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HIGHLIGHT

Croup review: comparative analysis of acute and recurrent croup

CPAP delivered via a helmet interface in lightly sedated patients with moderate to severe ARDS: predictors of success outside the ICU

Recommendations for the diagnosis and treatment of alpha-1 antitrypsin deficiency

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

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

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

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

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

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

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

COVIS PHARMA

Material exclusivo de uso do representante comercial
para promoção junto a profissionais de saúde habilitados
a prescrever e/ou dispensar medicamentos.
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ELMO-CPAP: an effective approach in the management of patients with acute hypoxemic respiratory failure

Erich Vidal Carvalho[1,2], Lídia Maria Carneiro da Fonseca[1,2,3], Bruno Valle Pinheiro[1,2,3]

The benefits of non-invasive ventilation (NIV) are well established in the treatment of exacerbations of COPD and cardiogenic acute pulmonary edema, conditions in which the application of NIV can reduce rates of endotracheal intubation and mortality.[1] However, in cases of acute hypoxemic respiratory failure (AHRF), particularly in ARDS, the use of NIV remains a subject of controversy. The European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines for NIV in acute respiratory failure, for instance, do not provide a recommendation regarding the use of NIV in AHRF, citing the uncertainty of the evidence.[2] A similar position is found in the guidelines from the European Society of Intensive Care Medicine on ARDS, although, in that document, the authors suggest the use of CPAP over conventional oxygen therapy in patients with AHRF due to COVID-19.[3]

Several concerns have been raised regarding the use of NIV in AHRF. The primary concern relates to delays in the decision to proceed with endotracheal intubation, which is associated with an increased risk of mortality.[4] Another concern involves the administration of high tidal volumes, particularly when two levels of positive pressure are employed, as this may increase the inflammatory lung injury and worsen prognosis.[5] Additionally, many patients do not tolerate, for prolonged periods, higher levels of positive pressure, which are theoretically desired in cases of moderate to severe hypoxemia, thereby limiting the benefits of NIV.[2,3]

The application of NIV via a helmet interface may overcome some of these limitations. The helmet interface enhances patient tolerance to elevated PEEP levels and allows prolonged application of NIV, which improves oxygenation. Furthermore, higher PEEP levels increase functional residual capacity and reduce ventilatory inhomogeneity, which might prevent the occurrence of ventilator-induced lung injury (VILI).[6] In a randomized clinical trial, Grieco et al. demonstrated that patients with moderate to severe AHRF due to COVID-19 who received NIV through a helmet interface presented lower rates of tracheal intubation, compared with those who received high-flow nasal oxygen.[7] In a previous randomized clinical trial, Patel et al. compared NIV delivered by a helmet with NIV delivered by face mask in patients with non-COVID-19 ARDS. They found that patients who received NIV through the helmet interface presented lower intubation rates (18.2% vs. 61.5% in the face mask group), and lower mortality at 90 days (34.1% vs. 56.4% in the face mask group).[8]

The results of these two studies are in line with those of a network meta-analysis[9] that evaluated randomized clinical trials including patients with AHRF and compared the following treatments: high-flow nasal oxygen, face mask NIV, helmet NIV, or standard oxygen therapy. That meta-analysis found that helmet NIV was associated with a lower risk of endotracheal intubation when compared with standard oxygen therapy, high-flow nasal oxygen, and face mask NIV. Additionally, helmet NIV was also associated with a lower risk of mortality compared with the other three treatments.[9]

In this issue of the *Jornal Brasileiro de Pneumologia*, Matos et al. present their experience with the application of CPAP in patients with AHRF due to COVID-19 through a new helmet interface, known as ELMO, in a retrospective cohort study.[10] The ELMO interface was developed in the of state of Ceará, Brazil, during the COVID-19 pandemic and allows the application of CPAP levels ranging from 6 to 15 cmH_2O, with a FIo_2 of up to 1. Positive pressure is generated by two compressed air flow meters and a PEEP valve adjusted to an air outlet, allowing the application of CPAP without the need for a ventilator. The lack of necessity for a ventilator constituted a significant advantage during the pandemic, when the number of mechanical ventilation devices available was insufficient. Furthermore, the ELMO-CPAP system facilitates the application of NIV outside the ICU.

The results obtained by Matos et al.[10] were consistent with the existing literature. The endotracheal intubation rate among the 180 patients who received ELMO-CPAP was 27.2%, and the in-hospital mortality rate was 18.9%. Among the nonintubated patients (n = 131), the mortality rate was 3.1%, while it was 61.2% among the intubated patients (n = 49). The high mortality rate among patients who are intubated following failure of NIV continues to be a challenge in the management of AHRF and highlights the need to avoid delays in endotracheal intubation. In this context, recognizing patients at a higher risk of failure is essential. The authors identified several factors associated with a higher risk of failure, including those related to greater severity (advanced age and pulmonary involvement on chest CT greater than 75%) and those related to the response to ELMO-CPAP application (ROX index after two hours of NIV and duration of the first NIV session < 24 h). These findings highlight the importance of closely monitoring

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patients undergoing NIV and providing appropriate ventilatory support for extended durations, conditions that require a trained and experienced team.

Another important finding in the study by Matos et al.[10] was the good tolerance of patients to ELMO-CPAP, which allowed for the application of NIV for prolonged periods, with a median duration of 39 h during the first session (IQR = 24-48 h). This tolerance to ELMO-CPAP, also described in other studies employing a helmet interface for NIV application, may have been facilitated by the judicious use of sedation by the team. The management of sedation also requires training and expertise to ensure that it does not compromise clinical assessment and early identification of failure in noninvasive ventilatory support.

In conclusion, the findings of this retrospective cohort study, consistent with recent literature, confirm that the appropriate application of NIV with a helmet interface is an effective approach in the management of patients with AHRF.

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Is asthma mortality decreasing or increasing in Brazil? The burden of proof

Marcia M M Pizzichini[1], Álvaro A Cruz[2,3], Emilio Pizzichini[1]

Asthma affects over 350 million people globally and is the most common chronic respiratory disease in children and young adults, although it affects people of all ages and it is an important cause of premature death. Also, it poses a significant public health challenge across and within different countries, with prevalence rates varying widely, but with a trend toward a decrease in its prevalence and mortality in several countries.[1] Therefore, it is important to monitor both the similarities and differences in asthma indicators across Brazil, a country characterized by significant social inequalities on top of regional economic and educational disparities.

Although asthma-related deaths are rare, they are unacceptable, as the disease is easily treatable for most patients and these fatalities are largely preventable. Most asthma-related deaths occur in low- and middle-income countries, or low-resource settings, highlighting a critical need to enhance our understanding of the risk factors, including issues about access to proper health care and management of various asthma phenotypes and endotypes.[1] Furthermore, improving the assessment of asthma's causes and treatments in less economically developed regions of the globe could lead to a deeper understanding of how equity in treatment access impacts on asthma control and remission.

A major disproportion between asthma prevalence, mortality, and morbidity still exists in many countries and must be addressed. For example, according to the publication "Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990–2019: A Systematic Analysis," released in 2020,[2] asthma ranked 24th among noncommunicable diseases in terms of disability-adjusted life years (DALY) for individuals aged 0-9 in 1990, moving to 19th in 2019. For the age groups 10-24, 50-74, and ≥ 75 years, there were notable changes: rankings shifted from 23rd to 27th, 15th to 28th, and 18th to 24th, respectively. Despite the noticeable improvement in asthma-related DALYs in the ages over 9 years, the burden of the disease remains significant.

Recently, two significant observational studies analysing trends in asthma mortality in Brazil were published in the JBP,[3,4] both authored by experts in the field. Yet they arrived at different conclusions. Pinheiro et al.[3] employed secondary data from the Information Technology Department of the Brazilian Unified Health Care System to estimate proportional hospitalization and in-hospital death rates per 100,000 population. Their analysis covered the years 2008 to 2021 and revealed that Brazil experienced over 8,000 deaths and more than 1.7 million hospitalizations due to asthma during this period. Particularly, both the number of deaths and hospitalizations significantly declined over the study years. On average, this corresponded to approximately one death per day and over 55,000 hospitalizations annually, with a mean length of hospital stay of three days.

Brum et al.[4], in a separate retrospective observational study, sourced their data on asthma mortality from the *Sistema de Informações sobre Mortalidade do Ministério da Saúde do Brasil* (SIM, Brazilian National Ministry of Health Mortality Database) covering the period from 2014 to 2021. This database is accessible at https://opendatasus.saude.gov.br/. The study population comprised all asthma-related deaths (ICD-10 codes J45 and J46) among individuals over 6 years of age.

During the study period, Brum et al.[4] reported a total of 18,854 asthma-related deaths in Brazil, with an annual increase of 2.6%, equating to 0.04 additional deaths per 100,000 population (95% CI, 0.02-0.06; $p < 0.01$). The northeastern region exhibited the highest prevalence of asthma deaths, at 1.60 deaths per 100,000 population, while the southern region experienced the greatest increase over the study period (37%). A higher proportion of deaths occurred among females and elderly patients. Notably, when analysing the location of these asthma-related deaths, it was found that 28% occurred at home. The authors also indicated that asthma death rates increased progressively over the years, with the highest peak occurring in 2020.

At first glance, the apparent contradictions between the two studies may be attributed to their data sources of secondary data: Pinheiro et al.[3] examined intra-hospital asthma deaths, while Brum et al.[4] analysed all death certificates in which asthma was the primary cause of death. Both forms of data registration may have inaccuracies that could not be prevented and impact the results of the studies. However, one could argue that these studies are not directly comparable due to the differing sources of data utilized in each.

Likewise, data source may not be the only explanation, as the significant disparity in reported asthma death rates—approximately one death per day in the first study[3] compared with six deaths per day in the second—suggests that additional contributing factors might be involved. Besides, it is important to emphasize that, in both studies, the authors thoroughly discussed their findings, along with the strengths and limitations that could have influenced the results.

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One notable aspect of the study by Pinheiro et al.[2] is the significant decline in hospital admissions—73% over the years—excluding the COVID-19 pandemic years. This decline has occurred progressively since the introduction of asthma medication at no cost in the Brazilian public health care system in 2008.[5] Consequently, the extent of this reduction in hospital admissions suggests that the corresponding decrease in hospital deaths due to asthma may primarily be associated with improved asthma management and a reduction in hospitalizations.

On the other hand, the study by Brum et al.[4] indicated that asthma death rates increased progressively over the years, reaching their highest peak in 2020, coinciding with the onset of the COVID-19 pandemic. The authors note that, despite excluding deaths directly related to COVID-19, the restricted access to health care during the pandemic may have influenced this particular peak.

Another factor that may have influenced the results of the study by Brum et al.[4] is that approximately one-third of the asthma-related deaths occurred at home, where determining the true primary cause of death may be complicated by potential over- or underdiagnosis of asthma. As the authors noted, it is essential to develop better public health care strategies to prevent such unacceptable outcomes. Additionally, the higher mortality rates among the elderly must be considered, as existing comorbidities can significantly impact asthma control and/or may contribute significantly to the deaths.

In summary, JBP published two distinct observational studies that reached different conclusions. These discrepancies may be attributed to the varying study source of information, and samples and should be confirmed by future research. It is important to highlight that, despite the significant decline in in-hospital asthma death rates, the overall rates of asthma-related deaths might be increasing, underscoring the need for improved public policies, as it suggests poor perception and possible negligence in handling emergencies in asthma at home.[6]

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Understanding the link between interstitial lung disease and obstructive sleep apnea: is lung volume involved?

Pedro Rodrigues Genta[1], Paulo Mateus Madureira Soares Mariano[1]

Obstructive sleep apnea (OSA) is associated with unfavorable cardiovascular, metabolic, and neurocognitive outcomes, resulting in significant deterioration in quality of life and increased mortality.[1] The coexistence of interstitial lung disease (ILD) and OSA represents an additional, potentially harmful combination.[2-4] Previous small studies assessed OSA in patients with idiopathic pulmonary fibrosis (IPF).[5-7] In this issue of the JBP, Cardoso et al. investigated the association between non-IPF ILD and OSA.[8] The relevance of the study and the contribution of the authors are emphasized, given the scarcity of data on this comorbidity. In addition, the authors provide additional evidence of the effect of CPAP in patients with both OSA and ILD.

In agreement with previous studies, the results by Cardoso et al.[8] highlight the limitations of anthropometric and demographic analyses and sleep questionnaires in the accurate identification of OSA in patients with ILD.[6,8-10] A high OSA prevalence (76%) was reported,[8] which is similar to the prevalence reported in a recent meta-analysis.[11] The similar prevalence of OSA in the study by Cardoso et al.[8] and in previous studies that mainly included patients with IPF suggests that the pathogenesis of OSA among both groups of patients is similar. Patients with OSA had significantly lower total lung capacity (TLC), suggesting TLC as a predictor of OSA risk.[8] A TLC < 80% of predicted was associated with an 82% probability of OSA.[8] Reduced lung volume may partially explain the high prevalence of OSA.[12-15] A lower lung volume may increase upper airway collapsibility due to reduced tracheal traction.[12-14] The high prevalence of OSA is also potentially attributable to the patients' age, as increasing age is an important risk factor for OSA.[16] Future studies that compare the prevalence of OSA among ILD patients and a control group consisting of patients without ILD of similar age, gender, and BMI are necessary to determine if ILD is associated with increased OSA prevalence.

Previous studies suggested that OSA is associated with clinical deterioration and reduced survival.[2-4] The majority of OSA patients in the study by Cardoso et al.[8] were not previously recognized. Underecognition of OSA precludes treatment and potentially leads to impaired quality of life and poorer prognosis. In the study by Cardoso et al., 12 patients underwent CPAP treatment.[8] After three months, 91% demonstrated effective control of OSA, with improvement in daytime sleepiness and a tendency to improve emotional well-being.[8] A previous observational study that included 55 subjects suggested that CPAP treatment improved survival.[3] However, a randomized controlled trial to test the benefit of CPAP among patients with ILD and OSA is necessary before active screening and treatment of OSA are recommended.

In addition to the lack of a control group and the observational nature of the study, the authors acknowledged some additional limitations of their study. The sample was relatively small and came from a single center, which restricts the overall applicability of the results and their representativeness in different clinical settings. In addition, adherence to PAP therapy was under optimal (66%). Low adherence to CPAP is a common feature in previous studies and may compromise the potential long-term benefits of the treatment.[17] The heterogeneity of the lung disease across patients may also influence the results, due to variations in the evolution and response to treatment between the different fibrotic conditions.

The findings of the study conducted by Cardoso et al.[8] may influence medical practice. They emphasize the need for further investigation of sleep disorders in patients with ILD. These patients may benefit from early screening, especially when associated with reduced TLC. The study also demonstrates that PAP treatment in patients with ILD may improve quality of life. Controlled trials are necessary to determine the impact of OSA treatment among patients with ILD.

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Pulmonary laceration

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

A 38-year-old man with no comorbidities was admitted to the emergency room after a motorcycle accident, complaining of chest pain, cough, and hemoptysis. A CT scan of the chest showed ground-glass opacities in the left lung, interspersed with oval formations with air and fluid content, forming air-fluid levels (Figure 1). A diagnosis of pulmonary laceration was made. The patient was treated conservatively, with no complications.

Pulmonary laceration (traumatic pneumatocele or traumatic pulmonary pseudocyst) is an uncommon injury associated with chest trauma that occurs as a consequence of traumatic rupture of the lung parenchyma. Due to the elastic nature of lung tissue, lacerations occur secondary to rapid compression and decompression of the parenchyma, forming cavities that fill with air or blood. Pulmonary lacerations are more commonly seen in children and young adults because of the greater flexibility of the chest wall in these age groups.[1-4]

The most common CT finding is a round or oval cystic mass with or without an air-fluid level. The lesion is usually surrounded by ground-glass opacities or consolidations resulting from pulmonary contusion. In the first 48 to 72 hours after trauma, pulmonary lacerations may be obscured on imaging by the underlying contusion. Once the contusion resolves, lacerations become apparent. They may be single or multiple, uniloculated or multiloculated, and rarely appear bilaterally. Associated CT findings may include pneumothorax, hemopneumothorax, rib fracture, or pneumomediastinum. Pulmonary lacerations usually resolve within 3-5 weeks. Treatment is primarily supportive, as the clinical course is usually benign. Serial imaging studies are helpful in demonstrating the gradual reduction in lesion size. Spontaneous resolution is expected within weeks to months.[1-4]

The diagnosis of pulmonary laceration is based on a history of chest trauma and imaging findings. Patients may be asymptomatic or present with cough, chest pain, dyspnea, hypoxemia, and hemoptysis. Hemoptysis may persist for up to 2 weeks. Because lesions may persist for weeks after trauma, correct diagnosis is critical to avoid confusing these alterations with cavitated lung lesions of other etiologies (abscess, tuberculosis, fungal diseases, malignancies, and others).[1-4]

Slow resolution, sometimes combined with a lack of details of the medical history of the patient, can lead to unnecessary invasive procedures due to suspicion of neoplasia or other diseases in some cases.

