($p = 0.013$), as shown in Table 2. In multiple comparisons with the Mann-Whitney test, Score 3 showed a statistical difference between groups A and C ($p = 0.015$) and between groups B and C ($p = 0.037$), but not between groups A and B ($p = 0.22$).

Regarding the assessment of the ability to recognize ultrasound patterns evaluated in Score 4, there was a significant difference between the scores of the groups ($p = 0.008$). When comparing groups pairwise, differences were observed between groups A and C ($p = 0.005$) and between groups B and C ($p = 0.026$), but not between groups A and B ($p = 0.46$). The scores for each group are shown in Table 2 and Figure 3.

The mean execution time of the BLUE protocol in the practical test during the 4th meeting was 346 ± 94 seconds, with means of 380 ± 98 s for group A, 333 ± 70 s for group B, and 326 ± 107 s for group C. Runtime data were missing for 5 participants (1, 2, and 2 in groups A, B, and C, respectively). There was no difference in execution time between the groups (ANOVA; $p = 0.199$).

In Test 4, when students were asked to report in descending order of importance which method provided them with greater learning, practical training was considered the most effective method for learning by 73.8% (n = 31) of the participants, followed by written material in 59.5% (n = 25) and classes in 54.8% (n = 23).

The subjective assessment of the importance of learning POCUS and the ability to benefit from the course were evaluated in Test 4 using a Likert scale. Thirty-nine participants (92.9%) fully agreed that the course provided relevant knowledge for medical practice that had not yet been addressed in the current curriculum of the medical school. There was almost unanimous agreement that POCUS improves the accuracy of clinical diagnosis (n = 41; 97.6%). Furthermore, there was total agreement that the course content was suitable for learning the BLUE protocol (100%) and that the inclusion of POCUS content in medical education is relevant (100%).

When asked about whether the practical training time was sufficient, 28 (66.6%) of the students partially agreed or fully agreed with the statement, while 7 (16.7%) disagreed. Although there was no statistically significant difference between the groups (Pearson's chi-square; $p = 0.136$), 14 students (93.4%) in group C agreed with the statement, whereas only 6 (46.2%)

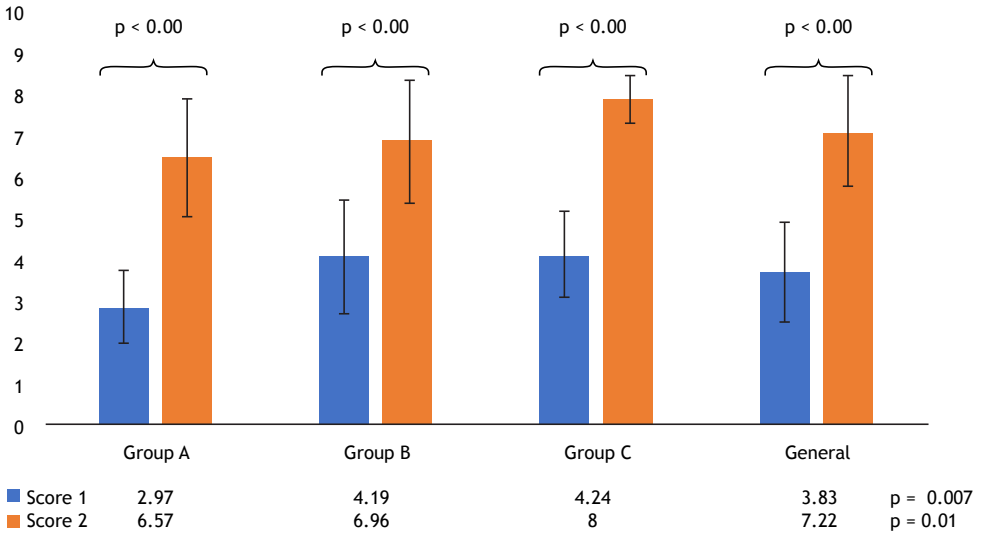

Figure 2. Mean pre- and post-intervention scores in Test 1 (cognitive test) in the sample as a whole and by group.

Table 2. Comparison scores among all groups, and execution time of the bedside lung ultrasound in emergency protocol.

Score	Group A	p (A and B)	Group B	p (B and C)	Group C	p (A and C)	p (A, B and C)	General
Score 1	2.97 ± 0.87	0.02	4.19 ± 1.38	1.00	4.24 ± 1.03	0.01	0.007	3.83 ± 1.23
Score 2	6.57 ± 1.41	1.00	6.98 ± 1.49	0.09	8.00 ± 0.59	0.01	0.01	7.22 ± 1.33
p (Score 1 and Score 2)	< 0.01		< 0.01		< 0.01			< 0.01
Score 3	8.18 (6.36-10.0)	0.22	9.09 (8.86-10.0)	0.037	10 (9.09-10.0)	0.015	0.013	9.09 (8.18-10.0)
Score 4	6 (4-8)	0.46	6 (4-8)	0.026	8 (8-10)	0.005	0.008	8 (4-8)
Execution time, s	380 ±98		333 ± 70		326 ± 107		0.199	346 ± 94

Score 1: score of the first assessment of cognitive knowledge pre-pedagogical intervention; Score 2: score of the repetition of the cognitive test after the pedagogical intervention; Score 3: score from the practical performance test; and Score 4: score from the recognizing ultrasound patterns test. Data are expressed as mean ± SD or as median (IQR).

in group A and 8 (57.1%) in group B provided the same response.

The only item with a statistical difference between the groups in Test 4 (Pearson's Chi-square; $p < 0.001$) was related to whether their stage of education would be suitable for teaching POCUS; 34 (80.9%) of the participants fully or partially agreed with the statement. When broken down by groups, all of the participants (n = 15) in group C fully agreed, 13 students (92.9%) in group B fully or partially agreed, and only 6 (46.2%) in group A agreed with the statement.

DISCUSSION

The present study demonstrates that short-term teaching of POCUS and lung ultrasound can improve cognitive performance in these areas, regardless of the medical education level. The comparison between knowledge about the subject before the intervention showed a significant difference in general, except between students in the clinical cycle and the medical internship cycle. The post-course knowledge was only different between the extremes (i.e., between the basic cycle and the medical internship cycle). The growing median of the scores in Test 3 (i.e., execution and recognition of pathologies) showed a significant difference between the groups, suggesting that the more advanced the students are in medical education, the better the ability to perform and interpret exams correctly is, after a brief training. On the other hand, the medical education level does not seem to influence execution time.

Students generally agreed that POCUS is an important topic for medical practice, capable of improving diagnostic ability, and therefore important to be addressed in the medical curriculum. The perception that teaching time was sufficient was pointed out in general, with less homogeneity between the earlier stages. This, combined with the fact that most of the basic cycle group disagreed that their course phase is suitable for teaching POCUS, suggests that teaching the subject has a greater yield from the clinical cycle onward, more consistently in the internship cycle, which was perceived objectively by the results of the

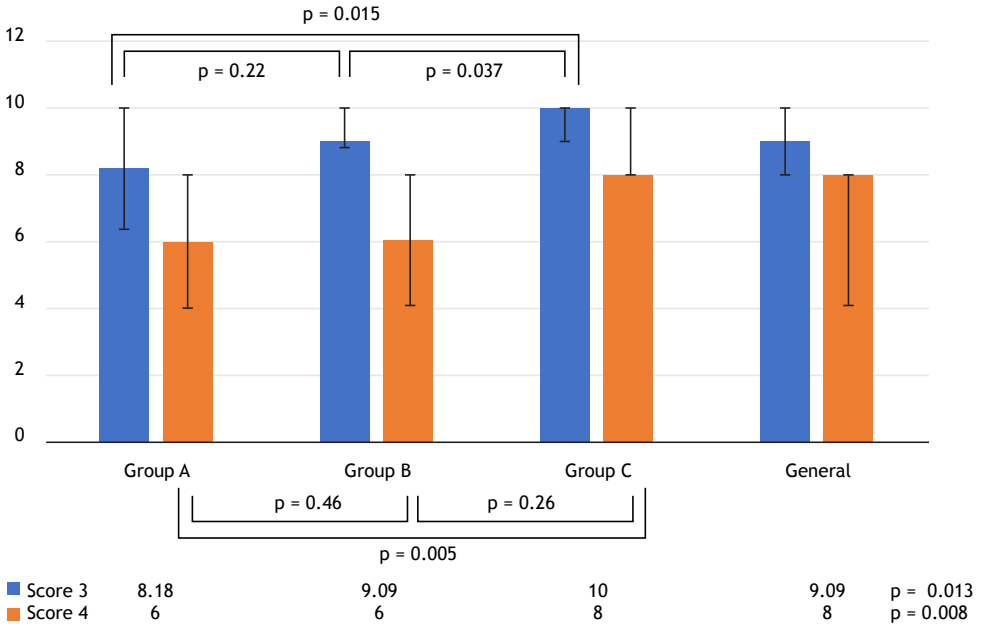

Figure 3. Median of Score 3 and Score 4 in the sample as a whole and by group.; Score 3: score from the practical performance test; and Score 4: score from the recognizing ultrasound patterns test.

post-training cognitive test and the self-perception of knowledge acquisition by students in the qualitative questionnaire.

The present study is unprecedented, and, to our knowledge, there is no study in the Brazilian literature on medical education that compares the learning ability of POCUS in relation to medical education years. In addition, training was offered by professionals with extensive experience in POCUS and addressed cognitive aspects, performance skills, pattern recognition, and qualitative learning assessment.

The inclusion of ultrasound teaching in the curriculum, in the cognitive sphere and practical training, is positive by students' perception.[14-16] Although different ways of including teaching are described in the literature, there is emphasis and encouragement on the introduction of longitudinally teaching during medical education, from the basic cycle in correlation with anatomy to the clinical cycle.[10,17,18]

Even with a brief training, the teaching of POCUS involving the study of didactic material, theoretical classes, and practical training in a simulator or in live models can improve the quality of execution of the exam and cognitive knowledge when compared with no training.[8,19]

Regarding the best moment for teaching ultrasound use in academic life, training either medical students or resident physicians seems to provide them with adequate, specialist-like skills when undergoing adequate training and supervision.[8,20] According to a study, performing cardiac ultrasound at the bedside by medical students after limited training improves the accuracy of cardiac diagnoses[21] and can confer a sensitivity and specificity of diagnoses superior to those by cardiologists equipped only with a physical exam, evidencing the importance of cardiac imaging even if performed by future, non-specialist physicians with short training.[22]

Regarding the students' perception about the appropriate moment for learning, the perception of students in the first and second years of medical school regarding the theoretical and practical teaching of POCUS showed that the initial phases were already considered to be adequate for teaching and that the training was already capable of increasing confidence in performing the exam.[23]

Although it is not a consensus, especially in Brazil, with the increased number of publications on the subject, the importance and need to introduce POCUS teaching is already evident in medical schools and not just in medical residency programs. Although the model, teaching methodology, and the stage that teaching should be introduced are still unclear, longitudinal programs with integration into the preclinical and clinical curriculum seem to be preferable.[10,11]

Among the numerous existing POCUS protocols, the BLUE protocol was chosen for its simple organization, which facilitates its reproducibility, ease of execution and interpretation of findings, and its ability to improve the accuracy of diagnoses in cases of acute respiratory failure.[12]

This study must be interpreted in the context of its limitations. A study with a small sample, in a single center, with more than one evaluator, the use of non-validated tests, and a short follow-up time are important limiting factors. In addition, the variables excluded from the study because the practical

evaluation took place in a controlled environment with healthy models may not express the same result as care in a real medical emergency with patients in acute respiratory failure.

In Brazil, the teaching of POCUS is recent for specialist physicians, residents, and medical students. The absence of formal training on the subject, the small number of professionals trained to perform it and teach it, associated with the difficulties of large-scale access to ultrasound devices in medical schools, and the absence of a consensus on the expected basic skills are key obstacles to be overcome so that the introduction of this topic in medical schools can be achieved on a large scale.

For the future, gaps such as the existence or not of an ideal teaching moment and the creation of valid tools that are capable of quantifying theoretical and practical knowledge must be attained.

"A generation of doctors will need to be trained to see this technology as an extension of their senses, just as many generations saw the stethoscope. This development will require the medical education community to embrace and incorporate technology throughout the medical curriculum."[9]

Since all technology requires training and experience, POCUS is not different. Its diffusion depends on the rupture of skepticism and traditionalism, as well as rewriting what are in fact the minimum skills expected of a doctor in training in 2024.

In conclusion, the findings of this study demonstrate that the theoretical teaching and practical training of lung ultrasound and the BLUE protocol, even for a short time, can significantly improve cognitive performance at all stages of the medical course, including the end of the basic cycle, the end of the clinical cycle, and during the medical internship. Moreover, practical training enhances the execution and interpretation of lung ultrasound and the BLUE protocol progressively throughout the medical course, particularly among students in the medical internship phase. These results align with the data indicating an increasing self-perception of learning lung ultrasound as students progress through their medical education.

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AUTHOR CONTRIBUTIONS

GTPD: conceptualization (lead); data curation (lead); formal analysis (lead); funding acquisition (lead); investigation (lead); methodology (lead); project administration (lead); resources (lead); software (equal); visualization (equal); writing – original draft (lead); and writing – review & editing (equal). ACBG: conceptualization (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); and writing – review & editing (equal). MPP: data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); resources (equal); software (equal); supervision (equal); validation (equal); visualization (equal); and writing – review & editing (equal). LJS: resources (equal); supervision (equal); validation (equal); visualization (equal); and writing – review & editing (equal).

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Microbial variations in sputum cultures among hospitalized patients with community-acquired pneumonia: differences in sputum microbiota between asthma and COPD patients

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Study carried out at the Akdeniz University Medical School Hospital, Antalya, Turkey.

ABSTRACT

Objective: To assess differences in the sputum microbiota of community-acquired pneumonia (CAP) patients with either COPD or asthma, specifically focusing on a patient population in Turkey. **Methods:** This retrospective study included hospitalized patients > 18 years of age with a diagnosis of pneumonia between January of 2021 and January of 2023. Participants were recruited from two hospitals, and three patient groups were considered: CAP patients with asthma, CAP patients with COPD, and CAP patients without COPD or asthma. **Results:** A total of 246 patients with CAP were included in the study, 184 (74.8%) and 62 (25.2%) being males and females, with a mean age of 66 ± 14 years. Among the participants, 52.9% had COPD, 14.2% had asthma, and 32.9% had CAP but no COPD or asthma. Upon analysis of sputum cultures, positive sputum culture growth was observed in 52.9% of patients. The most commonly isolated microorganisms were *Pseudomonas aeruginosa* (n = 40), *Acinetobacter baumannii* (n = 20), *Klebsiella pneumoniae* (n = 16), and *Moraxella catarrhalis* (n = 8). CAP patients with COPD were more likely to have a positive sputum culture ($p = 0.038$), a history of antibiotic use within the past three months ($p = 0.03$), utilization of long-term home oxygen therapy ($p < 0.001$), and use of noninvasive ventilation ($p = 0.001$) when compared with the other patient groups. Additionally, CAP patients with COPD had a higher CURB-65 score when compared with CAP patients with asthma ($p = 0.004$). **Conclusions:** This study demonstrates that CAP patients with COPD tend to have more severe presentations, while CAP patients with asthma show varied microbial profiles, underscoring the need for patient-specific management strategies in CAP.

Keywords: Community-acquired infections; Pulmonary disease, chronic obstructive; Asthma; Patient admission; Sputum; Culture techniques.

INTRODUCTION

Pneumonia continues to be a significant public health concern, resulting in an annual mortality of over 3 million individuals.[1] In the elderly, pneumonia constitutes 20-40% of hospital admissions, impacting an estimate of 2-13 individuals per 1,000 in the community. This results in heightened healthcare utilization, increased morbidity, and elevated mortality rates.[2] Individuals with underlying obstructive lung diseases, such as asthma and COPD, are particularly susceptible to the development of pneumonia. Community-acquired pneumonia (CAP) encompasses a diverse range of microbiological agents as causative factors. *Streptococcus pneumoniae* is the most commonly identified pathogen, responsible for approximately 25% of cases.[3] The causative agents of pneumonia may vary geographically.[4,5] In a review compiling studies conducted in Asian countries, it was observed that pathogens such as *S. pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila* are more prevalent in Western countries, whereas gram-negative bacilli and *Mycobacterium tuberculosis* are more commonly encountered in the Northeast.[4]

Chronic respiratory diseases such as COPD and asthma contribute to airway inflammation, airflow limitation, and increased sputum production, providing a favorable milieu for colonization and proliferation of microorganisms within the respiratory tract. Consequently, understanding the clinical manifestations and complications associated with pneumonia in patients with asthma and COPD is of utmost importance. Studies in the literature generally focus on sputum samples collected during exacerbations of both diseases.[6] However, few investigations have suggested the possibility of divergent etiological agents in hospitalized CAP patients with either asthma or

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COPD.[7-10] Additionally, microbiological investigation of CAP in the context of coexisting asthma and COPD has not been sufficiently explored in Turkey.

A review by Beasley et al.[6] highlighted that the bacterial flora in COPD patients varies with the severity of the condition. During stable periods and exacerbations in severe COPD, gram-negative organisms such as *Pseudomonas aeruginosa* are more common. Meanwhile, the presence of *Haemophilus parainfluenzae* and *Staphylococcus aureus* is less frequent, and their significance in COPD remains debatable.[6] In contrast, studies focusing specifically on COPD patients with CAP have revealed a different microbial pattern. In the study by Pascual-Guardia et al.,[11] *P. aeruginosa* was identified as the most frequently isolated microorganism in patients with bronchiectasis, low FEV_1 levels, and recent hospitalization. However, Sethi reported that *Haemophilus influenzae* was the most common microorganism causing exacerbations in COPD patients.[12] Separately, a study by Bari et al.[7] explored the microbial landscape in COPD exacerbations. They found culture positivity in 65% of such patients, with *P. aeruginosa* again being the most frequently isolated microorganism.[7] This distinction between the microbial profiles of COPD exacerbations and CAP patients with COPD underscores the complexity of microbial involvement in COPD. In the realm of asthma, in 27% of asthma patients with worsened symptoms, organisms such as *S. pneumoniae, Streptococcus pyogenes, S. aureus, Moraxella catarrhalis*, and *H. influenzae* were identified.[13] The use of 16S rRNA sequencing has further elucidated bacterial taxa associated with different inflammatory phenotypes in asthma, such as dominance of *Streptococcus* spp. in eosinophilic asthma and of *H. influenzae* in neutrophilic asthma.[14,15] However, the microbial profile in CAP patients with asthma does not show significant differences in etiological pathogens,[16] suggesting a complex interplay between these respiratory conditions and their associated microbial environments.

The primary aim of this study was to assess differences in the sputum microbiota of CAP patients with either COPD or asthma, specifically focusing on a patient population in Turkey.

METHODS

This retrospective study included hospitalized patients > 18 years of age diagnosed with CAP between January of 2021 and January of 2023. Participants were drawn from the Chest Disease clinics at the Akdeniz University School of Medicine and the Antalya Atatürk State Hospital. The study comprised three distinct patient groups: CAP patients with asthma, CAP patients with COPD, and CAP patients without either COPD or asthma. Inclusion criteria encompassed patients diagnosed with COPD following the GOLD guidelines.[17] Within the asthma group, individuals exhibiting variable symptoms, such as wheezing, shortness of breath, cough, chest tightness, and variable expiratory airflow limitation, and who had previously received a formal diagnosis of asthma and undergone treatment for the disease were included in the study.[18]

The data of 937 patients who had been hospitalized for the treatment of CAP were evaluated. Patients who were immunosuppressed, had interstitial lung disease, were receiving treatment for active tuberculosis, had asthma-COPD overlap syndrome, were diagnosed with bronchiectasis, and those for whom cultures were not obtained were excluded, resulting in a total of 246 patients included in the study. The flow chart of the study is presented in Figure 1.

The data of the patients were retrospectively evaluated by accessing their hospital records and electronic medical records. Age, gender, smoking history, use of inhaled corticosteroids prior to hospital admission, comorbidities, sputum culture results, radiological data, and 30-day mortality rates were recorded for all patients. Sputum cultures were obtained prior to initiating antibiotic treatment. Sputum cultures reached the laboratory within 30 minutes in both centers and were examined by experienced technicians. Inadequate samples were not processed by the laboratories and were not reported in the database. No data were available on viral pathogens.

To be classified as pneumonia cases, patients needed to meet the following criteria within the first 48 h of hospital admission: identification of pulmonary infiltrations on chest X-ray or CT, presence of productive or dry cough, body temperature above 37.8°C or hypothermia below 36°C, and presence of at least one systemic inflammatory marker (leukocytosis > 10,000 mm^3, leukopenia < 4,000 mm^3, and elevated CRP or procalcitonin values).[11]

We used the mental Confusion, Urea, Respiratory rate, Blood pressure, and age = 65 years (CURB-65) scoring system to assess the risk of mortality in CAP patients. A score of 1 is given to each of the criteria: presence of mental confusion; blood urea nitrogen level > 7 mmol/L or > 20 mg/dL; RR > 30 breaths/min; systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg; and age > 65 years.[19] Scores were categorized as follows: a score of 0 to 1 indicates low risk, the patient being typically managed as an outpatient; a score of 2 is considered intermediate risk, suggesting the need for close monitoring or a short hospital stay; and a score of 3 to 5 is classified as high risk, generally requiring hospitalization and possible intensive care.

The study received ethical approval from the Non-interventional Ethics Committee of the Faculty of Medicine, Akdeniz University, on April 5, 2023 (decision number 293).

Statistical analysis

Statistical analysis of the data was conducted using the IBM SPSS Statistics software package,

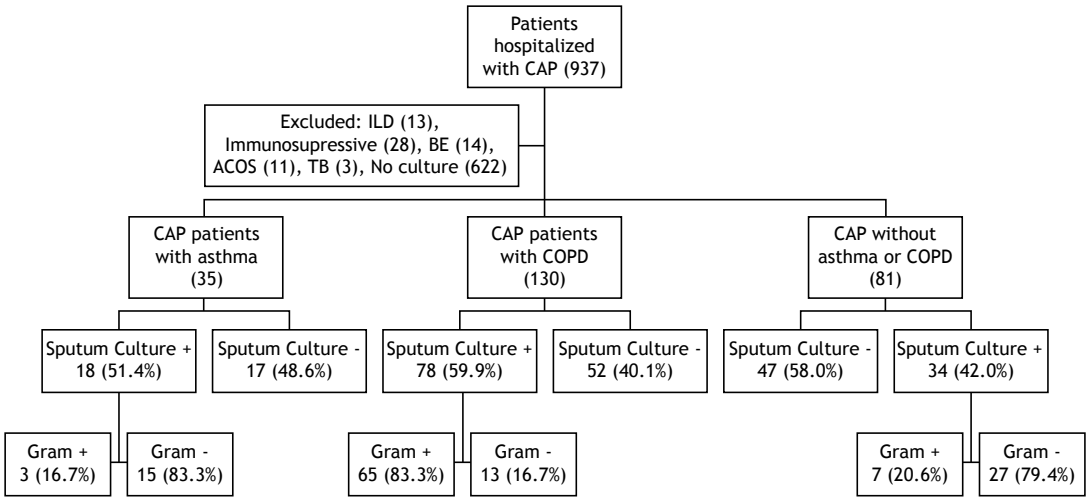

Figure 1. Flow chart of the patients. CAP: community-acquired pneumonia; ILD: interstitial lung disease; BE: bronchiectasis; ACOS: asthma-COPD overlap syndrome; and TB: tuberculosis.

version 23.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were described as absolute and relative frequencies, while continuous variables were described as means and standard deviations. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. For normally distributed data, the means of two groups were compared using the Student's t-test, and the means of more than two groups were compared using one-way ANOVA. For non-normally distributed data, the medians of two groups were compared using the Mann-Whitney U test, and the significance of categorical variables was analyzed using the chi-square test. The correlation between continuous variables was evaluated using the Spearman's correlation test. A significance level of 0.05 was considered for statistical significance in the study.

RESULTS

The study involved a total of 246 patients, comprising 184 males (74.8%) and 62 females (25.2%), with a mean age of 66.0 ± 14.3 years. Among them, 130 (52.9%) had COPD, 35 (14.2%) had asthma, and 81 (32.9%) had CAP without either COPD or asthma. Additionally, 150 (60.6%) of the patients had a history of smoking, and 120 (48.8%) had a history of hospitalization in the previous year. The proportion of males was higher in CAP patients with COPD when compared with CAP patients with asthma and CAP patients with no asthma or COPD ($p < 0.001$), as was the history of smoking more prevalent in that group ($p < 0.001$). Furthermore, CAP patients with COPD had a significantly higher rate of antibiotic use within the past three months ($p = 0.01$), a higher prevalence of long-term home oxygen therapy ($p < 0.001$), and an increased use of noninvasive ventilation (NIV) when compared with the other groups ($p = 0.001$). Before the onset of pneumonia, 30 (85.7%) of patients with asthma and 110 (84.6%) of patients with COPD were utilizing inhaled corticosteroids. Demographic and clinical characteristics of patients are presented in Table 1, and the outcomes of the study are presented in Table 2.