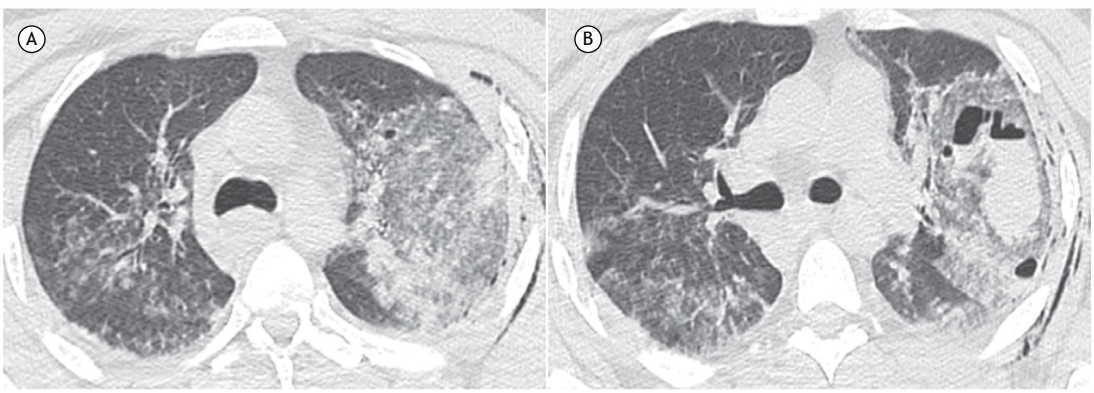

Figure 1. Axial CT scans with lung window settings showing extensive ground-glass opacities in the left lung (pulmonary contusion), interspersed with oval images with air and fluid content, forming air-fluid levels (pulmonary lacerations). Also note soft tissue emphysema and discrete ground-glass opacities on the right.

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How to become a productive academic writer?

Juliana C Ferreira[1,2], Cecilia M Patino[1,3]

PRACTICAL SCENARIO

As two clinical investigators and educators passionate about building research capacity in Latin America, we designed this scientific methodology short article series in 2015. Since then, more than fifty articles have been published in each issue of the Journal.[1] Many people have asked us how to keep this pace of writing bimonthly research articles over the years. While many factors contributed to it, the most important determinant for the success of this continued series has been discipline. We carefully planned the series, made a schedule, were very committed, and stuck to it.

WRITING IS HARD

Writing papers and publishing them is a core activity for clinician-scientists. However, as health professionals, we are trained to care for patients primarily and then conduct research if we choose an academic path. Writing skills are outside the top of the list of most training programs, and early investigators are expected to learn by doing. However, writing is hard, especially when you are a beginner. Consequently, many investigators procrastinate and feel guilty for not writing as much as they should. Procrastination can lead to frustration and impact career choices. Therefore, how do we prevent or overcome the barriers to writing manuscripts and becoming productive scientific writers? In his book: "How to write a lot,"[2] Paul J Silvia discusses barriers to becoming a productive academic writer and how to overcome these barriers.

BARRIERS TO WRITING

Among the barriers listed by Silvia, the most important one is the misconception that, in order to write a paper, the investigator must find a large block of time to sit and complete the paper almost all at once, known as binge writing. However, binge writing, as it turns out, is less productive than regular, paced, and scheduled writing. Finding time to write—on weekends, long nights, or during the holidays—does not usually work for the busy clinician-scientist. Instead, allocating periods of time to write in your weekly calendar, for example, 1-2 hours a day, just as you schedule meetings, is very useful. However, it is essential that you stick to the plan, respect that allotted time, and use the time exclusively for writing purposes, just as you allot time in your schedule to go to meetings and to teach your classes.

Other common barriers to avoiding writing include focusing on doing the research (collecting data), reading more papers about the subject matter, or running more data analysis. According to Silvia, the best strategy to overcome these barriers is formally alloting writing time into your schedule. Any activity necessary to complete a writing project can be done during that time.

Finally, a common misconception is that one must be inspired to write. This is a dangerous barrier because we do not control inspiration. However, we can control our schedules. So, instead of waiting for inspiration, like a poet, we suggest coming up with concrete writing goals and committing to writing by scheduling writing time on your calendar. Writing a manuscript can be broken down into small and doable tasks, and you can strategically schedule the most tedious ones for those slow Monday mornings when you are less inspired.

SETTING GOALS AND MONITORING PROGRESS

After you have allocated time in your schedule to write regularly, the next step is setting your writing goals. These goals are initially broad, such as writing a grant proposal, resubmitting a rejected paper, or starting to write a manuscript of a recently finished clinical study. Make a list of your research projects and set priorities from high to low. Projects with deadlines, such as sending a grant proposal for an open call or replying to reviewers on a paper that has not been rejected but needs revision, are typically high priority since missing the deadline has negative consequences. Then, make a detailed list of tasks for each project. For example, writing a grant proposal may include writing all the specific sections of the grant, updating your CV, and collecting letters of support from co-investigators. A list of small tasks that can be completed in one of your scheduled writing slots is shown in Chart 1.

Make sure you always have your list of writing projects and the specific tasks handy, possibly taped to your office wall, on an app on your phone, or as a digital document you frequently consult. Finally, monitor your progress by tracking your adherence to scheduled writing and

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Chart 1. Examples of writing tasks that can be completed during scheduled writing time:

Write 200 words within the data collection subheading of the Methods section
Draw Figure 1
Prepare a table with baseline characteristics of participants in the research study
Add references to the manuscript using a reference manager
Read the reviewers' comments and make a list of changes to be made to the paper
Check article proofs of an accepted manuscript
Prepare and submit the copyright agreement form for a manuscript you co-authored

completed tasks. Monitoring does not need to be complicated. Crossing out completed tasks on a task list or sticking post-its onto your computer screen is very rewarding and will help you monitor your pace and boost your confidence as you move towards completing projects.

Finally, Silvia suggests that writing with peers (team writing) can be very helpful. Team writing is a framework that promotes supporting and learning from each other, monitoring each other's progress, and, ideally, having fun writing together.

KEY MESSAGES

- Writing is part of your job as a researcher. Allocate time on your weekly schedule to write and stick to it. Avoid binge writing.
- Create a list of writing projects, prioritize, and break each project into small tasks that you can complete during your scheduled writing times.
- Do not wait for inspiration; writing scientific manuscripts requires discipline and regularity. Sit down on your scheduled writing time and complete a writing task. You can start now!

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The role of the pulmonary function laboratory in the management of hematologic diseases

José Alberto Neder[1], Denis E O'Donnell[1], Danilo C Berton[2]

BACKGROUND

Pulmonary complications can occur in 40-60% of patients with hematologic disorders. Although acute manifestations such as infection and hemorrhage are a major concern because of their life-threatening nature, chronic respiratory complications often also increase morbidity and mortality in such patients.[1] In this context, pulmonary function tests (PFTs) are vital for evaluating respiratory symptoms and for informing the management and follow-up of patients.

OVERVIEW

A 52-year-old male never-smoker (Case 1) presented with complaints of progressive dyspnea and dry cough 15 months after an allogeneic hematopoietic stem cell transplantation (HSCT) for acute myeloid leukemia. In relation to the preserved pre-HSCT values, FVC and FEV_1, expressed as percentages of the predicted value, had both decreased (to 63% and 49%, respectively). The new onset obstructive ventilatory defect (FEV_1/FVC ratio=0.60) indicated post-HSCT bronchiolitis obliterans. This diagnosis was supported by the presence of air trapping in plethysmography (RV, 147% of predicted) and expiratory HRCT scan. A 24-year-old female never-smoker with sickle cell disease (Case 2) presented with dyspnea (with a modified Medical Research Council scale score of 3) after recurrent episodes of acute chest syndrome (new segmental opacity on chest radiograph accompanied by fever, cough, and phlegm). Spirometry revealed a proportional reduction in FVC (to 69% of predicted) and FEV_1 (to 66% of predicted), together with a reduction in TLC (to 70% of predicted), indicative of a restrictive pattern. A mild reduction (to 70% of predicted) in DL_{CO} corrected for hemoglobin (9.6 mg/dL) and HRCT revealed chronic scarring of the lung parenchyma (pulmonary fibrosis) due to repeated episodes of acute chest syndrome with pulmonary infarction. Notably, echocardiography findings were unremarkable.

With improved management leading to a reduction in infection-related mortality, noninfectious complications are becoming increasingly common after HSCT.[2] Bronchiolitis obliterans syndrome (BOS) is a subtype of a broader category of chronic graft-versus-host disease (GVHD) involving the lungs that usually develops after the first 100 days and typically within the first 2 years after HSCT. Although BOS is characterized by the new onset of an obstructive ventilatory defect usually associated with dyspnea, cough, or wheezing, many patients are asymptomatic early in the disease process. Historically, biopsy-proven bronchiolitis obliterans was considered the only diagnostic pulmonary manifestation of chronic GVHD; that is, without the need for further testing or evidence of other organ involvement.[3] However, because of the risks of invasive lung biopsy, PFT findings can be used as "clinical" diagnostic criteria for BOS in the right clinical context.[4] Therefore, baseline and regular follow-up PFTs are recommended after HSCT (Chart 1). In sickle cell disease, chronic dyspnea is usually multifactorial. Common causes of such dyspnea include anemia, deconditioning, asthma, pulmonary hypertension, venous thromboembolism, and pulmonary fibrosis. Although the benefit of universal screening PFTs and echocardiography in asymptomatic individuals has yet to be determined, they should be performed in individuals with respiratory symptoms and other risk factors.[5]

CLINICAL MESSAGE

Several hematologic diseases and their treatments can chronically affect pulmonary function by causing direct damage to the lung tissue, impairing pulmonary immune responses, or affecting pulmonary vascular function. These are diverse, heterogeneous conditions that frequently course with respiratory symptoms and complications. The use of PFTs can shed light on the underlying mechanisms and guide the management of these conditions.

AUTHOR CONTRIBUTIONS

All of the authors contributed equally to this manuscript.

CONFLICTS OF INTEREST

None declared.

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Chart 1. Hematologic disorders and related treatments that can cause chronic respiratory manifestations, together with general recommendations for pulmonary function testing and the main findings indicative of each respiratory complication.

	General considerations	PFT recommendation	PFT findings
HSCT	• BOS is characterized by new-onset airflow limitation after allogeneic HSCT and is the pulmonary manifestation of chronic GVHD. • GVHD occurs when immune cells transplanted from a nonidentical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby initiating an immune reaction that causes disease in the recipient. • The confirmation of a diagnosis of BOS requires surgical lung biopsy, which is rarely performed in HSCT recipients. As a result, BOS is commonly diagnosed on the basis of the findings on PFT and chest imaging. • The magnitude of dyspnea and reduction in FEV_1 (% pred) are the parameters considered in the organ-specific score to grade the severity of pulmonary involvement in chronic GVHD.	• The current recommended work-up for BOS includes spirometry, and, in the presence of suggestive alterations, supporting features from plethysmography, expiratory CT, or both. • Screening spirometry is recommended pre-HSCT, at day 100 after transplantation, at diagnosis of chronic GVHD, at 1 year after transplantation, and at 6-month intervals for the first 2 years after the initial diagnosis of chronic GVHD. • More frequent PFT monitoring is recommended in patients diagnosed with BOS and in those with a significant decline in lung volumes but not yet meeting the criteria for BOS.	• In the presence of a distinctive* manifestation of GVHD in another organ or organs, a clinical diagnosis of BOS is sufficient to establish the diagnosis of chronic GVHD when all the following criteria are met: 1. FEV_1/FVC ratio < 0.70 or < 5th percentile of pred 2. FEV_1 post bronchodilator < 75% of pred with >10% decline in 2 years 3. Absence of infection in the respiratory tract 4. One of two supporting features**: a. evidence of air trapping on expiratory CT, small airway thickening, or bronchiectasis on HRCT b. evidence of air trapping by RV or RV/TLC ratio > 95th percentile of pred • Restrictive ventilatory defect is not characteristic of BOS but can reflect extra-pulmonary conditions like advanced sclerotic GVHD of the chest wall or intrapulmonary processes not related to GVHD, such as cryptogenic organizing pneumonia or pulmonary fibrosis.
Sickle Cell Disease	• Acute chest syndrome and PH are the most common causes of death. • The probable etiology of PH includes hemolysis, impaired nitric oxide bioavailability, chronic hypoxemia, thromboembolism, and parenchymal/vascular injury due to sequestration of sickle erythrocytes. • Venous thromboembolism and pulmonary arterial thrombosis are also increased secondary to a hypercoagulable state. • Pulmonary fibrosis is occasionally seen after recurrent episodes of acute chest syndrome with pulmonary infarction.	• There is variable practice related to routine PFT recommendation. • Some experts recommend against performing routine screening PFTs for asymptomatic children and adults. • However, diagnostic PFTs should be performed in the presence of any of the following: • respiratory symptoms • impaired exercise capacity • history of syncope or recurrent acute chest syndrome	The most common PFT abnormality is • restrictive ventilatory defect (↓TLC with or without accompanying ↓FEV_1 and ↓FVC with an FEV_1/FVC ratio > 0.70). Mechanisms of restrictive physiology could be ineffective inspiration due to chest wall discomfort, prior rib infarctions or vertebral disease. It could also be caused by pulmonary fibrosis related to more frequent episodes of acute chest syndrome. • Isolated ↓DL_{CO} (corrected for hemoglobin) can be a marker of early ILD or, more commonly, can be associated with PH.

Continue...▶

Chart 1. Hematologic disorders and related treatments that can cause chronic respiratory manifestations, together with general recommendations for pulmonary function testing and the main findings indicative of each respiratory complication. (Continued...)

	General considerations	PFT recommendation	PFT findings
Amyloidosis	Lung involvement is mainly caused by systemic AL amyloidosis due to deposition of protein derived from immunoglobulin light chain fragments. It is a potential complication of any plasma cell dyscrasia that produces monoclonal Ig light chains. • In the systemic form, Ig light chains are produced in the bone marrow and deposited in the lung interstitium, vasculature, lymph nodes, pleura, phrenic nerves, or diaphragm. • In the localized form, precursor amyloidogenic proteins are locally produced and most frequently deposited in lung parenchyma (nodules and cysts) and/or airways	• PFTs are usually performed to assess the presence, type, and severity of respiratory impairment. • PFTs are also often performed prior to lung biopsy to document baseline function.	• PFTs are generally not affected by the presence of limited amyloid nodules or cysts (localized amyloidosis). • Restrictive ventilatory defect (↓TLC) associated with ↓DL_{CO} and exertional desaturation is typical of amyloidosis ILD. • ↓TLC with preserved DL_{CO} (and especially K_{CO}) is indicative of diaphragmatic/phrenic dysfunction. • Patients with mild airway narrowing usually present normal PFT results. However, severe airway wall thickening can induce airflow obstruction and air trapping. Of note, blunted inspiratory and expiratory limbs of the flow volume loop might be the only abnormal spirometric finding.
Histiocytosis	• Pulmonary Langerhans cell histiocytosis (PLCH) is an uncommon tobacco-related cystic ILD caused by a disorder of myeloid dendritic cells.	• Same as mentioned above for amyloidosis	• In general, spirometry and plethysmography results are preserved. • Nevertheless, obstructive and restrictive ventilatory defects can be observed in some patients. • DL_{CO} is usually reduced disproportionately in relation to the changes in lung volume.
Leukemias & Lymphomas	• Although classic Hodgkin lymphoma accounts for ≈10% of all lymphomas, more than 75% of treated patients experience long-term survival at risk for pulmonary complications: pulmonary fibrosis, bronchiectasis, chronic pleural effusions, and recurrent pneumonia. Factors that contribute to lung injury include bleomycin use, radiation therapy, and smoking. • Patients with myeloproliferative neoplasms and chronic myeloid leukemia have been shown to develop PH. Potential mechanisms include CTEPH, portal hypertension, extramedullary hematopoiesis, drug toxicity, and occlusion of the pulmonary capillary bed due to aberrant, excessive, or immature cells.	• There is a lack of data on the value of screening with PFTs following treatment for Hodgkin lymphoma. Baseline PFTs should be considered for patients who have undergone chest wall radiation with or without bleomycin treatment. Follow-up PFTs and imaging are recommended for those with chronic or progressive respiratory symptoms (dyspnea, fatigue, wheezing, or cough). • Unexplained respiratory symptoms in patients with myeloproliferative neoplasms require further evaluation, including chest imaging, echocardiography, PFTs, and testing for cardiac biomarkers such as NT-proBNP.	• Restrictive ventilatory defect (↓TLC) with ↓DL_{CO} is indicative of ILD. If DL_{CO} and K_{CO} are within normal limits, an extrapulmonary cause of restriction should be considered. • Isolated ↓DL_{CO} should raise the suspicion of PH. • An obstructive or mixed ventilatory defect is suggestive of bronchiectasis.

HSCT: hematopoietic stem cell transplantation; BOS: bronchiolitis obliterans syndrome; GVHD: graft-versus-host disease; PFT: pulmonary function testing; % pred: % of predicted; PH: pulmonary hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; NT-proBNP: N-terminal pro-brain natriuretic peptide; ILD: interstitial lung disease; and KCO: carbon monoxide transfer coefficient. *Manifestations that are not ordinarily found in acute GVHD but are not considered sufficient to establish an unequivocal diagnosis of chronic GVHD without further testing or evidence of additional organ involvement. **If a patient already has "definite" diagnostic signs and/or symptoms of chronic GVHD by organ involvement elsewhere, then these supporting features are unnecessary. If BOS is the only clinical manifestation in a patient without a prior diagnosis of chronic GVHD, a lung biopsy is required to establish the diagnosis of chronic GVHD.

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Croup review: comparative analysis of acute and recurrent croup

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Croup is a common respiratory illness of the larynx, trachea, and bronchi which is manifested by stridor and a barking cough. Laryngotracheitis and laryngotracheobronchitis have been included in the croup spectrum. It involves the narrowing of the laryngeal lumen and subglottic region, leading to airway inflammation and edema.[1] Croup is typically self-limited, occurring predominantly during the fall and winter. It is more common in boys than in girls (1.5:1 ratio). Croup affects approximately 3% of children between six months and six years of age.[1] However, it can occur in children up to six years of age, or even before six months.[2-4]

Most patients present with mild conditions (less than 5% requiring hospitalization), and, of these, less than 3% may require tracheal intubation. Parainfluenza virus (types 1 to 3) accounts for 75% of all cases, and human parainfluenza virus 1 is the most common type. Other viral etiologies include influenza A and B, adenovirus, respiratory syncytial virus, rhinovirus, enterovirus and SARS-CoV-2. Spasmodic croup is also caused by the same viruses, but lacks signs of infection. Bacterial causes are rare. *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* may be involved.[2,5,6]

Viral croup often presents similarly to an upper respiratory infection, with 12-72 h of low-grade fever and coryza. Narrowing of the larynx leads to stridor, increased respiratory rate, respiratory retractions, and a barking cough. Symptoms worsen at night and peak between 24 and 48 h. In most cases it improves spontaneously within 48 h to a week. Croup is a clinical diagnosis, and there is no need for additional tests to confirm it in most cases.[2,5]

In patients with recurrent croup (more than two episodes per year), bronchoscopic abnormalities may be associated with risk factors: previous intubation, prematurity, and young age. Gastroesophageal reflux disease, asthma, and atopy are also more prevalent in recurrent croup, but do not usually show abnormalities at bronchoscopy.[2] Chart 1 shows useful clinical manifestations for the differential diagnosis of obstructive diseases of the upper airway.[2,7]

Management of croup is based on the severity of illness. Clinical signs of level of consciousness, as well as presence of cyanosis, stridor, air entry, and retractions, have been used to structure severity scores. However, they are not mandatory in the clinical context. They can be useful when the team has less expertise and experience. More recently, the incorporation of the number of doses of racemic epinephrine in the emergency department (ED), previous administration of dexamethasone, and history of intubation have been used to improve the predictive accuracy of the need for hospitalization.[1,2,7]

The management of acute viral croup includes corticosteroids that may be administered orally, inhaled, or intramuscularly, considering different criteria as the severity of the condition. However, further studies are necessary to elucidate the potential dose-dependent effects of the medication and to evaluate the benefits of administering multiple doses to children assisted in the ED. Additionally, nebulized epinephrine can be prescribed as it is recommended for cases of moderate to severe upper airway obstruction, characterized specially by increased difficulty of breathing. The effects of mild viral croup are usually transient, and epinephrine does not provide sustained benefits in cases with mild symptoms.[2,5,7]

Historically, recurrent croup had been considered an anatomical issue related to airway abnormalities, prompting evaluations with laryngoscopy or bronchoscopy procedures under anesthesia. However, recently experts described that it resembles airway reactivity similar to asthma.[8] Previously, inhaled corticosteroids (ICS) were used for acute croup episodes because of suggested benefits as a preventative therapy. In a large cohort study,[5] it was hypothesized that prophylactic ICS could potentially decrease both the frequency and severity of recurrent croup episodes in patients with no fixed airway lesions. Another study[6] retrospectively reviewed charts of children referred to outpatient clinics for recurrent croup between June of 2019 and January of 2021. In that study, recurrent croup was defined as three or more episodes occurring within a lifetime.[6]

Among the patients who underwent imaging or diagnostic laryngoscopy/bronchoscopy, there were few airway abnormalities, and none required surgical intervention. Most patients treated with medical therapy used fluticasone propionate inhalers twice daily upon the onset of an upper respiratory infection. Nearly 90% of parents reported improvement in symptoms. There were no significant differences in past medical history or comorbidities between patients who improved on ICS and those who did not, and no reported adverse drug reactions. ICS treatment seemed to be particularly effective in patients with more than five episodes of croup.

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Chart 1. Clinical manifestations, differential diagnosis, and management recommendations of croup in children.

MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS		
Etiology	**Age range**	**CLINICAL MANIFESTATIONS**
Croup	6 months to 3 years	Acute onset of barking cough, stridor, and hoarseness
Bacterial tracheitis	< 6 years	High fever, barking cough, respiratory distress, and rapid deterioration
Congenital or acquired airway lesions	< 6 months to 4.5 years	Recurrent episodes of barking cough and stridor
Foreign body aspiration	< 3 years	Acute onset of choking and/or drooling
Hemangioma	< 6 months	Stridor worse with crying
Laryngomalacia	< 18-24 months	Stridor that worsens with crying and feeding. Symptoms related to position.
Neoplasm	No age predilection	Progressive airway symptoms
Retropharyngeal, parapharyngeal, peritonsillar abscesses	6 months to 35 years	High fever, neck pain, sore throat, and dysphagia followed by torticollis, drooling, and stridor
MANAGEMENT		
ACUTE MANAGEMENT	• Corticosteroids administered orally, inhaled, or intramuscularly • Nebulized epinephrine may be recommended for moderate to severe airway obstruction	
RECURRENT CROUP MANAGEMENT	• Endoscopic airway evaluation may help identification of underlying airway disorder • In the acute management of recurrent croup, patients may receive the standard treatment above • Inhaled steroids may be used to reduce recurrence	

In addition, some patients with gastroesophageal reflux disease or eosinophilic esophagitis also reported improvements with ICS therapy.[6] The initiation of ICS at the first sign of a viral upper respiratory infection in order to reduce episodes of recurrent croup is a relatively a novel preventative treatment. It is necessary to conduct randomized control trials to validate its effectiveness in the future.

CONCLUSION

Although croup is a condition that is often resolved on its own, it can be a difficult illness to deal with due to the need of regular doctor visits and usage of health care resources. Further research is needed, and it is likely that early intervention with oral or inhaled corticosteroids will still be the primary approach to croup management, given its importance in lowering mortality and morbidity.

AUTHOR CONTRIBUTIONS

SPCA, LGBB, JGK contributed to literature search and writing the first draft. SLA and LAP contributed to writing, reviewing, and editing.

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ORIGINAL ARTICLE

Obstructive sleep apnea in patients with fibrotic interstitial lung disease (non-idiopathic pulmonary fibrosis): what should be offered?

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Study carried out in the Departamento de Pneumologia, Unidade Local de Saúde de São João, Porto, Portugal.

ABSTRACT:

Objective: The frequency of obstructive sleep apnea (OSA) in patients with idiopathic pulmonary fibrosis (IPF) is high. The clinical course of non-IPF interstitial lung disease (ILD) can be similar to that of IPF. We sought to assess the frequency and predictors of OSA in patients with non-IPF fibrotic ILD, as well as the impact of positive airway pressure (PAP) therapy on the quality of life of such patients. **Methods:** This was a prospective study in which non-IPF fibrotic ILD patients underwent a home sleep apnea test. The patients with and without OSA were compared, and a multivariate logistic regression model was used to identify independent predictors of OSA. At 3 months after initiation of PAP therapy, we evaluated the participating patients for respiratory events, nocturnal hypoxemia, and changes in quality of life. **Results:** Of a total of 50 patients, 50% were male, and 76% were diagnosed with OSA. The mean age was 67.8 ± 8.3 years. The patients with OSA had significantly lower TLC (p = 0.033) and awake SpO_2 (p = 0.023) than did those without OSA. In the multivariate logistic regression model, SpO_2 (OR = 0.46; p = 0.016) and TLC (OR = 0.95; p = 0.026) remained significantly associated with OSA risk. A total of 12 patients received PAP therapy. At 3 months after initiation of PAP therapy, 91.7% were well controlled, Epworth Sleepiness Scale scores decreased significantly (p = 0.006), and emotional well-being tended to improve (p = 0.068). PAP therapy corrected nocturnal hypoxemia in all patients. **Conclusions:** We found a high frequency of OSA in patients with non-IPF fibrotic ILD. A low TLC was an independent predictor of a higher risk of OSA. PAP therapy can correct nocturnal hypoxemia. There should be a low threshold for suspicion of OSA and initiation of PAP therapy in patients with non-IPF fibrotic ILD.

Keywords: Sleep apnea, obstructive; Fibrosis, pulmonary; Total lung capacity; Hypoxia; Quality of life.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common and heterogeneous disease[1] caused by recurrent episodes of airway collapse during sleep.[2] A chronic condition, OSA is associated with intermittent hypoxia, intrathoracic pressure swings, arousals, sleep fragmentation, metabolic dysfunction, and cardiovascular morbidity.[2-4]

The incidence of interstitial lung disease (ILD) is increasing globally; ILD comprises a heterogeneous group of inflammatory and fibrotic conditions.[5,6] Numerous studies have shown a high (20-80%) frequency of OSA in patients with ILD,[7-9] especially those with idiopathic pulmonary fibrosis (IPF).[10-13] Pulmonary fibrosis can occur in association with many forms of ILD, including connective tissue disease-associated ILD, hypersensitivity pneumonitis, sarcoidosis, idiopathic nonspecific interstitial pneumonia, and unclassifiable ILD.[14] Non-IPF fibrotic ILD patients show a combination of inflammatory and self-sustained fibrotic processes, the clinical course of which can be similar to that of IPF, progressing with lung function decline and risk of early death, especially if a usual interstitial pneumonia (UIP) pattern is present.[14]

Although the relationship between OSA and ILD remains undetermined—as does the effect of coexisting OSA on the natural history of ILD—there appears to be a bidirectional relationship.[10,15] ILD can predispose to OSA, given that decreased lung volumes and compliance can reduce upper airway stability and induce traction that could facilitate collapse.[10,12] This is especially true during rapid eye movement sleep, when muscle atonia is more significant and, consequently, functional residual capacity is more severely impaired.[16]

Because OSA is associated with recurrent hypoxia, it promotes—much like lung fibrosis—oxidative stress,

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systemic inflammation, and tissue damage as a result of production of TGF-β, a profibrotic cytokine.[5,10] Hypoxia-inducible factor 1-alpha and Krebs von den Lungen-6, biomarkers linked with epithelial proliferation, as well as with lung injury and fibrosis, have also been shown to be increased in the lung tissue and blood, respectively, of OSA patients.[17-20] Additionally, oxygen desaturation during sleep can contribute to pulmonary arterial hypertension and poor outcomes in patients with ILD.[15]

The guidelines for the diagnosis and management of IPF recognize OSA as a common comorbidity,[21] which is associated with worse quality of sleep and worse quality of life, as well as with potentially worse outcomes.[8,22,23] OSA treatment with positive airway pressure (PAP) therapy is recommended, as it has been shown to improve sleep-related quality of life and potentially mortality.[8] Nevertheless, it can be more challenging to provide PAP therapy to ILD patients than it is to provide it to the general population.[24]

The objective of this prospective study was to assess the frequency and predictors of OSA in patients with non-IPF fibrotic ILD, as well as adherence to PAP therapy and its impact on the quality of life of such patients.

METHODS

This was a prospective study. The study was performed in the Pulmonology Department of the *Unidade Local de Saúde de São João*, located in the city of Porto, Portugal.

Patients

Consecutive patients ≥ 18 years of age diagnosed with non-IPF fibrotic ILD between 2020 and 2021 were eligible for enrollment. All diagnoses of non-IPF fibrotic ILD were established after discussion in a multidisciplinary meeting.

The exclusion criteria were as follows: previously diagnosed pulmonary arterial hypertension; daytime hypoxemia (a resting PaO_2 of < 60 mmHg on room air); and hospital admission for ILD exacerbation during the preceding 3 months. Other exclusion criteria included previously diagnosed OSA; sleep-related breathing disorders other than OSA; neuromuscular disease; therapy with PAP for other causes; loss to follow-up; refusal to participate in the study; and inability to provide written informed consent.

Intervention

Demographic data, clinical data, smoking history, comorbidities, and anthropometric measurements were assessed for all patients. The Epworth Sleepiness Scale (ESS) was used, and a score ≥ 11 defined subjective daytime sleepiness.[25]

All patients underwent pulmonary function tests, chest HRCT, and a home sleep apnea test (HSAT).

Spirometry, static lung volume measurements, and single-breath DL_{CO} measurements were performed with a MasterScreen Body-PFT device (Jaeger, Würzburg, Germany), with the patient in a seated position.

All chest HRCT images were independently evaluated by two thoracic radiologists. Each HRCT image was evaluated for a UIP pattern, in accordance with the most recent guidelines,[26] and the extent of fibrosis (< 10% or ≥ 10%).

The HSAT was performed with an ambulatory sleep recorder (Embletta® MPR PSG Sleep Study System; Natus Medical Incorporated, Middleton, WI, USA), including 6-channel monitoring and recording of the following: oronasal flow signals by nasal cannula; snoring; body position and respiratory effort by thoracic and abdominal bands; and oxygen saturation and pulse rate by pulse oximetry. All recordings were manually scored by experienced sleep technicians.

The apnea-hypopnea index (AHI) was determined as the total number of apnea and hypopnea events per hour of time recorded. Apnea and hypopnea events were categorized in accordance with American Academy of Sleep Medicine criteria.[27,28] OSA was considered mild if the AHI was ≥ 5 events/h and < 15 events/h, moderate if the AHI was ≥ 15 events/h and < 30 events/h, and severe if the AHI was ≥ 30 events/h.[27] The oxygen desaturation index (ODI) was determined as the total number of arterial oxygen desaturations ≥ 3% per hour of sleep.[27] Nocturnal hypoxemia was considered significant when the total sleep time spent below an SpO_2 of 90% (T90) was > 20%.[29]

Study assessments and treatment plan

Every patient diagnosed with OSA (an AHI ≥ 5 events/h) was given instructions for sleep hygiene, an active lifestyle, weight control, and avoidance of sedative drugs. PAP therapy was provided to all patients with severe OSA. Patients with mild or moderate OSA were given PAP therapy if they presented with daytime sleepiness, cardiovascular disease, or both. Positional therapy was recommended in cases of positional OSA.

The patients who underwent PAP therapy rated their perception of cough and dyspnea on a scale of 0 (minimum) to 10 (maximum) and filled out the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) prior to initiation of PAP therapy and at 3 months after initiation of PAP therapy. The SF-36 is a measure of health-related quality-of-life,[30] previously translated and validated for use in Portugal.[31,32] A higher SF-36 score translates to a more favorable health status.

At 3 months after initiation of PAP therapy, patients were assessed by a sleep physician for adherence to PAP therapy, daytime sleepiness (using the ESS), and PAP-related side effects. Information on the PAP device pressure, residual AHI, and leaks was obtained through telemonitoring or the memory card of the device. OSA patients with nocturnal hypoxemia at diagnosis underwent repeated nocturnal oximetry testing while receiving PAP therapy. Adherence was

considered adequate if patients used PAP at least 4 h a day and for ≥ 70% of nights.[33]

The study protocol was reviewed and approved by the local research ethics committee (Ruling no. 214/22), and the study was performed in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and continuous variables are presented as means and standard deviations or medians and interquartile ranges for variables with skewed distribution. Normality of distribution was tested by skewness and kurtosis. The chi-square test or Fisher's exact test was used in order to compare categorical variables.

The independent samples t-test and the Mann-Whitney U test were used in order to assess differences in continuous variables with normal and skewed distributions, respectively. Comparisons between identical quantitative variables with normal distribution were performed with the paired t-test, whereas comparisons between identical quantitative variables with skewed distribution were performed with the Wilcoxon signed-rank test.

Univariate and multivariate binary logistic regression analyses were performed to determine predictors of OSA in patients with non-IPF fibrotic ILD. Factors that were statistically significant in the univariate analysis and those that were considered relevant to the study were included in the multivariate analysis.

To understand the impact of the extent of lung fibrosis on nocturnal hypoxemia, a linear regression analysis was performed to determine whether DL_{CO} and carbon monoxide transfer coefficient (K_{CO}) were significantly associated with the ODI, T90, or mean nocturnal SpO_2. Values of $p < 0.05$ were considered significant.

Data were analyzed with the IBM SPSS Statistics software package, version 29.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Of a total of 122 patients diagnosed with non-IPF fibrotic ILD, 24 (19.7%) had a previous diagnosis of OSA; 23 (18.9%) had daytime hypoxemia and/or had recently experienced exacerbations of ILD; 16 (13.1%) were lost to follow-up; and 9 (7.4%) declined to participate in the study.

A total of 50 patients were included in the study. Of those, 50% were male (mean age, 67.8 ± 8.3 years), 60% were smokers or former smokers, and 52% were diagnosed with fibrotic hypersensitivity pneumonitis (Table 1). The diagnosis of OSA was confirmed in 38 patients (76%). Of those, 20 (52.6%) presented with mild OSA, 13 (34.2%) presented with moderate OSA, and 5 (13.2%) presented with severe OSA (Table 2). The patients with OSA had significantly lower TLC (84% vs. 98.3%; $p = 0.033$), had lower awake SpO_2 (96% vs. 98%; $p = 0.023$), and tended to have a higher FEV_1/FVC ratio (82.3 vs. 77.6; $p = 0.079$). No significant differences were observed between the groups of patients with and without OSA regarding demographic data, smoking history, comorbidities, BMI, ESS scores, DL_{CO} measurements, a UIP pattern on HRCT scans, or the extent of fibrosis on HRCT scans (Table 1).