Among the patients hospitalized with CAP, 622 (66.4%) had no sputum cultures performed, while among those who had sputum cultures obtained (n = 246), 130 samples (52.9%) showed growth. Sputum cultures were positive in 18 (51.4%) of CAP patients with asthma; in 78 (59.9%) of CAP patients with COPD; and in 34 (42.0%) of CAP patients with no asthma or COPD ($p = 0.038$; Figure 1). Among the positive sputum cultures, the most commonly isolated microorganisms were *P. aeruginosa* (n = 40), *Acinetobacter baumannii* (n = 20), *Klebsiella pneumoniae* (n =16), and *M. catarrhalis* (n = 8). The distribution of microorganism growth according to the underlying disease is shown in Figure 2. In CAP patients with asthma, the most frequently isolated microorganisms were *P. aeruginosa* (n = 8; 22.9%), *K. pneumoniae* (n = 3; 8.6%), and *M. catarrhalis* (n = 3; 8.6%). In CAP patients with COPD, the most commonly isolated microorganisms in cultures were *P. aeruginosa* (n = 29; 22.3%), *A. baumannii* (n = 17; 13.1%), *Escherichia coli* (n = 6; 4.6%), and *S. pneumoniae* (n = 5; 3.8%). However, in CAP patients with no asthma or COPD, the most commonly isolated microorganisms were *K. pneumoniae* (n = 12; 14.8%), *P. aeruginosa* (n = 3; 3.7%), and *A. baumannii* (n = 3; 3.7%). CAP patients with asthma had a significantly higher rate of multiple organism growth in sputum (14.3%) when compared with CAP patients with COPD (6.9%) and CAP patients with no asthma or COPD (9.9%; $p = 0.031$; Figure 3). The mean CURB-65 score of the patients included in the study was found to be 1.30 ± 0.94, and it was higher in patients with COPD when compared with patients with asthma ($p = 0.004$; Figure 4). Patients with positive sputum culture showed a higher tendency to be homebound intensive

Table 1. Demographic and clinical characteristics of patients.[a]

Characteristic	CAP patients with asthma (n = 35)	CAP patients with COPD (n = 130)	CAP patients with no asthma or COPD (n = 81)	Total sample (N = 246)	p
Gender, male[†]	14 (40.0)	117 (90.0)	53 (65.4)	184 (74.8)	< 0.001*
Age, years	62.1 ± 16.5	68.0 ± 10.8	65.2 ± 17.4	66.2 ± 14.3	0.090
Current or former smoker[†]	9 (25.7)	105 (80.8)	35 (43.2)	149 (60.6)	< 0.001*
Coronary artery disease[†]	27 (77.1)	87 (66.9)	61 (75.3)	71 (28.9)	0.297
Hypertension[†]	12 (34.3)	68 (52.3)	39 (48.1)	127 (51.6)	0.166
Diabetes mellitus[†]	24 (68.6)	94 (72.3)	54 (66.7)	74 (30.1)	0.674
Hospitalization within the previous year[†]	17 (48.6)	71 (54.6)	32 (39.5)	120 (48.8)	0.102
Antibiotic use (last 3 months) [a]	11 (31.4)	65 (50.0)	22 (27.2)	98 (39.6)	0.010*
ICS use[†]	30 (85.7)	110 (84.6)	-	139 (56.5)	0.872
LTOT[†]	5 (14.3)	38 (29.2)	3 (3.7)	46 (18.7)	< 0.001*
Homebound intensive care patient[†]	1 (2.9)	8 (6.2)	13 (16.0)	22 (8.9)	0.069
NIV[†]	14 (40.0)	77 (59.2)	27 (33.3)	118 (48.0)	0.001*
CURB-65 score[‡]	1.1 ± 0.7	1.5 ± 0.9	1.2 ± 1.0	1.3 ± 0.94	0.029*

CAP: community-acquired pneumonia; ICS: Inhaled corticosteroid, LTOT: long-term oxygen therapy; NIV: noninvasive ventilation, CURB-65: mental Confusion, Urea, Respiratory rate, Blood pressure, age > 65 years. [a]Data are expressed as n (%) or as mean ± SD. *They were statistically significantly higher in COPD patients with CAP when compared with the other groups. The data conforms to a normal distribution as confirmed by the Kolmogorov-Smirnov test. [†]Chi-square test. [‡]Kruskal-Wallis test.

Table 2. Study outcomes.[a]

Outcome	CAP patients with asthma (n = 35)	CAP patients with COPD (n = 130)	CAP patients with no asthma or COPD (n = 81)	p
Culture positivity[†]	17 (51.4)	78 (59.9)	34 (42.0)	0.038*
Gram staining, gram-positive[†]	3 (8.6)	15 (11.5)	7 (8.6)	0.156
Length of hospitalization, days[‡]	10.3 ± 8.1	11.0 ± 10.8	15.1 ± 15.4	0.078
Mortality rate[†]	0 (0.0)	11 (8.5)	4 (4.9)	0.155

[a] Data were expressed as n (%) or as mean ± SD. *Statistically significant increase in CAP patients with COPD. [†]Chi-square test. [‡]Kruskal-Wallis test.

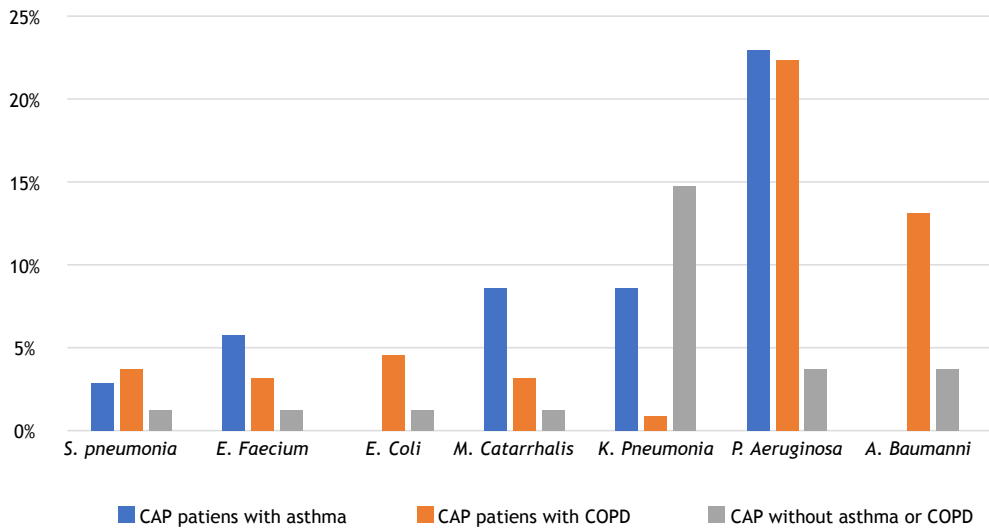

Figure 2. Sputum culture growths in patients hospitalized with community-acquired pneumonia (CAP).

care patients (p = 0.040), receive long-term oxygen therapy (p < 0.001), and have a higher CURB-65 score (p = 0.014). Patients with a medical history of diabetes mellitus (p = 0.017) and hypertension (p = 0.026) had a lower incidence of positive sputum culture. When patients with multiple microorganism growth in sputum cultures were compared with those having a single microorganism growth, it was observed

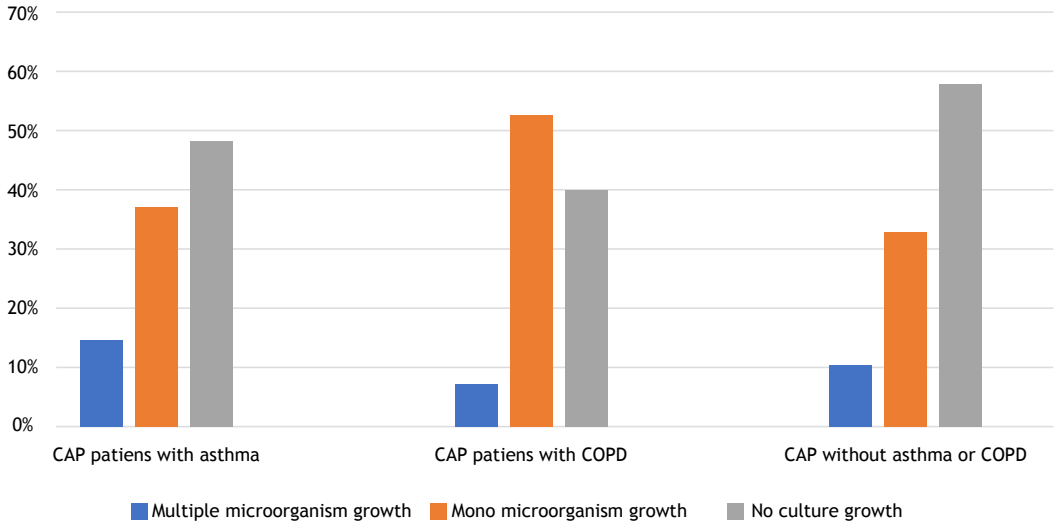

Figure 3. Multiple growth in sputum cultures of patients. The chi-square test showed that community-acquired pneumonia (CAP) patients with asthma had a significantly higher rate of multiple organisms (p = 0.031).

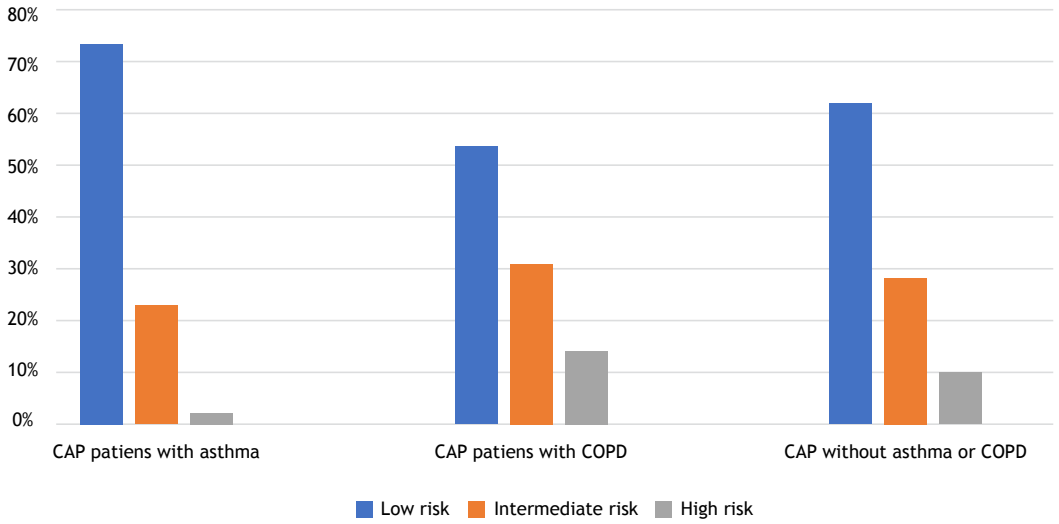

Figure 4. Distribution of CURB-65 scores among community-acquired pneumonia (CAP) patients, highlighting higher scores in CAP patients with COPD when compared with CAP patients with asthma (p = 0.004; Kruskal-Wallis test. The CURB-65 score categorizes patients into low- (0-1 points), intermediate- (2 points), and high- (3-5 points) risk groups.

that the smoking history was significantly higher in the group with a single microorganism growth (35 pack-years vs. 20 pack-years; p = 0.016). Apart from this, no significant differences were found in the demographic and clinical characteristics between patients with multiple microorganism growth and those with a single microorganism growth.

DISCUSSION

This study showed that CAP patients with COPD exhibited a higher predominance of males and smokers, along with increased antibiotic use and reliance on long-term home oxygen therapy and NIV. Sputum cultures revealed higher culture positivity in CAP patients with COPD. The most common microorganisms in sputum culture were identified as *P. aeruginosa, A. baumannii, K. pneumoniae*, and *M. catarrhalis*. The frequency of microorganism growth varied according to the underlying disease. In CAP patients with COPD, the most identified microorganisms were *P. aeruginosa* and *A. baumannii*. In CAP patients with asthma, the most frequently identified microorganisms were *P. aeruginosa, K. pneumoniae*, and *M. catarrhalis*. Patients with a positive sputum culture were more likely to require homebound intensive care and long-term oxygen therapy, and exhibited higher CURB-65 scores, whereas those with a history of diabetes mellitus and hypertension demonstrated a lower incidence of positive sputum cultures. Smoking was more

pronounced in patients with a single microorganism growth in sputum cultures.

COPD affects more than 250 million people and is a leading cause of death for millions worldwide.[11,17] CAP in COPD patients is associated with increased mortality and imposes a significant burden on hospitalizations and healthcare costs. Pneumonia treatment guidelines recommend empirical antibiotic treatment targeting *P. aeruginosa* in patients with underlying chronic lung diseases.[20] In fact, a recent multicenter international study by Pascual-Guardia et al.[11] reported *P. aeruginosa* as the most frequently isolated microorganism in CAP patients with COPD. Similarly, in our study, *P. aeruginosa* was the most commonly isolated microorganism in both CAP with asthma patients and CAP with COPD patients.

Patients with CAP may be infected by multiple microorganisms. In a study by Wark et al.,[21] multiple microorganism growth was detected in 4 (9.8%) out of 45 patients with obstructive lung disease. The same study also found that COPD patients with signs of infection had a longer hospital stay when compared with asthma patients. A review by Yu et al.[22] highlighted that COPD patients hospitalized with CAP tend to have a higher incidence of ICU admissions, increased need for mechanical ventilation support, and a higher mortality rate. In our study, it was observed that asthma patients had a higher frequency of multiple organism growth in sputum cultures than did COPD patients. Furthermore, CAP patients with COPD had a higher CURB-65 score than did the other groups. This suggests that the severity of pneumonia-related illness may be higher in COPD patients. In COPD patients, there is a higher likelihood of being male, having a smoking history, having recent antibiotic use, being on long-term oxygen therapy, using home NIV, and having an increased probability of microbial growth in sputum cultures when compared with asthma patients. These findings suggest that CAP patients with COPD may require different approaches in treatment.

The coexistence of pneumonia and COPD has been found to be associated with increased mortality.[22,23] In a case-control study conducted in Switzerland, the coexistence of asthma or COPD with pneumonia has resulted in lower mortality rates when compared with a control group, contrary to the existing literature.[24] There was no statistically significant different difference in mortality among the three groups of patients in our study

A. baumannii and *E. coli* showed a predominance in sputum cultures of CAP patients with COPD, whereas *M. catarrhalis* and *Enterococcus faecium* were more common in those with asthma. Additionally, there was no significant difference in the prevalence of *P. aeruginosa* between CAP patients with COPD or with asthma. Furthermore, *K. pneumoniae* was found to be more prevalent in sputum cultures of CAP patients with no asthma or COPD. Our study results indicate differences in sputum culture growth between CAP patients with asthma and with COPD, a higher frequency of multiple organism growth being observed in CAP patients with asthma. These findings highlight the necessity for reevaluation of treatment strategies and approaches in this at-risk patient group for pneumonia.

According to guidelines, routine sputum culture is not recommended for all patients hospitalized with pneumonia. The decision to obtain a sputum culture should be based on various factors, such as the severity of illness, presence of risk factors, and clinical judgment of the healthcare provider.[20] In an assessment of the diagnostic utility of sputum culture in CAP, only 15.8% of a total of 1,669 patients included in the study received a microbiological diagnosis.[25] However, more than 40% of the patients did not undergo sputum specimen collection, and, of the specimens collected, 46% were deemed inadequate and were therefore not subjected to culture analysis.[25] In our study, sputum culture was not performed in 66.4% of the patients. Among the patients who had sputum cultures performed, growth was detected in 52.9% of them. Since our primary aim was to assess culture growth, the evaluation of treatment modifications based on culture results was not conducted. Therefore, it is not possible to make a definitive interpretation regarding whether cultures are necessary for all patients hospitalized with CAP.

Although our research was conducted in only two centers and with a limited number of cases, it offers valuable insights into the etiology of CAP in Turkey. This approach will facilitate a careful and measured interpretation of our findings. We did not assess the impact of microbiological culture results on treatment decisions and on the evaluation of airflow limitation in obstructive lung diseases, constituting additional constraints. Nevertheless, the study elucidated the distinct course of pneumonia among asthma and COPD patients, highlighting the significance of the microbiological profile in shaping treatment and management strategies. To strengthen future research further, we recommend larger sample sizes, microbiota analysis, and diverse clinical parameters for more comprehensive assessments. Additionally, exploring treatment outcomes, disease severity, and long-term prognosis differences among patient groups will yield valuable insights.

In conclusion, this study reveals distinct patterns in sputum culture growths in CAP patients with asthma or with COPD. Specifically, CAP patients with COPD tend to have higher CURB-65 scores, indicating a potentially more severe disease course, while those with asthma often show multiple culture growths. These findings suggest a link between specific microorganisms and the clinical manifestations and complications of CAP in these patient groups. Consequently, for CAP patients with COPD, a heightened awareness of severity is recommended, and for those with asthma, treatment strategies should consider the likelihood of multiple organisms.

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AUTHOR CONTRIBUTIONS

FU: conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; original drafting; and reviewing and editing of the manuscript. BK: conceptualization; data curation; resources; software; and supervision. AGÇ: formal analysis; funding acquisition; investigation; project administration; visualization; and original drafting. NK: data curation; funding acquisition; investigation; project administration; resources; software; and validation. RBG: investigation; resources; software; and visualization. AAD: data curation; and visualization. UBI: data curation; formal analysis; and visualization. MA: formal analysis; funding acquisition; investigation; software; supervision; validation; original drafting; and reviewing and editing of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

A critical analysis of the decreasing trends in tuberculosis cure indicators in Brazil, 2001–2022

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ABSTRACT

Objective: To analyze the temporal trend of tuberculosis cure indicators in Brazil. **Methods:** An ecological time-series study using administrative data of reported cases of the disease nationwide between 2001 and 2022. We estimated cure indicators for each federative unit (FU) considering individuals with pulmonary tuberculosis, tuberculosis-HIV coinfection, and those in tuberculosis retreatment. We used regression models using joinpoint regression for trend analysis, reporting the annual percentage change and the average annual percentage change. **Results:** For the three groups analyzed, we observed heterogeneity in the annual percentage change in the Brazilian FUs, with a predominance of significantly decreasing trends in the cure indicator in most FUs, especially at the end of the time series. When considering national indicators, an average annual percentage change of −0.97% (95% CI: −1.23 to −0.74) was identified for the cure of people with pulmonary tuberculosis, of −1.11% (95% CI: −1.42 to −0.85) for the cure of people with tuberculosis-HIV coinfection, and of −1.44% (95% CI: −1.62 to −1.31) for the cure of people in tuberculosis retreatment. **Conclusions:** The decreasing trends of cure indicators in Brazil are concerning and underscore a warning to public authorities, as it points to the possible occurrence of other treatment outcomes, such as treatment discontinuity and death. This finding contradicts current public health care policies and requires urgent strategies aiming to promote follow-up of patients during tuberculosis treatment in Brazil.

Keywords: Tuberculosis; Time factors; Retrospective studies; Brazil.

INTRODUCTION

Despite its ancient origin and global efforts for control, tuberculosis remains an important public health problem.[1] In 2022, the WHO estimated that 10.6 million individuals fell ill worldwide, and 1.3 million died from the disease.[1] This scenario becomes even more complex and worrying when we consider that tuberculosis disproportionately affects underdeveloped and developing countries and the most socioeconomic vulnerable groups.[2]

Regarding this context, WHO launched the "End Tuberculosis Strategy", an international proposal that aims to eliminate the global tuberculosis epidemic.[3] This strategy is anchored in pillars of research and innovation, support systems, and integrated patient-centered care and prevention.[3] The objectives are to reduce the incidence rate of tuberculosis by 90% and the number of deaths caused by the disease by 95% by 2035, according to data released in 2015.[3]

In relation to this issue, Sustainable Development Goals (SDGs) were also highlighted, which are directly related to combating tuberculosis as a public health problem. These include ending hunger and poverty, as well as reducing inequities, given that the disease has a strong social determination.[4] In general, the SDGs presented by the United Nations aim to guarantee to the global population the end of persistent social inequalities, and environmental and climate protection.[4]

Brazil is one of the countries with the highest number of tuberculosis cases. As part of efforts to achieve global goals, the Ministry of Health launched the "National Plan to End Tuberculosis as a Public Health Problem", which recognizes the WHO international pacts and the 2030 SDG agenda.[5] However, recently, the COVID-19 pandemic caused negative effects on global health and reversed advances in tuberculosis control, including on a national level.[6]

Among the efforts towards the elimination of tuberculosis as a public health problem, the importance of actions aimed at linking individuals to health services for effective treatment follow-up stands out.[3] This requires unique strategies focused on the specificities of individuals affected by the disease, with a focus on therapy adherence to increase cure rates, on reducing unfavorable outcomes (e.g., loss to follow-up and death), and controlling the transmission chain.[3]

However, a country with continental dimensions and regional inequalities, such as Brazil, implies the possibility

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of dissimilarity of indicators in geopolitical areas, which shape different actions and responses to tuberculosis.[5] Therefore, with the aim of understanding the evolution of cure indicators in light of the history of actions already developed and identifying barriers towards achieving global goals, we analyzed the temporal trend of tuberculosis cure indicators in Brazil.

METHODS

We conducted an ecological study that presented the Brazilian Federative Units (FUs) as the unit of analysis. We followed all the recommendations of the Reporting of Studies Conducted using Observational Routinely Collected Health Data (RECORD).[7] Also, as this study used aggregated, anonymous, and publicly available data, it did not require an evaluation by a research ethics committee, in accordance with the Ordinance No. 674 of May 6, 2022, issued by the Brazilian National Health Council.

Brazil has over 200 million inhabitants and is stratified into 26 states and the *Distrito Federal*, organized into five regions: North, Northeast, South, Southeast, and Central-West. This organization ensures the adoption of different programmatic responses for the prevention and management of tuberculosis. The country has a gross domestic product per capita estimated at R$ 42,247.52, an unemployment rate of 7.7%, and an illiteracy rate among people over 15 years of age of 5.6%.[8]

We collected data from the Brazilian *Sistema de Informação de Agravos de Notificação* (SINAN, Notifiable Diseases Information System) via the *Departamento de Informática do Sistema Único de Saúde* (DATASUS, Information Technology Department of the Unified Health System), accessed in November of 2023. Regarding cases of tuberculosis, we should note that only people with a confirmed diagnosis are reported by health professionals at all levels of the health care network.[9]

For the study population, we included all tuberculosis cases reported between 2001 and 2022, considering that this period refers, respectively, to the initial availability of data on SINAN and the last year with qualified data until the date of access to DATASUS. Concerning the cure indicators studied, we considered the following definitions and formulas established in the recently released "Tuberculosis Indicators Booklet", elaborated by the Brazilian Ministry of Health.[10]

- Percentage of cure among new cases of laboratory-confirmed pulmonary tuberculosis: the total number of laboratory-confirmed new cases of pulmonary tuberculosis that presented a status of closure as cure, in the year and locality, divided by the total number of new laboratory-confirmed cases of pulmonary tuberculosis in the year and locality, and then multiplied by 100;
- Percentage of cure among new cases of tuberculosis in people with HIV: the total number of new cases of tuberculosis among people with a positive test for HIV that presented a status of cure for tuberculosis, in the year and locality, divided by the total number of new tuberculosis cases among people with a positive test for HIV, in the year and locality, and then multiplied by 100;
- Percentage of cure of tuberculosis retreatment cases: the total number of tuberculosis retreatment cases cured, in the year and locality, divided by the total number of retreatment cases, in the year and locality, and then multiplied by 100.

We selected these indicators to explain tuberculosis cure over time in three different groups. Reported cases that had essential information (such as year of diagnosis, place of residence, and closure status) filled in as ignored or blank were not included, because these are data points do not allow a reliable analysis. We proceeded to data tabulation in an electronic spreadsheet (Microsoft Excel®), with indicators calculated according to the year of diagnosis and the FU of residence.[10]

Considering that a reduced number of events could generate important random variations in the proportion measurements, we decided to use the strategy of smoothing the historical series using the three-point moving average.[10] Based on the initially calculated indicators, we averaged the values from the previous year, the current year, and the following year. This process resulted in series with 20 points (considered as the years after smoothing) for trend analysis.

We applied regression models via the Joinpoint Regression Program®, version 5.0 (National Cancer Institute, Bethesda, MD, USA), which aimed to visualize whether the insertion of several straight segments, verified by the identification of inflection points (joinpoints), is capable of better explaining the behavior of the set of data than are fewer segments or just one straight line.[11] Based on the assumption defined in the literature,[11] as 20 years were considered for the analysis, we postulated a maximum of three joinpoints per series.

The aforementioned indicators were defined as the dependent variable and, as the independent variable, the years of the historical series after smoothing (i.e., 2002–2021). To build the models, we applied the grid selection method, using the following parameters: natural logarithmic transformation of the dependent variable; adjustment of the models by the standard error of the percentages; and adjustment for first-order autocorrelation, verified by the "estimated from the data" function.[11]

The best model was the one with the lowest value in the weighted Bayesian criterion. We calculated the annual percentage change (APC), the average annual percentage change (AAPC), and corresponding 95% CIs using the empirical quantile method.[11] The APC indicated the change in the segments, and the AAPC, which consists of the geometric mean of the APC, demonstrated the behavior across the entire series. The interpretation of the APC and AAPC was as follows:

- Increasing trend (↑): indicated by positive values of APC or AAPC with a 95% CI that did not encompass the null point (zero);

- Decreasing trend (↓): indicated by negative values of APC or AAPC with a 95% CI that did not encompass the null point (zero);
- Stationary trend (↔): characterized when the APC or AAPC, whether positive or negative, encompassed the null point (zero) within the 95% CI.

RESULTS

Between 2001 and 2022, 994,081 new laboratory-confirmed cases of pulmonary tuberculosis were registered, of which 709,096 (71.33%) were declared cured. Regarding the trend of the cure indicator, we observed heterogeneity in the APC across FUs. We detected moments of increasing and decreasing trends throughout the analyzed period, but with a negative AAPC in most FUs (n = 24; 88.88%), except for Acre, Amapá, and Rio de Janeiro, as described in Table 1.

Concerning tuberculosis-HIV coinfection, we observed 143,361 cases during the study period, of which 69,794 (48.68%) were cured. It is noteworthy the divergence of APC across FUs, yet a declining trend at the conclusion of the series was observed for most states, except for Acre, Roraima, Tocantins, Rio Grande do Norte, and Mato Grosso. Acre, Amapá, and Rio de Janeiro exhibited an upward trajectory in AAPC, contrasting with the declining (n = 19; 70.37%) or stationary (n = 5; 18.51%) trends in the other FUs (Table 2).

Regarding tuberculosis retreatment cases, we identified that, between 2001 and 2022, a total of 275,255 cases were registered, and 134,740 (48.95%) progressed to cure. We observed that, except for Rondônia, all FUs experienced a decreasing trend at the end of the historical series, particularly between 2019 and 2021. According to AAPC, we also detected a decreasing trend in the period for all FUs of analysis (n = 23; 85.18%), except for Acre, Amapá, Tocantins, and Rio de Janeiro (Table 3).

DISCUSSION

Between 2002 and 2021, we identified a decreasing trend in cure indicators for new cases of pulmonary tuberculosis, cases of tuberculosis-HIV coinfection, and cases of retreatment in Brazil, with heterogeneity among the FUs. The reduction in the cure indicator is worrisome and issues a warning to public authorities, as it points to the possible occurrence of worse outcomes. Thus, these findings go against current public policies and underscore the need of immediate interventions in Brazil.

A time series analysis conducted in Brazilian capitals with data between 2001 and 2015 found significant heterogeneity in the temporal pattern of tuberculosis outcomes.[12] Despite the disparity among locations, the authors showed an increasing trend of loss to follow-up during tuberculosis treatment in the country, while the cure rate remained stationary.[12] This scenario already indicated difficulties related to improving adherence to treatment and cure rates in Brazil.

Similarly, a research conducted in the city of São Paulo between 2006 and 2017 pointed to an annual increase of 1.60% (95% CI, 0.02-3.48) in cases of treatment abandonment.[13] Furthermore, a study in a state in the northeast of Brazil, analyzing over nine thousand tuberculosis cases, found a decreasing trend in the percentage of people cured, dropping from 81.78% in 2001 to 57.81% in 2016.[14] This evidence corroborates and reinforces the findings obtained in this investigation.

Especially at the end of the time series, the effects of the COVID-19 pandemic can be attributed as one of the explanatory factors for the decreasing trends, which may also have influenced the general trend during the period. Researchers from several countries, such as Mozambique,[15] Brazil,[16] and Italy[17] reported that the health situation that prevailed during the pandemic caused underdiagnosing and underreporting, an increase in treatment interruptions, and a reduction in the cure rates for tuberculosis.