Regarding HSAT results, there was a predominance of obstructive respiratory events, especially hypopneas (Table 1). The patients with OSA had a higher ODI (12.6 vs. 3.7; $p < 0.001$) and a lower minimum nocturnal SpO_2 (82.3% vs. 87.2%; $p < 0.001$; Table 1). Of the 38 patients with OSA, 8 had T90 > 20%, but the median T90 was not significantly different between the groups of patients with and without OSA ($p = 0.169$; Table 1).

In the univariate logistic regression model, a lower SpO_2 (OR = 0.56; $p = 0.031$) and a lower TLC (OR = 0.97; $p = 0.045$) were associated with a higher risk of OSA (Table 3). In the multivariate logistic regression model (adjusted for age, BMI, and extent of fibrosis), SpO_2 (OR = 0.46; $p = 0.016$) and TLC (OR = 0.95; $p = 0.026$) remained statistically significant (Table 3).

A TLC of ≤ 80% was associated with a predicted probability of OSA > 82% (Figure 1). The linear regression model showed that neither DL_{CO} nor K_{CO} were associated with the ODI, T90, or mean nocturnal SpO_2.

In comparison with the patients who had mild OSA, those who had moderate to severe OSA were significantly older ($p = 0.008$) and presented with a higher ODI ($p < 0.001$), a greater T90 ($p = 0.007$), and a lower minimum nocturnal SpO_2 ($p = 0.002$; Table 2).

Of the 38 patients with OSA, 14 were offered PAP therapy. Of those, 5 had severe OSA, 7 had moderate OSA, and 2 had mild OSA. Of the 14 patients, 11 were started on continuous/automatic PAP, 2 declined PAP therapy, and 1 switched to BiPAP because of intolerance to continuous PAP. Two patients with positional OSA were encouraged to use positional devices. Six patients had significant nocturnal hypoxemia. None required oxygen therapy.

At 3 months after initiation of PAP therapy, 8 patients (66.7%) showed adequate adherence, 11 patients (91.7%) presented with well-controlled OSA (a residual AHI of < 5 events/h), and 6 patients (50.0%) reported improvement in daytime sleepiness (Table 4). Of those with inadequate adherence, 4 had complaints such as dry mouth (n = 2), claustrophobia (n = 1), and nasal obstruction (n = 1), all of which were managed. Nocturnal hypoxemia was corrected in all patients (Table 4). Subjective daytime sleepiness decreased significantly ($p = 0.006$), and emotional well-being (as evaluated by the SF-36) showed a trend toward improvement ($p = 0.068$) at 3 months after initiation of PAP therapy (Table 4). Changes in patient

Table 1. Comparisons among all of the patients included in the study, those with obstructive sleep apnea, and those without obstructive sleep apnea.[a]

Variable	All patients (n = 50)	OSA (n = 38)	No OSA (n = 12)	p
Age, years	67.8 ± 8.3	67.8 ± 8.6	68.0 ± 7.4	0.932
Male	25 (50.0%)	21 (55.3%)	4 (33.3%)	0.321
Current or former smoker	30 (60.0%)	25 (65.8%)	5 (41.7%)	0.182
ESS score	3.0 (1.0-7.0)	3.0 (1.0-7.0)	3.5 (0.0-7.5)	0.837
BMI, kg/m^2	26.7 ± 4.1	27.2 ± 4.1	25.3 ± 4.0	0.164
ILD				
HP	26 (52.0%)	20 (52.6%)	6 (50.0%)	1.000
CTD-ILD	7 (14.0%)	6 (15.8%)	1 (8.3%)	1.000
Idiopathic NSIP	6 (12.0%)	6 (15.8%)	0 (0.0%)	0.314
PPFE	4 (8.0%)	1 (2.6%)	3 (25.0%)	0.038
Unclassifiable ILD	4 (8.0%)	3 (7.9%)	1 (8.3%)	1.000
Sarcoidosis	1 (2.0%)	1 (2.6%)	0 (0.0%)	1.000
Organizing pneumonia	1 (2.0%)	0 (0.0%)	1 (8.3%)	0.240
Desquamative interstitial pneumonia	1 (2.0%)	1 (2.6%)	0 (0.0%)	0.314
Comorbidities				
Diabetes mellitus	10 (20.0%)	9 (23.7%)	1 (8.3%)	0.416
Arterial hypertension	22 (44.0%)	17 (44.7%)	5 (41.7%)	1.000
Dyslipidemia	30 (60.0%)	22 (57.9%)	8 (66.7%)	0.740
Stroke	4 (8.0%)	3 (7.9%)	1 (8.3%)	1.000
Coronary artery disease	3 (6.0%)	3 (7.9%)	0 (0.0%)	1.000
Heart failure	2 (4.0%)	2 (5.3%)	0 (0.0%)	1.000
COPD	5 (10.0%)	4 (10.5%)	1 (8.3%)	1.000
Asthma	9 (18.0%)	7 (18.4%)	2 (16.7%)	1.000
Pulmonary function tests				
Awake SpO_2, %	97.0 (96.0-98.0)	96.0 (96.0-97.5)	98.0 (97.0-99.0)	0.023
FEV_1/FVC ratio, %	81.2 ± 8.1	82.3 ± 7.4	77.6 ± 9.3	0.079
FEV_1, %	92.2 ± 18.0	92.8 ± 17.8	90.5 ± 19.5	0.706
FVC, %	89.0 ± 17.4	88.9 ± 18.2	89.6 ± 15.4	0.900
TLC, %	87.5 ± 20.4	84.0 ± 19.8	98.3 ± 19.2	0.033
DL_{CO}, %	59.9 ± 16.2	59.0 ± 14.4	62.5 ± 21.4	0.515
K_{CO}, %	81.2 ± 20.1	82.3 ± 21.4	77.6 ± 15.4	0.483
HRCT pattern				
UIP	10 (20.0%)	6 (15.8%)	4 (33.3%)	0.225
Probable UIP	8 (16.0%)	8 (21.1%)	0 (0.0%)	0.173
Indeterminate for UIP	8 (16.0%)	8 (21.1%)	0 (0.0%)	0.173
Alternative diagnosis	24 (48.0%)	16 (42.1%)	8 (66.7%)	0.190
Extent of fibrosis > 10%	33 (66.0%)	26 (68.4%)	7 (58.3%)	0.728
HSAT results				
Snoring, %	6.4 (2.9-25.1)	6.7 (3.2-25.5)	5.7 (2.6-25.3)	0.474
AHI, events/h	7.7 (4.8-18.7)	14.3 (6.9-25.5)	3.4 (1.8-3.7)	< 0.001
Apnea index, events/h	1.3 (0.2-6.3)	2.0 (0.3-7.7)	0.5 (0.0-1.1)	0.006
Hypopnea index, events/h	6.8 (3.6-15.7)	9.3 (6.1-16.8)	2.2 (1.5-3.1)	< 0.001
Obstructive events, events/h	5.9 (2.6-14.3)	6.8 (4.9-17.0)	2.0 (1.2-2.7)	< 0.001
Central events, events/h	0.3 (0.0-2.1)	0.3 (0.0-2.6)	0.1 (0.0-0.8)	0.330
ODI	9.3 (5.5-21.8)	12.6 (8.2-26.0)	3.7 (2.8-5.0)	< 0.001
Mean nocturnal SpO_2, %	92.5 ± 2.1	92.3 ± 2.1	93.1 ± 2.1	0.267
Minimum nocturnal SpO_2, %	83.5 ± 5.7	82.3 ± 5.8	87.2 ± 2.9	< 0.001
T90, %	2.2 (0.2-12.9)	2.8 (0.3-17.2)	0.6 (0.0-9.5)	0.169
T90 scores > 20%	9 (18.0%)	8 (21.1%)	1 (8.3%)	0.425

OSA: obstructive sleep apnea; ESS: Epworth Sleepiness Scale; ILD: interstitial lung disease; HP: hypersensitivity pneumonitis; CTD-ILD: connective tissue disease-associated interstitial lung disease; NSIP: nonspecific interstitial pneumonia; PPFE: pleuroparenchymal fibroelastosis; K_{CO}: carbon monoxide transfer coefficient; UIP: usual interstitial pneumonia; HSAT: home sleep apnea test; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; and T90: total sleep time spent below an SpO_2 of 90%. [a]Values expressed as mean ± SD, n (%), or median (IQR).

Table 2. Comparisons among obstructive sleep apnea patients as a whole, those with mild disease, and those with moderate to severe disease.[a]

Variable	OSA (n = 38)	Mild OSA (n = 20)	Moderate to severe OSA (n = 18)*	p
Age, years	67.8 ± 8.6	64.4 ± 9.5	71.5 ± 5.9	0.008
Male	21 (55.3%)	9 (45.0%)	12 (66.7%)	0.210
Current or former smoker	25 (65.8%)	12 (60.0%)	13 (72.2%)	0.506
ESS score	3.0 (1.0-7.0)	2.5 (1.0-7.0)	3.0 (1.8-6.3)	0.508
BMI, kg/m^2	27.2 ± 4.1	26.4 ± 4.7	28.0 ± 3.2	0.248
ILD				
HP	20 (52.6%)	8 (40.0%)	12 (66.7%)	0.119
CTD-ILD	6 (15.8%)	3 (15.0%)	3 (16.7%)	1.000
Idiopathic NSIP	6 (15.8%)	5 (25.0%)	1 (5.6%)	0.184
PPFE	1 (2.6%)	1 (5.0%)	0 (0.0%)	1.000
Unclassifiable ILD	3 (7.9%)	1 (5.0%)	2 (11.1%)	0.595
Organizing pneumonia	1 (2.6%)	1 (5.0%)	0 (0.0%)	1.000
Desquamative interstitial pneumonia	1 (2.6%)	1 (5.0%)	0 (0.0%)	1.000
Comorbidities				
Diabetes mellitus	9 (23.7%)	5 (25.0%)	4 (22.2%)	1.000
Arterial hypertension	17 (44.7%)	7 (35.0%)	10 (55.6%)	0.328
Dyslipidemia	22 (57.9%)	11 (55.0%)	11 (61.1%)	0.752
Stroke	3 (7.9%)	0 (0.0%)	3 (16.7%)	0.097
Coronary artery disease	3 (7.9%)	1 (5.0%)	2 (11.1%)	0.595
Heart failure	2 (5.3%)	1 (5.0%)	1 (5.6%)	1.000
COPD	4 (10.5%)	3 (15.0%)	1 (5.6%)	0.606
Asthma	7 (18.4%)	4 (20.0%)	1 (5.6%)	1.000
Pulmonary function tests				
Awake SpO_2, %	96.0 (96.0-97.5)	96.0 (96.0-98.0)	96.0 (95.8-97.3)	0.593
FEV_1/FVC ratio, %	82.3 ± 7.4	81.53 ± 8.3	83.3 ± 6.4	0.486
FEV_1, %	92.8 ± 17.8	90.4 ± 17.3	95.6 ± 18.4	0.377
FVC, %	88.9 ± 18.2	89.6 ± 18.1	88.0 ± 18.9	0.791
TLC, %	84.0 ± 19.8	86.7 ± 20.7	80.8 ± 18.7	0.371
DL_{CO}, %	59.0 ± 14.4	56.8 ± 11.9	61.6 ± 16.9	0.314
K_{CO}, %	82.3 ± 21.4	76.2 ± 16.0	89.5 ± 25.1	0.059
HRCT pattern				
UIP	6 (15.8%)	4 (20.0%)	2 (11.1%)	0.663
Probable UIP	8 (21.1%)	3 (15.0%)	5 (27.8%)	0.438
Indeterminate for UIP	8 (21.1%)	3 (15.0%)	5 (27.8%)	0.438
Alternative diagnosis	16 (42.1%)	10 (50.0%)	6 (33.3%)	0.342
Extent of fibrosis > 10%	26 (68.4%)	14 (70.0%)	12 (66.7%)	1.000
HSAT results				
Snoring, %	6.7 (3.2-25.5)	5.2 (2.8-23.2)	9.6 (4.3-34.3)	0.105
AHI, events/h	14.3 (6.9-25.5)	7.0 (6.6-9.7)	25.6 (17.9-32.3)	< 0.001
Apnea index, events/h	2.0 (0.3-7.7)	0.8 (0.1-1.9)	7.8 (2.9-11.4)	< 0.001
Hypopnea index, events/h	9.3 (6.1-16.8)	6.5 (5.1-8.2)	17.0 (13.0-23.4)	< 0.001
Obstructive events, events/h	6.8 (4.9-17.0)	6.4 (4.4-6.8)	17 (6.9-24.5)	0.001
Central events, events/h	0.3 (0.0-2.6)	0.3 (0.0-1.3)	0.9 (0.0-4.3)	0.743
ODI	12.6 (8.2-26.0)	8.3 (7.0-10.8)	26.0 (20.4-35.7)	< 0.001
Mean nocturnal SpO_2, %	92.3 ± 2.1	93.0 ± 2.1	91.7 ± 2.0	0.059
Minimum nocturnal SpO_2, %	82.3 ± 5.8	85.0 ± 4.5	79.3 ± 5.8	0.002
T90, %	2.8 (0.3-17.2)	0.6 (0.1-6.5)	8.5 (2.3-29.8)	0.007
T90 scores > 20%	8 (21.1%)	3 (15.0%)	5 (27.8%)	0.438

OSA: obstructive sleep apnea; ESS: Epworth Sleepiness Scale; ILD: interstitial lung disease; HP: hypersensitivity pneumonitis; CTD-ILD: connective tissue disease-associated interstitial lung disease; NSIP: nonspecific interstitial pneumonia; PPFE: pleuroparenchymal fibroelastosis; K_{CO}: carbon monoxide transfer coefficient; UIP: usual interstitial pneumonia; HSAT: home sleep apnea test; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; and T90: total sleep time spent below an SpO_2 of 90%. [a]Values expressed as mean ± SD, n (%), or median (IQR). *Moderate OSA (n = 13); severe OSA (n = 5).

Table 3. Univariate and multivariate analyses to determine risk factors for obstructive sleep apnea.

Variable	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.00 (0.92-1.08)	0.930	0.90 (0.79-1.02)	0.104
Male	0.41 (0.10-1.58)	0.192		
BMI, kg/m^2	1.13 (0.95-1.34)	0.166	1.02 (0.83-1.26)	0.848
Awake SpO_2, %	0.56 (0.33-0.9)	0.031	0.46 (0.25-0.87)	0.016
FEV_1/FVC ratio, %	1.07 (0.99-1.16)	0.088		
FEV_1, %	1.01 (0.97-1.05)	0.700		
FVC, %	1.00 (0.96-1.04)	0.897		
TLC, %	0.97 (0.93-0.99)	0.045	0.95 (0.92-0.99)	0.026
DL_{CO}, %	0.99 (0.95-1.03)	0.508		
K_{CO}, %	1.01 (0.98-1.05)	0.475		
Extent of fibrosis > 10%	1.55 (0.41-5.89)	0.522	0.27 (0.03-2.82)	0.271
ESS score	1.00 (0.82-1.22)	0.970		
ODI	22.80 (0.67-777.78)	0.083		
Mean nocturnal SpO_2, %	0.82 (0.57-1.17)	0.266		
T90, %	1.01 (0.98-1.05)	0.542		

K_{CO}: carbon monoxide transfer coefficient; ESS: Epworth Sleepiness Scale; ODI: oxygen desaturation index; and T90: total sleep time spent below an SpO_2 of 90%.

Table 4. Comparison of patient symptoms and nocturnal oxygenation at baseline and at 3 months after initiation of positive airway pressure therapy.[a]

Variable	Baseline	At 3 months after initiation of PAP therapy	p
Mean nocturnal SpO_2, %	90.1 ± 2.2	94.0 ± 0.5	0.015
Minimum nocturnal SpO_2, %	78.8 ± 4.9	86.3 ± 1.2	0.011
T90, %	36.8 (21.3-63.8)	0.1 (0.1-0.2)	0.046
Nocturnal hypoxemia*	6.0 (50.0%)	0.0 (0.0%)	0.014
ESS score	5.0 (2.0-8.5)	3.5 (0.3-5.0)	0.006
Cough score	2.0 (1.0-5.5)	1.0 (2.5-4.8)	0.931
Dyspnea score	1.5 (0.3-4.5)	1.0 (0.0-2.8)	0.307
SF-36 physical functioning, %	72.5 (47.5-85.0)	80 (57.5-88.8)	0.928
SF-36 role-physical, %	100.0 (75.0-100.0)	100.0 (56.3-100.0)	0.854
SF-36 role-emotional, %	100.0 (100.0-100.0)	100.0 (100.0-100.0)	0.317
SF-36 vitality, %	57.5 (35.0-77.5)	62.5 (50.0-75.0)	0.541
SF-36 mental health, %	72.0 (38.0-92.0)	78.0 (68.0-96.0)	0.068
SF-36 social functioning, %	100.0 (87.5-100.0)	100.0 (90.6-100.0)	0.180
SF-36 bodily pain, %	100.0 (51.3-100.0)	100.0 (60.0-100.0)	0.892
SF-36 general health, %	52.5 (42.5-63.8)	50.0 (41.3-60.0)	0.377

PAP: positive airway pressure; T90: total sleep time spent below an SpO_2 of 90%; ESS: Epworth Sleepiness Scale; and SF-36: Medical Outcomes Study 36-item Short-Form Health Survey. [a]Values expressed as mean ± SD, median (IQR), or n (%). *Nocturnal hypoxemia was defined as a T90 > 20%.