In a scenario of national inequalities, the importance of targeting specific strategies to groups most socially vulnerable to the disease stands out. Considering the daily barriers that prevent adequate access to health services and the continuity of care,[18,19] people deprived of liberty,[19] people living with HIV, and people undergoing retreatment for the disease, for example,[20] are more susceptible to the worst outcomes (e.g., loss to follow-up and death) of tuberculosis.

A meta-analysis investigating the results and predictors of tuberculosis treatment on the African continent observed that the treatment success rate varied between 53% (95% CI: 47-58%) in Nigeria and 92% (95% CI: 90-93%) in Ethiopia.[20] The worst outcomes, such as death and loss of follow-up, were more associated with people living with HIV (relative risk [RR] = 1.53; 95% CI, 1.36-1.71) and people undergoing tuberculosis retreatment (RR = 1.48; 95% CI, 1.14-1.94).[20]

In the Brazilian context, a retrospective cohort study identified factors leading to loss of follow-up for tuberculosis treatment when compared with the cure outcome.[21] Among the vulnerabilities, the following stood out: male gender (adjusted OR [aOR] = 1.35; 95% CI: 1.23-1.46); non-white ethnicity/race (aOR = 1.16; 95% CI: 1.07-1.26); drug use (aOR = 1.84; 95% CI: 1.66-2.04); and entry as recurrence (aOR = 1.33; 95% CI: 1.15-1.53) or re-entry after abandonment (aOR = 4.31; 95% CI: 3.90-4.77).[21]

To achieve the goals of reducing new cases and deaths from the disease by 2030, it is necessary and urgent to advance and overcome existing care gaps. To this end, we suggest expanding diagnostic testing, timely and adequate reporting of new cases, guaranteeing general access to health care for treatment follow-up, mitigation of disease risk factors (focusing on countries with the highest burden and among vulnerable populations), and expanding investments in research.[22]

Table 1. Temporal trend in the cure percentage of new cases of laboratory-confirmed pulmonary tuberculosis in the Brazilian federative units between 2002 and 2021.

Federative Unit	Period	APC (95% CI)	Trend	AAPC (95% CI)	Trend
North region					
Rondônia	2002-2008	0.27 (−0.30;2.19)	↔	−1.55 (−1.90;−1.22)	↓
	2008-2012	−2.08 (−3.63;−0.89)	↓		
	2012-2019	0.79 (0.28;2.41)	↑		
	2019-2021	−13.22 (−16.57;−7.74)	↓		
Acre	2002-2007	3.03 (1.97;5.17)	↑	0.05 (−0.22;0.39)	↔
	2007-2019	0.29 (0.07;0.54)	↑		
	2019-2021	−8.39 (−10.67;−4.67)	↓		
Amazonas	2002-2004	−3.66 (−5.62;−0.86)	↓	−1.59 (−1.86;−1.33)	↓
	2004-2010	0.69 (0.16;2.16)	↑		
	2010-2019	−0.72 (−1.10;−0.39)	↓		
	2019-2021	−9.80 (−12.15;−6.12)	↓		
Roraima	2002-2013	−0.40 (−0.78;0.20)	↔	−1.68 (−2.08;−1.36)	↓
	2013-2016	−5.67 (−7.71;−2.82)	↓		
	2016-2019	3.84 (1.10;6.56)	↑		
	2019-2021	−10.25 (−14.53;−5.87)	↓		
Pará	2002-2013	0.17 (0.02;0.40)	↑	−1.23 (−1.46;−1.08)	↓
	2013-2016	−2.49 (−3.25;−1.36)	↓		
	2016-2019	2.67 (1.51;3.69)	↑		
	2019-2021	−12.05 (−14.33;−10.14)	↓		
Amapá	2002-2012	2.57 (1.15;7.83)	↑	0.38 (−0.17;1.14)	↔
	2012-2019	0.13 (−1.23;2.88)	↔		
	2019-2021	−9.07 (−14.57;−2.30)	↓		
Tocantins	2002-2007	2.16 (1.16;4.54)	↑	−1.06 (−1.52;−0.67)	↓
	2007-2019	−0.45 (−0.83;−0.10)	↓		
	2019-2021	−12.00 (−15.95;−6.79)	↓		
Northeast region					
Maranhão	2002-2007	1.12 (0.24;3.13)	↑	−0.85 (−1.16;−0.58)	↓
	2007-2016	−0.51 (−2.16;−0.04)	↓		
	2016-2019	1.08 (−0.25;2.27)	↔		
	2019-2021	−9.75 (−12.59;−5.82)	↓		
Piauí	2002-2004	−2.11 (−4.03;1.11)	↔	−1.58 (−1.91;−1.31)	↓
	2004-2007	3.09 (−0.70;4.19)	↔		
	2007-2018	−0.52 (−0.87;−0.16)	↓		
	2018-2021	−9.34 (−11.58;−6.50)	↓		
Ceará	2002-2006	4.04 (2.70;5.72)	↑	−1.52 (−1.95;−1.23)	↓
	2006-2019	−1.27 (−1.48;−1.07)	↓		
	2019-2021	−13.22 (−16.68;−8.29)	↓		
Rio Grande do Norte	2002-2021	−0.62 (−1.13;−0.11)	↓	−0.62 (−1.13;−0.11)	↓
Paraíba	2002-2021	−1.18 (−1.80;−0.65)	↓	−1.18 (−1.80;−0.65)	↓
Pernambuco	2002-2019	0.16 (−0.11;0.56)	↔	−0.99 (−1.52;−0.46)	↓
	2019-2021	−10.20 (−15.08;−3.45)	↓		
Alagoas	2002-2006	2.29 (0.81;5.31)	↑	−1.63 (−2.17;−1.11)	↓
	2006-2019	−1.64;(−2.03;−1.13)	↓		
	2019-2021	−9.02 (−13.54;−2.71)	↓		
Sergipe	2002-2012	−0.20 (−0.72;1.79)	↔	−1.26 (−1.81;−0.79)	↓
	2012-2016	−3.15 (−6.52;−1.23)	↓		
	2016-2019	4.59 (1.69;7.68)	↑		
	2019-2021	−10.76 (−16.33;−4.97)	↓		
Bahia	2002-2006	3.44 (2.47;5.05)	↑	−1.28 (−1.59;−0.99)	↓
	2006-2010	−1.40 (−2.45;−0.59)	↓		
	2010-2019	−0.29 (−0.57;0.78)	↔		
	2019-2021	−13.78 (−16.56;−8.72)	↓		

Continue...▶

Table 1. Temporal trend in the cure percentage of new cases of laboratory-confirmed pulmonary tuberculosis in the Brazilian federative units between 2002 and 2021. (Continued...)

Federative Unit	Period	APC (95% CI)	Trend	AAPC (95% CI)	Trend
Southeast region					
Minas Gerais	2002-2008	1.41 (0.83;2.13)	↑	−1.36 (−1.64;−1.14)	↓
	2008-2016	−1.18 (−2.23;0.43)	↔		
	2016-2019	0.61 (−0.82;1.51)	↔		
	2019-2021	−12.53 (−15.11;−9.82)	↓		
Espírito Santo	2002-2006	1.34 (0.52;3.30)	↑	−2.75 (−3.19;−2.49)	↓
	2006-2016	−0.89 (−1.14;−0.53)	↓		
	2016-2019	−3.38 (−4.46;−1.45)	↓		
	2019-2021	−17.73 (−21.60;−13.06)	↓		
Rio de Janeiro	2002-2006	6.25 (4.37;9.84)	↑	0.32 (−0.07;0.70)	↔
	2006-2019	0.04 (−0.21;0.36)	↔		
	2019-2021	−8.98 (−12.04;−4.66)	↓		
São Paulo	2002-2012	0.55 (0.39;0.78)	↑	−0.95 (−1.12;−0.82)	↓
	2012-2019	−0.60 (−0.93;−0.33)	↓		
	2019-2021	−9.31 (−10.84;−7.93)	↓		
South region					
Paraná	2002-2004	−1.04 (−2.36;0.94)	↔	−1.84 (−2.16;−1.58)	↓
	2004-2013	1.00 (−1.49;2.08)	↔		
	2013-2019	−2.33 (−2.93;−1.59)	↓		
	2019-2021	−13.06 (−15.98;−8.88)	↓		
Santa Catarina	2002-2012	0.05 (−0.25;0.53)	↔	−1.55 (−1.91;−1.26)	↓
	2012-2019	−1.79 (−2.34;−1.06)	↓		
	2019-2021	−8.41 (−11.77;−4.23)	↓		
Rio Grande do Sul	2002-2006	1.00 (0.30;2.21)	↑	−1.75 (−1.99;−1.56)	↓
	2006-2011	−1.98 (−3.00;−1.42)	↓		
	2011-2019	−0.69 (−0.94;0.17)	↔		
	2019-2021	−10.44 (−12.68;−6.67)	↓		
Central-West region					
Mato Grosso do Sul	2002-2007	1.06 (0.44;1.90)	↑	−1.74 (−1.96;−1.57)	↓
	2007-2016	−1.93 (−2.38;−1.69)	↓		
	2016-2019	1.85 (0.51;2.70)	↑		
	2019-2021	−12.40 (−14.49;−10.47)	↓		
Mato Grosso	2002-2007	0.54 (−0.28;2.83)	↔	−1.60 (−1.99;−1.19)	↓
	2007-2010	−3.00 (−4.08;−1.35)	↓		
	2010-2019	−0.51 (−0.85;1.46)	↔		
	2019-2021	−9.33 (−13.24;−3.94)	↓		
Goiás	2002-2004	−2.96 (−5.97;1.30)	↔	−1.29 (−1.70;−0.90)	↓
	2004-2009	2.24 (−2.45;5.00)	↔		
	2009-2019	−1.01 (−1.46;0.42)	↔		
	2019-2021	−9.33 (−12.98;−4.80)	↓		
Distrito Federal	2002-2008	0.19 (−1.79;1.72)	↔	−4.28 (−4.98;−3.81)	↓
	2008-2015	−2.16 (−3.90;1.69)	↔		
	2015-2019	−8.82 (−10.13;−0.34)	↓		
	2019-2021	−14.82 (−21.01;−9.57)	↓		
Brazil	2002-2007	1.60 (0.94;2.78)	↑	−0.97 (−1.23;−0.74)	↓
	2007-2019	−0.47 (−0.67;−0.27)	↓		
	2019-2021	−9.88 (−12.14;−5.96)	↓		

APC: annual percentage change; AAPC: average annual percentage change; and (↑: increasing; ↔: stationary; and ↓: decreasing).

The literature reported several useful strategies that focus on promoting care for people affected by tuberculosis that can be used to provide access to health services, adequate follow-up, and treatment. Directly observed treatment, for example, has been crucial to guarantee the bond between health professionals and affected people, allowing early identification of possible loss to follow-up and favoring the chances of curing the disease.[21,23,24]

Table 2. Temporal trend in the percentage of cure of new cases of tuberculosis with HIV coinfection in the Brazilian federative units between 2002 and 2021.

Federative Unit	Period	APC (95% CI)	Trend	AAPC (95% CI)	Trend
North region					
Rondônia	2002-2006	1.66 (−1.73;10.70)	↔	−1.25 (−1.98;−0.35)	↓
	2006-2010	−7.25 (−11.90;−3.22)	↓		
	2010-2019	2.23 (1.37;6.45)	↑		
	2019-2021	−9.59 (−16.02;−1.50)	↓		
Acre	2002-2006	19.24 (11.29;32.47)	↑	2.33 (1.42;3.90)	↑
	2006-2011	−8.89 (−15.53;−5.57)	↓		
	2011-2015	7.78 (3.36;14.51)	↑		
	2015-2021	−1.65 (−5.83;0.05)	↔		
Amazonas	2002-2005	−2.81 (−12.14;4.52)	↔	−0.84 (−1.48;0.04)	↔
	2005-2009	7.80 (−1.48;12.98)	↔		
	2009-2019	−1.27 (−1.72;−0.50)	↓		
	2019-2021	−11.63 (−15.29;−6.27)	↓		
Roraima	2002-2019	−1.14 (−7.57;24.79)	↔	−2.80 (−4.83;0.59)	↔
	2019-2021	−15.86 (−31.13;1.06)	↔		
Pará	2002-2004	−5.02 (−10.51;3.26)	↔	−1.56 (−2.11;−0.80)	↓
	2004-2010	4.16 (−2.40;9.04)	↔		
	2010-2019	−0.86 (−1.66;0.68)	↔		
	2019-2021	−16.57 (−20.28;−10.70)	↓		
Amapá	2002-2011	13.38 (12.20;16.46)	↑	2.48 (1.86;3.58)	↑
	2011-2014	−9.89 (−12.60;−4.49)	↓		
	2014-2018	3.69 (1.03;8.66)	↑		
	2018-2021	−15.27 (−21.40;−10.92)	↓		
Tocantins	2002-2004	25.95 (6.89;59.03)	↑	1.22 (0.98;3.65)	↔
	2004-2009	7.12 (−14.29;12.69)	↔		
	2009-2014	−11.00 (−17.66;6.91)	↔		
	2014-2021	0.10 (−13.58;9.51)	↔		
Northeast region					
Maranhão	2002-2019	0.22 (−1.23;7.07)	↔	−1.20 (−2.57;1.24)	↓
	2019-2021	−12.51 (−22.27;−0.08)	↓		
Piauí	2002-2012	0.77 (−4.73;8.74)	↔	−2.33 (−3.21;−1.13)	↓
	2012-2019	−2.89 (−5.27;4.50)	↔		
	2019-2021	−14.78 (−22.32;−3.93)	↓		
Ceará	2002-2004	15.10 (7.18;22.87)	↑	−1.69 (−2.21;−1.06)	↓
	2004-2007	−4.26 (−5.88;−1.24)	↓		
	2007-2018	−0.09 (−0.40;0.85)	↔		
	2018-2021	−14.34 (−16.43;−10.60)	↓		
Rio Grande do Norte	2002-2019	1.13 (0.38;30.49)	↑	−0.28 (−1.56;3.63)	↔
	2019-2021	−11.50 (−23.88;0.45)	↔		
Paraíba	2002-2011	−2.24 (−2.83;0.81)	↔	−3.03 (−3.74;−2.48)	↓
	2011-2014	−7.13 (−10.07;−3.72)	↓		
	2014-2017	6.21 (1.24;9.73)	↑		
	2017-2021	−8.11 (−14.54;−6.25)	↓		
Pernambuco	2002-2007	1.04 (0.03;2.92)	↑	−1.22 (−1.52;−0.94)	↓
	2007-2013	−2.47 (−4.21;−1.74)	↓		
	2013-2018	1.83 (0.78;3.81)	↑		
	2018-2021	−7.24 (−10.98;−4.84)	↓		
Alagoas	2002-2005	10.00 (2.19;23.84)	↑	−3.50 (−4.79;−2.05)	↓
	2005-2009	−13.32 (−18.85;−8.14)	↓		
	2009-2019	−0.73 (−1.91;7.18)	↔		
	2019-2021	−14.67 (−24.69;−3.83)	↓		
Sergipe	2002-2011	−0.35 (−1.59;2.84)	↔	−1.49 (−2.49;−0.54)	↓
	2011-2014	−12.69 (−17.62;−5.68)	↓		
	2014-2018	12.92 (8.44;23.54)	↑		
	2018-2021	−10.46 (−20.72;−4.81)	↓		

Continue...▶

Table 2. Temporal trend in the percentage of cure of new cases of tuberculosis with HIV coinfection in the Brazilian federative units between 2002 and 2021. (Continued...)

Federative Unit	Period	APC (95% CI)	Trend	AAPC (95% CI)	Trend
Bahia	2002-2007	10.00 (8.64;12.52)	↑	−0.11 (−0.54;0.36)	↔
	2007-2010	−5.81 (−7.03;−2.69)	↓		
	2010-2019	−0.59 (−0.99;0.50)	↔		
	2019-2021	−12.38 (−15.96;−7.29)	↓		
Southeast region					
Minas Gerais	2002-2011	2.17 (1.69;2.67)	↑	−0.52 (−0.91;−0.26)	↓
	2011-2016	−3.45 (−5.92;−2.45)	↓		
	2016-2019	2.88 (0.74;4.51)	↑		
	2019-2021	−9.61 (−13.40;−5.47)	↓		
Espírito Santo	2002-2010	1.65 (−0.75;3.29)	↔	−3.16 (−3.74;−2.72)	↓
	2010-2013	−3.65 (−5.32;3.43)	↔		
	2013-2018	0.22 (−1.61;3.28)	↔		
	2018-2021	−19.25 (−23.01;−14.80)	↓		
Rio de Janeiro	2002-2006	15.43 (13.72;17.78)	↑	2.25 (1.88;2.67)	↑
	2006-2010	−2.92 (−4.94;−1.32)	↓		
	2010-2019	1.41 (1.01;2.45)	↑		
	2019-2021	−7.61 (−10.77;−3.16)	↓		
São Paulo	2002-2008	0.23 (−2.21;1.24)	↔	−1.32 (−1.75;−1.02)	↓
	2008-2011	2.34 (−1.67;3.49)	↔		
	2011-2019	−0.48 (−1.35;1.06)	↔		
	2019-2021	−13.78 (−17.37;−8.57)	↓		
South region					
Paraná	2002-2010	2.40 (2.06;2.84)	↑	−1.49 (−1.73;−1.31)	↓
	2010-2016	−0.07 (−0.48;0.88)	↔		
	2016-2019	−2.34 (−3.20;−1.10)	↓		
	2019-2021	−18.07 (−20.41;−16.27)	↓		
Santa Catarina	2002-2012	1.70 (−1.25;5.62)	↔	−1.46 (−2.20;−0.82)	↓
	2012-2015	−5.11 (−7.29;4.15)	↔		
	2015-2019	−0.99 (−3.51;3.00)	↔		
	2019-2021	−11.74 (−18.84;−3.66)	↓		
Rio Grande do Sul	2002-2007	3.18 (2.42;3.82)	↑	−1.99 (−2.25;−1.79)	↓
	2007-2015	−2.11 (−2.83;−1.81)	↓		
	2015-2019	−0.79 (−1.65;0.33)	↔		
	2019-2021	−15.51 (−17.87;−13.30)	↓		
Central-West region					
Mato Grosso do Sul	2002-2008	−0.87 (−2.92;6.84)	↔	−3.93 (−5.31;−2.80)	↓
	2008-2011	−10.43 (−14.90;−4.37)	↓		
	2011-2019	1.22 (−0.41;11.14)	↔		
	2019-2021	−21.20 (−32.82;−9.74)	↓		
Mato Grosso	2002-2015	−3.73 (−7.45;4.39)	↔	−3.38 (−4.75;−1.63)	↓
	2015-2019	3.60 (−8.20;9.48)	↔		
	2019-2021	−13.96 (−26.26;0.21)	↔		
Goiás	2002-2011	−0.53 (−1.26;1.04)	↔	−1.92 (−2.60;−1.41)	↓
	2011-2014	−7.30 (−9.80;−3.50)	↓		
	2014-2018	4.25 (1.56;8.99)	↑		
	2018-2021	−8.30 (−17.10;−4.23)	↓		
Distrito Federal	2002-2015	−0.71 (−1.25;−0.08)	↓	−3.03 (−3.72;−2.62)	↓
	2015-2021	−7.88 (−11.15;−6.02)	↓		
Brazil	2002-2006	3.08 (1.88;5.24)	↑	−1.11 (−1.42;−0.85)	↓
	2006-2019	−0.54 (−0.74;−0.32)	↓		
	2019-2021	−12.37 (−14.84;−7.71)	↓		

APC: annual percentage change; AAPC: average annual percentage change; and (↑: increasing; ↔: stationary; and ↓: decreasing).

Table 3. Temporal trend in the cure percentage of tuberculosis retreatment cases in the Brazilian federative units between 2002 and 2021.

Federative Unit	Period	APC (95% CI)	Trend	AAPC (95% CI)	Trend
North region					
Rondônia	2002-2012	−1.42 (−10.20;12.92)	↔	−1.84 (−3.23;−0.38)	↓
	2012-2015	−7.85 (−15.35;9.57)	↔		
	2015-2019	8.34 (−6.85;20.06)	↔		
	2019-2021	−13.23 (−26.53;2.34)	↔		
Acre	2002-2019	1.67 (1.32;2.43)	↑	0.09 (−0.63;0.80)	↔
	2019-2021	−12.44 (−19.06;−5.52)	↓		
Amazonas	2002-2010	0.47 (−0.13;1.59)	↔	−2.18 (−2.46;−1.85)	↓
	2010-2013	−4.28 (−5.40;−2.21)	↓		
	2013-2019	−0.77 (−1.39;1.09)	↔		
	2019-2021	−13.06 (−15.78;−8.62)	↓		
Roraima	2002-2006	7.81 (4.27;11.51)	↑	−1.37 (−1.78;−0.83)	↓
	2006-2013	−10.37 (−12.74;−9.25)	↓		
	2013-2016	21.42 (14.66;25.66)	↑		
	2016-2021	−7.31 (−8.86;−5.91)	↓		
Pará	2002-2016	−0.51 (−2.32;−0.02)	↓	−1.33 (−1.92;−0.92)	↓
	2016-2019	4.70 (0.85;7.08)	↑		
	2019-2021	−14.81 (−20.04;−8.25)	↓		
Amapá	2002-2004	−12.65 (−25.59;6.93)	↔	0.05 (−0.83;1.68)	↔
	2004-2008	12.98 (−6.15;27.68)	↔		
	2008-2019	−0.15 (−1.32;6.35)	↔		
	2019-2021	−9.10 (−16.66;−1.83)	↓		
Tocantins	2002-2007	10.95 (2.49;26.19)	↑	−1.28 (−2.99;0.72)	↔
	2007-2019	−3.20 (−5.32;13.53)	↔		
	2019-2021	−17.01 (−29.86;−3.18)	↓		
Northeast region					
Maranhão	2002-2006	−0.38 (−1.39;1.96)	↔	−2.54 (−2.81;−2.29)	↓
	2006-2016	−2.10 (−3.72;−1.86)	↓		
	2016-2019	1.42 (−0.54;2.75)	↔		
	2019-2021	−14.07 (−16.63;−11.34)	↓		
Piauí	2002-2006	1.17 (−0.66;4.77)	↔	−1.67 (−2.09;−1.33)	↓
	2006-2011	−4.71 (−8.68;−3.18)	↓		
	2011-2014	5.36 (1.06;8.14)	↑		
	2014-2021	−3.94 (−5.90;−2.90)	↓		
Ceará	2002-2006	3.99 (2.73;6.21)	↑	−2.50 (−2.86;−2.20)	↓
	2006-2009	−4.35 (−5.35;−2.55)	↓		
	2009-2019	−2.19 (−2.49;−0.76)	↓		
	2019-2021	−13.17 (−16.42;−8.58)	↓		
Rio Grande do Norte	2002-2013	−4.45 (−4.73;−4.19)	↓	−1.74 (−1.99;−1.52)	↓
	2013-2019	6.55 (5.97;7.29)	↑		
	2019-2021	−10.16 (−12.56;−7.50)	↓		
Paraíba	2002-2006	−1.86 (−3.13;−0.01)	↓	−4.03 (−4.34;−3.81)	↓
	2006-2015	−6.78 (−7.32;−6.35)	↓		
	2015-2018	8.85 (6.93;10.39)	↑		
	2018-2021	−10.42 (−12.60;−8.64)	↓		
Pernambuco	2002-2007	0.24 (−1.55;5.54)	↔	−1.62 (−2.14;−1.09)	↓
	2007-2011	−2.85 (−5.67;2.28)	↔		
	2011-2019	1.74 (0.85;4.14)	↑		
	2019-2021	−15.89 (−20.55;−20.55)	↓		
Alagoas	2002-2007	−1.84 (−2.97;0.26)	↔	3.92 (−4.37;−3.56)	↓
	2007-2010	−10.49 (−12.60;−6.85)	↓		
	2010-2015	2.89 (0.95;8.06)	↑		
	2015-2021	−7.63 (−9.84;−5.98)	↓		

Continue...▶

Table 3. Temporal trend in the cure percentage of tuberculosis retreatment cases in the Brazilian federative units between 2002 and 2021. (Continued...)

Federative Unit	Period	APC (95% CI)	Trend	AAPC (95% CI)	Trend
Sergipe	2002-2005	−8.93 (−12.78;−6.55)	↓	−2.98 (−3.41;−2.64)	↓
	2005-2011	−3.21 (−5.07;−1.27)	↓		
	2011-2019	0.28 (−0.26;3.25)	↔		
	2019-2021	−5.84 (−10.06;−1.49)	↓		
Bahia	2002-2019	−0.69 (−1.40;1.31)	↔	−2.53 (−4.15;−1.10)	↓
	2019-2021	−16.80 (−29.53;−2.00)	↓		
Southeast region					
Minas Gerais	2002-2007	0.78 (0.01;1.82)	↑	−2.07 (−2.40;−1.82)	↓
	2007-2015	−3.01 (−3.72;−2.59)	↓		
	2015-2019	2.94 (1.60;5.44)	↑		
	2019-2021	−14.26 (−17.39;−9.23)	↓		
Espírito Santo	2002-2017	0.19 (−0.87;0.64)	↔	−4.62 (−5.81;−3.95)	↓
	2017-2021	−19.57 (−25.35;−14.61)	↓		
Rio de Janeiro	2002-2005	4.03 (0.75;10.62)	↑	−0.41 (−1.03;0.19)	↔
	2005-2019	0.70 (−0.28;1.65)	↔		
	2019-2021	−13.71 (−18.56;−8.04)	↓		
São Paulo	2002-2005	3.31 (0.97;7.89)	↑	−0.86 (−1.22;−0.47)	↓
	2005-2019	0.18 (−0.24;0.44)	↔		
	2019-2021	−13.33 (−15.95;−8.17)	↓		
South region					
Paraná	2002-2004	−4.82 (−6.05;−2.45)	↓	−2.53 (−2.75;−2.33)	↓
	2004-2011	2.50 (2.09;3.14)	↑		
	2011-2019	−1.76 (−2.14;−1.42)	↓		
	2019-2021	−18.84 (−20.66;−17.17)	↓		
Santa Catarina	2002-2009	−1.12 (−4.90;0.30)	↔	−2.90 (−3.56;−2.43)	↓
	2009-2013	1.78 (−0.50;4.52)	↔		
	2013-2019	−3.72 (−5.27;−1.91)	↓		
	2019-2021	−14.97 (−20.30;−8.91)	↓		
Rio Grande do Sul	2002-2006	−0.34 (−1.56;2.03)	↔	−2.70 (−2.98;−2.42)	↓
	2006-2013	−3.55 (−5.08;−2.97)	↓		
	2013-2019	−0.08 (−0.74;1.33)	↔		
	2019-2021	−11.65 (−14.20;−7.47)	↓		
Central-West region					
Mato Grosso do Sul	2002-2011	0.89 (0.11;2.05)	↑	−2.54 (−3.01;−2.08)	↓
	2011-2014	−11.72 (−14.03;−6.97)	↓		
	2014-2019	4.88 (3.31;8.68)	↑		
	2019-2021	−19.49 (−23.65;−14.82)	↓		
Mato Grosso	2002-2008	−2.05 (−3.24;0.88)	↔	−2.87 (−3.37;−2.49)	↓
	2008-2011	−4.89 (−6.62;2.37)	↔		
	2011-2019	1.06 (0.03;2.91)	↑		
	2019-2021	−16.56 (−21.01;−10.41)	↓		
Goiás	2002-2007	1.89 (−3.25;10.55)	↔	−1.35 (−2.11;−0.48)	↓
	2007-2019	−1.31 (−3.62;5.44)	↔		
	2019-2021	−9.24 (−15.71;−1.45)	↓		
Distrito Federal	2002-2006	−6.00 (−10.84;−3.35)	↓	−5.40 (−6.32;−4.77)	↓
	2006-2010	7.93 (4.33;12.84)	↑		
	2010-2019	−7.20 (−8.03;−5.87)	↓		
	2019-2021	−19.75 (−26.84;−10.99)	↓		
Brazil	2002-2006	2.36 (1.78;3.41)	↑	−1.44 (−1.62;−1.31)	↓
	2006-2009	−2.77 (−3.32;−1.39)	↓		
	2009-2019	0.03 (−0.14;0.30)	↔		
	2019-2021	−13.99 (−14.92;−12.40)	↓		

APC: annual percentage change; AAPC: average annual percentage change; and (↑: increasing; ↔: stationary; and ↓: decreasing).