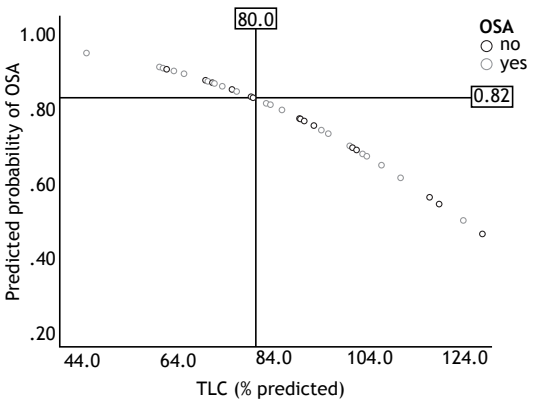

Figure 1. Predicted probability of obstructive sleep apnea (OSA) based on TLC values.

perception of cough and dyspnea, as well as in most of the SF-36 domains, were not significant (Table 4).

DISCUSSION

In a group of 122 non-IPF fibrotic ILD patients, only 19.7% of whom had a previous diagnosis of OSA, we found a much higher frequency of OSA (76%) when an HSAT was performed systematically, even in the absence of typical OSA symptoms. The high frequency of OSA observed in this study is similar to that observed in previous studies involving IPF patients,[10-13] a finding that may reflect similar underlying mechanisms of pulmonary fibrosis. In this study, respiratory events were mostly obstructive hypopneas (rather than apneas or central events), and

the severity of OSA was mostly mild, in agreement with previous studies.[11,34]

Current evidence has shown that the anatomical endotype is present in all OSA patients, although with different underlying causes and magnitude,[35] being related to impaired pharyngeal anatomy and being strongly associated with obesity and reduced lung volumes.[5,35] A higher BMI does not seem to be a significant contributing factor to OSA in ILD patients,[5,36] as shown in our study. However, we showed that a lower TLC was associated with a higher risk of OSA, reinforcing the idea that decreased lung volumes can reduce upper airway stability and induce upper airway traction, facilitating collapse.[5,13,37]

It has been hypothesized that chronic hypoxia, a common feature of ILD, can increase chemosensitivity and therefore increase controller gain and loop gain, leading to an unstable respiratory system.[5,38] We did not address this issue, because patients presenting with daytime hypoxemia (a resting PaO_2 of < 60 mmHg on room air) were excluded. In our study, neither DL_{CO} nor K_{CO} were associated with the ODI, T90, or mean nocturnal SpO_2. Therefore, we assume that nocturnal hypoxemia is mostly related to obstructive events rather than to the extent of lung parenchymal fibrosis.

In this study, the ILD patients with a diagnosis of OSA did not show higher ESS scores when compared with non-OSA patients, which is consistent with the literature.[11] Therefore, there should be a lower threshold of suspicion in this group of patients, and new tools should be sought to evaluate the probability of OSA. We found that a TLC of < 80% was associated with a higher predicted probability of OSA (> 82%). Although more studies should be performed to confirm this finding, TLC might be a potential marker in non-IPF fibrotic ILD to decide which patients should undergo an HSAT for the diagnosis of OSA.

In non-IPF fibrotic ILD patients, OSA may contribute to poorer sleep quality and poorer overall quality of life, contributing to disease progression and mortality.[8,13,22] Effective PAP therapy has been shown to improve quality of sleep, quality of life, and potentially mortality in this population.[8] Therefore, an effort must be made to diagnose OSA correctly in patients with non-IPF fibrotic ILD and to achieve good adherence to PAP therapy, when applicable. Several studies have evaluated adherence to PAP therapy in patients with ILD, with heterogeneous results, although the majority reports high incidences of nonacceptance and poor adherence.[13,22,24] The main reason is the underrecognition of OSA as a medical condition, given that patients may be asymptomatic or paucisymptomatic, as well as complaints related to PAP therapy.[24] Although the Portuguese national health system fully reimburses the cost of PAP therapy, this may be an obstacle to treatment adherence in other countries. In the present study, we showed that, after initiation of PAP therapy, patients reported an improvement in daytime sleepiness and emotional well-being. Although the number of patients was small and the follow-up period was short, our findings show a trend toward clinical improvement with PAP therapy and should be further evaluated in future studies. In addition, patients with significant baseline nocturnal hypoxemia had complete resolution, not requiring oxygen therapy. This is clinically relevant because nocturnal hypoxemia[13] and oxygen therapy[39] may be related to fibrosis progression and worse outcomes in patients with fibrotic ILD. To optimize adherence, a close follow-up is crucial, especially at the beginning of the treatment, with group educational sessions.

One of the limitations of our study is the small sample size. However, this is currently the largest study of patients with non-IPF fibrotic ILD. Although our study showed a high frequency of OSA in this population, the lack of a control group may constitute a limitation preventing the prevalence of OSA from being accurately defined. Another limitation is the heterogeneity of the study population. A larger group of patients with different forms of ILD might allow more robust conclusions regarding OSA in patients with non-IPF fibrotic ILD and other forms of ILD. Yet another limitation is that the HSAT may have underestimated the frequency and severity of OSA. Level 1 polysomnography is more appropriate in this population because it can provide more information on sleep stages and different sleep-related breathing disorders. Further studies, addressing these issues and including longer follow-up periods, are warranted.

In conclusion, we found a high frequency of OSA in a population of patients with non-IPF fibrotic ILD, even in the absence of typical symptoms such as daytime sleepiness. A lower TLC correlated with a higher risk of OSA. Therefore, a TLC cutoff of 80% is suggested to decide which patients should undergo an HSAT for OSA screening. There should be a low threshold for suspicion of OSA and initiation of PAP therapy in patients with non-IPF fibrotic ILD because PAP therapy can correct nocturnal hypoxemia.

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AUTHOR CONTRIBUTIONS

CGC and MS: conceptualization, methodology, investigation, data curation, resources, software, formal analysis, writing—original draft, visualization, and writing—review and editing. CV, IR, and AC: conceptualization, investigation, resources, and visualization. DBC, HNB, PCM, AM, and MD: conceptualization, investigation, resources, visualization, and writing—review and editing.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

CPAP delivered via a helmet interface in lightly sedated patients with moderate to severe ARDS: predictors of success outside the ICU

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Study carried out in the Hospital of Messejana Dr. Carlos Alberto Studart Gomes, Fortaleza (CE) Brasil.

ABSTRACT

Objective: This study aimed to describe the outcomes and explore predictors of intubation and mortality in patients with ARDS due to COVID-19 treated with CPAP delivered via a helmet interface and light sedation. **Methods:** This was a retrospective cohort study involving patients with COVID-19-related ARDS who received CPAP using a helmet developed in Brazil (ELMO™), associated with a light sedation protocol in a pulmonology ward. Demographic, clinical, imaging, and laboratory data, as well as the duration and response to the ELMO-CPAP sessions, were analyzed. **Results:** The sample comprised 180 patients. The intubation avoidance rate was 72.8%. The lack of necessity for intubation was positively correlated with younger age, > 24-h continuous HELMET-CPAP use in the first session, < 75% pulmonary involvement on CT, and ROX index > 4.88 in the second hour. The overall in-hospital mortality rate was 18.9%, whereas those in the nonintubated and intubated groups were 3.0% and 61.2%, respectively. Advanced age increased the mortality risk by 2.8 times, escalating to 13 times post-intubation. **Conclusions:** ELMO-CPAP with light sedation in a pulmonology ward was successful in > 70% of patients with moderate to severe ARDS due to COVID-19. Younger age, pulmonary involvement, ROX index, and prolonged first Helmet-CPAP session duration were associated with no need for intubation. Older age and intubation are associated with mortality.

Keywords: Respiratory distress syndrome; COVID-19; Continuous positive airway pressure; helmets ; Dexmedetomidine.

INTRODUCTION

Respiratory involvement in COVID-19 has a clinical spectrum ranging from asymptomatic or oligosymptomatic patients to those with severe acute hypoxemic respiratory failure (AHRF) and ARDS.[1] The persistence of the latter condition has remained the main risk factor for COVID-19-related endotracheal intubation (ETI) and mortality since the beginning of the pandemic.[2-4] Noninvasive respiratory support strategies using helmet interfaces have become important for avoiding invasive measures.[5-7] However, insistence on these strategies can delay ETI and worsen patient outcomes.[8,9] Factors for predicting ETI and mortality continue to be a subject of debate.[10,11]

Helmet-CPAP has been used in ARDS patients with COVID-19 to provide prolonged and continuous treatments with high positive airway pressure (CPAP or PEEP) to reduce self-inflicted lung injuries.[12] In association with noninvasive respiratory support, light sedation has been gaining prominence with the advantage of reducing anxiety, decreasing respiratory rate, and decreasing tidal volumes, factors that can aggravate lung injury if elevated, as well as improving patient compliance and tolerance to therapy.[13-15] However, the association of CPAP with helmets and light sedation is limited to a few cases in the literature and little explored in ARDS outcomes.[13,16]

Helmet-CPAP is commonly implemented with an oxygen flow generator: it is simple to apply, does not require mechanical ventilators, and is usable outside the ICU.[13,17,18] It is particularly useful in low-resource locations and during pandemics.[6,7,19,20]

During the second wave of the COVID-19 pandemic in Brazil, a helmet known as ELMO™ was used in thousands of patients. It was designed for the application of CPAP outside of overwhelmed ICUs during a pandemic emergency and does not require a mechanical ventilator.[21,22] Respiratory wards were opened for non-intubated patients with AHRF with team training and structured protocols.

Patients with COVID-19 are especially anxious and frightened because of the disease. This factor potentially increases respiratory drive and respiratory rate and

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reduces patient tolerance to therapy.[1,23] Therefore, we added pharmacological intravenous continuous light sedation with dexmedetomidine, a drug recommended for sedating patients during noninvasive respiratory support.[13]

We hypothesized that applying Helmet-CPAP with light sedation would augment patient tolerance, allowing prolonged periods of helmet application in patients with moderate to severe ARDS and COVID-19 treated outside the ICU, and that we would find predictors for ETI and mortality yet to be reported in the literature, such as the duration of Helmet-CPAP sessions. This study aimed to describe the outcomes of intubation and mortality and to explore their predictors in patients with ARDS secondary to COVID-19 treated with ELMO-CPAP (the specific helmet used in these patients) associated with light sedation with dexmedetomidine.

METHODS

Study design and population

This retrospective cohort study was performed at a specialized noninvasive respiratory support pulmonology ward for patients with AHRF and ARDS due to COVID-19 at the Hospital of Messejana Dr Carlos Alberto Studart Gomes, a tertiary referral hospital for respiratory diseases in the state of Ceará, Brazil. This study was performed in strict accordance with the Declaration of Helsinki and approved by the Brazilian National Research Ethics Committee (Protocol number. 4.902.781). The requirement for informed consent was waived owing to the retrospective nature of the study.

Eligible patients were adults > 18 years of age, of both sexes, diagnosed with COVID-19 confirmed by positive RT-PCR nasopharyngeal swab test,[24] with hypoxemic respiratory failure submitted to noninvasive respiratory support therapy using ELMO-CPAP during the study period. ARDS was classified according to the new definition, which includes criteria such as assessment of the Pao_2/FIo_2 ratio when using CPAP > 5 cmH_2O (201-300 = mild; 101-200 = moderate; and ≤ 100 = severe), bilateral opacities on chest CT, and a compatible underlying cause.[25]

The patients met the following criteria: 1. Being alert, oriented, and cooperative; 2. Oxygen therapy by nasal cannula with a flow > 4 L/min or by nonrebreathing reservoir mask > 8 L/min, maintaining SpO_2 higher than 92%; 3. Arterial blood gas analysis with pH > 7.35 (no acidosis), Pao_2 > 60 mmHg up to 30 min before starting therapy, and no hypercapnia ($PaCo_2$ < 46 mmHg); and 4. Chest CT scan obtained within the preceding 24 h showing bilateral parenchymal opacities.[7]

Exclusion criteria were as follows: 1. first use of ELMO-CPAP after extubation; 2. Exacerbation of asthma or COPD; 3. Need for more than 0.5 mcg/kg/min of i.v. norepinephrine infusion; 4. Persistent signs of respiratory fatigue (use of accessory respiratory muscles and paradoxical breathing); 6. Uncontrolled claustrophobia; 7. Uncontained vomiting or nausea; and 8. Imminent risk of cardiorespiratory arrest.

The respiratory ward was monitored with a multiparameter monitor for vital signs (e.g. continuous pulse oximetry, frequency of blood pressure measurements). It was covered 24 h by doctors, nurses, and respiratory therapists, with a ratio of such professionals of 1:6 per patient, with daily shifts of fixed pulmonologists. The patients who underwent ELMO-CPAP support followed a standardized protocol (Figure 1) developed by the interdisciplinary team, all adequately trained and headed by a pulmonologist responsible for the continuous efforts to improve the team's performance every day.

The ELMO-CPAP works by delivering a continuous flow of a mixture of oxygen and compressed medicinal gases directly into the inspiratory circuit; a PEEP valve in the exhalation port allows the application of a stable, adjustable CPAP of 8-15 cmH_2O, which can be measured with a simple analog tracheal tube cuff pressure manometer.[21]

All patients started therapy with a total flow rate of 60 L/min (O_2 and compressed air), with sufficient FIo_2 to maintain an Spo_2 in the range of 92-96%, and a CPAP of 10 cmH_2O checked with the cuff pressure manometer.[22]

To reduce anxiety and improve patient compliance and comfort, patients were administered dexmedetomidine by continuous intravenous infusion (0.2-0.6 mcg/kg/min) and clonazepam oral drops (1 mg every 8 h) during ELMO-CPAP. Sedation was gradually adjusted to achieve a Richmond Agitation Sedation Scale score of 0 or −1.[5] Some precautions were adopted as follows: the use of lubricating eye drops (before each CPAP session), nasal lavage with 0.9% sodium chloride saline, lactulose, and ear protectors. Spontaneous prone position was encouraged, adopted according to the patient's tolerance, and maintained as long as possible. Figure S1 and S2 (supplementary material) shows details of the ELMO-CPAP application protocol and weaning from therapy, respectively.

Data collection plan

Data were extracted from the electronic medical records using standardized forms, keeping the identity of each patient confidential. Data collection was performed by a single researcher who was adequately trained to use the data-collection instrument.

Baseline clinical data were collected on hospital admission. An arterial blood gas sample was collected before the start of therapy and during the first therapy session (with a time interval of 2-24 h of continuous ELMO-CPAP use). A qualitative description of chest CT performed within 24 h after admission was also analyzed by a board-certified radiologist who described the following items: degree of lung parenchymal involvement with findings suggestive of viral pneumonia (graduated as < 25%, 25-50%, > 50-75%, and

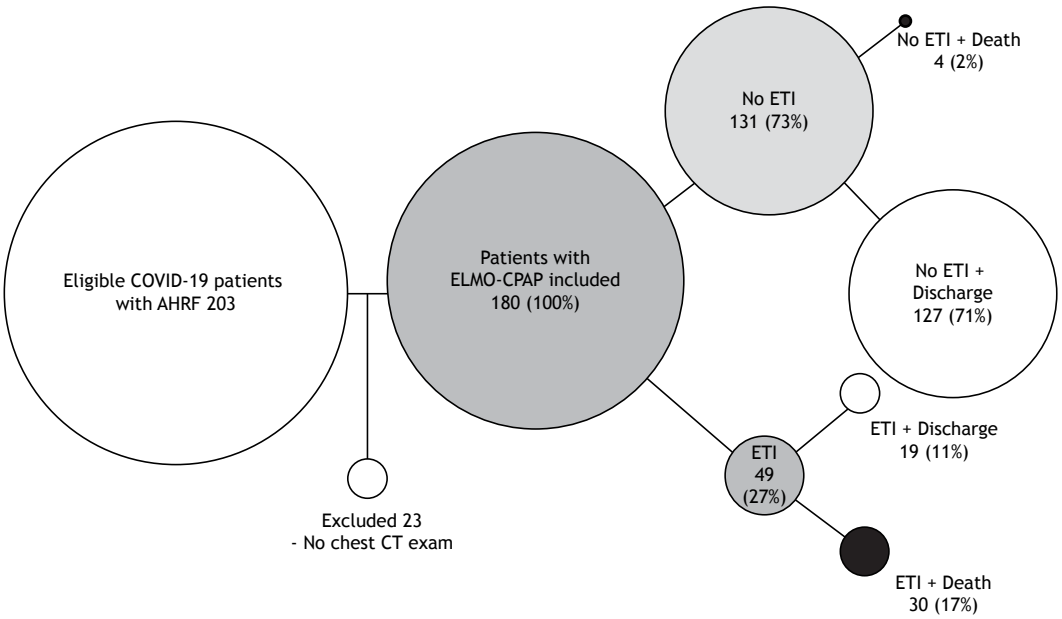


Figure. 1. Flow chart of the study and outcomes. AHRF: acute hypoxemic respiratory failure; and ETI: endotracheal intubation.

> 75% of lung involvement). Subsequently, for statistical analysis, these categories were grouped as ≤ 50%, 51-75%, and > 75%. Complications such as pneumomediastinum or pneumothorax, if present, were recorded.

Data on clinical evolution of the disease were obtained, such as the beginning and type of symptoms before admission, time of therapy initiation after admission to the respiratory ward, total duration of ELMO-CPAP use in the first 48 h, and duration in days.

Patients who did not require ETI were considered successful, whereas those who needed it were considered failure.

The primary objective of this study was to assess the factors related to the success of ELMO-CPAP respiratory support. The secondary objective was to evaluate the factors associated with in-hospital mortality, including intubation.

Statistical analysis

The normality test for quantitative variables was performed using the Shapiro-Wilk and Kolmogorov-Smirnov tests. For the descriptive analysis of quantitative variables, the mean and standard deviation or the median and interquartile range were calculated according to the sample distribution. Categorical variables were described as absolute and relative frequencies.

The Student's t-test and Mann-Whitney U tests were used to compare continuous variables with normal and non-normal distributions, respectively. Association analysis between categorical variables was performed using the Pearson's chi-square test.

Multivariate analysis and Poisson regression with robust estimator examined variables associated with ETI (primary outcome) and in-hospital death (secondary outcome). The variables considered relevant to the model were selected from those found significant in the univariate analyses ($p < 0.05$), according to clinical importance and biological plausibility, and others as potential confounders: age, C-reactive protein, chest CT involvement, Pa_{O_2}/FI_{O_2} ratio at baseline, and duration of first ELMO-CPAP section. The results are presented as relative risk (RR) and 95% CI. Statistical significance was set at $p < 0.05$. We used the IBM SPSS Statistics software, version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 203 patients diagnosed with AHRF secondary to COVID-19 were admitted to the respiratory ward. All patients were eligible for ELMO-CPAP therapy. After applying the inclusion criteria, 180 patients were included in the analysis (Figure 1). Of these, 116 (81%) were male, and the median age of the sample was 55 years. Table 1 shows the patient characteristics, treatments applied, and hospital outcomes of the nonintubated (success) and intubated (failure) groups. A total of 131 (72.8%) patients did not need ETI after ELMO-CPAP, while 49 (27.2%) failed and received invasive mechanical ventilation.

Older age [57.5 years (50-67) vs. 54 years (41.2-62.0); $p = 0.01$], higher levels of C-reactive protein [11.9 mg/L (9.1-15.2) vs. 9 mg/L (6.2-14.5); $p = 0.01$], lower Pa_{O_2}/FI_{O_2} ratio [117.5 (100.0-141.0) vs. 142.5 (121.0-163.0); $p = 0.001$], more than 75% of pulmonary involvement on chest CT images [19 (38.8%) vs. 21 (16%); $p = 0.03$], and fewer hours during the first ELMO-CPAP session [24 h (17-42) vs 44 h (32.2-48.0); $p < 0.001$] were associated with

Table 1. Patient characteristics, treatments applied, and hospital outcomes comparing the nonintubated (success) with the intubated (failure) groups.[a]

Variables	Whole sample	Group		p
		Nonintubated	Intubated	
	N = 180	n = 131	n = 49	
Demographic data				
Age, years	55 (45-63)	54 (41-62)	57.5 (50.0-67.0)	0.01
Male	116 (81.0)	87 (66.4)	29 (59.2)	0.38
SOFA score	2 (2-2)	2 (2-2)	2 (2-3)	0.06
Comorbidities				
Hypertension	77 (42.8)	53 (40.4)	24 (48.9)	0.34
Diabetes mellitus	51 (28.3)	34 (25.9)	17 (34.6)	0.24
Obesity	46 (25.5)	36 (27.4)	10 (20.4)	0.33
Heart failure	22 (12.2)	17 (12.9)	5 (10.2)	0.61
Cerebrovascular accident	3 (1.7)	1 (0.7)	2 (4.0)	0.12
Atrial fibrillation	2 (1.1)	2 (1.5)	0 (0.0)	0.38
COPD	5 (2.8)	2 (1.5)	3 (6.1)	0.95
Asthma	6 (3.3)	6 (4.5)	0 (0.0)	0.12
Anxiety	4 (2.2)	3 (2.2)	1 (2.0)	0.92
Other	17 (9.4)	12 (9.1)	5 (10.2)	0.83
None	53 (29.4)	43 (32.8)	10 (20.4)	0.10
Radiological and laboratory data				
Pulmonary involvement on chest CT				
≤ 50%	39 (21.7)	33 (25.2)	6 (12.2)	0.03
51-75%	101 (56.1)	77 (58.0)	24 (49.0)	
> 75%	40 (22.2)	21 (16.0)	19 (38.8)	
Hemoglobin = 13-18 g/dL	13.5 (12.6-14.5)	13.6 (12.6-14.5)	12.5 (11.0-13.1)	0.12
Haematocrit = 40-54%	40.4 (37.7-43.0)	40.8 (37.9-43.3)	39.3 (36.8-42.8)	0.39
Leucocytes = 4,000-10,000/mm3	9050 (7000-12350)	9700 (7600-13100)	7700 (5850-9750)	0.10
Lymphocytes = 1,500-4,500/mm3	864 (630-1170)	911 (634-1283)	791 (600-975)	0.02
D-dimer < 0.500 µg/mL)	810 (530-1160)	795 (508-1127)	870 (643-1450)	0.36
LDH = 140-271UI/L	381 (303-512)	365 (285-470)	407 (261-589)	0.11
C-reactive protein, mg/dL	9.6 (6.52-14.6)	9.0 (6.2-14.5)	11.9 (9.1-15.2)	0.01
Urea, mg/dL	32 (25-42)	32 (24-41)	31 (26-43)	0.84
Creatinine, mg/dL	0.8 (0.66-0.96)	0.7 (0.6-0.9)	0.8 (0.6-1.0)	0.41
Arterial blood gas analysis				
pH	7.45 (7.43-7.47)	7.45 (7.43-7.47)	7.45 (7.42-7.48)	0.55
$PaCO_2$, mmHg	35.8 (32.9-38.2)	36.8 (33.4-39.1)	33.7 (31-38.0)	0.05
PaO_2, mmHg	76 (67.5-89.0)	76 (68.9-90.5)	76.2 (62.1-85.3)	0.18
SaO_2, %	95.2 (93.5-96.6)	96 (94-98)	95 (93.0-96.7)	0.008
Lactate, mmol/L	1.68 (1.28-2.39)	1.7 (1.2-2.4)	1.5 (0.9-2.3)	0.54
PaO_2/FIO_2	138 (116.5-163)	142.5 (121.0-163.0)	117.5 (100.0-141.0)	0.001
Concomitant medications				
Dexamethasone	180 (100)	131 (100)	49 (100)	NA
Albendazole or ivermectin	180 (100)	131 (100)	49 (100)	NA
Deep vein thrombosis prophylaxis	167 (92.7)	107 (81.6)	25 (51.0)	0.01
Anticoagulation	13 (7.2)	24 (18.3)	24 (48.9)	0.01
Antibiotics	173 (96.1)	124 (94.7)	49 (100)	0.1
Days of symptoms preceding ELMO-CPAP use	10 (8-12)	10 (8-12)	10 (7.5-11.5)	0.86
Duration of 1st ELMO-CPAP session, h	39 (24-48)	44 (32.2-48.0)	24 (17-42)	< 0.001
Total duration of ELMO-CPAP, days	4 (2-5)	4 (3-5)	3 (2-4)	0.104
Outcomes				
Length of hospital stay, days	13 (9-23)	11 (9-15)	25 (20-32.7)	< 0.01
In-hospital mortality	34 (18.9)	4 (3.0)	30 (61.2)	0.001
Complications				
Pneumothorax	2 (1.1)	0 (0.0)	2 (4.1)	0.001
Pneumomediastinum	9 (5.0)	5 (3.8)	4 (8.2)	0.23

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

ETI in univariate analysis (Table 1). All patients used light sedatives, as described in the study protocol.

The length of hospital stay for intubated patients was more than double of that for nonintubated patients [25 days (20.0-32.7) vs. 11 (9.0-15.0); p < 0.01]. Overall, the in-hospital mortality was 18.9%, and there was a statistically significant difference between the intubated and nonintubated groups [30 (61.2%) vs. 4 (3%); p = 0.001; Table 1].

Considering the secondary outcome, when comparing death versus hospital discharge, mortality was higher in older patients who presented with higher levels of C-reactive protein, LDH, and D-dimer; those who were hyperventilated; those with lower levels of Pao_2/FIo_2 ratio; those who presented more than 75% of pulmonary involvement on chest CT images; and those who spent fewer continuous hours during the first ELMO-CPAP session (28 h vs. 42 h; p = 0.048), as detailed in Table S1.

Table 2 shows the response to ELMO-CPAP in arterial blood gases and Spo_2 collected at 2-24 h, variation to baseline, and respiratory rate-oxygenation (ROX) index at 2 h during the first ELMO-CPAP application in nonintubated and intubated patients. An improvement in oxygenation was observed in the nonintubated group, which was reflected in the increase in Pao_2, Spo_2, and Pao_2/FIo_2 during the use of ELMO-CPAP. In addition, there was an early response in the ROX index after 2 h, with a median of 5.56 vs 4.84 (p = 0.003) in nonintubated and intubated patients, respectively. Most patients had moderate to severe ARDS. The latter was more frequent in the intubation group and was associated with failure (Table 2).

Multivariate analysis with Poisson regression was used to examine the factors associated with ETI and mortality. The relevant variables for the model were age, C-reactive protein level, involvement on chest CT, Pao_2/FIo_2 ratio at the beginning of the study, and duration of the first ELMO section.

For intubation, multivariate analysis showed that patients over 60 years of age, with more than 75% pulmonary involvement on chest CT images, an ROX index < 4.88, and less than 24 h duration of the first ELMO-CPAP session were associated with a higher risk for intubation (Figure 2).

Regarding mortality, advanced age was associated with an increase of 2.8 times in the risk of mortality, and this risk escalated to a 13-time increase in individuals who underwent intubation. The other variables were not associated with mortality (Figure 2).

DISCUSSION

This retrospective cohort study included 180 patients with AHRF and ARDS secondary to COVID-19 treated with CPAP without mechanical ventilation using the first Brazilian helmet interface (ELMO), light sedation, and outside the ICU. In our sample, 131 (72.8%) of

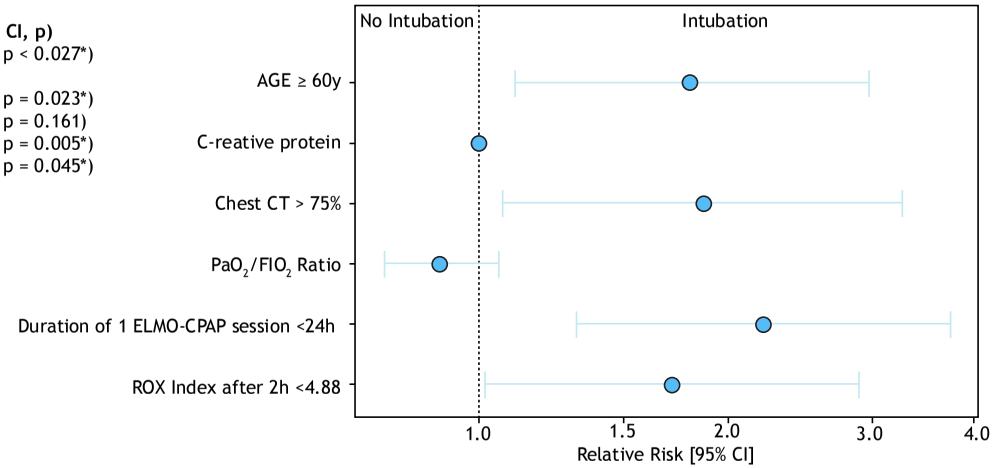
Table 2. Arterial blood gas analysis and SpO_2 collected at 2-24 h after admission, variation in relation to baseline, and respiratory rate-oxygenation index at 2 h during the first ELMO-CPAP application.[a]

Variable	Whole sample	Group		p
		Nonintubated	Intubated	
	N = 180	n = 131	n = 49	
Arterial blood gas (ABG)				
pH	7.44 (7.41-7.47)	7.44 (7.41-7.47)	7.44 (7.42-7.47)	0.71
$PaCO_2$, mmHg	37.3 (33.3-40.9)	37.7 (34.5-41.0)	36.4 (32.8-39.9)	0.20
PaO_2, mmHg	90.1 (75.6-115-7)	94 (77-119)	83 (69.9-107.3)	0.03
PaO_2/FIO_2	160 (125-205)	176 (135-221)	127 (106-159)	0.01
Lactate, mg/dL	1.79 (1.38-2.34)	1.8 (1.35-2.34)	1.78 (1.57-2.38)	0.41
SpO_2, %	97 (95-98)	97 (95-98)	95.9 (93.7-97.9)	0.03
ARDS classification				
Mild (PaO_2/FIO_2 = 300-201)	30 (16.7)	25 (19.1)	5 (10.2)	
Moderate (PaO_2/FIO_2 = 200-101)	108 (60.0)	78 (59.5)	30 (61.2)	
Severe ($PaO_2/FIO_2 \leq 100$)	19 (10.6)	8 (6.1)[a]	11 (22.4)[b]	0.005
Variation in ABG in relation to baseline				
ΔpH	−0.01 (−0.04 to 0.01)	to 0.01 (−0.04 to 0.01)	to 0.01 (−0.05 to 0.02)	0.14
$\Delta PaCO_2$	1.5 (−0.97 to 4.8)	1.5 (−1.0 to 4.8)	1.9 (−1.2 to 4.45)	0.37
ΔPaO_2	13.2 (−2.71 to 37)	14.3 (−2.0 to 40.5)	16.9 (−8.5 to 38.5)	0.96
$\Delta PaO_2/FIO_2$	20 (−10.7 to 61.5)	25 (−11 to 64)	16 (−16 to 60)	0.61
Δlactate	−0.34 (−0.81 to 0.22)	0.09 (−0.43 to 0.81)	−0.19 (−1.0 to 0.5)	0.86
ΔSpO_2	1.2 (−0.4 to 3.27)	1.3 (−0.3 to 3.7)	1.3 (−1.95 to 3.3)	0.79
ROX[b] index at 2 h	5.39 (4.3-6.1)	5.56 (4.63-6.15)	4.84 (4.08-5.75)	0.003

ROX: respiratory rate-oxygenation. [a]Data expressed as n (%) or median (IQR). [b]The ROX index is defined as the ratio SpO_2/FIO_2 to the respiratory rate. In case of missing data, statistics were performed on available data. Differences in frequencies were tested with the chi-square test. Differences in continuous variables were tested with the Mann-Whitney test. [a] Chi-square test and post hoc analysis for pairwise comparisons for success group. [b] Chi-square test and post hoc analysis for pairwise comparisons for failure group.

ELMO-CPAP - Factors for Intubation	Relative Risk (95% CI, p)
Age ≥ 60 years	1.81 (1.07 to 3.04, p < 0.027*)
C-reative protein	1.00 (p = 0.683)
Chest CT > 75% involvement	1.87 (1.08 to 3.17, p = 0.023*)
PaO_2/FIO_2 ratio	0.90 (0.77 to 1.03, p = 0.161)
Duration of 1st ELMO-CPAP session <24h	2.21 (1.27 to 3.80, p = 0.005*)
ROX Index after 2h <4.88	1.72 (1.02 to 2.93, p = 0.045*)

*p <0.05, significant



ELMO-CPAP - Factors for Death	Relative Risk (95% CI, p)
Age ≥ 60 years	2.82 (1.60 to 5.08, p < 0.001*)
C-reative protein	1.00 (p = 0.892)
Chest CT > 75% involvement	1.32 (0.78 to 2.22, p = 0.298)
$PaO_2/FI0_2$ Ratio	0.99 (0.84 to 1.15, p = 0.916)
Duration of 1st ELMO-CPAP session <24h	1.22 (0.70 to 2.11, p = 0.471)
ROX Index after 2h <4,88	1.13 (0.66 to 1.94, p = 0.646)
Intubation	13.3 (6.32 to 31.9, p < 0.001*)

*p < 0.05, significant

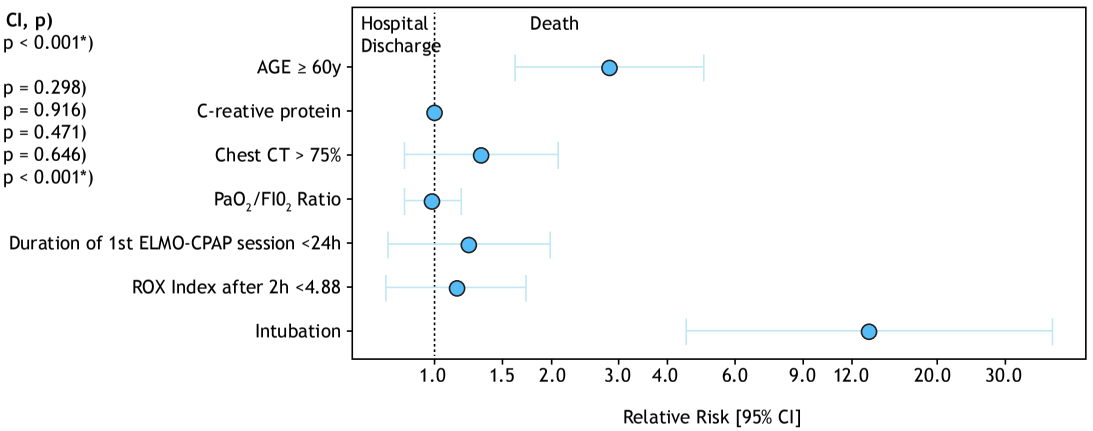


Figure 2. Multivariate logistic regression analysis with independent variables of factors for intubation and death.

the patients did not need ETI. To our knowledge, this is the highest success rate reported in the literature. The overall in-hospital mortality rate was 18.9%, and almost all deaths occurred in the intubation group.