Furthermore, to effectively combat tuberculosis, it is crucial to reinforce actions aimed at controlling and managing cases of latent *Mycobacterium tuberculosis* infection (LTBI), also known as tuberculosis infection.[25] In these situations, people are not sick, but when exposed to risk factors, such as immunosuppression or malnutrition, they can develop an active condition, and, eventually, spread tuberculosis among contacts, maintaining the transmission chain.[26]

The Brazilian Ministry of Health has focused efforts on screening and treating cases of tuberculosis infection since 2018, when a surveillance protocol for latent *Mycobacterium tuberculosis* infection was published.[27] A descriptive study that analyzed the indications for treatment of tuberculosis infection between January of 2018 and June of 2022 identified 85,822 cases of LTBI treatment in the country, especially among contacts of people with tuberculosis (57.2%) and people living with HIV (16.7%).[28]

In addition to the national plan that directs control strategies,[5] the Brazilian Ministry of Health intensified the strengthening of actions that deal with social protection for people and families affected by tuberculosis, considering the close relationship between poverty and the disease.[29] Intersectoral actions, focused mainly on education and social assistance, can be particularly important for ensuring comprehensive care and well-being for individuals and groups with tuberculosis.[20]

On this topic, in 2024, Decree No. 11,908 established the *Programa Brasil Saudável*, coordinated by the *Comitê Interministerial para a Eliminação da Tuberculose e de Outras Doenças Socialmente Determinadas*.[30] The aim is to promote the integration of ministries, with the goal of quickly improving access to health care and mitigating existing inequalities in the country.[30] One of the objectives is to eliminate tuberculosis as a public health problem by the end of this decade.[28]

However, given the worrying scenario of tuberculosis cure indicators in our study, we highlight the need to strengthen the health care network constantly, especially primary care. Primary health care has autonomy on the prevention, diagnosis, and treatment of tuberculosis.[31] Also, the activities and coverage of primary health care teams are directly related to the detection of the disease in Brazil,[32] playing a crucial role in monitoring cases and interrupting the transmission chain.

This study needs to be interpreted in light of some limitations: (i) the use of secondary data is subject to filling errors and underreporting, especially during the COVID-19 pandemic period; (ii) ignored/blank records about the outcome or location were excluded; (iii) there is the possibility of reviewing preliminary data between 2018 and 2022 by the Brazilian Ministry of Health; and (iv) the use of the percentage as a measure makes the dependent variable more susceptible to variations.

Therefore, it must be considered that the data employed in this study may not accurately reflect the actual scenario of the tuberculosis cure trend in the country. Undiagnosed, unreported, and/or inaccurately filled cases may overestimate or underestimate the calculated indicators. However, it is reiterated that smoothing strategies using a three-point moving average and the selection of complete cases were applied in an attempt to minimize these effects.

In short, this study highlighted the need for new efforts to mitigate the scenario of reduction in the cure rate among tuberculosis cases, especially in the most vulnerable populations. The coordination between health care services, social assistance, and other sectors of society is a key element in tackling this problem. Moreover, this is essential for achieving the goals agreed in the national plan for the elimination of tuberculosis by 2030, mainly in the post-pandemic period.

The need to evaluate local scenarios for monitoring tuberculosis indicators at a national level is highlighted, considering that there are particularities that lead to the adoption, or lack thereof, of different strategies for controlling the disease. In this sense, the results of our study are essential for managers, particularly those at a federal level, to understand the different epidemiological contexts and promote the redirecting of interventions to locations with the most alarming indicators.

AUTHOR CONTRIBUTIONS

GP and LVL: conception and planning of the study; interpretation of the results; drafting and revising of the manuscript; and approval of the final version. PHPB, JRD, BRS, and GTM: drafting and revising of the manuscript; and approval of the final version.

CONFLICTS OF INTEREST

None declared.

ADDITIONAL INFORMATION

This investigation was conducted by scholars affiliated with the *Grupo de Estudo e Pesquisa em Vigilância do HIV/aids e Tuberculose* (GEPVHAT, Study and Research Group on HIV/AIDS and Tuberculosis Surveillance), associated with the Graduate Program in Nursing at the State University of Maringá. Additionally, collaborative efforts were carried out by members from the State University of Londrina and the *Rede Brasileira de Pesquisa em Tuberculose* (REDE-TB, Brazilian Tuberculosis Research Network).

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ORIGINAL ARTICLE

Lung function and quality of life one year after severe COVID-19 in Brazil

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Study carried out at the Hospital das Clínicas da Universidade Federal de Minas Gerais, Hospital Júlia Kubitschek, and Hospital Eduardo de Menezes, all located in Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: To evaluate symptoms, lung function, and quality of life of a cohort of patients hospitalized for severe COVID-19 12 months after hospital admission. **Methods:** This was a cross-sectional study. We included severe COVID-19 survivors hospitalized in one of three tertiary referral hospitals for COVID-19 in the city of Belo Horizonte, Brazil. Participants were submitted to lung function and six-minute walk tests and completed the EQ-5D-3L questionnaire. **Results:** The whole sample comprised 189 COVID-19 survivors (mean age = 59.6 ± 13.4 years) who had been admitted to a ward only (n = 96; 50.8%) or to an ICU (n = 93; 49.2%). At 12 months of follow-up, 43% of patients presented with dyspnea, 27% of whom had a restrictive ventilatory disorder and 18% of whom presented with impaired DL_{CO}. There were no significant differences in FVC, FEV_1, and TLC between the survivors with or without dyspnea. However, those who still had dyspnea had significantly more impaired DL_{CO} (14.9% vs. 22.4%; $p < 0.020$) and poorer quality of life. **Conclusions:** After one year, survivors of severe COVID-19 in a middle-income country still present with high symptom burden, restrictive ventilatory changes, and loss of quality of life. Ongoing follow-up is needed to characterize long COVID-19 and identify strategies to mitigate its consequences.

Keywords: COVID-19; Respiratory function tests; Spirometry; Dyspnea; Quality of life.

INTRODUCTION

COVID-19, caused by SARS-CoV-2, has been acknowledged to be responsible for a multisystemic disorder.[1] Similarly to other coronaviruses, there are also reports of prolonged symptoms after COVID-19.[2]

There are various mechanisms that may be involved in symptom persistence.[1,3] In a prospective cohort from Wuhan, China, dyspnea was reported in 26% of patients after 6 months.[4] Interstitial abnormalities were observed in 55.7% of patients after a mean of 90 days from hospital discharge.[5] A reduced DL_{CO} has been the most frequently detected alteration in the long term.[6] Scientific studies comparing clinical data and pulmonary function after 45 days or 3 months and 6 months of hospitalization for severe COVID-19 showed that there was improvement in pulmonary function at 6 months.[4,7-9]

Physical fitness deficit was associated with dyspnea and fatigue in studies of persistent symptoms after COVID-19.[10,11] However, in a study that evaluated six-minute walk test (6MWT) results after hospital discharge and then again after 3 months, no differences were found in demographic, anthropometric, physiological, and clinical characteristics or in the perception of health status between patients with and without exercise limitation.[12]

Poor quality of life (QoL) has been detected in 59% of 1,108 participants pooled in a systematic review and meta-analysis with survivors of COVID-19.[13] Another review, including only studies involving hospitalized patients, identified that COVID-19 patients had worse health-related QoL (HRQoL) when compared with hospitalized patients without COVID-19.[14]

The aim of this study was to describe alterations in lung function and perceived HRQoL in a cohort of patients 1 year after hospital admission for severe COVID-19 in Brazil and to compare COVID-19 patients who were admitted to a ward only and those admitted to an ICU.

METHODS

This is a nested cross-sectional study in a multicenter cohort of COVID-19 survivors evaluating patients 12 months after admission to one of three public referral hospitals for COVID-19 in the city of Belo Horizonte, Minas Gerais, Brazil, namely, *Hospital das Clínicas da Universidade Federal de Minas Gerais*, *Hospital Júlia Kubitschek*, and *Hospital Eduardo de Menezes*, between May 25, 2020 and December 28, 2020, during the first wave of COVID-19. During that period, vaccination was unavailable in the country. Patients were stratified into two groups: patients admitted only to a ward, that is,

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who never required admission to an ICU; and patients admitted to an ICU, who required high-flow oxygen therapy, mechanical ventilation, or use of vasopressors during ICU stay.

Patients ≥ 18 years of age who had ARDS upon hospital admission were included. COVID-19 was confirmed by a positive RT-PCR result of a nasal swab sample. A case of ARDS was defined as an individual with fever and cough or sore throat, associated with dyspnea, chest tightness, or Sp_{O_2} < 95%.[15] Eligible patients at hospital admission were invited to participate in outpatient follow-up and were included in the study when they attended the outpatient clinic 360 days after admission and completed the study protocol. Patients who withdrew consent were excluded from the analysis.

The study was approved by the Brazilian National Research Ethics Committee under protocol number 5.416.966. All participants were invited to participate in the study and were included after the participant signed an informed consent form.

Demographic data, clinical manifestations, comorbidities, continuous medication, smoking, date of respiratory symptom onset, date of hospital admission, length of hospital stay, length of ICU stay, duration of mechanical ventilation, and complications during hospitalization were recorded.

During consultations at the outpatient clinics, information on the participants' QoL was collected using the EQ-5D-3L questionnaire (EuroQoL Research Foundation).[16] The instrument consists of a descriptive form, comprising five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each dimension there are three levels: no problems, moderate problems, and extreme problems. Patients were asked to indicate their health status by checking the box next to the most appropriate statement in each of the five dimensions. Finally, the patient assigned a value to their QoL using a visual analog scale from 0 (worst health) to 100 (best health).

The main outcomes studied were lung function (spirometry, lung volumes, and DL_{CO}), physical exercise capacity measured by the distance covered in six minutes (6MWD), respiratory muscle strength (MIP and MEP), and perceived QoL at 12 months after hospital admission.

According to the WHO, the post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, generally 3 months after the onset of COVID-19, with symptoms lasting at least 2 months that cannot be explained by alternative diagnoses.[17]

At follow-up, the persistence of cough and dyspnea (according to the modified Medical Research Council scale),[18] vital data, weight, and height were recorded. Lung function tests were performed in the Pulmonary Function Laboratory of the University Hospital of the Federal University of Minas Gerais. Lung volumes were measured using a Vyntus™ body plethysmograph (Vyaire Medical Inc., Höchberg, Germany) of variable pressure equipped with a pneumotachograph in accordance with the standards proposed by the American Thoracic Society and the European Respiratory Society.[19,20] The following variables were studied: TLC, slow vital capacity, FVC, FEV_1, and the FEV_1/FVC ratio. Measurements were expressed in absolute values and in percentage of predicted (%pred) values for the Brazilian population.[21,22] The single breath method was used to determine DL_{CO}, considering the values suggested by Guimarães et al.[23]

The 6MWT was performed in a 30-m corridor using a portable oximeter (Nonin Medical Inc, Plymouth, MN, USA) according to international recommendations.[24] The following variables were recorded: oxygen saturation (Sp_{O_2}), heart rate (HR), respiratory rate (RR), dyspnea score on the Borg scale at the beginning and end of the 6MWT, HR in %pred relative to the maximum HR in %pred for adults, HR at the end of the 6MWT, HR after 1 min of recovery from the 6MWT (HRR_1), and 6MWD. A fall in oxygen saturation ≥ 4% or a reduction in HR after 1 min of 6MWT recovery < 12 bpm were considered altered results.[24] The 6MWD was expressed in absolute values and in %pred for the Brazilian population.[25]

MIP and MEP were measured with an analog manometer (Makil, Londrina, Brazil) as described by Laveneziana et al.[26] The maneuver was repeated five to eight times, respecting a reproducibility of 10%. The highest value obtained was recorded. The predicted values were calculated according to Neder et al.[27] The lower limit of normality (LLN) for each variable was calculated from predictive equations.[20]

Possible sources of bias were the diagnosis of COVID-19, lung function measurements, and selection bias. Diagnosis was defined by RT-PCR; the equipment was calibrated according to recommendations of the manufacturers, and clinical evaluation was based on standardized questionnaires. Selection bias was minimized by the multicenter design.

Data were collected using the REDCap platform (Vanderbilt University, Nashville, TN, USA)[28] and analyzed with the IBM SPSS Statistics software package, version 28.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were described as frequencies and ratios. Continuous variables with normal distribution were described as means and standard deviations, while those with non-normal distribution were described as medians and interquartile ranges. The predicted values and the LLN were used as risk to categorize continuous variables. The parametric Student's t-test or the nonparametric Mann-Whitney U test were used to check the differences in means and medians, respectively, between groups, and the Pearson's chi-square test for ratios. Binary logistic regression analysis was used to adjust associations by BMI, use of mechanical ventilation, acute kidney injury, and length of hospital stay. Hypothesis testing

was two-sided, and the significance level was set at $p < 0.05$.

RESULTS

At hospital admission during the study period, 454 patients were considered eligible, but 252 did not attend the evaluation at 360 days, 4 withdrew consent, and 9 died. The final sample consisted of 189 patients evaluated 360 days after hospitalization for severe COVID-19 (Figure 1). Among those lost to follow-up, a greater proportion corresponded to patients who had been admitted to the ICU (p = 0,032; Supplementary Table 1)

The Ward and ICU groups were composed of 96 (50.79%) and 93 (49.20%) of participants, respectively. The groups were homogeneous regarding demographic variables: age (59.6 ± 13.4 years), gender (49.2% were male), presence of comorbidities (88.8%), schooling, family income, and self-declared skin color. Among the pre-existing conditions, there was a difference between the groups only regarding the presence of obesity, which was more frequent in the ICU group (p = 0.018). In the sample as a whole, asthma and COPD were reported in 11.1% and 6.7%, respectively, and 26.6% of the patients were smokers (Table 1).

After 12 months, we found persistence of cough and dyspnea in 19% and 43% of patients in the Ward and ICU groups, respectively, but with no statistical difference. In the logistic regression analysis, no significant difference was observed between the groups regarding spirometry variables, lung volumes, DL_{CO}, 6MWT, and muscle strength ($p > 0.05$; Table 2).

After stratifying the patients into two groups, with and without dyspnea, we observed that cough was more common in the first group, as well as higher BMI values. Lung function variables (VC, FVC, FEV_1, FEV_1/FVC ratio, TLC, DL_{CO}, MIP, and MEP) obtained in the group with dyspnea were significantly lower. However, the frequency of altered variables did not differ significantly between the groups, except for DL_{CO} [(dyspnea: 15 (14.9%) vs. no dyspnea: 17 (22.4%); p = 0.011]. The dyspnea group had shorter 6MWD, with a higher percentage of patients with a final Borg scale score ≥ 4, (44.4% vs. 8.9%; p = 0.001; Table 3).

In the assessment of QoL, the group with dyspnea had worse mobility problems, self-care, usual activities, pain/discomfort, anxiety, and depression. The mean follow-up duration was 364 days (Table 4).

DISCUSSION

The main results of this study show that dyspnea was present in 43% of the cohort at 12 months. Symptoms of cough and dyspnea in the acute phase predominated in the ICU group; however, at 12 months, there was no difference between the groups. About 27% of the cohort still had a restrictive ventilatory pattern, and 18% had altered DL_{CO} at 12 months.

Corroborating our results, post-COVID-19 persistent symptoms were still observed in 30% of the subjects in the Wuhan cohort, China, at one-year follow-up, regardless of initial severity. These symptoms were related to decreased QoL, lower functional capacity, and abnormal mental health.[29] A possible explanation for persistent dyspnea is a combination of peripheral and psychological factors.[30]

In another Brazilian cohort study, one year after hospital discharge, more than one-third of patients still had persistent COVID-19-related symptoms, regardless of acute disease severity. The most common symptoms were dyspnea (54.5%), fatigue (50.0%), myalgia, and muscle weakness (46.6%), which decreased over time. Obese patients also had a greater risk of dyspnea, although this was not significant after adjustment.[31] In our dataset, BMI > 30 kg/m^2 was not associated with persistent dyspnea.

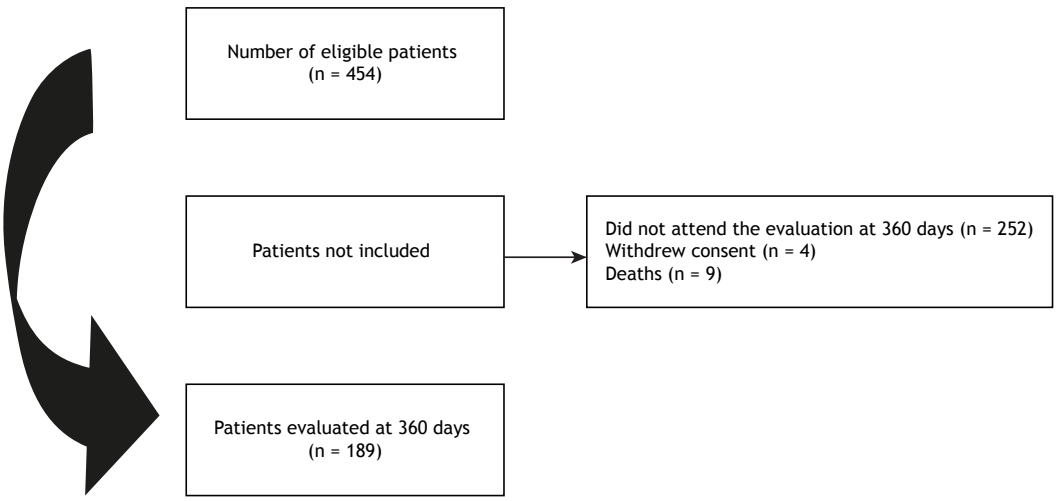

Figure 1. Flow chart of the participant selection process.

Table 1. Sociodemographic and clinical characteristics, as well as pre-existing conditions, at baseline in the sample as a whole and by group (Ward vs. ICU).[a]

Variable		Total sample	Group		p
			Ward	ICU	
		N = 189	n = 96	n = 93	
Age, years		59.6 ± 13.4	60.9 ± 14.3	58.4 ± 12.4	0.197
Men, n (%)		93 (49.2)	49 (51.0)	44 (47.3)	0.608
Comorbidities[b]		167 (88.8)	85 (89.5)	82 (88.2)	0.777
Variable	**Category**		**n (%)**		
Schooling[b]	Undergraduate/graduate education	17 (9.7)	7 (7.8)	10 (11.6)	0.165
	Middle to high school	76 (43.2)	45 (50.0)	31 (36.0)	
	No education or incomplete elementary school (< 8 years)	83 (47.2)	38 (42.2)	45 (52.3)	
Income[b]	> 3 MW	33 (19.4)	18 (20.7)	15 (18.1)	0.633
	< 3 MW	131 (77.1)	67 (77.0)	64 (77.1)	
	No income	6 (3.5)	2 (2.3)	4 (4.8)	
Self-reported skin color[b]	White	56 (29.8)	30 (31.3)	26 (28.3)	0.654
	Non-White[d]	132 (70.2)	66 (68.8)	66 (71.7)	
Prevailing circumstances					
Hypertension[c]		118 (71.1)	56 (66.7)	62 (75.6)	0.204
Obesity[c]		66 (42.0)	28 (33.3)	38 (52.1)	0.018
Diabetes mellitus[c]		53 (31.9)	22 (25.9)	31 (38.3)	0.087
Other cardiovascular diseases[c]		20 (12.4)	11 (13.1)	9 (11.7)	0.787
Asthma[c]		18 (11.1)	10 (11.9)	8 (10.3)	0.739
COPD[c]		11 (6.7)	4 (4.8)	7 (8.9)	0.297
Chronic kidney disease[c]		8 (5.0)	3 (3.6)	5 (6.5)	0.394
Other comorbid disorders[c]		76 (46.3)	43 (50.6)	33 (41.8)	0.258
Smoking[b]		49 (26.6)	28 (30.1)	21 (23.1)	0.281
Use of immunosuppressive drugs[c,e]		8 (5.1)	6 (7.6)	2 (2.6)	0.157
Solid organ transplantation[c]		5 (3.1)	3 (3.6)	2 (2.6)	0.711
Acute COVID-19					
Cough[b]		133 (70.7)	61 (63.5)	72 (78.3)	0.027
Dyspnea[b]		151 (80.7)	70 (73.7)	81 (88.0)	0.013
Invasive mechanical ventilation[b]		34 (18.5)	0 (0.0)	34 (38,6)	< 0.001
Acute kidney failure[b]		13 (7.1%)	3 (3.1)	10 (11.4)	0.029
Length of stay, days		15,92 ± 17.7	9.56 ± 11.3	22,47 ± 20.6	< 0.001

MW: minimum wage (3 MW = R$ 613.50); and CVD: cardiovascular disease. [a]Values expressed as n (%) or mean ± SD. [b]Missing data ≤ 10%. [c]Missing data between 10-20%.[d]Non-White: black (20.7%), brown (48.9%), and yellow (0.5%). [e]Prednisone > 20 mg/day for more than two weeks, cyclosporine, cyclophosphamide, mycophenolate, rituximab, azathioprine, and/or chemotherapy in the last 30 days.

According to plethysmography, pulmonary function still remained impaired in part of the cohort (27% restriction), regardless of the unit of admission (ward or ICU). After stratification by groups with and without dyspnea, reduced DL_{CO} was the only variable significantly associated with dyspnea at 12 months (p = 0.02). Huang et al.,[32] when evaluating survivors of COVID-19 after 12 months, described 29% of restriction and 54% of altered DL_{CO} in individuals who required ICU admission. Meanwhile, Steinbeis et al.[33] reported 44-50% restriction and 61-76% altered DL_{CO} among survivors who required high-flow oxygen and invasive mechanical ventilation, showing that these differences still persist after 12 months of follow-up.

Pulmonary fibrosis after COVID-19 may be related to restriction and altered DL_{CO} and may be explained by the duration of illness and mechanical ventilation use.[34] Impaired DL_{CO} may also be attributable to vascular abnormalities.[35] These data suggest that changes in lung function after 1 year are not enough to explain the late presence of dyspnea.

Regarding the exercise capacity assessment by 6MWT, individuals with persistent dyspnea walked a shorter distance (440.3 m vs. 512.0 m, p < 0.001). They also had a worse assessment of sensory stress (final Borg score ≥ 4). However, no differences were observed in gas exchange during exercise (desaturation ≥ 4%), in Δ(final HR, HRR_1), suggesting that the worse 6MWD in individuals with persistent dyspnea may be due to the peripheral muscle component. Razak et al.,[2] in their analysis of 119 survivors of COVID-19 in 12 months, also justified the shorter 6MWD in their patients as a result of muscle weakness.

Table 2. Symptoms, spirometry, lung volumes, DL_{CO}, respiratory muscle strength, and six-minute walk test 360 days after hospitalization for COVID-19 (D360) in the whole sample and by group (Ward vs. ICU).[a,*]

Variable	Total sample	Group		Crude p-value	Adjusted p-value**
		Ward	ICU		
	N = 189	n = 96	n = 93		
Follow-up time on the D360, days	363.9 ± 13.8	363,6 ± 13.6	364.2 ± 13.8	0.784	-
Symptoms of long COVID-19					
Cough[b]	35 (19.0)	18 (19.4)	17 (18.7)	0.907	0.443
Dyspnea[b]	80 (43.0)	38 (40.0)	42 (46.2)	0.397	0.274
Spirometry					
VC, L[b]	3.0 ± 0.8	3.1 ± 0.8	3.1 ± 0.8	0.934	0.145
VC, % pred[b]	90.1 [79.5-99.8]	92.8 [83.0-99.2]	87.0 [76.0-100.4]	0.285	0.931
VC < LLN, %[b]	40 (23.0)	16 (17.6)	24 (28.9)	0.076	0.229
FVC, Ls [b]	3.0 ± 0.8	3.0 ± 0.8	3.0 ± 0.8	0.807	0.188
FVC, % pred[b]	86.8 ± 15.2	87.1 ± 13.7	86.4 ± 16.8	0.750	0.710
FVC < LLN[b]	55 (29.3)	24 (25.0)	31(33.7)	0.190	0.539
FEV_1, L[b]	2.3 ± 0.6	2.3 ± 0.7	2.3 ± 0.6	0.508	0.247
FEV_1, % pred[b]	83.0 ± 16.7	83.2 ± 17.1	82.8 ± 16.5	0.886	0.980
FEV_1 < LLN[b]	65 (34.6)	32 (33.3)	33 (35.9)	0.715	0.635
FEV_1/FVC[b]	77.5 [72.3-82.1]	77.9 [71.8-82.4]	77.3 [72.4-81.7]	0.695	0.913
FEV_1/FVC < LLN[b]	84 (44.7)	42 (43.8)	42(45.7)	0.793	0.279
Lung volumes					
TLC, L[b]	4.7 ± 1.1	4.8 ± 1.0	4.6 ± 1.1	0.171	0.776
TLC, % pred[b]	87.2 ± 14.0	89.4 ± 13.5	84.8 ± 14.2	0.025	0.450
TLC < LLN[b]	50 (27.3)	17 (18.3)	33 (36.7)	0.005	0.085
RV, L[b]	1.6 ± 0.6	1.7 ± 0.5	1.5 ± 0.6	0.067	0.308
RV, % pred[b]	83.0 ± 25.5	86.9 ± 25.4	79.0 ± 25.1	0.039	0.253
RV/TLC, % pred[b]	96.9 ± 24.2	100.4 ± 23.9	93.2 ± 24.1	0.045	0.101
		DL_{CO}			
DL_{CO}, mL.min^{-1}.mmHg[b]	19.7 ± 5.4	20.1 ± 5.8	19.2 ± 4.9	0.284	0.690
DL_{CO}, % pred[c]	93.1 ± 19.6	96.6 ± 19.9	89.4 ± 18.7	0.013	0.145
DL_{CO} < LLN[c*]	32 (17.8)	12 (12.9)	20 (23.0)	0.077	0.069
Respiratory muscle strength					
MIP, cmH_2O[c]	76.6 ± 26.7	75.1 ± 28.9	78.2 ± 24.4	0.444	0.290
MIP, % pred[c]	85.5 ± 27.2	83.0 ± 27.7	88.0 ± 26.6	0.222	0.373
MIP < LIN[c]	35 (19.7)	20 (22.2)	15 (17.0)	0.385	0.297
MEP, cmH_2O[c]	82.9 ± 30.2	81.0 ± 31.1	84.8 ± 29.3	0.400	0.578
MEP, % pred[c]	48.9 ± 16.3	48.4 ± 17.2	49.4 ± 15.4	0.680	0.788
MEP < LIN[c]	146 (82.0)	71 (78.9)	75 (85.2)	0.271	0.659
Six-minute walk test					
Distance, m[b]	486.4 [409.7-532.4]	492.2 [397.4-559.9)	466.0 [430.7-512.0]	0.099	0.220
Distance, % pred[b]	91.7 ± 17.1	94.0 [81.2-101.5]	90.0 [75.2-102.7]	0.368	0.820
Saturation drop during the test ($\Delta SpO_2 \leq 4\%$)[b]	53 (30.1)	25 (28.4)	28 (31.8)	0.622	0.685
HRR_1, bpm[b]	91.0 [78.0-102.0]	91.7 ± 13.7	85.0 ± 19.3	0.616	0.990
Δ(final HR, HRR_1), bpm[b]	22.7 ± 15.6	22.8 ± 15.7	22.7 ± 15.7	0.969	0.444
%HRmax[b]	71.3 ± 11.8	72.7 ± 11.9	69.9 ± 11.6	0.109	0.516
Final Borg scale score ≥ 4[b]	41 (23.3)	19 (21.6)	22 (25.0)	0.593	0.559

% pred: % of predicted values; LLN: lower limit of normality; HRR_1: recovery heart rate in the first minute; and %HRmax: percentage of maximum HR achieved. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]Missing data ≤ 10%. [c]Missing data in 11-12%. *Variables expressed as median [IQR] were calculated with the nonparametric Mann-Whitney U test. **Adjusted for BMI, invasive mechanical ventilation, and length of hospital stay.