The independent predictive factors associated with ETI were old age, > 75% pulmonary involvement on chest CT images, ROX index < 4.88 after 2 h, and duration of first ELMO-CPAP session less than 24 h. Advanced age was associated with an increase of up to 2.8 times in the risk of death, and this risk escalated by more than 10 times in individuals who underwent intubation.

The application of noninvasive respiratory support outside the ICU in the patient profile of this study is feasible when performed by an experienced, trained team and is associated with favorable outcomes, such as lower rates of intubation and mortality.[10,19] These settings have become known as specialized wards, with institutional protocols and well-defined criteria for initiating therapy, guided by pulmonologists and a multidisciplinary team. These factors may be associated with a learning curve for the team in managing ELMO-CPAP, thereby influencing the high success rate. Compared with other studies that used CPAP with a helmet interface, our success rate is currently the highest reported in the literature. Previously, other researchers reported success rates of 63%,[26] 69%,[27] and 56%.[28]

The high nonintubation rate in patients using ELMO-CPAP with light sedation obtained in our investigation can be explained by the improvement in oxygenation, probably due to alveolar recruitment, improvement in the ventilation-perfusion ratio, and dyspnea relief.[12] This result can be potentiated with helmet-type interfaces, such as ours, by providing a greater tolerance for high CPAP levels for prolonged periods. To the best of our knowledge, the present study is the first to routinely use light sedation with Helmet-CPAP in all patients, which may have contributed to their success. Light sedation may favorably modulate the respiratory drive, a factor that, in theory, may contribute to reducing the propensity to self-inflicted lung injury.[12] Dexmedetomidine is the preferred agent for sedating patients receiving Helmet-CPAP in the ICU when necessary and promotes lower rates of delirium.[13,29] In previous similar studies, the overall in-hospital mortality rates were 34.3%[30] and 36.3%[26] compared with 18.9% in the present investigation. The relatively lower mortality rate in our study may be related to the lower ETI rate.

Two factors related to the patient and disease extension were independently associated with intubation: older age and extensive lung parenchymal involvement on chest CT, respectively. In fact, for every one-year increase in lifetime, the risk of ETI and mortality increased. This is consistent with the study by De Vita et al.,[31] in which age and markers of disease severity, leukocytes, LDH, and Pao_2/FIo_2 were predictive factors of CPAP failure. In our study, lung parenchymal involvement on chest CT images < 75% at hospital admission was associated with an increased chance of no intubation. Patients with COVID-19 and greater extension of lung parenchyma infiltrates on chest CT have a reduced surface area for respiratory gas exchange with worsening during the course of the disease, which can lead to ETI.[32] Considerable lung involvement can also predispose patients to complications such as pneumothorax and the need to be admitted to the ICU.[33]

We found a direct relationship between prolonged duration of the first ELMO-CPAP session and avoidance of ETI: a session for more than 24 h reduced the risk of intubation. Of the four retrospective cohort studies published to date,[11,30,31,34] none associated the duration of continuous CPAP use in the first session with a decrease in intubation rate in patients with COVID-19 and AHRF, a new finding of the present investigation.

Our study has several limitations. It had a retrospective, single-center design, which limits the generalizability of the results. Arterial blood gas measurements were obtained within a broad timeframe of 2-24 h from therapy initiation, a software-based quantitative analysis of lung involvement on chest CT images was not used, and the measurement of the ROX index was performed at a single point in time. Therefore, it was not possible to include a control group in this study. However, the protocol and respiratory support were standardized for a single disease, limiting the variability of treatment and the number of confounding variables.

The clinical implications of this study are as follows. This study provides new predictors of intubation and mortality using Helmet-CPAP in severely ill patients with ARDS due to SARS-CoV-2. Furthermore, CPAP therapy, which is much simpler than noninvasive ventilation with pressure-support ventilation, can be applied in scenarios of public health emergencies or catastrophes with favorable outcomes, mainly in low-income communities or countries. Moreover, predictors related to the patient, disease extension, tolerance, and response to Helmet-CPAP use can help identify patients who need more attention and early recognition of failure, avoiding delayed intubations and possible increases in mortality.[35] Future clinical trials are warranted to study the applications of Helmet-CPAP designed to implement the earliest and most prolonged duration possible in patients with AHRF and ARDS due to viral pneumonia or other causes combined with light sedation with dexmedetomidine or other sedatives, whenever needed, in comparison with alternatives such as high-flow nasal cannula or standard noninvasive ventilation.[36]

In conclusion, the use of a new helmet, ELMO, with CPAP and light sedation applied outside the ICU, resulted in more than 70% of COVID-19 patients with AHRF and ARDS not requiring ETI. Intubation and mortality rates were higher for elderly patients with more than 75% pulmonary involvement on chest CT images and less than 24 h duration for the first ELMO-CPAP session. The design of future investigations with Helmet-CPAP use in ARDS and AHRF should consider the present results.

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AUTHOR CONTRIBUTIONS

IMM: designed the study, collected the data, had full access to all of the data in the study, took responsibility for the integrity of the data, analyzed the data, and drafted the manuscript. BST: designed the study, drafted the manuscript, and reviewed the manuscript. MPUS: designed the study and reviewed the manuscript. GCG: reviewed the manuscript. ABVJ: statistician that analyzed the data. MRG: review of the manuscript. MAH: drafting and reviewing the manuscript. EDBP: designed the study, analyzed the data, drafted the manuscript, and reviewed the manuscript. All authors revised, read, and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Risk of mycobacterial infections in a cohort of silicosis patients with autoimmune rheumatic diseases

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ABSTRACT

Objective: To evaluate the incidence rates of mycobacterial infections in silicosis patients with systemic autoimmune rheumatic disease (ARD). **Methods:** This was a retrospective cohort of silicosis patients between January of 1999 and December of 2023. We compared the incidence of tuberculosis and nontuberculous mycobacterial disease (NTM) in patients with silicosis with and without ARD. We also compared the tuberculosis incidence in the overall cohort with general Brazilian population estimates. **Results:** The study comprised 369 silicosis patients, of whom 35 (9.5%) had ARD. Having ARD did not affect the cumulative incidence of mycobacterial diseases. The risk of tuberculosis was higher in the cohort when compared with that in the adult Brazilian male population (age-adjusted incidence rate ratio = 20.46; 95% CI 14.89-28.13). **Conclusions:** In this cohort of patients with silicosis, ARD was not associated with the incidence of mycobacterial diseases.

Keywords: Silicosis; Tuberculosis; Mycobacterium infections, nontuberculous; Arthritis, rheumatoid; Scleroderma, systemic; Lupus erythematosus, systemic.

INTRODUCTION

There is increasing evidence that silica exposure may trigger the pathogenesis of several systemic autoimmune rheumatic diseases (ARD), such as rheumatoid arthritis (RA),[1-3] systemic sclerosis (SSc),[2-4] systemic lupus erythematosus (SLE),[5] and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).[3,6] Also, silica exposure and silicosis are known risk factors for developing mycobacterial infections.[1,7,8] Furthermore, patients with ARD receiving systemic glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and biologic/targeted synthetic treatment (b/tsDMARD) are at high risk of mycobacterial infections.[9,10]

Although there is biologic plausibility for a triple association of silicosis, ARD, and mycobacterial infections, there are only a few case reports in the literature exploring this topic,[11-14] including an interim case series of our center.[15]

We hypothesized that patients with silicosis and ARD have a higher risk of mycobacterial infections than those without ARD. Therefore, we assessed the data of our silicosis patients to compare the incidence rate of mycobacterial infections between patients with silicosis and ARD and those without ARD, and to explore variables possibly associated with mycobacterial infections. We also compared the prevalence of ARD and the incidence of tuberculosis in this cohort with general population estimates in Brazil.

METHODS

Consecutive patients with silicosis from a single tertiary care hospital with specialized services in occupational respiratory diseases in the city of São Paulo, Brazil, who had been followed between January of 1999 and December of 2023 were analyzed using a retrospective longitudinal cohort design.

Case definition

Patients with silicosis and ARD were included in the case group. Silicosis was defined as the presence of compatible radiological features on HRCT[16] in patients with occupational exposure to inhaled silica (for further information, see supplementary material, Table S1). Diagnoses of ARD were defined according to disease definitions stated by the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) Classification Criteria for Rheumatoid Arthritis[17]; the 2013 ACR/EULAR Classification Criteria for Systemic Sclerosis[18]; the 2019 ACR/EULAR Classification Criteria for Systemic Lupus Erythematosus[19]; and the 2012 Chapel Hill Consensus Conference for Nomenclature of Vasculitides.[20] Patients with symptoms, signs, and serological manifestations of ARD but with insufficient criteria for a specific disease were classified as having undifferentiated connective tissue disease (UCTD) as described by Mosca et al. in 2014.[21]

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◄ Voltar ao sumário

Selection of control group

The remaining patients with silicosis were included in the control group. Patients using systemic glucocorticoids or synthetic immunosuppressive or biologic medications due to conditions other than ARD were excluded. Patients with a single evaluation in our service were also excluded.

Mycobacterial infection definition

Tuberculosis was defined as a positive *Mycobacterium tuberculosis* culture or a positive molecular testing (nuclear amplification assays or Xpert® MTB/RIF assay) in sputum, bronchoalveolar lavage, biopsy fragment, or other biologic samples.[22] Nontuberculous mycobacterial (NTM) disease was defined by the criteria of the 2007 American Thoracic Society/Infectious Disease Society of America Statement for Nontuberculous Mycobacterial Diseases.[23]

Procedures

The study was approved by the University of São Paulo Research Ethics Committee (protocol number 5.360.480), which waived the requirement to obtain informed consent since data were collected from regular follow-up records and anonymized for analysis.

Patients were evaluated regarding their age at the start of follow-up; gender; tobacco consumption; occupational history of silica exposure; comorbidities; general and ARD-specific symptoms; serological tests and ARD-specific diagnostic evaluation; use of systemic corticosteroids; csDMARD or b/tsDMARD treatment; last available pulmonary function test before censoring, tuberculin skin test positivity (≥ 10 mm), tuberculosis or NTM diagnosis and/or treatment before follow-up; and positive AFB smear, mycobacterial culture or *M. tuberculosis* molecular assays.

We reviewed follow-up records of patients with silicosis since their first medical appointment in our center. Patients were considered to have had an event if they were diagnosed with tuberculosis or NTM during follow-up. Patients were censored after lung transplant, death for any cause, or at the last available appointment date if lost to follow-up. If none of these conditions were met, they were censored at December 31st, 2023.

Statistical analysis

We compared characteristics of ARD and control groups using the Student's t-test for normally distributed continuous variables, the Mann-Whitney test for non-normally distributed continuous variables, and the Fisher's exact test for categorical variables.

Cumulative incidence rates of tuberculosis, NTM, and any mycobacterial disease in the ARD and control groups were analyzed using the Kaplan-Meier method and log-rank for comparisons.

Cox proportional hazards model was used to calculate unadjusted hazard risk of mycobacterial infections for the following variables: age at start of follow-up, tobacco consumption, diabetes, total occupational silica exposure time, FVC in percentage of predicted value (FVC%), FEV_1%, any ARD diagnosis, use of systemic glucocorticoids for a period longer than six months, use of any csDMARD ever, use of any b/tsDMARD ever, prior tuberculosis, and latent tuberculosis treatment during follow-up.

Brazilian population estimates from 2001 to 2021 were retrieved using the Brazilian Institute of Geography and Statistics database.[24] An age-adjusted incidence rate ratio (IRR) of tuberculosis in the overall cohort was calculated and compared with the tuberculosis incidence in the adult (> 20 years of age) Brazilian male population during the same time period using the Brazilian Case Registry Database,[25] the national system for notification of diseases that is maintained by the Brazilian Ministry of Health. Because NTM notification is not mandatory in Brazil, there were no reliable Brazilian incidence estimates for NTM.[26]

We calculated the prevalence ratios (PR) of RA, SLE, and SSc and compared them with those in the Brazilian population using estimates described by Senna et al.[27] for RA and SLE, and by Horimoto et al.[28] for SSc. We did not find studies with prevalence estimates for AAV in Brazil.

All statistical analyses were performed with the statistical package R, version 4.3.3 (R Development Core Team, Auckland, New Zealand).

RESULTS

Between January of 1999 and December of 2023, a total of 423 patients were diagnosed with silicosis at our center. However, 54 patients were excluded from analysis due to the following reasons: 39 patients never came to any follow-up evaluation nor contributed to follow-up period; 13 patients had sarcoidosis and silicosis and required systemic glucocorticoid treatment; and 2 patients received kidney transplantation before starting follow-up and were under immunosuppressive therapy. The ARD group and the control group comprised 35 (9.5%) and 334 (90.5%) patients, respectively (Table 1). Compared with the control group, the ARD group had lower mean FVC% and lower mean TLC%. The remaining characteristics were similar in both groups (Table 1). Patients were followed for a median time of 3.8 years (IQR: 1.1-8.2).

Autoimmune rheumatic diseases

Of the 35 patients in the ARD group, 12, 9, 6, 6, and 2 were diagnosed with RA, SSc, SLE, UCTD, and AAV, respectively (Table S2). Regarding their treatment, 24 patients (68.6%) received systemic glucocorticoids for more than six months; in addition, 21 (60.0%) and 5 (14.2%) patients received any csDMARD ever and any b/tsDMARD ever, respectively (Table S2).

Compared with Brazilian estimates, the PRs of RA, SLE, and SSc were 6.87 (95% CI: 3.20-14.74), 10.87 (95% CI: 2.44-48.38), and 225.49 (95% CI: 114.45-444.25), respectively.

Risk of mycobacterial infections

Before starting follow-up, 55 patients reported having had a diagnosis of tuberculosis (4 and 51 in the ARD and control groups, respectively). We had no access to any AFB smear or culture results to check whether these diagnoses were accurate.

During follow-up, 38 patients developed tuberculosis, 23 patients developed NTM, and 76 patients were diagnosed with latent tuberculosis (Table 2). All patients were referred to a tertiary care service for tuberculosis treatment. The cumulative incidence of mycobacterial infections did not differ between groups (Figures 1 and 2). We evaluated the univariate hazard risks of mycobacterial infections using the Cox proportional hazards model (Table 3). The risk of symptomatic tuberculosis was lower in patients who received treatment for latent tuberculosis during follow-up (hazard ratio [HR] = 0.34; 95% CI: 0.12-0.95). FVC% and FEV_1% in higher quartiles were associated with a lower risk of NTM (HR = 0.43; 95% CI: 0.26-0.71; and HR = 0.46; 95% CI: 0.29-0.75, respectively).

The IR of tuberculosis and NTM in the overall cohort was 21.72 per 1.000 person-years (95% CI: 14.19-29.25) and 15.61 per 1.000 person-years (95% CI: 9.23-22.00), respectively. Compared with the adult Brazilian male population, the age-adjusted IRR of tuberculosis was 20.46 (95% CI: 14.89-28.13).