The data presented here have shown that some mobility problems, and anxiety/depression were present in more than 50% of the individuals with dyspnea. Similarly to our results, Schlemmer et al.[36] found that although most participants recovered overall, high percentages had functional sequelae and residual symptoms over the course of follow-up, all of which may have affected their HRQoL.

Table 3. Symptoms, spirometry, lung volumes, DL_{CO}, respiratory muscle strength, and six-minute walk test 360 days after hospitalization for COVID-19 (D360) in the whole sample and by group (absence of dyspnea vs. presence of dyspnea).[a,*]

Variable	Total sample	Group		Crude p-value	Adjusted p-value**
		No dyspnea	Dyspnea		
	N = 186	n = 106	n = 80		
Follow-up time on the D360, days	363.9 ± 13.8	363,7 ± 13.4	364.3 ± 14.3	0.768	-
Symptoms of long COVID-19					
Cough[b]	35 (19.0)	11 (10.5)	24 (30.4)	0.001	0.010
BMI, kg/m^2	32.3 ± 7.0	31.0 ± 6.4	34.1 ± 7.4	0.002	-
Spirometry					
VC, L[b]	3.0 [2.5-3.8]	3.3 [2.8-4.0]	2.7 [2.4-3.1]	< 0.001	< 0.001
VC, % pred[b]	90.1 ± 15.2	92.0 ± 14.8	87.3 ± 15.5	0.049	0.083
VC < LLN, %[b]	39 (22.8)	22 (21.6)	17 (24.6)	0.639	0.964
FVC, Ls [b]	2.9 [2.5-3.6]	3.2 [2.7-3.8]	2.6 [2.3-3.1]	< 0.001	< 0.001
FVC, % pred[b]	86.8 ± 15.2	89.0 ± 15.0	83.8 ± 15.2	0.021	0.051
FVC < LLN[b]	54 (29.2)	25 (23.8)	29 (36.3)	0.065	0.077
FEV_1, L[b]	2.3 ± 0.6	2.5 ± 0.6	2.0 ± 0.6	< 0.001	< 0.001
FEV_1, % pred[b]	83.1 ± 16.8	86.6 ± 15.2	78.6 ± 17.7	0.001	0.001
FEV_1 < LLN[b]	63 (34.1)	30 (28.6)	33 (41.3)	0.071	0.100
FEV_1/FVC[b]	76.2 ± 9.1	77.5 ± 7.5	74.6 ± 10.6	0.027	0.002
FEV_1/FVC < LLN[b]	81 (43.8)	46 (43.8)	35 (43.8)	0.994	0.576
Lung volumes					
TLC, L[b]	4.7 ± 1.1	4.9 ± 1.1	4.4 ± 1.1	0.001	0.012
TLC, % pred[b]	85.9 [79.6-95.2]	86.9 [79.9-95.2]	84.2 [77.4-95.0]	0.455	0.923
TLC < LLN[b]	49 (27.2)	27 (26.0)	22 (28.9)	0.657	0.718
RV, L[b]	1.6 ± 0.6	1.6 ± 0.5	1.6 ± 0.7	0.907	0.240
RV, % pred[b]	82.8 ± 25.5	80.3 ± 20.5	86.4 ± 30.9	0.115	0.035
RV/TLC, % pred[b]	97.0 ± 23.9	92.5 ± 22.0	103.0 ± 25.0	0.003	0.005
DL_{CO}					
DL_{CO}, mL.min^{-1}.mmHg[b]	19.7 ± 5.4	20.9 ± 5.6	17.9 ± 4.7	< 0,001	< 0,001
DL_{CO}, % pred[c]	93.0 ± 19.7	94.0 ± 19.3	91.6 ± 20.4	0.408	0.021
DL_{CO} < LLN[c]*	32 (18.1)	15 (14.9)	17 (22.4)	0.198	0.011
Respiratory muscle strength					
MIP, cmH_2O[c]	76.1 ± 26.7	80.1 ± 28.6	70.9 ± 23.1	0.024	0.026
MIP, % pred[c]	85.0 ± 27.1	82.9 ± 26.9	87.9 ± 27.2	0.222	0.479
MIP < LIN[c]	35 (20.0)	22 (22.0)	13 (17.3)	0.445	0.750
MEP, cmH_2O[c]	82.3 ± 29.8	85.8 ± 32.0	77.7 ± 26.2	0.077	0.085
MEP, % pred[c]	48.6 ± 16.3	48.0 ± 16.2	49.5 ± 16.4	0.568	0.912
MEP < LIN[c]	145 (82.9)	81 (81.0)	64 (85.3)	0.452	0.373
Six-minute walk test					
Distance, m[b]	486.4 [409.7-532.4]	512.0 [457.0-553.3)	440.3 [358.4-486.4]	< 0.001	< 0.001
Distance, % pred[b]	94.3 [82.7-103.2]	98.2 [87.8-105.4]	87.1 [75.4-99.3]	< 0.001	< 0.001
Saturation drop during the test ($\Delta SpO_2 \leq 4\%$)[b]	53 (30.6)	30 (29.7)	23 (319)	0.753	0.929
HRR_1, bpm[b]	89.8 ± 18.7	91.7 ± 13.7	85.0 ± 19.3	0.118	0.062
Δ(final HR, $HRR_{1.}$), bpm[b]	22.7 ± 15.6	22.8 ± 15.3	22.7 ± 16.1	0.944	0.992
%HRmax[b]	71.3 ± 11.8	72.1 ± 11.5	70.1 ± 12.3	0.277	0.329
Final Borg scale score ≥ 4[b]	41 (23.7)	9 (8.9)	32 (44.4)	< 0.001	< 0.001

% pred: % of predicted values; LLN: lower limit of normality; HRR_1: recovery heart rate in the first minute; and %HRmax: percentage of maximum HR achieved. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]Missing data ≤ 10%. [c]Missing data in 11-12%. *Variables expressed as median [IQR] were calculated with the nonparametric Mann-Whitney U test. **Adjusted for BMI, invasive mechanical ventilation, and length of hospital stay.

Evidence is insufficient to determine conclusions about the underlying mechanisms of post-COVID breathlessness. A previous review study reported inconsistent results of impaired lung function or lung pathologies, although correlations between mental health disorders (depression and anxiety) and post-COVID-19 breathlessness appear to be more consistent.[37] Sakai et al.[38] suggest that rehabilitation

Table 4. Description of the dimensions of quality of life according to the EQ-5D3L questionnaire 360 days after hospitalization for COVID-19 in the whole sample and by group (absence of dyspnea vs. presence of dyspnea).[a]

Variable	Total sample	Group		p
		No dyspnea	Dyspnea	
	N = 186	n = 106	n = 80	
Mobility				
No problems	112 (60.2)	76 (71.7)	36 (45.0)	< 0.001
Some problems or inability	74 (39.8)	30 (28.3)	44 (55.0)	
Self-care				
No problems	155 (83.3)	100 (94.3)	55 (68.8)	< 0.001
Some problems or inability	31 (16.7)	6 (5.7)	25 (31.3)	
Regular activities				
No problems	132 (71.0)	88 (83.0)	44 (55.0)	< 0.001
Some problems or inability	54 (29.0)	18 (17.0)	36 (45.0)	
Pain/malaise				
Absent	78 (41.9)	58 (54.7)	20 (25.0)	< 0.001
Moderate/extreme	108 (58.1)	48 (45.3)	60 (75.0)	
Anxiety/Depression				
Absent	94 (50.5)	70 (66.0)	24 (30.0)	< 0.001
Moderate/extreme	92 (49.5)	36 (34.0)	56 (70.0)	
Comprehensive overview on health	80.0 [70.0 - 90.0]	87.5 [70.0 - 98.2]	80.0 [50.0 - 83.7]	< 0.001

[a]Values expressed as n (%) or median [IQR].

after COVID-19 should be considered an effective therapeutic strategy to improve the functional capacity and QoL of patients with COVID-19.

The strength of our study is its multicenter design, in which regional public referral hospitals for the treatment of patients with COVID-19 participated. Specialized trained teams, including undergraduate and graduate students, as well as research professors, carried out data collection systematically and were able to identify patients according to their disease severity using a standardized questionnaire through REDcap.

This study has limitations. There was no information on return to work, use of health care services, and mental health status of the patients after discharge. Therefore, longitudinal analysis of these outcomes was not possible. Similarly to most COVID-19 follow-up studies, there is a potential information bias regarding self-reported comorbidities during the acute phase and during convalescence. The outcome of patients who missed follow-up and were not assessed 1 year after admission is unknown, and most of the patients were those who had been admitted to an ICU.

Twelve months after acute infection, survivors of severe COVID-19 still had a high burden of symptoms, such as dyspnea, restrictive ventilatory changes in lung function, and loss of QoL, identified in an established cohort in a middle-income country that had been highly impacted by the pandemic.

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AUTHOR CONTRIBUTIONS

TAP, GLLMC, CCM, and EM: study conception, design, and planning; data analysis; and drafting and reviewing of the manuscript. ASL and VMA: study conception, design, and planning; data analysis; and reviewing of the manuscript. DCB, BHA, and JGFO: reviewing of the manuscript. APB: data analysis, and reviewing of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Asthma in the Brazilian Unified Health Care System: an epidemiological analysis from 2008 to 2021

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ABSTRACT

Objective: To analyze the number of hospitalizations, the length of hospital stay, and mortality due to asthma, as well as the costs to the Unified Health Care System in Brazil between 2008 and 2021. **Methods:** This was a cross-sectional epidemiological study using data from the Information Technology Department of the Brazilian Unified Health Care System. Proportional hospitalization and death rates were estimated per 100,000 population by age, microregion, and year. **Results:** The number of hospitalizations and deaths due to asthma decreased from 2008 to 2021 (205,392 vs. 55,009 and 822 vs. 327, respectively). In addition, a between-sex difference was observed in asthma-related hospitalizations in 2008, and more men were hospitalized in 2021 (51.8%). Asthma mortality rates were similar for both sexes (50.0% each) in 2008, and a slight increase was observed in women's deaths in 2021 (52.9%). Even so, approximately one death/day and more than 55,000 hospitalizations were observed yearly, with a mean length of hospital stay of three days. Additionally, the Southeast region allocated more financial resources to asthma-related hospitalizations. **Conclusions:** Our results showed that the number of deaths and hospitalizations due to asthma substantially declined during the study period.

Keywords: Asthma/mortality; Asthma/epidemiology; Hospitalization; National health programs.

INTRODUCTION

Asthma is the second most common chronic respiratory disease and affects around approximately 300 million people worldwide.[1] Moreover, it is estimated that 20 million people are affected by this disease in Brazil.[2]

A recent study showed that the prevalence of asthma in Brazil is 4.6% and 12.1% in adults and children, respectively.[3] Although most cases are manageable with pharmacological treatment, such as inhaled corticosteroids (ICSs) and long-acting β_2 agonists (LABAs), up to 10% of patients have severe asthma and require further treatment.[4] Severe asthma is associated with increased morbidity and mortality and negatively impacts a patient's psychological condition and socioeconomic status.[5]

The costs per patient with severe asthma can be up to ten times greater than those per patient with the mild form of the disease,[6] and severe asthma accounts for more than 60% of health expenses related to asthma. The costs of asthma can be high when the disease is not controlled.[7] In Brazil, 71.5% of the population depends on the public health care system, which provides services at all levels of care.[8] Considering the number of people with asthma in the country, this disease generates high costs for the government through health services.

Throughout the current century, there have been changes in Brazilian health policies. Some Brazilian cities have offered ICSs free of charge to their inhabitants since 2003[9]; however, in 2009, the Unified Health Care System (UHCS) included ICSs for people with asthma.[10] This represented higher expenses associated with medication but potentially lower expenses associated with hospitalization.

The WHO calls for "better surveillance to map the magnitude of chronic respiratory diseases and analyze their determinants and monitor future trends."[11] Although the *Departamento de Informática do Sistema Único de Saúde* (DATASUS, Information Technology Department of the Brazilian Unified Health Care System) continuously updates the data on asthma, it is necessary to organize and analyze these data to draw conclusions and identify room for improvement in public policies. To the best of our knowledge, the latest study systematically assessed data related to the economic impact of asthma nationally through 2013.[10]

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Assessing the regional impacts of asthma is important, particularly in countries with a vast area such as Brazil, characterized by substantial variations among its macroregions. A study showed a downward trend in asthma mortality in the early 2000s in Brazil, although regional disparities persisted.[12] The Northeast region was the sole area where mortality rates did not decrease, likely influenced by variations in health care access and climatic conditions.[12-14]

Considering the reported advances in asthma management in the last decade, it is important to update the data regarding this disease. The Global Asthma Report,[15] prepared by the WHO, reinforces the need for continuous monitoring of asthma to investigate trends in this disease. The present study aimed to update the data referring to hospitalization, mortality, and expenses associated with asthma by the Brazilian UHCS by examining regional differences and relevant changes according to changes in public policies.

METHODS

This epidemiological study, conducted in October 2022, assessed hospitalization and mortality rates due to asthma and status asthmaticus as defined by the International Classification of Diseases, 10th revision (ICD-10) according to the sex and the subject's geographic macroregion within Brazil. The inclusion criteria were defined as living in Brazil between January of 2008 and December of 2021.

The financial costs, hospitalization numbers, length of hospital stay, and mortality data were extracted from the DATASUS Ministry of Health of Brazil website.[16] The data available in DATASUS are part of the universal accessibility policy of the Brazilian UHCS and include the Hospital Information System and Mortality Information System (hospitalization and mortality data, respectively), which are composed of registers collected through city hall health departments. The data collection methodology did not change during the study period. Therefore, the individuals whose information was extracted were deidentified. This study did not require approval from a research ethics committee.

The DATASUS information includes the basic and associated causes based on the ICD-10 codes, in which the codes 'J45' and 'J46' represent asthma and status asthmaticus, respectively. The demographic data were collected from the *Instituto Brasileiro de Geografia e Estatística* (IBGE, Brazilian Institute of Geography and Statistics) website.[17] The IBGE runs a census every 10 years to verify the Brazilian population profile by collecting a number of variables from every household in the country; the sociodemographic profiles in the years between censuses are estimated through projections.

Data analysis

For the proportional hospitalization and death rates, we used the number of hospital admissions or deaths by sex, region, or calendar year as the numerator and the respective number of people in this range as the denominator, as shown in the following equations[18]:

$$Hospitalization \ \frac{age}{\frac{region}{year}} = \frac{number\ of\ hospitalizations}{total\ population\ in\ the\ range} \ x10^5$$

and

$$Mortality \ \frac{age}{\frac{region}{year}} = \frac{number\ of\ deaths}{total\ population\ in\ the\ range} \ x10^5$$

The monetary restatement was calculated with the *Índice de Preços ao Consumidor* (IPCA, National Consumer Price Index), one of Brazil's most traditional and important inflation indices. The following formula was used to calculate the monetary restatement during the study period:

$$Corrected\ cost = \frac{Average\ cost}{1000} \ x\ Year\ IPCA\ tax$$

Data analyses were conducted using Prism, version 8.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

From 2008 to 2021, Brazil had more than 8,000 deaths and more than 1.7 million hospitalizations due to asthma. The Northeast region had the highest absolute number of deaths and hospitalizations among men and women, and the Central-West region had the lowest during this period. The Southeast was the only region where more men than women were hospitalized, and in the North and Central-West regions, there were more deaths among men than among women, as opposed to the other three regions. Table 1 and Table 2 show the total number of hospitalizations and deaths per year from 2008 to 2021 and those numbers by region and sex.

During the study period, there was a decrease in hospitalizations in the general population among men and women (Figure 1A). When the respective populations of inhabitants were evaluated separately, the same trend was observed (Figures 1B and 1C). Among the macroregions, the Northeast had the highest absolute number of hospitalizations, followed by the Southeast, South, North, and Central-West (Figure 1A). When analyzed by the number of inhabitants, the Northeast still had the highest hospitalization rate, followed by the North, South, Central-West, and Southeast (Figure 1D). When analyzed by the number of inhabitants and sex, the Northeast still had the highest hospitalization rate, followed by the North, South, Central-West, and Southeast (Figures 1E and F), according to sex.

To understand the characteristics of the hospitalization profile according to the macroregions, we calculated the mean number of hospitalization days from 2008 to 2021 and per year (Figure 2). Interestingly, the Southeast region had the greatest number of days per hospitalization, followed by the North, South, Northeast, and Central-West (Figure 2A). However,

Table 1. Frequency of hospitalization and deaths from asthma and status asthmaticus per year.[a]

Year	Hospitalization				Death			
	Men		Women		Men		Women	
	n	Per 100,000	n	Per 100,000	n	Per 100,000	n	Per 100,000
2008	101,993	107.6	103,399	106.9	411	0.43	411	0.42
2009	99,950	104.4	103,247	105.6	411	0.43	448	0.46
2010	95,576	98.8	97,621	98.8	442	0.46	447	0.45
2011	86,951	89.1	91,271	91.5	394	0.40	378	0.38
2012	73,110	74.2	75,092	74.5	346	0.35	407	0.40
2013	65,822	66.3	68,500	67.4	314	0.32	383	0.38
2014	56,740	56.6	59,659	58.1	254	0.25	333	0.32
2015	56,285	55.8	57,445	55.5	243	0.24	300	0.29
2016	47,125	46.3	47,893	45.9	256	0.25	303	0.29
2017	46,587	45.5	46,590	44.3	197	0.19	288	0.27
2018	43,495	42.	43,601	41.1	189	0.18	242	0.23
2019	39,712	38.2	40,235	37.7	204	0.20	241	0.23
2020	23,787	22.8	24,175	22.5	150	0.14	178	0.16
2021	28,493	27.1	26,516	24.5	154	0.15	173	0.16
Total	865,626		885.244		3,965		4.532	

[a]Hospitalizations and deaths normalized per 100,000 population per year.

Table 2. Frequency of hospitalization and deaths from asthma and status asthmaticus per region.[a]

Region	Hospitalization				Death			
	Men		Women		Men		Women	
	n	Per 100,000	n	Per 100,000	n	Per 100,000	n	Per 100,000
North	92,534	75.3	95,461	80.0	209	0.17	193	0.16
Northeast	374,155	96.9	385,193	96.0	1,430	0.37	1,702	0.42
Southeast	212,393	36.1	202,834	33.5	1,375	0.23	1,601	0.26
South	124,374	61.8	138,274	67.2	597	0.30	719	0.35
Central-West	62,170	58.3	63,482	59.0	354	0.33	317	0.29
Total	865,626		885,244		3,965		4,532	

[a]Hospitalizations and deaths normalized per 100,000 population per region.

all regions exhibited high variability over the years (Figure 2B).

To analyze whether the length of hospital stay was associated with hospital expenditure, we analyzed the costs of hospital stay. The Southeast region spent a greater amount of financial resources, followed by the South, North, Northeast, and Central-West regions. From 2008 to 2021, financial resources decreased in all regions. When corrected by the IPCA, which represents the Brazilian inflation-targeting system, spending in all regions overlapped with peaks in 2015 and 2021 (Figure 3).

Regarding hospitalizations, the mortality rate also declined over the years. When analyzed by absolute numbers, the Southeast region presented the highest mortality, followed by the Northeast, South, North, and Central-West when both sexes were analyzed (Figure 4A). When the respective populations were evaluated separately, the same trend of reduction in mortality was observed (Figures 4B and 4C). When normalized, the proportional mortality rates also differed from the hospitalization rates, with the Northeast region having the highest proportion of deaths, followed by the Southeast, Central-West, and North regions (Figure 4D). When the data were normalized by population separately, we observed a reduction in mortality for both sexes in different regions (Figures 4E and F).

DISCUSSION

The total number of hospitalizations and deaths due to asthma significantly decreased from 2008 to 2021. In the last year analyzed, 327 people died of asthma, approximately one death/day, and there were approximately 55,000 hospitalizations in Brazil. In the last thirteen years, there were reductions of 73% and 60% in the absolute number of hospitalizations and deaths due to asthma, respectively. The mean length of hospital stay for patients with asthma was approximately 3 days, irrespective of the region in Brazil. The costs of hospital admissions for asthma in Brazil decreased during the study period despite economic inflation or political instability.

In 2021, the last year analyzed, we observed approximately 1 death/day. Previous studies reported up to 5 deaths/day[12,19] related to asthma in Brazil

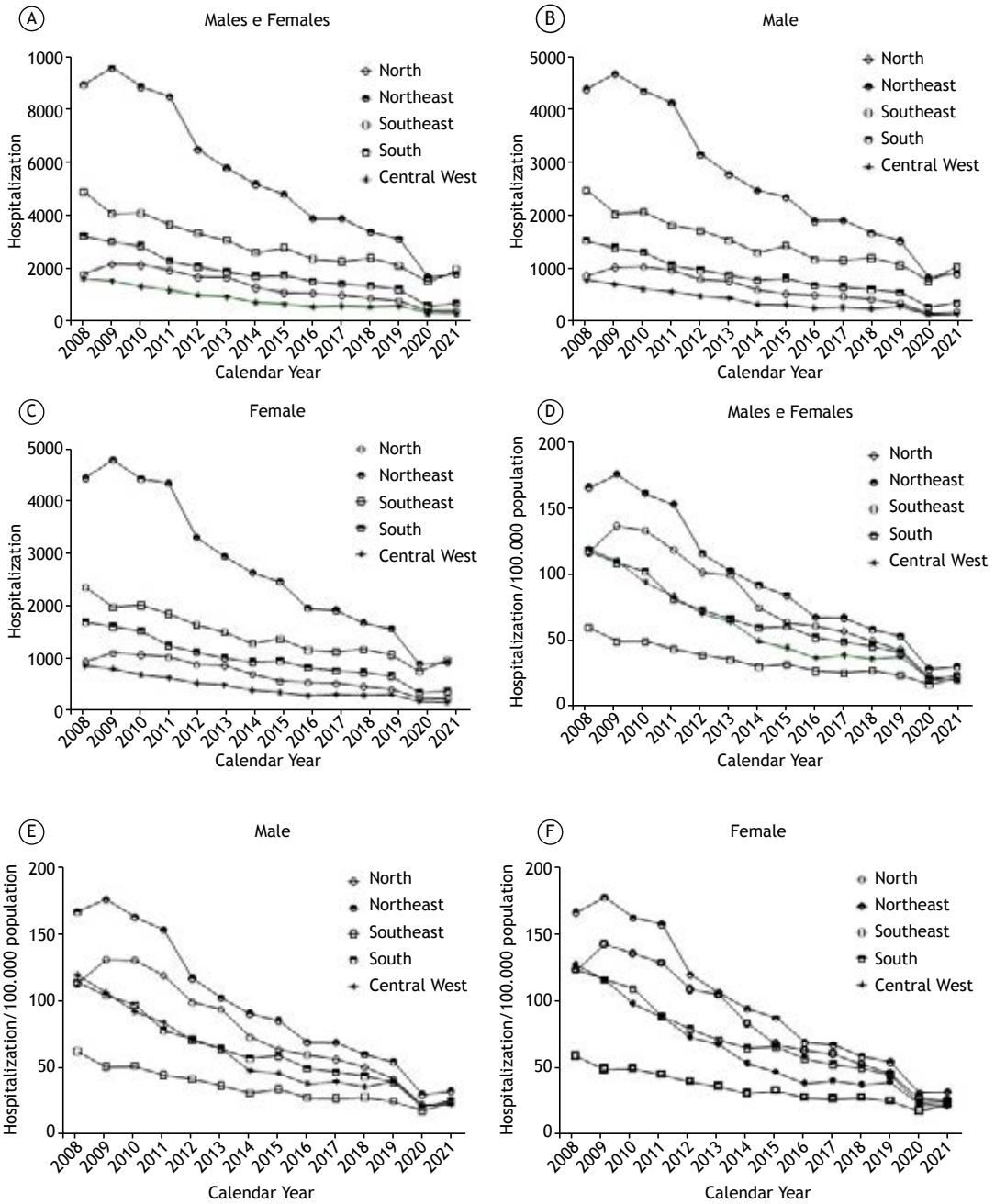

Figure 1. Number of hospitalizations due to asthma per year by Brazilian macroregions. In A, hospitalizations in total population. In B, hospitalizations in the male population. In C, hospitalizations in the female population. In D, hospitalizations per 100,000 population. In E, hospitalizations per 100,000 males. In F, hospitalizations per 100,000 females.

in the 2000s; however, they considered the total number of deaths related to the disease, such as people who may have died at home and/or who had died from other associated factors. On the other hand, our study reported deaths among hospitalized patients specifically due to asthma. Although the comparison is difficult, we can consider that the number of deaths reported in our study are more precise since the information presented can have fewer mistakes in determining the cause of death than those previously reported.[12,19] A study carried out by Cardoso et al.[10] reported that, in 2013, 2,047 people died from asthma in Brazil (approximately 5 deaths/day), which was a greater number than that in our study. This is an important result for the Brazilian UHCS and can be explained by the use of pharmacological therapy for asthma (beclomethasone and albuterol), which was made available throughout the country free of charge by the Brazilian National Ministry of Health in 2009.[10]

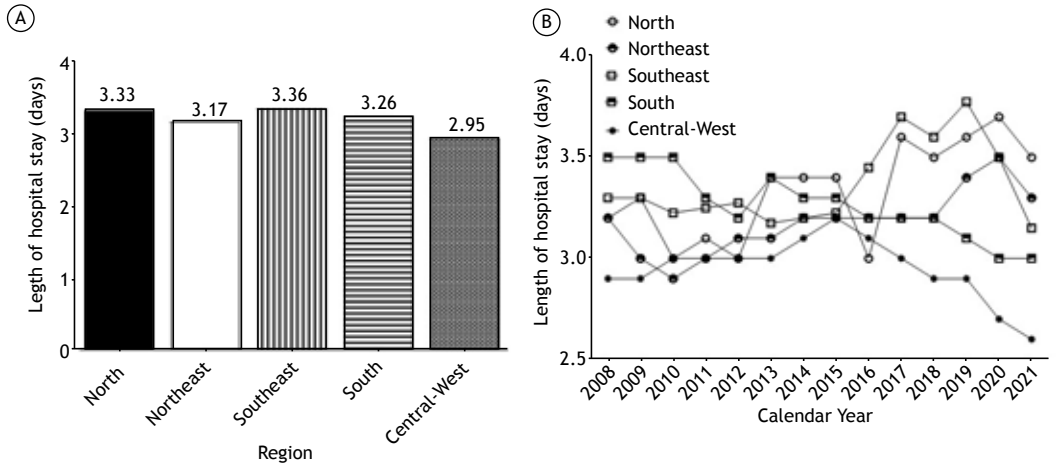

Figure 2. Mean length of hospital stay (in days) due to asthma and status asthmaticus by region throughout the study period (in A) and per year (in B).

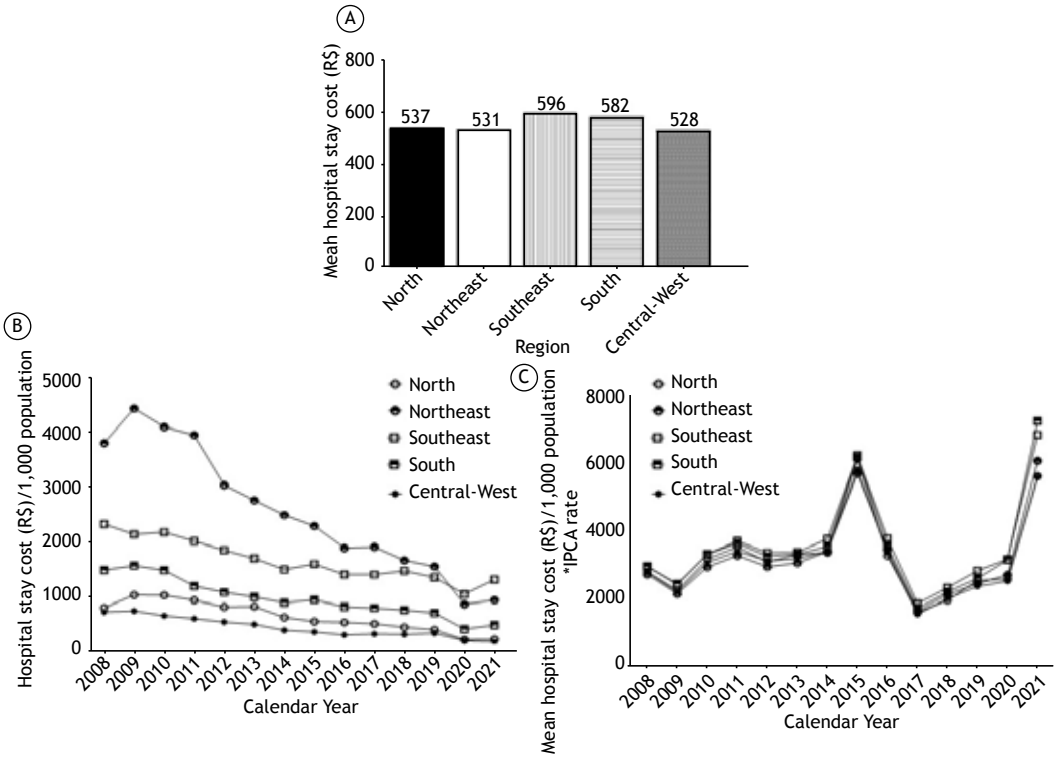

Figure 3. Mean hospital stay costs per region (in A). Total hospital stay costs by region per 1,000 population per year (in B). Mean hospital stay costs by region per 1,000 population normalized by monetary correction per year (in C). R$: Brazilian Real. *IPCA rate: monetary correction.

Our results strongly suggest that asthma management in Brazil has improved over the years, as demonstrated by the reduction in hospitalizations and mortality. Decreases in hospitalization rates in the last two decades have been reported in other countries, such as Canada,[20] Costa Rica,[21] and Kuwait.[22] This may be related to advances in pharmacological (e.g., immunobiologics) and nonpharmacological (e.g., education, exercise, and physical activity) treatments,[21] as well as to the advancement of public policies aimed at this population. Tavakoli et al.[23] observed a major increase in the use of ICSs in combination with LABAs starting in 2002 in the Canadian population, which coincided with the decline in hospital admission rates.[20] Similarly, our study showed a substantial decrease in hospitalizations coinciding with the implementation of pharmacological therapy for asthma free of charge, made available throughout the country starting in 2011.[24]

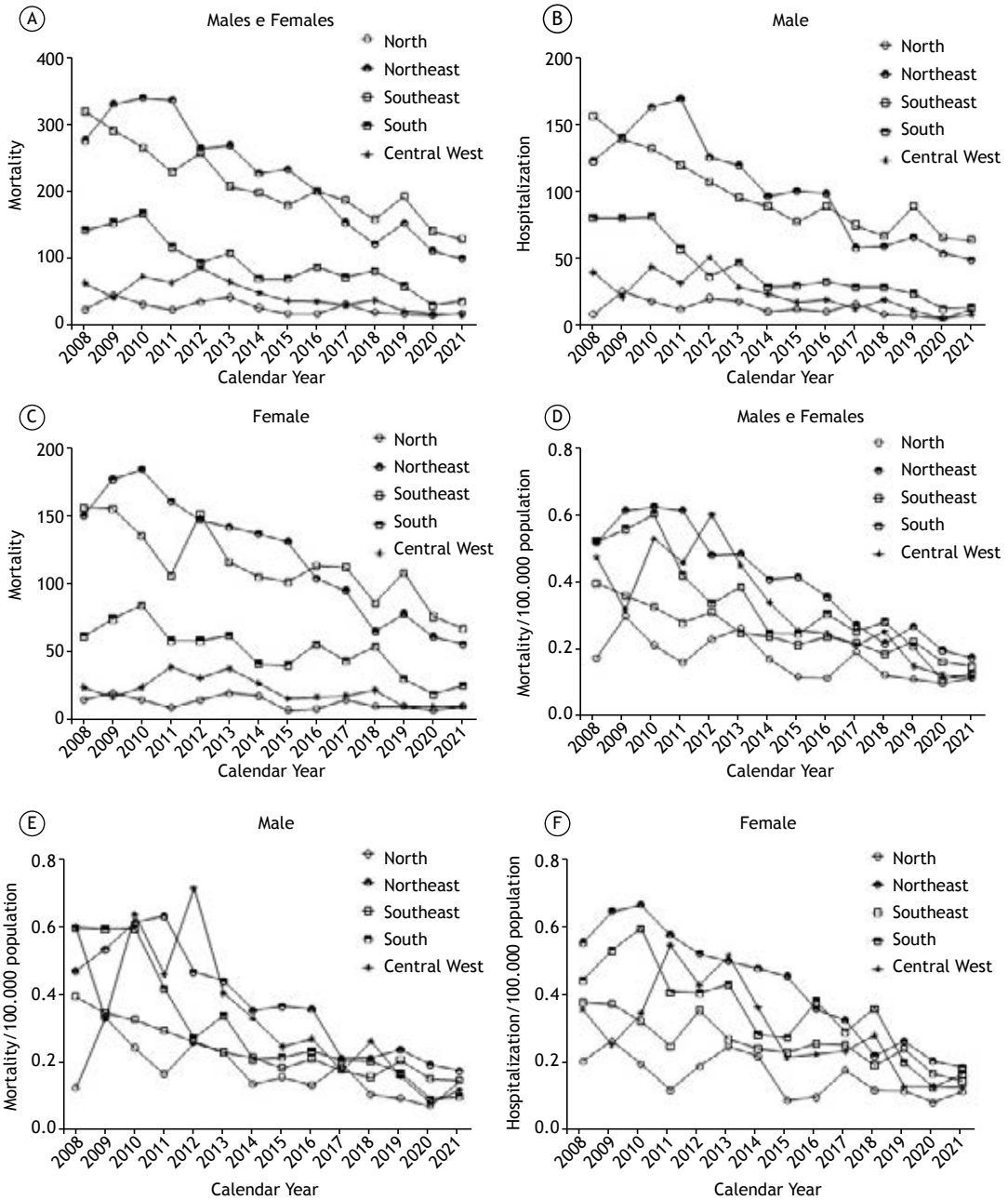

Figure 4. Asthma mortality per year by Brazilian region. In A, mortality in total population. In B, mortality in the male population. In C, mortality in the female population. In D, mortality per 100,000 population. In E, mortality per 100,000 males. In F, mortality per 100,000 females.

The medication provided by the UHCS was previously shown to be cost-effective for asthma management.[25] Even though there was a significant increase in asthma-related costs when ICS therapy was included in the "Popular Pharmacy Program" in 2011, our study showed a decrease in values in subsequent years, suggesting that improved pharmacotherapy was able to reduce other costs related to the disease. Another important aspect observed in our study was the significant decrease in hospitalizations and mortality from 2020 on, which may have been associated with the repercussions of COVID-19 and the measures employed by the WHO, such as stay-at-home orders.[26] Our results corroborate the findings in the literature, in which there was a 36% reduction in hospitalizations in Scotland and Wales.[27] Additionally, Shah et al.[28] observed a significant reduction in primary care attendance for asthma exacerbations during the pandemic.

Indeed, at the beginning of the pandemic, there was a fear that SARS-CoV-2 could contribute to asthma exacerbations similarly to those caused by

other respiratory viruses[29]; however, a meta-analysis suggested that individuals with asthma have a reduced risk of contracting COVID-19 when compared with those without the disease.[30] Shah et al. also reported a significant reduction in the use of primary care for asthma exacerbations during the pandemic, likely due to social distancing measures and the increase in mask usage worldwide.[28]

We found that asthma hospitalization costs showed reduction differences among the Brazilian regions. The Southeast region had the highest economic expenditure, approximately R$ 596 (Brazilian real) or USD 119 per hospitalization. However, despite the decrease in asthma hospitalizations, the cost balance was still high when all Brazilian regions were included. Approximately R$ 2,776.50 were spent on hospital admissions for asthma between 2008 and 2021.

Indeed, spending on hospitalizations and medication may be the main cause of health system costs in Brazil related to COPD and severe asthma.[31,32] Asthma contributes to high costs at the individual level that are directly associated with disease management and indirectly associated with social factors (impaired quality of life, absenteeism from school/work, and mental health impairment).[31] A systematic review[32] found that the cost from the perspective of the UHCS in Brazil, derived from two studies,[33,34] revealed mean annual hospital costs per patient of USD 135 and USD 733, respectively. A study performed in the USA between 2008 and 2013 showed that the total annual cost of asthma, including medical care, absenteeism, and mortality, was USD 81.9 billion.[35] In addition, the annual per-person medical cost of asthma was approximately USD 3,266. From the total budget, USD 1,830 were spent for prescriptions, USD 640 were spent for consultations, USD 529 were spent for hospitalizations, USD 176 were spent for outpatient visits, and USD 105 were spent for emergency care in the USA.

Our results are important for updating the asthma situation in Brazil. Despite the decrease in hospitalizations and deaths from asthma in Brazil, it is extremely important that new policies be employed to reduce both variables, for example, by improving education about disease management and physical activity in daily life, which has been demonstrated to contribute to better asthma control in this population.[36,37]

Our study has several limitations. The data analyzed were collected from electronic records. Although notification is mandatory, there is potential for missing data and inclusion of incorrect records, which may lead to underreporting of the disease. Another important aspect is the reduction in the number of hospitalizations from 2020 to 2021, which can be associated with the restriction measures recommended by the WHO due to COVID-19.

Our results showed that the number of asthma deaths and hospitalizations has decreased in Brazil in the last fifteen years. Although there is still much to be done regarding asthma, these data suggest that national asthma has improved in Brazil.

AUTHOR CONTRIBUTIONS

DHAP and JVHS equally contributed to this work.

DHAP, JVHS, AFOJ, FFL, RMCP, and CRFC designed the study. JVHS and AFOJ collected the data. DHAP, JVHS, AFOJ, FFL, and CRFC analyzed and interpreted the data. All authors were responsible for significant manuscript writing and/or critical revisions for important intellectual content. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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Management of pediatric pleural empyema: a national survey of pediatric surgeons in Brazil

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ABSTRACT

Objective: To identify how pediatric surgeons manage children with pneumonia and parapneumonic pleural effusion in Brazil. **Methods:** An online cross-sectional survey with 27 questions was applied to pediatric surgeons in Brazil through the Brazilian Association of Pediatric Surgery. The questionnaire had questions about type of treatment, exams, hospital structure, and epidemiological data. **Results:** A total of 131 respondents completed the questionnaire. The mean age of respondents was 44 ± 11 years, and more than half (51%) had been practicing pediatric surgery for more than 10 years. The majority of respondents (33.6%) reported performing chest drainage and fibrinolysis when facing a case of fibrinopurulent parapneumonic pleural effusion. A preference for video-assisted thoracic surgery instead of chest drainage plus fibrinolysis was noted only in the Northeast region. **Conclusions:** Chest drainage plus fibrinolysis was the treatment adopted by most of the respondents in this Brazilian sample. There was a preference for large drains; in contrast, smaller drains were preferred by those who perform chest drainage plus fibrinolysis. Respondents would rather change treatment when facing treatment failure or in critically ill children.

Keywords: Empyema, pleural; Thoracic surgery, video-assisted; Fibrinolysis; Surveys and questionnaires; Pediatric surgery .

INTRODUCTION

Pleural effusion is a serious complication of pneumonia in children. Although pleural effusion is rare, it is responsible for almost half of hospital admissions in Brazil.[1,2] Parapneumonic pleural effusion (PPE) has a three-stage evolution, and its treatment depends on the phase in which it is found. In the beginning, the increase in capillary permeability promotes an accumulation of free fluid in pleural space. The infectious process leads to fibrin and septal formation in the pleural space. In this phase, known as fibrinopurulent, it is possible to identify these loculations or septations on chest ultrasound.[3] This is a good method to confirm the presence of pleural fluid and to characterize the nature of a PPE and guide management. It was shown that classifying the stage of PPE and individualizing the treatment leads to shorter length of hospital stay.[4] The treatment of PPE is carried out according to the quality of the pleural fluid.[5,6] The gold standard of treatment is not defined and may depend on medical and equipment availability, as well as the experience of some centers. Chest drainage and administration of a fibrinolytic agent promote evacuation of pleural cavity and pulmonary expansion.[5,6] In several countries, the association of chest drainage and administration of fibrinolytic agents is the first line treatment. In Brazil, the number of centers using chest drainage and fibrinolysis in these patients is unknown. However, video-assisted thoracoscopic surgery (VATS) is routinely preferred, because it allows adequate visualization of the effusion and helps position the chest drain. Many surgeons have conducted it according to the availability of thoracoscopic equipment.[7,8]

Necrotizing pneumonia may be difficult to diagnose on chest radiography in its initial phase, although it may show cavitations (pneumatoceles) later. Chest CT is not routinely recommended for evaluating empyema, but it could be used to detect parenchymal lung abnormalities, endobronchial obstruction, lung abscesses, and mediastinal abnormalities.[9]

Therefore, it is necessary to know and establish protocols for the treatment of empyema in children. Surveys can help answer several questions related to pediatric surgeons' practice in managing pleural empyema.[10] An international survey applied to physicians who treat pleural empyema in adults identified that the practices adopted were very divergent. There was also a wide variation in fibrinolytic dosing.[11] This study aimed to identify how PPE in children is managed by means of an online questionnaire applied to pediatric surgeons in Brazil.

METHODS

The Research Ethics Committee of *Hospital Infantil Joana de Gusmão* approved the study (CAAE no.

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58259922.8.0000.5361). A pilot survey with 29 questions was developed and randomly applied to 10 regional pediatric surgeons in the city of Florianópolis, Brazil. After the pilot, the researchers have selected a total of 27 questions, and the definitive questionnaire was applied to pediatric surgeons participating in the Brazilian Association of Pediatric Surgery mailing system between February and March of 2023. Google Forms was chosen to produce and distribute the questionnaire. All of the respondents were an active member of the Association. Invitations to participate in the survey were sent via e-mail sent by the Association. Participants who did not complete the questionnaire within 21 days were contacted again. Descriptive analysis was performed using absolute data and reported as absolute and relative frequencies. Continuous variables were reported as medians or means. The Shapiro-Wilk test was used for the evaluation of variables with normal distribution. Categorical variables were evaluated using the chi-square test, and numerical variables were evaluated using the t-test. The Cramer's V test was used to assess the effect size. ANOVA was performed to compare means and categorical variables. The chi-square test and the Fisher's exact test were used for comparative analysis and the value of $p < 0.05$ was considered significant for testing the hypotheses.

RESULTS

There were 131 respondents who completed the questionnaire. Table 1 shows the distribution of responses. The Shapiro-Wilk test demonstrated normal distribution of the responses. The mean age of respondents was 44 ± 11 years, and 67 (51%) of the respondents had been practicing pediatric surgery for more than 10 years. When asked about the frequency of being called to evaluate children with pleural effusion, the majority answered that this always or almost always happened (61.8%). More than half of respondents stated that they had treated 16 or more children within the last 12 months.

The correlation of chest drain size, Brazilian macroregion, treatment in case of illness, and type of treatment is shown in Table 2. No significant differences were found regarding respondents' mean age and type of surgical treatment of patients for fibrinopurulent PPE (ANOVA: 218.673; df: 4; $p = 0.7$). However, the mean age of respondents (51 years) who performed thoracotomy was higher than that of those who performed other types of treatment, as shown in Figure 1.

Pediatric thoracic surgeries represented less than 25% of the surgeries performed by most respondents. Only 11 respondents used more than 50% of their working time with pediatric thoracic surgery. Only 21.4% of respondents reported not performing other thoracoscopic procedures. Stage II pleural effusion was treated only with chest drainage, with or without saline, by 68% of the participating pediatric surgeons.

Table 1. Characteristics of the respondents (N = 131).

Characteristic		
Age, years (mean ± SD)	44 ± 11	
	n	%
Gender		
Male	59	45,0
Female	72	55,0
Region		
North	5	3.8
Northeast	31	23.7
Central-West	17	13,0
South	29	22.1
Southeast	48	36.6
Effusion stage at admission		
I - Exudative	37	28.2
II - Fibrin-purulent	90	68.7
III - Organized	3	2.3
Unknown	1	0.8
Treatment		
Chest drainage with or without saline	41	31.3
Chest drainage plus fibrinolysis	44	33.6
VATS	35	26.7
Thoracotomy	3	2.3
Other	8	6.1
Chest drain size		
Small drain (≤ 14Fr)	22	16.8
Large drain (≥ 16Fr)	99	75.6
Pigtail	4	3.1
Other	6	4.6
Time of practice		
Less than 5 years	37	28.2
Between 6-10 years	30	19.8
Between 11-20 years	4	21.4
More than 20 years	30	30.5

VATS: video-assisted thoracic surgery.

Intervention

Most of the patients were hospitalized with fibrinopurulent PPE according to 68.7% of the respondents. Additionally, the most common surgical treatment was chest drainage followed by the administration of fibrinolytics (32.8% of respondents), and the most commonly used fibrinolytic was alteplase (in 97%). Nevertheless, 31.3% of respondents reported that they performed chest drainage with or without the use of saline solution.

The surgeon or resident was responsible for administering the fibrinolytic agent in 88.3% of the responses. None of the respondents reported that interventional radiologists had administrated fibrinolytics.

When asked about the size of the thoracic drain, there was a preference for using larger drains (in 75%). However, those who reported to perform thoracostomy and fibrinolysis were associated with the use of small drains (< 14 Fr; Fisher's: 22.947; df: −12; $p < 0.001$; Cramer's V: 0,251). The analysis of

Table 2. Correlations between chest drain size, macroregions of Brazil, and types of treatment.

Variable	Treatment				Total	Cramer's V	p*
	Thoracostomy plus saline solution	Thoracostomy plus fibrinolytic agent	VATS	Thoracotomy			
Drain size							
Small drain (≤ 14Fr)	3 (14.3%)	15 (71.4%)	3 (14.3%)	0 (0,0%)	21 (16.2%)	Moderate (0.251)	0.07
Large drain (≥ 16Fr)	34 (36.5%)	25 (26.8%)	31 (33.3%)	3 (3.2%)	93 (70.9%)		
Pigtail	0 (0.0%)	3 (75.0%)	1 (25.0%)	0 (0.0%)	4 (3.1%)		
Other	4 (80.0%)	1 (20.0%)	0 (0.0%)	0 (0.0%)	5 (3.8%)		
Valid responses					131 (100%)		
Change in treatment							
Yes, if VATS	11 (61.1%)	4 (22.2%)	0 (0.0%)	3 (16.7%)	18 (14.6%)	Moderate (0.459)	< 0.01
Yes, if fibrinolytic agent	22 (48.9%)	1 (2.2%)	22 (48.9%)	0 (0.0%)	45 (36.6%)		
No	7 (11.9%)	39 (66.1%)	13 (22.0%)	0 (0.0%)	59 (48.0%)		
Valid responses					122 (100%)[a]		
Different treatment if unstable							
Yes, always	12 (44.4%)	5 (18.5%)	8 (29.6%)	2 (7.4%)	27 (24.8%)	Weak (0.231)	0.07
No, only in necrosis	12 (26.1%)	18 (39.1%)	15 (32.6%)	1 (2.2%)	46 (42.2%)		
No	14 (38.9%)	17 (47.2%)	5 (13.9%)	0 (0.0%)	36 (33.0%)		
Valid responses					109(100%)[a]		
Region							
North	1 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	3 (2.8%)	Moderate (0.282)	< 0.01
Northeast	15 (60.0%)	0 (0.0%)	8 (32.0%)	2 (8.0%)	25 (23.1%)		
Center-west	5 (35.7%)	7 (50.0%)	2 (14.3%)	0 (0.0%)	14 (13.0%)		
Southeast	14 (35.0%)	20 (50.0%)	6 (15.0%)	0 (0.0%)	40 (37.0%)		
South	3 (11.5%)	10 (38.5%)	12 (46.2%)	1 (3.8%)	26 (24.1%)		

VATS: video-assisted thoracic surgery. *Chi-square test and Fisher's exact test. [a]Some missing data.

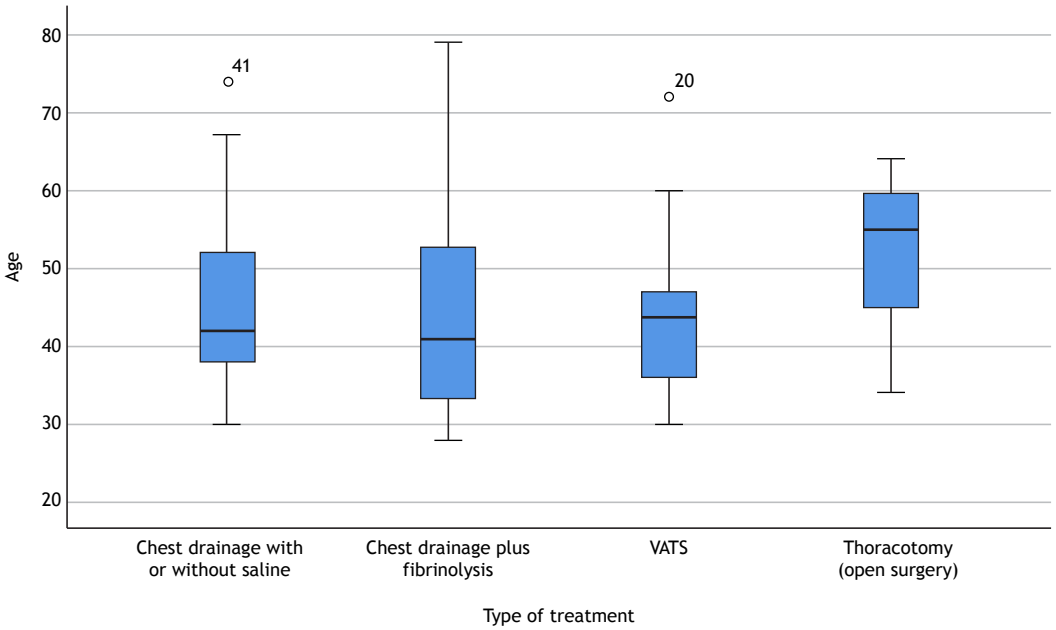

Figure 1. Type of treatment selected by age of respondents (mean age: black line in the rectangle). VATS: video-assisted thoracic surgery.

the adjusted residuals indicated that, for the group who reported using chest drainage and fibrinolysis (CDF), there was a higher than expected frequency regarding the use of small drains.

We also asked the participants that if they had other treatment options available, they would adopt them. In the CDF group, 88.6% would not change their conduct if they had other treatment methods. On the other hand, those who would change if they had fibrinolytics available were mostly those who reported using VATS or drainage plus saline solution. (Fisher's: 84.031; gL : 12; p < 0.001).

When compared by Brazilian macroregions, many of the respondents in the Northeast performed chest drainage with or without saline (n = 17; 41%), as shown in Figure 2. Meanwhile, the Southeast region had the highest number of respondents who performed VATS (40%).

None of the respondents in the Northeast region performs CDF. There was an association between respondents who were in the Northeast and performed thoracostomy and pleural drainage with or without saline. The Southern region had the highest number of respondents who performed VATS.

Complications and treatment failure

Therapeutic failure was considered as the persistence of fever, need for supplemental oxygen, and lack of appetite for 51.5% of respondents. Most respondents (66.4%) chose another surgical treatment when a therapeutic failure was considered.

When asked whether the patient should be treated differently if he/she was clinically ill, 28 (21.4%) of respondents reported that they agreed with the change, 49 (37.4%) replied that they would treat him/her differently if there was pulmonary necrosis, and another 38 (29.0%) said that they would not change treatment.

Almost half of the respondents reported having followed the children regardless of the treatment performed. When there is pulmonary necrosis, 61 (46.6%) of respondents stated that they would maintain the conduct according to the treatment of the pleural disease; however, another 29 (22.1%) answered that they would perform VATS, and 34 (26%) said they would perform thoracotomy to manage pulmonary necrosis. Surgery for bronchopleural fistula was said to be carried out mostly when the fistula is persistent (60% of respondents). In contrast, 41 (31.3%) of respondents would not choose a surgical procedure when facing a bronchopleural fistula.

DISCUSSION

The result of this survey shows that CDF is the most common treatment adopted in Brazil (n = 44; 33.6%). However, 41 respondents (31.3%) reported performing chest drainage with or without saline solution. One randomized trial found a reduction in length of hospital stay comparing the use of urokinase and saline in children.[12] In adults, another study reported a lower risk of treatment failure using fibrinolytics.[13] Treatment for fibrinopurulent PPE using CDF as the first line treatment and VATS in case of failure are recommendations of the British Thoracic Society (BTS) and the American Pediatric Surgical Association.[5,6] Various centers have adopted this type of approach. However, 35 (26.7%) of respondents preferred VATS as the first line treatment for fibrinopurulent PPE. In

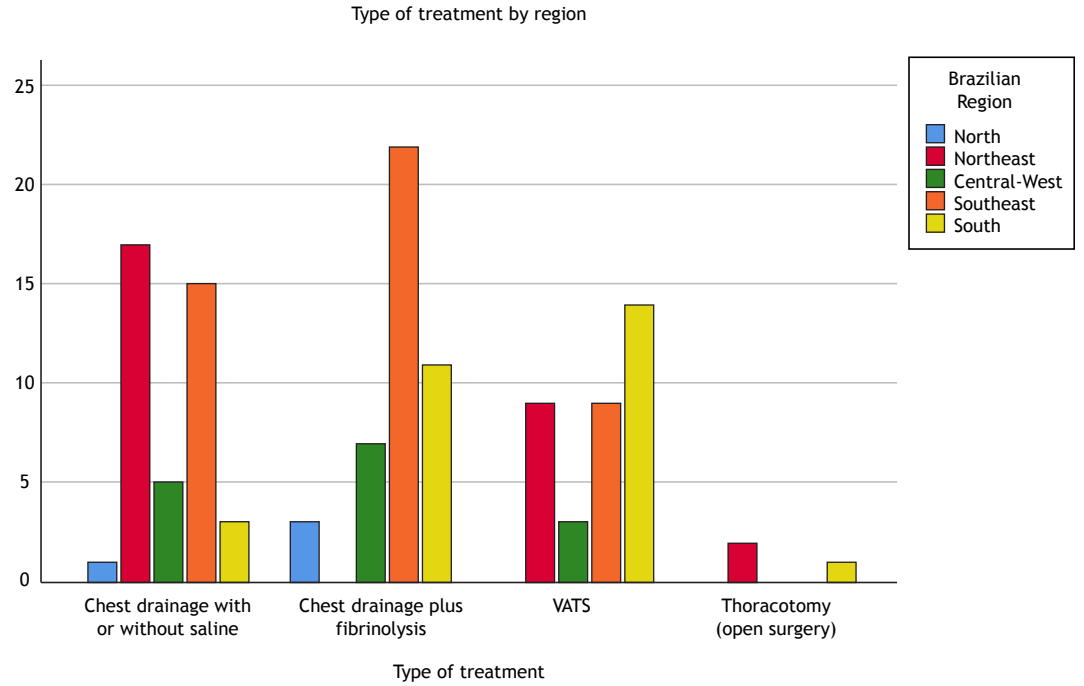

Figure 2. Number of respondents by Brazilian macroregion and type of treatment selected. VATS: video-assisted thoracic surgery.

2017, a systematic review[14] stated that VATS can reduce the length of hospital stay when compared with thoracostomy and drainage alone by almost 3 days. The evaluation of the use of fibrinolytics in that review was disadvantaged by insufficient evidence. Thoracotomy was also superior to thoracostomy and pleural drainage in terms of length of hospital stay in children.[14]

St Peter et al.[15] performed a randomized clinical trial with 36 participants, comparing fibrinolysis with alteplase and VATS, and found equal length of hospital stay and drainage time; however, the costs in the VATS group were more expensive. Sonnappa et al.,[16] in a randomized clinical trial involving 60 participants, compared fibrinolysis using urokinase with VATS and found no differences in terms of mean length of hospital stay and number of days for chest drain removal. The abovementioned systematic review[14] showed no difference in mortality between surgical or nonsurgical treatment.

Administration of alteplase has an advantage over VATS, because it is less invasive and does not require general anesthesia. Nevertheless, a retrospective study found advantages in applying a fibrinolytic (urokinase) after thoracoscopy performed with moderate sedation.[17] However, the medication used (propofol+remifentanil+sevoflurane) might be considered as general anesthesia in some centers.

There is no evidence to determine which treatment for fibrinopurulent PPE in children is the best. The use of CDF, VATS, or chest drainage alone in Brazil might result from the unavailability of thoracoscopic equipment or fibrinolytic agents. Certainty, most of the participants who chose CDF (n = 39; 88.6%) stated that they would not change the treatment if VATS was available. In contrast, those who reported using VATS or chest drainage with or without a fibrinolytic—22 (62%) and 22 (53%), respectively—stated that they would change treatment if a fibrinolytic agent was available (Fisher: 84.031; gL: 12; $p < 0.001$; Cramer's V: 0,463).

Large drains were preferred by most of the respondents (75%), but those who chose CDF used smaller drains. An open randomized study[18] with 130 children compared drainage of empyema with small catheters (less than 14Fr) and large catheters (greater than 14Fr) and found no differences between length of hospital stay, chest drainage time, and volume drained. They also concluded that smaller drains caused less pain without any impact on the clinical outcome.[18] The BTS guidelines recommend the use of small drains (including pigtail catheters) to minimize patient discomfort.[6]

Brazil is a continental country with inequitable distribution of investments in health. Besides that, income inequality could affect the management of some cases of PPE. There was an association with the macroregion of Brazil and the type of intervention. The Fisher's exact test showed significance for those who reported being in the Northeast and treating for PPE with drainage and saline solution in comparison with those in other regions ($p < 0.001$). In addition, there was an association of those who responded being in the South and treating for PPE with VATS ($p < 0.001$; Cramer's V: 0.282). On the other hand, there was an association between those who reported they would change treatment if VATS was available and being in the Northeast ($p = 0.04$; Cramer's V: 0.216). Some authors from developing countries reported no significant differences between treatment with CDF and with VATS in their centers. In a randomized trial with 41 children,[19] the use of fibrinolytic agents were not inferior to VATS in the Indian subcontinent. In addition, the need of blood transfusion was significantly higher in the VATS group in that study.[19] To sum up, VATS might require more medical equipment (hospital apparatus), and it is difficult to compare surgical management between different countries or centers with different number of patients or different health care structures.

Failure in the treatment of empyema is considered when fever, prolonged supplemental oxygen requirement, and loss of appetite occur. The majority of respondents agreed with that statement. Most of them chose another type of treatment when facing failure. There is a preference for surgical treatment (VATS or thoracotomy) when there is treatment failure or necrosis. Indeed, consideration for VATS after chemical debridement should occur when the patient is persistently ill after chest tube drainage diminishes and imaging proves substantial disease in pleural space.[5] Meanwhile, some authors showed that, instead of performing VATS, it would be possible to do an additional course of fibrinolysis or replace the chest drain in other non-contemplated loculations in order to avoid surgery in children with symptomatic pleural disease.[20]

Dealing with the experience in chest ultrasound, 71% of respondents reported not being experienced. However, 91.6% of respondents reported using chest CT for the diagnosis of pulmonary necrosis. Chest ultrasound is portable, easy to perform, and involves no radiation. Likewise, it is superior to chest CT to show pleural problems.[21] The ultrasonographic aspect of a pleural effusion should indicate the treatment and can be carried out by the surgical team. The use of point-of-care chest ultrasound should be encouraged to improve management of pleural empyema. The BTS guidelines advise the use of ultrasound to guide thoracentesis and to identify the best place for drain insertion.[6] In addition, ultrasound could be used before thoracoscopy to assess the best site of trocar insertion according to presence, quantity, and characteristics of pleural effusion.[22]

It is estimated that there are 1,720 pediatric surgeons registered in Brazil and probably less than half of this number is not active in the specialty, although we only obtained 131 responses.[23] The low rate of respondents was a limitation. The interest in

responding may represent a biased sample of those surgeons who perform most thoracic procedures and might not represent reality. Thoracic surgeons and pediatric pulmonologists are responsible for caring for children with pleural effusion, and they were not included in this survey, which might be a bias.

In a nutshell, chest drainage with fibrinolysis is the treatment adopted by most of the respondents in Brazil. Besides that, VATS could be more used if it is widely available. Moreover, there was a preference for using larger drains in this sample. The majority of respondents would prefer to do another procedure when facing treatment failure. The point-of-care chest ultrasound should routinely be used in the diagnosis and selection of treatment strategies.

AUTHOR CONTRIBUTIONS

All authors participated in the study design analysis, interpretation of data, and drafting and revising of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Methylprednisolone intravenous pulse therapy for pediatric patients with post-infectious bronchiolitis obliterans: an update

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TO THE EDITOR:

Post-infectious bronchiolitis obliterans (PIBO) is a rare form of chronic obstructive lung disease that follows a lower respiratory tract infection and results in partial or complete obliteration of the small airways.[1,2]

The use of corticosteroids is the most common anti-inflammatory therapy for PIBO; nonetheless, there has been no controlled trials to prove its efficacy and safety.[1,2] High-dose methylprednisolone intravenous pulse therapy has been proposed to enhance the therapeutic effect and reduce side effects of prolonged corticosteroid therapy.[1,3]

We reported our first experience in children with PIBO treated with corticosteroid pulse therapy between 1996 and 2007.[4] The objective of the current study is to describe our experience with this approach in the subsequent period (2007-2019).

We included PIBO patients attending our outpatient clinic (≤ 18 years of age) who were treated with monthly intravenous high-dose methylprednisolone pulse (MP) therapy cycles (30 mg/kg body weight/day for three consecutive days) between 2007 and 2019. The diagnosis of PIBO was given upon a combination of clinical and radiological findings; none of the patients was submitted to lung biopsy. Clinical criteria included signs of persistent and severe airway obstruction that persisted for over six weeks following a severe acute respiratory infection in a previously healthy child, excluding other chronic obstructive lung diseases. Radiological criteria were based on HRCT findings, including significant air trapping, mosaic pattern, and/or bronchiectasis.

Data were obtained from the medical records and included the number of acute wheezing attacks and hospitalizations within the six-month period before treatment, and at 6, 12, 18, and 24 months thereafter. Description of growth, the need of supplemental oxygen, and chronic oral corticosteroid usage, as well as lung function results and MP therapy-related adverse effects were also registered when available. The nonparametric ANOVA (Friedman test) with post hoc Dunnett's test was performed to compare wheezing attacks and hospitalization frequencies between periods; anthropometric comparisons used t-test for paired samples. Statistical analysis was performed using the IBM SPSS Statistics software package, version 23.0 (IBM Corporation, Armonk, NY, USA). Statistical significance defined as $\alpha = 5\%$. This study was approved by the research ethics committee of the institution (CAPPesq HCFMUSP, protocol no. 0695/07).

A total of 17 patients (9 boys = 53%) diagnosed between 10-59 months of age (median = 22 months) were included in the study. The interval between the onset of the disease and diagnosis was 1-28 months (median = 10 months).

While the presumed etiology was post-infectious, most of the referring hospitals did not perform studies of viral etiology and therefore only two patients had a previous result of an adenovirus infection.

The most common radiological finding was mosaic perfusion pattern (in 88%), followed by atelectasis (in 59%), bronchiectasis (in 35%), bronchial wall thickening (in 41%), alveolar filling (in 17%), air trapping (in 17%) and Swyer-James-MacLeod syndrome (in 12%).

The median number of MP cycles was 9 (range, 5-17). The median age at MP start was 23 months (range, 10-60 months), and the median interval between the onset of disease and MP therapy was 11 months (range, 2-28 months). In addition, all 17 patients were given inhaled corticosteroids with long-acting β_2-agonist bronchodilators during the entire follow-up period. Other treatments included therapy for gastroesophageal reflux (n = 8; 47%), azithromycin (n = 9; 52%) and anti-hypertensive drugs (n =3; 17%).

The median numbers of acute wheezing attacks and hospitalizations were significantly reduced after starting MP therapy when compared with the previous period ($p = 0.001$ and $p < 0.001$, respectively). Half of the patients were able to discontinue supplemental oxygen use, and most of those who remained dependent were able to step down the flow or duration needed. We also observed improvement of growth in the first year after MP therapy started (Table 1).

Spirometry results were available during follow-up in 9 patients (median age = 6.0 years; range, 5.5-8.1 years), and depicted moderate-to-severe obstructive disease with reduced vital capacity—median [IQR] in % of predicted values: $FEV_1\%$ = 41 [40-42]; $FEV_1/FVC\%$ = 76 [67.8-80.0]; and $FEF_{25-75\%}$ = 22 [19-26]—and no significant response to bronchodilators.[5]

Safety of MP therapy was overall very good, and adverse effects were transient and of minor concern. No patient was diagnosed with arterial hypertension after starting MP therapy, and no one was diagnosed with diabetes mellitus in the follow-up. Few patients were actively screened for long-term effects of steroid therapy such as fundoscopy, urinary tract lithiasis, or bone density, but results were normal in those investigated.

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Table 1. Clinical and laboratory evaluation before and after methylprednisolone pulse therapy (n = 17)

Variable	Before	After	Time needed to discontinue
Prolonged oral corticosteroid therapy	8 patients (47%)	0 patient	4.5 months (range, 2-13 months)
Domiciliary oxygen therapy			
Total	13 patients (76%)	7 patients (41%)	11 months (range, 8-13 months)
Full-time	10 patients	1 patient	
Overnight	1 patient	6 patients	
Anthropometric measurements	Before	After one year	p
Length for age (mean Z score)	−1.37	−0.84	0.016
Weight for age (mean Z score)	−0.70	−0.19	0.20
BMI (mean Z score)	0.09	0.49	0.25

We started MP therapy with corticosteroids for PIBO cases some years ago, aiming to maximize therapeutic effect and reduce side effects of prolonged systemic corticosteroid use. However, we had no reference to judge how long the treatment should be kept for, and which patients would benefit the most. We now believe that treatment for some patients was longer than necessary. After learning from the results of our initial study,[4] we established that if the patient shows no improvement after 6 cycles of MP therapy, it should be discontinued, and we also agreed to reduce the total number of cycles, preferably up to 12 months of treatment.

In this current study, 17 children with PIBO treated with MP therapy presented with significant clinical improvement: fewer wheezing exacerbations and hospitalizations, and improved oxygen saturation. This accumulated experience allowed us to establish that the most important factors to indicate MP therapy for BO patients should be dependence of chronic systemic corticosteroid therapy or the need for home oxygen therapy, as well as prolonged or frequent hospitalizations due to respiratory impairment.

An additional aspect that needs to be considered is the lag before starting the treatment. In our previous study,[4] the median interval between the onset of the disease and the start of MP therapy was 18.5 months. In the current study, this interval was 11 months. Presumably, the effectiveness of anti-inflammatory treatment would be reduced if the initial event has taken place too long before its start, due to airway fibrosis. A retrospective and controlled study[6] evaluated the responsiveness of 17 patients with PIBO who were treated with MP therapy and the responder group had a significantly shorter median interval between the initial episode (4 months) and the start of MP therapy than did the non-responder group (50 months), indicating that MP therapy works better when indicated earlier.

Regarding the side effects, all acute effects observed during the methylprednisolone intravenous infusion were transient and not considered serious in our series. Even linear growth of the patients showed to improve, possibly due to clinical stabilization and discontinuation of chronic oral use of corticosteroids.

We conclude that MP therapy may be an effective and safe strategy to improve the clinical course of PIBO but to be used for shorter periods of time than we previously recommended.

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AUTHOR CONTRIBUTIONS

All of the authors equally contributed to the study and gave final approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Clinical remission after biologic therapy discontinuation in pediatric patients with severe asthma: a case series from a tertiary center

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TO THE EDITOR:

Given the complex interactions between genetic and environmental factors, asthma is a heterogeneous chronic lung disease, characterized by different patterns of inflammation and bronchial remodelling.[1] The treatment aims at clinical disease control with optimized or normal lung function, applying different steps for treatment, from inhaled corticosteroids (ICS) as monotherapy to add-on therapies, including biologics. Severe asthma is a major clinical challenge, but the access to biologics resulted in better control of disease.[1] In Brazil, omalizumab was the first biologic therapy approved for severe asthma in the pediatric population, demonstrating significant reductions in the number of exacerbations, in the use of rescue medications, and in emergency room visits during the first year of treatment, maintaining clinical improvement.[2,3] These clinical effects arise the possibility of clinical remission on and off treatment, becoming an important scientific topic worldwide.[4]

Aiming to describe the characteristics and the course of clinical remission with omalizumab therapy discontinuation, we contacted patients from a previous cohort of Brazilian pediatric patients with severe asthma, aged 14-21 years, followed in a tertiary center. Between 2012 and 2018, the patients underwent a clinical protocol approach to diagnose severe asthma based on GINA criteria[5] and used omalizumab as an add-on therapy. Of the 21 eligible patients with severe asthma, 8 agreed to participate in this follow-up case series (mean age = 17.2 ± 1.9 years; 4 were female). The patients were assessed through an in-person visit or a web conference. Patient-reported outcomes included clinical history, dose of medications, assessment of disease control (GINA questionnaire), and history of hospitalizations. For those patients who visited the tertiary center, pulmonary function was assessed by measuring FEV_1 and FEV_1/FVC ratio. Data were also collected from standardized electronic medical records. The study was approved by the research ethics committee of the institution (CAAE n. 50818220.0.0000.5345).

Lack of disease control was defined as the presence of poor symptom control (GINA criteria), > 2 severe or serious exacerbations in the previous year (with the use of oral corticosteroids [OCS] or hospitalization, respectively), or persistent airflow limitation.[1] Clinical remission on- and off-treatment with omalizumab was defined by the sustained absence of significant symptoms (> 12 months of total control of disease and no exacerbations).[4]

All of the 8 patients were previously classified as having atopic severe asthma (positive skin-prick test), uncontrolled asthma symptoms, normal or mild airway obstruction, and a history of hospitalization in the year before the initiation of omalizumab therapy. Six patients showed allergic rhinitis, and 4 patients had as a comorbidity being overweight/obese. The mean duration of omalizumab treatment was 46 ± 25 months. The mean age at initiation of omalizumab therapy was 9.0 ± 1.6 years, and the mean age at discontinuation was 13.0 ± 2.9 years. Only 1 patient did not achieve clinical remission to discontinue the omalizumab treatment. The 7 patients who discontinued omalizumab had from 3 to 7 years off-treatment with omalizumab until the follow-up visit. Figure 1 shows disease control and the course of treatment for each patient. After omalizumab prescription, hospital admissions were significantly reduced, from pre-treatment, post-treatment to follow-up, with no report of hospital admission in the last 12 months before data collection.

On clinical follow-up, 4 of the 7 patients who discontinued omalizumab reported uncontrolled disease. All patients are currently on continuous ICS. The mean daily dose of ICS was significantly reduced from pre-treatment to follow-up (at pre-treatment: 537.5 µg/day; at post-treatment: 425.0 µg/day; and at follow-up: 212.5 µg/day; $p = 0.0179$—comparisons performed with Friedman test). Also, symptom control was significantly improved after omalizumab treatment; 1 patient reported partially controlled symptoms, and 1 reported uncontrolled symptoms (a 40% reduction; $p = 0.0373$). The 4 patients originally on continuous OCS discontinued this treatment by six weeks after initiating omalizumab. No serious adverse events from omalizumab were observed. Lung function, considered a less important tool for assessing the severity of asthma in children,[6] was not significantly changed by omalizumab treatment for all variables analyzed during pre-treatment, post-treatment, and follow-up (comparisons using mixed effect analysis).

Three patients (42.8%) are in clinical remission 4-6 years after discontinuing omalizumab. In their medical records, all of these patients had a history of multiple hospitalizations before omalizumab treatment. This

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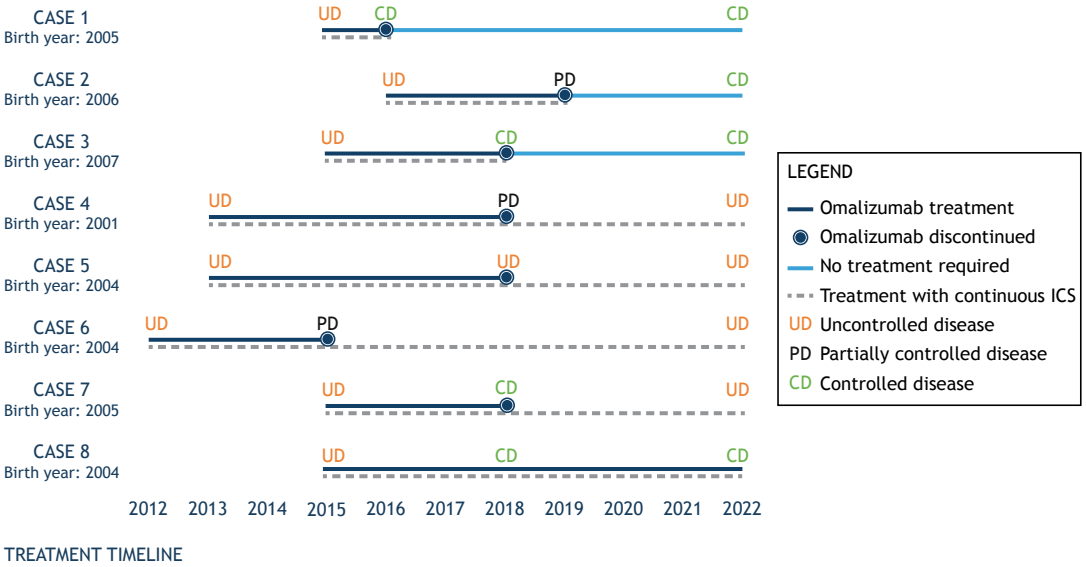

Figure 1. Evolution of clinical and disease control with omalizumab treatment. Each line on the Y-axis represents one individual of this case series. Data from medical records and interviews comprise a period of up to 10 years of registry. Outcomes are depicted for each individual at pre-treatment, post-treatment, and follow-up. ICS: inhaled corticosteroids.

is probably the most important clinical goal for any severe presentation of a chronic disease.

One previous real-life study including our case series showed that omalizumab significantly reduced hospitalizations, OCS use, and improved disease control.[7] In this report, we demonstrated that, after omalizumab discontinuation, 3 of the 8 patients achieved long-term total control of disease (off-treatment clinical remission), being treated only with inhaled controller medications. However, despite preventing further hospitalizations in all cases, 4 patients did not show clinical remission off-treatment, but none of them returned to show a severe phenotype.

The first real-life study of omalizumab discontinuation conducted with 35 children showed that patients with well-controlled disease generally maintained disease control when the drug was discontinued. However, 22% had to resume omalizumab therapy due to worsening of symptoms.[8] Two other large cohort studies with pediatric patients with severe asthma showed that long-term off-treatment clinical remission after the use of omalizumab was observed in 27% (n = 100) and in 33% (n = 1,082) of the patients, respectively.[8,9] Our report also shows, in a Brazilian population, that clinical remission after discontinuation of a biologic in pediatric patients with severe asthma may not be an uncommon outcome. Despite the limitations of this report, because data were retrospectively collected from medical records, and a self-report questionnaire regarding the previous 12 months was applied, which is dependent on patient and parent recall, we were able to demonstrate that long-term clinical off-treatment remission of asthma after omalizumab use may be achieved in the management of Brazilian pediatric patients with severe asthma.

Off-treatment clinical remission is one of the most important clinical targets in asthma, and our case series of pediatric patients suggests that this outcome may be achieved in almost half of the patients with severe asthma treated with biologics. Large national multicenter prospective cohort studies in pediatric patients with severe asthma are urgently needed to better define off-treatment asthma remission, the prevalence of this outcome, and predictors of success.

AUTHOR CONTRIBUTIONS

GDMC: wrote the paper, collected data, and performed the analysis. FF: collected data and reviewed the analysis. AFW: collected data, performed the investigation, and reviewed the analysis. GS: data curation and analysis review. PMP: conceptualization, analysis design, and revision of the manuscript. All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Freezing mediastinal lymph node: first case of mediastinal cryobiopsy guided by EBUS in Brazil

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TO THE EDITOR,

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is currently considered the method of choice for the invasive mediastinal staging of lung cancer. The samples obtained through EBUS-TBNA have proven suitable for tumor subtyping, immunohistochemistry, and molecular analysis. Transbronchial cryobiopsy is a technique used in the diagnosis of interstitial lung diseases that enables obtaining more tissue and samples with preserved architecture. A combination of EBUS and cryobiopsy, known as transbronchial mediastinal cryobiopsy guided by EBUS (EBUS-TBMC), is being developed as a novel mediastinal sampling strategy.[1] EBUS-TBMC can be considered a complementary method to EBUS-TBNA in cases where material is difficult to obtain through a cytological needle (metastatic lymph nodes after chemotherapy, immunotherapy, or radiotherapy) and in cases of difficult diagnosis, such as lymphoproliferative diseases and benign infectious and inflammatory lesions, in which histological material offers advantages over cytological samples.[2,3] In the present letter, we describe the first case of EBUS-TBMC performed in Brazil.

We present a case of a 50-year-old female patient, a former smoker, who presented with mediastinal lymph node enlargement, periodic fever, and cough over the past three months. We chose to perform EBUS-TBMC due to the need for a differential diagnosis between lymphoproliferative disease, sarcoidosis, granulomatous infection, or lung cancer. After providing informed consent, EBUS-TBMC was performed. The procedure was conducted on an outpatient basis, under general anesthesia, using an orotracheal tube and endobronchial blocker. An infracarinal lymph node measuring 15 mm was identified. After four passes of TBNA with a 22-gauge needle, a 1.1 cryoprobe was introduced through the working channel of the EBUS bronchoscope. The cryoprobe was then advanced into the target lesion through the bronchial-wall orifice created by the needle. Upon confirming the cryoprobe's position inside the lymph node through ultrasound visualization, transbronchial mediastinal cryobiopsy (EBUS-TBMC) (Figure1) was performed by cooling down for 3 seconds, followed by en bloc endoscopic removal. A total of 4 cryobiopsies were carried out, with subsequent sample fixation in formalin. No significant bleeding, pneumothorax, or other clinical complications were observed. Histopathological analyses revealed chronic granulomatous lymphadenitis without necrosis, with negative staining for microorganisms, suggesting a diagnosis of sarcoidosis.

We aimed to present the first EBUS-TBMC performed in Brazil, an innovative biopsy technique that allows for the retrieval of larger mediastinal tissue samples with preserved architecture. Traditionally, EBUS is performed by needle aspiration and has shown good performance in diagnosing and staging lung cancer. Combining transbronchial cryobiopsy with linear EBUS provides histopathological samples with preserved architecture, which can be helpful in cases where histological material has advantages over cytological samples.

The primary technical challenge encountered was the perforation of the bronchial wall and the lymph node capsule with the cryoprobe, given its lack of sharpness. We utilized a 22-gauge needle to perform the TBNA, and introduced the cryoprobe through the same puncture site. Some authors have suggested alternative techniques, such as using a 21G needle to create a larger puncture hole or a knife with electrocoagulation.[2] Another method described in the literature involves making multiple puncture holes with the TBNA needle to break the capsule and facilitate the passage of the cryoprobe.[4] Following the initial cryobiopsy, the already created pathway can be used for subsequent biopsies without major difficulties. The cryosamples analyzed by the pathologist were compared with the TBNA samples. Although both sample types were adequate for establishing the diagnosis of sarcoidosis, the EBUS-TBMC sample allowed for the visualization of the preserved architecture of the granuloma and the delineation of how the histiocytes were organized.

In this report, we share our pioneering experience in Brazil with this promising new biopsy technique. The procedure was uneventful, and the histopathological result played a decisive role in establishing the diagnosis of the patient in question. We will soon draft an original article describing the EBUS-TBMC case series currently under study at our center.

AUTHOR CONTRIBUTIONS

JPSM: study conceptualization and procedure performance. AS: study conceptualization and procedure supervision. BPPL: writing of the manuscript. MCB: writing of the manuscript. LHC: formal analysis.

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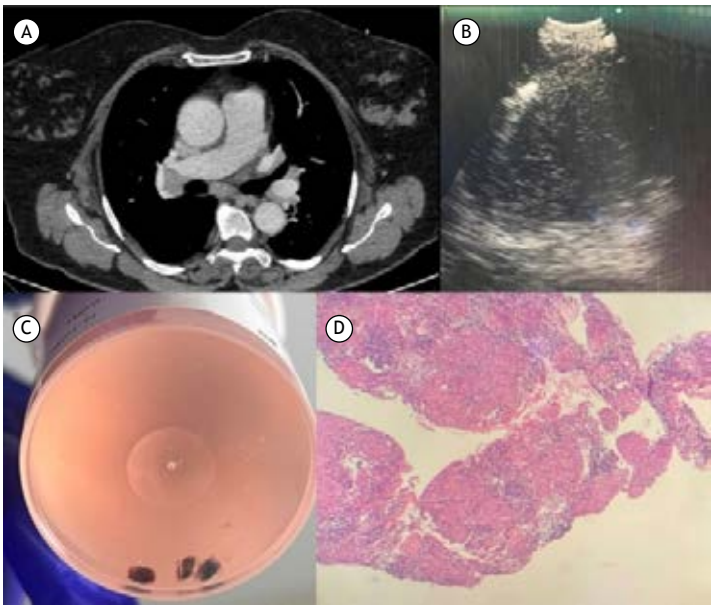

Figure 1. (A) Chest tomography with infracarinal and right hilar lymph node enlargement. (B) EBUS image showing the cryoprobe inside the lymph node. (C) EBUS-TBMC samples. (D) Histopathological image of the granuloma.

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Impact of telehealth during the COVID-19 pandemic on clinical and nutritional conditions of adolescents with cystic fibrosis

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TO THE EDITOR:

Cystic fibrosis (CF) is a severe, progressive, and multisystemic genetic disease that requires a regular, in-person treatment routine.[1,2] In 2020, with the advent of the COVID-19 pandemic, given the quarantine situation imposed by the authorities, self-care was encouraged, and services were provided remotely, thus establishing a routine of multiprofessional teleconsultations. Given this, we sought to verify how the impacts of telehealth during the COVID-19 pandemic reflected on the clinical and nutritional characteristics of adolescents monitored at a CF referral center (CFRC) in the state of Rio de Janeiro, Brazil.

A retrospective longitudinal study was carried out in which data from adolescents with CF (≥ 12 years of age) who were monitored between March and December of 2020 were evaluated. Teleconsultations were scheduled by the pulmonology team, with the participation of other specialties, such as physiotherapy, nutrition, nursing, and social assistance, all of which being involved in the treatment of CF. Teleconsultations were carried out via video calls or phone calls, depending on the availability of the patient. In addition to that, emergency consultations were available when requested by the patient or caregiver if deemed necessary. Telemonitoring was also carried out in patients considered to have more severe disease. The configuration of this service was only available in 2020.

The variables studied were as follows: BMI, height for age (H/A), percentile of arm muscle circumference (pAMC), percentile of BMI for age (pBMI/A), percentile of FEV_1 in percentage of the predicted value ($pFEV_1$%), percentile of predicted FVC (pFVC%), and FEV_1/FVC ratio. Results of these variables were compiled from the years 2017, 2018, 2019, 2021, and 2022 in order to establish the progression of the changes of the variables studied. Adolescents whose necessary data for the research were unavailable in their medical records were excluded from the study. Continuous data were presented as means and standard deviations, as were categorical data as absolute and relative frequencies. The mean differences between the years were also calculated, and the t-test for paired samples was used to compare them. Statistical significance was set at $p < 0.05$. This study was submitted to and approved by the research ethics committee of the institution (CAAE no. 52272115.0.0000.5269; opinion no. 1,431,706).

We evaluated 35 adolescents with a mean age of 11.0 ± 2.7 years, 54.3% of whom were female. It is possible to notice a reduction in the mean values of H/A and BMI/A over the years, which became more pronounced in the years following the online service period (Table 1). At the same time, the percentage of malnourished people according to the pAMC increased proportionally in the same years. In relation to lung function, a decline was also observed in the mean values of $pFEV_1$% and pFVC%, while the FEV_1/FVC ratio maintained stationary values throughout the study period. When evaluating year-to-year differences, statistical significance was observed only between 2018 and 2019 and between 2021 and 2022 in the $pFEV_1$% and pFVC%. There were no statistically significant differences between the period before the interruption of face-to-face meetings and after the return of consultations at the institution.

Although there was a decline in nutritional and lung function variables in the years studied, there were no statistically significant differences in the same characteristics between the period before and after the interruption of in-person consultations. This fact can be attributed to the almost immediate start of teleconsultations with the CFRC team that are knowledgeable of the specificities of patients with chronic and complex diseases.

It is noted that due to the progressive nature of the disease, nutritional and lung function data of these patients had already followed a course of decline even before the pandemic period. Some studies have shown high malnourishment indices in adolescents, especially in those with CF.[3,4] Adolescence in itself is a period of psychological and physiological changes and cognitive development, and experiencing it with a chronic and progressive disease impacts these changes even more. Given that nutritional status directly impacts functional capacity and, consequently, quality of life, adolescence requires primary attention not only from the multidisciplinary team, but also from the caregivers of these individuals.[5-7]

Because individuals with CF are considered a risk group vulnerable to complications from COVID-19, priority was given to keeping their health conditions as stable as possible through teleconsultations, telemonitoring, and encouragement of social isolation. Such strategies were extremely important to avoid worsening of lung function during that time. After the return of in-person consultations, the adolescents returned to the hospital frequently and returned to school, which explains the

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Table 1. Clinical and nutritional variables of adolescents with cystic fibrosis between 2017 and 2022 (N = 35).

Variable	2017	2018	p (2017-2018)	2019	p (2018-2019)	2021	p (2019-2021)	2022	p (2021-2022)
BMI	17.5 ± 3.43	18.0 ± 3.66	0.0062	18.1 ± 3.24	3.2443	19.3 ± 3.18	0.000	19.4 ± 3.48	0.7440
H/A	32.8 ± 24.99	31.1 ± 26.25	0.219	30.6 ± 27.16	0.7246	26.0 ± 24.60	0.5195	27.6 ± 25.39	0.6216
pBMI/A	45.7 ± 30.85	43.8 ± 32.58	0.3027	40.2 ± 30.47	0.1283	36.5 ± 29.41	0.4552	32.4 ± 28.06	0.2121
pAMC < 5, %	29.4	35.3		48.6		54.3		51.7	
$pFEV_1$%	82.0 ± 14.89	82.0 ± 14.06	0.8183	79.0 ± 17.98	0.0395	78.0 ± 18.30	0.5519	74.0 ± 19.59	0.0385
pFVC%	92.0 ± 13.05	91.0 ± 12.33	0.5436	87.0 ± 15.0	0.0065	89.0 ± 14.78	0.9911	85.0 ± 15.54	0.0536
FEV_1/FVC, %	83.0 ± 9.93	84.0 ± 8.08	0.3399	84.0 ± 9.03	0.4251	84.0 ± 10.86	0.5373	83.0 ± 12.94	0.7057

H/A: height for age; pBMI/A: percentile of BMI for age; pAMC: percentile of arm muscle circumference; $pFEV_1$%: percentile of predicted FEV_1; and pFVC%: percentile of predicted FVC.

recurrence of the pattern of decline in the variables studied.

Costa et al.[8] observed that most CF patients adhered to teleconsultations, demonstrating the relevance of remote assistance in the pandemic period. Teleconsultations were made available to the patients monitored quarterly, in a multidisciplinary manner, with different specialties that cover the treatment of CF, at the CFRC, where the study was carried out. This organization encouraged individuals with CF to join the online modality.

The distribution of CFRCs in Brazil is heterogeneous, the majority of them being in state capitals, so patients need to travel long distances to attend appointments.[9] Teleconsultation and telemonitoring in CF can be considered a possibility of accessing healthcare wherever the patient is and was considered a convenient option in comparison with outpatient care.[10]

Gur et al.[11] evaluated the perception of patients with CF and their families regarding the experience of remote care, and, although there were challenges, such as difficulty in accessing the Internet, patients were satisfied with the intervention and improved communication with the team. The authors highlighted that remote care is an acceptable and viable intervention.

Corroborating the literature, in our study, telehealth proved to be an important tool in the treatment of CF, since the values of the studied clinical and nutritional parameters were maintained. This finding can be justified by the rapid implementation of multidisciplinary teleconsultations at the CFRC, which evaluated and monitored individuals, carrying out interventions whenever necessary.

AUTHOR CONTRIBUTIONS

LMSS and NSS: study conception and planning; data interpretation; and drafting and reviewing of the manuscript. MASJ and CPG: study conception and planning; and data interpretation. All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Feasibility of EBUS-TBNA for the molecular characterization of non-small cell lung cancer

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TO THE EDITOR:

The accurate diagnosis of lung cancer (LC) relies on histopathological classification (HC) and molecular characterization (MC) for targeted therapies.[1] Clinicians that deal with LC face the dilemma of how to apply minimally invasive interventions that yield large and well-preserved samples suitable for the demands of the histopathologist and the molecular geneticist.

A milestone in this pathway has been achieved with the introduction of EBUS-TBNA, which is currently the first-choice procedure for mediastinal staging of LC.[2,3] On the other hand, MC of non-small cell LC (NSCLC) is a growing field of research with diverse strategies and heterogenous results.[4-7]

In this study we aimed to evaluate the current clinical practice of a large oncology referral centre concerning the feasibility of EBUS-TBNA-derived samples for MC of NSCLC.

We conducted a retrospective analysis (between January of 2019 and December of 2021) of all patients who underwent EBUS-TBNA for diagnosis and/or staging of NSCLC whose samples proceeded to MC. EBUS-TBNA was performed under general anesthesia with a BF-UC180F endoscope (Olympus, Tokyo, Japan) and 21G needles (ViziShot 2; Olympus). Samples were stored in formaldehyde and were processed as cell blocks for HC. *EGFR* status was determined by real-time polymerase chain reaction. If samples were negative, determination of *ALK* gene rearrangements by fluorescence in-situ hybridization followed.

Procedure and patient-related factors affecting sample adequacy were assessed. Finally, a timeframe was estimated from the initial endoscopic procedure and the final MC.

Descriptive and inferential statistical analysis was performed using the IBM SPSS Statistics software package, version 27 (IBM Corporation, Armonk, NY, USA). A logistic regression model was attempted to ascertain the presence of factors influencing MC results.

A total of 718 patients were subjected to EBUS-TBNA. Of these, 59 (8.2%) proceeded to MC, but only 38 (5.3%) had their MC performed in EBUS-TBNA samples. In the remaining 19 patients, MC was performed in other samples (6 in surgical specimens; 5 in bronchoscopy forceps biopsies; 4 in transthoracic CT-guided biopsies; and 4 in peripheral blood samples).

The patients included (N = 38) were mainly male (n = 25; 65.7%) with a median age of 67 years (range: 40-86 years). Nearly half had a relevant smoking history (12 former smokers and 8 current smokers). Most NSCLC were adenocarcinomas (n = 33; 86.8%), 3 were squamous cell carcinomas (SCC), and 2 were mixed adenocarcinoma and SCC (Table 1). All presented with locally advanced (stage IIIA, in 4; IIIB, in 6; and IIIC, in 3) or metastatic disease (IVA in 12; and IVB in 13). Programmed death-ligand 1 (PD-L1) status was ascertained in all patients and proved to be positive in 44.7% (in 2 patients with SCC and in 15 patients with adenocarcinoma), indeterminate in 5.2% (mixed adenocarcinoma and SCC, in 1; and adenocarcinoma, in 1), and negative in the remainder 50%.

A median of 2 lymph node stations were approached per patient (range: 1-4), with a median number of 3 needle passes (range: 3-8) per lymph node.

Overall, 34 out of the initial 38 cases (89.5%) were satisfactory for *EGFR* mutation testing, whereas 26 out of 32 (81.3%) were suitable for *ALK* rearrangement testing. Clinically relevant *EGFR* mutations were found in 6 patients (15.7%). *ALK* rearrangements were found in 2 cases (Table 1).

Mutated patients were mainly non-smoker males (5 out of 8) and presented with metastatic disease (stage IVB, in 4; and IVA, in 3).

The median time between EBUS-TBNA sampling and final MC was 20 days (range: 7-590 days). An in-depth analysis of this measure showed 11 cases (>30 group) in which this timeframe surpassed 30 days (median: 186 days; range: 48-590 days), whereas that was below 30 days in the ≤30 group (median: 18 days; range: 7-30 days). The patients in the >30 group were mainly in stage III (7 out of 11) whereas those in the ≤30 group were mainly in stage IV (20 out of 27).

MC was pivotal in determining the therapeutic options. All mutated patients were referred for targeted therapy (anti-EGFR, in 6; and anti-ALK, in 2). Immunotherapy was offered as frontline therapy in 15 non-mutated, PD-L1

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Table 1. Histopathological classification and mutational profiling of the sample of patients with non-small cell lung cancer (N = 38).

Histopathological classification	Mutational profiling	n (%)
Adenocarcinoma	Non-mutated	26 (68)
	EGFR mutated	5 (13)
	ALK rearrangements	2 (5)
Squamous cell carcinoma	Non-mutated	1 (3)
	EGFR mutated	1 (3)
	ALK rearrangements	1 (3)
Mixed squamous cell carcinoma	Non-mutated	1 (3)
	EGFR mutated	1 (3)

positive patients. Platinum-based chemotherapy was the option for 15 additional patients. Best supportive care was offered to 2 patients that suffered severe performance status deterioration (ECOG 3 and 4) throughout the course of diagnosis and staging.

Due to the small sample size, a logistic regression model could not be built to ascertain factors associated with the feasibility of EBUS-TBNA for MC. Nevertheless, the 4 cases whose samples were insufficient belonged mainly to the puncture of a single (in 3 cases) or dual (in 1 case) lymph node stations with a median of 4 needle passes per lymph node station (range: 3-8).

This study unveils a clear underutilization of EBUS-TBNA (5.3%) for the MC of NSCLC. Various reasons may account for this. First, NSCLC staging was determinant, since only candidates for systemic therapy (stages III or IV) were referred for MC. Secondly, there was preferential utilization of other biological samples that were perhaps considered more cell enriched, such as surgical or CT-guided biopsies. An intriguing finding of the study was the option for peripheral blood sampling, in 4 cases. The wider accessibility of peripheral blood samples may offer an explanation, but it is still surprising that this material was preferred over EBUS-TBNA samples.

As previously reported,[6,7] EBUS-TBNA was feasible for MC in most cases (89.5% for *EGFR* and 81.3% for *ALK*). Also, in agreement with previous reports,[6,7] *EGFR* analysis outperformed *ALK*. The sequential method applied in this study may offer an explanation. Samples were sequentially used for HC, *EGFR* testing, and only afterwards released for *ALK* testing, which means that only largely cellular samples could suffice all processes.

Two patient groups were identified based on the timeframe of MC. The >30 group mainly included patients with less advanced disease stages who probably undergone multimodal therapeutic strategies in which systemic therapy was likely delayed. In contrast, the ≤30 group included patients with metastatic disease in which systemic therapies came first and hence the prompter need for an up-front MC.

Our study showed a relatively low prevalence of mutations (Table 1). We observed 18% of mutated adenocarcinomas (*EGFR* mutations, in 13%; and *ALK* rearrangements, in 5%), and there was only 1 case of *EGFR*-mutated SCC (3%), as was there 1 case of *EGFR*-mutated mixed SCC and adenocarcinoma (3%), which agrees with publications reflecting Western populations.[8,9]

When assessing factors that could influence the feasibility of molecular profiling EBUS-TBNA samples, we could not safely establish statistically significant relationships. Nevertheless, we observed a trend toward lower yields in patients with a smaller number of lymph nodes approached despite a seemingly higher number of needle passes in these cases. This perhaps reflects the clinical perception of a lower probability of achieving a complete diagnosis in cases when just one lymph node station was approached.

In conclusion, our study highlights the value EBUS-TBNA on obtaining sufficient samples for MC of NSCLC. Nevertheless, questions are raised about sequential approaches and the time required for molecular results, for which additional studies, namely addressing the added value of multiplex simultaneous analysis, are still warranted.[6,10]

AUTHOR CONTRIBUTIONS

LVR, RC, LTB, and VS conceptualized and designed the study. LVR recruited patients and performed the EBUS-TBNA procedures. VS was responsible for histopathological analysis. MV was responsible for molecular analysis. RC and LTB provided input regarding statistical analysis. LVR and LTB were responsible for data collection, major statistical analysis, and main manuscript structure. All authors revised and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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Tracheobronchial amyloidosis and multiple myeloma

Luciana Volpon Soares Souza[1], Arthur Soares Souza Jr[1,2], Edson Marchiori[3]

An 86-year-old man was admitted with cough and weight loss. He reported episodes of mild hemoptysis and denied fever or other symptoms. He was a smoker (40 pack-years) with a previous history of multiple myeloma. Physical examination demonstrated wheezing. Laboratory test results were unremarkable. Chest CT revealed tracheal and bronchial wall thickening, and lytic lesions on the ribs and vertebral bodies with partial collapse (Figure 1).

The patient was referred for fiberoptic bronchoscopy with BAL. Bronchoscopy showed tracheal and bronchial wall thickening, with swelling and hypertrophy of a brittle, and easily bleeding mucosa, as well as submucosal plaques. BAL fluid was negative for neoplastic cells, bacteria, and fungi. Biopsy of the tracheal walls revealed a stroma occupied by an amorphous eosinophilic material that was positive on Congo red staining and exhibited apple-green birefringence under polarized light, consistent with amyloidosis.

Multiple myeloma and amyloidosis are characterized by abnormal accumulation and deposition of monoclonal plasma cells and extracellular protein fibrils. Multiple myeloma is often complicated with amyloidosis.[1] In the thoracic compartment, amyloidosis typically affects the heart, but it can also involve the pulmonary parenchyma, tracheobronchial tree, and other sites. Pulmonary involvement is rare, and amyloidosis is reported as tracheobronchial, diffuse/alveolar-septal, or nodular.[2]

AUTHOR CONTRIBUTIONS

All author equally contributed to this manuscript.

CONFLICTS OF INTEREST

None declared.

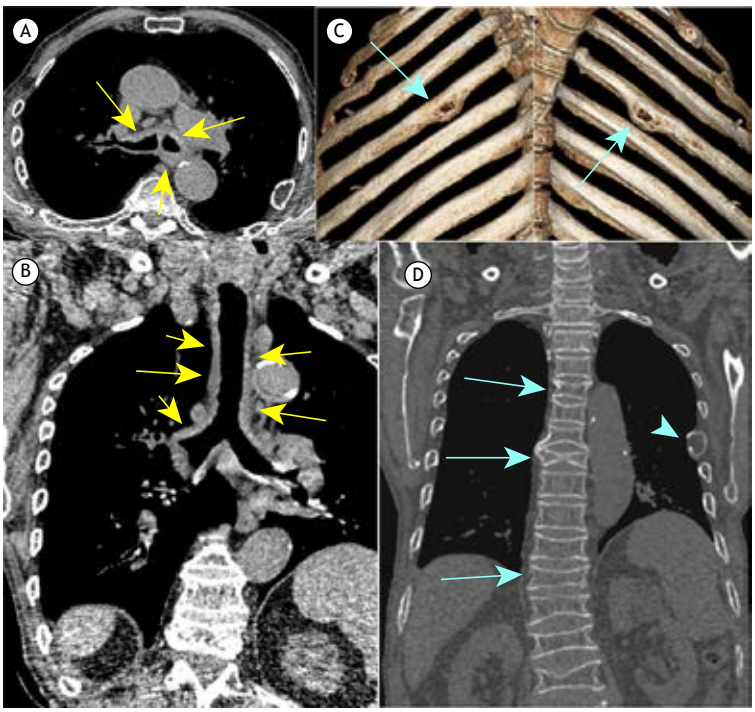

Figure 1. Axial CT of the chest (mediastinal window) at the level of the proximal segment of the bronchial bifurcation (in A) and a coronal reconstruction scan (in B) showing thickening of the tracheal wall and main bronchi (yellow arrows). In C, three-dimensional reconstruction of the chest wall demonstrating bilateral lytic lesions on the ribs (blue arrows). In D, coronal reconstruction showing partial collapse of multiple vertebral bodies (green arrows) and a lytic lesion on a left rib (arrowhead).

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Challenges in the treatment of cystic fibrosis in the era of CFTR modulators

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The paper entitled "Use of elexacaftor+tezacaftor+ivacaftor in individuals with cystic fibrosis and at least one F508del allele: a systematic review and meta-analysis," published in the Brazilian Journal of Pulmonology, highlighted the effects of triple combination therapy targeting the cystic fibrosis transmembrane conductance regulator (CFTR) protein—elexacaftor+tezacaftor+ivacaftor (ETI). However, we believe that it is important to emphasize some challenges emerging regarding the maintenance of symptom treatment for the disease.

The maintenance of airway clearance techniques (ACTs) after the use of ETI is a challenge for professionals, families, and individuals with cystic fibrosis (CF). In addition to improving lung function and quality of life, as well as reducing the number of exacerbations, patients report a decrease in lung secretions with this therapy, leading to anxiety about the reduction of inhaled therapies (ITs) and ACTs.[1,2]

To date, no literature data supports the long-term reduction of ITs and ACTs. A randomized clinical trial with adults using ETI evaluated the suspension of ITs with hypertonic saline solution (SSH) or dornase alfa for six weeks. The authors observed non-inferiority in lung function with the suspension of one of the nebulization during the study follow-up. However, the group that suspended one of the ITs (SSH or dornase alfa) experienced a higher number of adverse effects when compared with the group maintaining ITs.[3]

A study conducted in the United Kingdom demonstrated that ITs and ACTs are considered the most demanding parts of the treatment. Professional guidance to patients who experienced a reduction in respiratory symptoms was to reduce routines but never to suspend them. Even with the increased flexibility and individualization of routines, the assisting team is often resistant to changes in treatment routines due to the fear that patients will not implement them again in case of an exacerbation.[2]

It is important to note that, in both studies, the included population had preserved lung function, not being representative of most of the Brazilian population with CF. These findings still hinder the extrapolation of these data to our referral centers in terms of reducing ITs and ACTs in the long term.[2,3]

Physical exercise has become increasingly important in the daily lives of patients, representing a significant area of intervention for physiotherapists and physical education professionals. With the reduction of ACT routines, the encouragement of routine exercise, both aerobic and anaerobic, is important for maintaining physical conditioning and preventing excessive weight gain, which may become a reality for patients using ETI.

For the first time, patients are optimistic about their future due to a reduction in symptoms and the possibility of reducing the burden imposed by treatment. It is up to the teams to customize the treatment carefully for each patient according to their new reality. The positive effects of reducing ITs and ACTs are associated with improvements in well-being, mental health, and social life. However, their effects on long-term lung function are yet to be described. It is necessary to act with caution and rigorously monitor routine changes until more evidence can guide future treatment guidelines for patients undergoing ETI.

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Authors' reply

Luiz Vicente Ribeiro Ferreira da Silva Filho[1], Rodrigo Abensur Athanazio[2], Carolina Rodrigues Tonon[3], Juliana Carvalho Ferreira[2], Suzana Erico Tanni[3]

We received the correspondence entitled "Challenges in the treatment of cystic fibrosis in the era of CFTR modulators" and would like to thank the authors for bringing up such an important issue. As more evidence accumulates, CFTR modulators such as elexacaftor-tezacaftor-ivacaftor (ETI) stand for as a revolutionary therapeutic option for people with cystic fibrosis (CF). The magnitude of improvement in many key health outcomes of the disease is quite impressive[1] and will certainly transform the scenario of CF care in the next few years.

We do agree with the authors of the correspondence that many uncertainties about standard CF care will emerge, including management of respiratory infections, use of mucolytics, and airway clearance therapies (ACTs). As stated in the correspondence, nebulized therapies and ACTs are indeed responsible for most of the treatment burden in CF, and towards that, the SIMPLIFY study[2] aimed to investigate the safety of withdrawing hypertonic saline or dornase alfa use in people with CF treated with ETI. Although the study confirmed the non-inferiority outcome, it enrolled patients with well-maintained lung function and assessed the impact on lung function over a relatively brief period of six weeks.[2]. A recently published data from the SIMPLIFY substudy, however, focusing on individuals with CF and impaired lung function, demonstrated comparable results after discontinuation of hypertonic saline among those with FEV_1 levels ranging from 40% to 69%.[3] Consequently, we acknowledge that CF healthcare providers, while potentially making such decisions, should remain aware of associated risks and ensure vigilant and thorough monitoring of individuals when implementing these practices.

While we also believe that ACTs represent one of the main-stem aspects of CF care, a revision of the role of each professional composing the multidisciplinary team involved in CF care is anticipated. Doctors themselves should be observant to changes in life expectancy and possible complications related to aging. Psychologists should focus on behavior adjustments in the face of a new lifestyle and life expectancy. Physiotherapists may need to focus on muscular conditioning and rehabilitation of individuals who may have spent most of their lives with severe physical limitations.

Finally, we believe that we are witnessing a very exciting new era in CF. This is a much more optimistic scenario, although there is still plenty of uncertainties that must be adequately evaluated and investigated in the coming years in order to provide the best treatment options for individuals with CF.

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Homepages/URLs

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

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

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