DISCUSSION

In our 24-year cohort of patients with silicosis, having ARD did not affect the incidence of mycobacterial infections. Treatment of latent tuberculosis decreased the risk of symptomatic tuberculosis. Having higher FVC% and FEV_1% were associated with a lower risk of NTM. To our knowledge, this is the first study to assess the incidence of mycobacterial disease in patients with silicosis and ARD. Previous studies mainly focused on ARD diagnosis.[2-5,10-13]

The prevalence of ARD in our cohort was 9.5%, in line with previous studies.[2,29-31] Many recent silicosis registries reported high prevalence rates, ranging from 5% to 27%: the Michigan Surveillance System

Table 1. Group characteristics.[a]

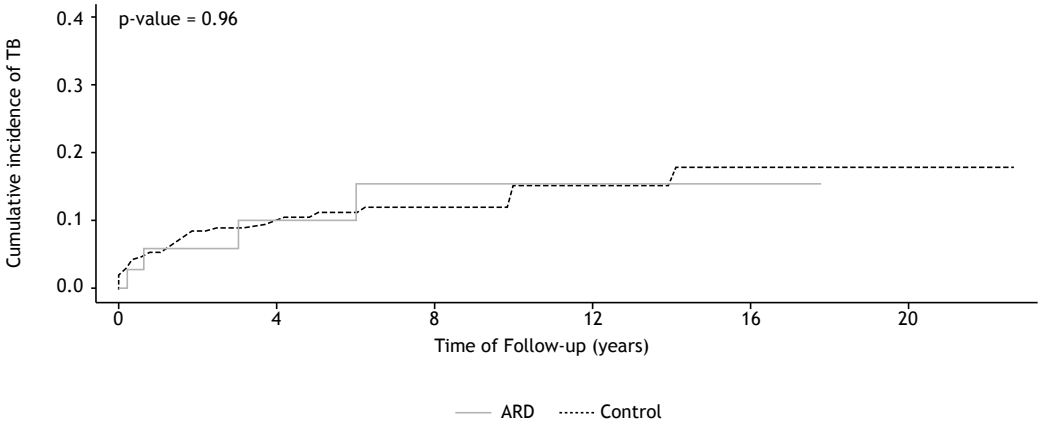
Characteristic	Group	
	ARD n = 35 (9.5%)	Control n = 334 (90.5%)
Female gender	2 (5.7%)	6 (1.8%)
Mean age, years	55.2 ± 9.6	52.7 ± 13.9
Tobacco use		
Never	16 (45.7)	160 (47.9)
Ever	16 (45.7)	168 (50.2)
No information	4 (11.4)	6 (1.8)
Diabetes	4 (11.1)	42 (9.3)
HIV	0 (0.0)	1 (0.3)
Median time of follow-up, years (IQR)	4.6 (2.0-11.3)	3.8 (1.1-7.5)
Median time of silica exposure, years (IQR)	15.0 (5.5-22.5)	16.0 (8.0-27.0)
Pulmonary function parameters		
Mean FVC%	64.7 ± 22.9	74.5 ± 21.2*
Mean FEV_1%	58.3 ± 18.8	62.4 ± 24.8
Mean TLC%	77.2 ± 18.9	88.9 ± 23.8*
Mean DL_{CO}%	58.1 ± 25.3	66.0 ± 28.7
FEV_1% > 80% pred	5 (14.3)	77 (23.1)
80% > FEV_1% > 50% pred	14 (40.0)	126 (37.7)
FEV_1% < 50%	10 (28.6)	92 (27.5)

[a]Values are expressed as n (%), except where otherwise indicated. ARD: autoimmune rheumatic disease. *p < 0.05 in a two-tailed Student's t-test.

Table 2. Prevalence of mycobacterial infections.

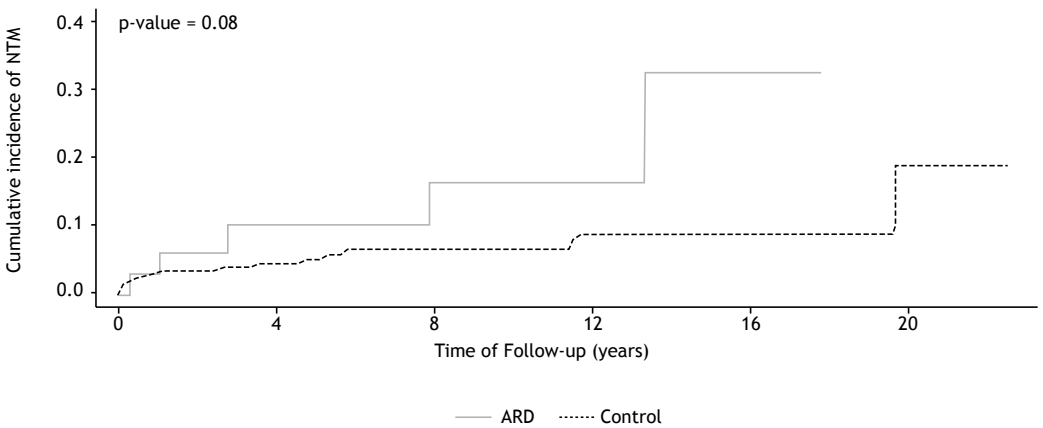
Mycobacterial Infections	Group	
	ARD	Control
Previous tuberculosis, n (%)	4 (11.4%)	51 (15.2%)
Latent tuberculosis, n (%)	8 (22.9%)	68 (20.4%)
Mycobacterial infection during follow-up, n (%)	7 (24.1%)	43 (12.9%)
M. tuberculosis	4	34
M. avium	1	1
M. kansasii	3	17
M. smegmatis	1	0

ARD: autoimmune rheumatic disease.



ARD						
At Risk	35	19	14	7	1	0
Events	0	3	4	4	4	4
Control						
At Risk	334	159	80	41	23	6
Events	0	28	31	33	34	34

Figure 1. Kaplan-Meier curve of cumulative incidence of tuberculosis and number at risk in each group. TB: tuberculosis; and ARD: autoimmune rheumatic disease group.



ARD						
At Risk	35	19	14	7	1	0
Events	0	3	4	4	5	5
Control						
At Risk	334	159	80	41	23	6
Events	0	13	16	17	17	18

Figure 2. Kaplan-Meier curve of cumulative incidence of nontuberculous mycobacteria disease and number at risk in each group. NTM: nontuberculous mycobacteria disease; ARD: autoimmune rheumatic disease group.

for Silicosis reported a prevalence of 5.5% (44/790) in a 1985-2006 cohort[2]; a Spanish study[29] reported a prevalence of 11.0% (54/489); an Israeli cohort of artificial stone silicosis[30] reported a prevalence of 22.5% (9/40); and a US case series of severe silicosis[31] reported a prevalence of 27.7% (5/18). Epidemiological data have strengthened the association between silica and ARD, and experimental studies have yet to understand the mechanisms by which silica exposure affects immune regulation and triggers autoimmunity.[32]

The IR of tuberculosis in our cohort was 20-fold the incidence in the adult Brazilian male population. We chose to compare it with the IR in the adult male population, because there were few women in our cohort (8/369; 2.2%) and the IR of tuberculosis in Brazil is higher in males than in females: in 2023, 69.2% of new cases of tuberculosis occurred in males.[25,33] The IR in our cohort was high, with rates comparable with a cohort of gold miners in South Africa in the 1990s, which reported an annual IR of 27 per 1,000 population in a sample with high HIV

Table 3. Risk of mycobacterial infections. Unadjusted hazard ratio (95% CI) for selected variables.

Variable	Tuberculosis	NTM
Age > 60 years	0.86 (0.43-1.7)	0.74 (0.29-1.9)
Tobacco use ever	0.90 (0.47-1.7)	0.46 (0.19-1.1)
Latent tuberculosis treatment	0.34* (0.12-0.95)	0.54 (0.18-1.6)
Diabetes	0.91 (0.32-2.6)	0.70 (0.16-3.0)
FVC%†	0.82 (0.6-1.1)	0.43* (0.26-0.71)
FEV_1%†	0.90 (0.66-1.2)	0.46* (0.29-0.75)
Time of exposure > 20 years	1.30 (0.64-2.5)	0.79 (0.32-1.9)
Any autoimmune rheumatic disease	0.97 (0.34-2.7)	2.40 (0.88-6.5)
Chronic glucocorticoid use	0.63 (0.15-2.6)	1.80 (0.53-6.1)
csDMARD therapy	0.36 (0.05-2.6)	2.10 (0.63-7.2)
b/tsDMARD therapy	1.9 (0.26-14.0)	3.0 (0.4-23.0)

NTM: nontuberculous mycobacteria disease; csDMARD: conventional synthetic disease-modifying antirheumatic drugs; and b/tsDMARD: biologic/targeted synthetic disease-modifying antirheumatic drugs. *p < 0.05 in a Wald test. †per higher quartile.

prevalence.[8] The high IR of tuberculosis in our cohort may be explained by the high proportion of severe silicosis in our cohort (27.6% had FEV_1% < 50%), as our hospital also hosts a national referral service of lung transplant. In this regard, it is possible that the IR of tuberculosis in this cohort is an overestimation of the true incidence of tuberculosis in individuals with silicosis in Brazil.

Diagnoses of NTM infections have been increasing in the past few decades worldwide due to multiple possible reasons, such as better laboratory techniques, increased tuberculosis/NTM awareness, ageing population, higher prevalence of chronic lung diseases, environmental/climatic changes, and immunosuppressive states.[34] In individuals with ARD, the incidence and the prevalence rates of NTM are higher than in non-ARD individuals,[35,36] and they may develop more severe NTM disease[37] due to the immunosuppressive treatment. In our cohort, the incidence of NTM was similar in both groups, but with a trend towards being higher in the ARD group; a possible explanation was the lower mean FVC% in this group, which is equivalent to more severe lung disease.

Biologic/targeted synthetic treatment changed the treatment of several rheumatic diseases in the early 2000s, but it was associated with increased mycobacterial infections, especially in TNF-α-targeted therapy users.[10] Because only 5 (14%) patients received b/tsDMARD therapy, we were unable to evaluate the risk of mycobacterial disease properly in these patients.

Our study had some limitations. First, we could not access patient data about previous mycobacterial infection diagnosis and treatment before commencing follow-up at our institution. As pulmonary tuberculosis and chronic silicosis have similar radiological features,[16] some patients with silicosis might have been misdiagnosed as having tuberculosis if the diagnosis was solely based on radiological evaluation with negative sputum. Previous tuberculosis is a known risk for development of both NTM[7] and recurrent tuberculosis.[38] Second, because the ARD sample was small, the analysis was underpowered to detect a significant difference in the cumulative incidence of NTM. Third, few ARD patients used b/tsDMARD therapy, so we were unable to assess properly this subset of patients with high risk of mycobacterial infection. Finally, because we did not have a negative control group (i.e., individuals without silicosis), we resorted to comparing our data with general population estimates, which might have overestimated our results, especially considering that the estimates of RA, SLE, and SSc were based on small scale studies in Brazil,[27,28] which may not reflect the actual prevalence of these diseases.

In conclusion, in our cohort of patients with silicosis, having ARD did not affect the incidence of mycobacterial infections. Prevalence rates of ARD were higher than in the general population, as was tuberculosis IR. Our findings strengthen the association between silicosis and ARD and further explore the risk of mycobacterial disease in these patients.

AUTHOR CONTRIBUTIONS

RFM: conceptualization (lead), data curation (lead), formal analysis (lead), methodology (equal), software (equal), visualization (equal), writing – original draft (lead), writing – review & editing (equal). UPS: conceptualization (equal), supervision (equal), validation (equal), writing – review & editing (equal). RKBS: validation (equal), writing – review & editing (equal). EFNY: methodology (supporting), writing – review & editing (equal). EMSL and LCDR: data curation (equal), writing – review & editing (supporting). MTF: project administration (equal), supervision (equal), visualization (equal), writing – review & editing (equal).

CONFLICTS OF INTEREST

RFM, UPS, RKBS, EMSL, and LCDR have no conflicts of interest to declare. EFNY received grants from Astra Zeneca and Glaxo-Smith-Kline for lectures and from GSK for a study on Shingrix vaccine in rheumatic patients (none related to the topics of this article). MTF

received grants from Janssen for board membership in a study related to chronic thromboembolic pulmonary hypertension; from Bayer for board membership in a study related to riociguat; and from Janssen and Bayer related to travel/accommodations/meeting expenses (none related to the topics of this article).

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Lung ultrasound score and diaphragm ultrasound in weaning from mechanical ventilation: are they different in patients with and without COVID-19?

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ABSTRACT

Objective: To compare pre-extubation physiological characteristics and ultrasound variables between patients intubated for COVID-19 compared to a clinical population and those intubated for other reasons. **Methods:** This was a secondary analysis of a prospective cohort study of patients undergoing invasive mechanical ventilation (IMV) for more than 48 h. Patients were divided into two groups: those intubated for COVID-19-induced ARDS and those intubated for other clinical reasons. Ultrasound assessment of lung and diaphragm function was performed before extubation. The results were compared between the two groups of patients. **Results:** In comparison with the patients without COVID-19, those with the disease were younger (a median age of 58 [46-76] years vs. a median age of 75 [69-85] years; $p = 0.01$), had fewer comorbidities (a median Charlson Comorbidity Index of 2 [1-4] vs. a median Charlson Comorbidity Index of 5 [4-6]; $p < 0.01$), and were less severely ill at admission (a median APACHE II score of 9 [8-14] vs. a median APACHE II score of 18 [13-22]; $p < 0.01$). In addition, the median duration of IMV was longer in the COVID-19 patients (11 [9-23] days vs. 6 [3-8] days; $p < 0.01$). Although extubation success rates were similar between the COVID-19 and non-COVID-19 groups (22 [71%] vs. 35 [77.8%]), median lung ultrasound score differed between the two groups (23 [18-25] vs. 15 [11-18]; $p < 0.01$), as did median diaphragmatic excursion (2.1 [1.7-2.4] vs. 1.7 [1.2-2.0]; $p < 0.01$). **Conclusions:** Although patients with COVID-19 requiring ventilatory support are younger and have fewer comorbidities than those intubated for other clinical reasons, they experience longer hospital stays. Although lung ultrasound score can differ between patients with and without COVID-19, these differences do not significantly translate into extubation success rates. Therefore, the utility of ultrasound scores in weaning COVID-19 patients from IMV needs further study.

Keywords: COVID-19; Ventilator weaning; Diaphragm; Ultrasound/diagnosis; Lung.

INTRODUCTION

The COVID-19 pandemic, caused by SARS-CoV-2, has posed an unprecedented challenge to health care systems worldwide.[1,2] In addition to the impact of COVID-19 on public health, the treatment of patients with severe COVID-19, which often leads to ARDS, has been a major focal point. Invasive mechanical ventilation (IMV) has become a crucial intervention for many COVID-19 patients who develop severe acute respiratory failure, such patients accounting for approximately 20% of all hospitalized COVID-19 patients.[3,4] However, successful weaning from IMV and extubation pose significant challenges, given the complexity of the disease and its specific complications. Extubation failure rates in this population appear to be as high as 40%,[5] resulting in high morbidity and mortality.[6,7]

Weaning from mechanical ventilation in COVID-19 patients can be particularly challenging because COVID-19 causes severe lung inflammation, blood clot formation, pulmonary fibrosis, and muscle weakness. These complications can prolong the need for ventilatory support. Therefore, weaning strategies must be adapted to meet the needs of COVID-19 patients, ensuring a safe transition to spontaneous breathing and minimizing the risk of relapse or reintubation. Lung ultrasound has proven to be a valuable tool in the diagnosis and prognosis of patients with COVID-19, helping to identify those at a higher risk of progression to IMV.[8-10] However, the use of lung ultrasound in weaning from ventilatory support has yet to be clarified.

In this context, the objective of the present study was to compare pre-extubation physiological characteristics and ultrasound variables between patients intubated

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for COVID-19 and those intubated for other reasons in the same period.

METHODS

This was a secondary analysis of an original study evaluating the accuracy of thoracic ultrasound in predicting extubation success in patients on IMV for more than 48 h. Because part of the study sample consisted of patients with COVID-19 pneumonia, we decided to compare the patients with and without COVID-19 in terms of physiological characteristics and ultrasound findings.

A prospective cohort study was conducted between January of 2021 and April of 2023 in the ICU of *Hospital Moinhos de Vento*, located in the city of Porto Alegre, southern Brazil. The ICU comprises 72 beds for clinical and surgical admissions. The study was approved by the local research ethics committee (Protocol no. 21991519.8.0000.5330) and was conducted in accordance with the Declaration of Helsinki. All responsible parties of the participating patients gave written informed consent.

The inclusion criteria were as follows: being > 18 years of age; and having been on IMV for more than 48 h because of COVID-19 pneumonia or other causes, the condition leading to IMV being resolved or controlled. After a successful spontaneous breathing trial (SBT) and prior to extubation, thoracic ultrasound was performed, including an assessment of lung aeration and diaphragm function. The exclusion criteria were as follows: having a tracheostomy; receiving exclusive palliative care; having advanced pulmonary fibrosis; having end-stage neuromuscular disease; being on home IMV; being pregnant or lactating; having previously failed extubation during the same hospitalization; and being clinically unable to undergo ultrasound examination. The SBT was performed either with a T-tube or on pressure support mode with reduced parameters.

Arterial blood gas data and vital signs were collected on the day of extubation. The following were also assessed: duration of ventilation until successful SBT; rate of tracheostomy; use of vasoactive drugs; need for renal replacement therapy; and mortality.

Thoracic ultrasound

Ultrasound evaluation was performed by two intensivists with experience in thoracic ultrasound. Calibration was achieved through 20 simultaneous examinations and was assessed with Pearson's correlation coefficient. Thoracic ultrasound, including assessment of lung aeration and diaphragm function, was performed at the end of the SBT, prior to extubation, with the patient in the supine position, with the head of the bed elevated at 30-45°.

Lung ultrasound was performed with a 2-4 MHz convex probe. To calculate the lung aeration score, the anterior, lateral, and posterior areas of the upper and lower intercostal spaces were examined, totaling 12 regions. Four lung aeration patterns were evaluated: normal aeration (0), characterized by pleural sliding with A-lines or a few B-lines (a maximum of 2); moderate loss of lung aeration (1), characterized by multiple well-defined B-lines; significant loss of lung aeration (2), characterized by multiple coalescent B-lines; and lung consolidation (3), characterized by complete loss of aeration. The lung ultrasound score (LUS) was calculated on the basis of the worst observed pattern and ranged from 0 to 36.[11]

Ultrasound assessment of diaphragm function included assessment of diaphragmatic excursion (DE) and diaphragm thickening fraction (DTF) on the right hemidiaphragm, the best ultrasound window being considered. To assess DE, a 2-4 MHz convex probe was used. The probe was placed in the lowest intercostal spaces, on the right anterior axillary line, with the liver as a window for imaging. Initially, the two-dimensional mode was used in order to determine the best approach and select the scanning line of the hemidiaphragm. The ultrasound beam was directed to the diaphragmatic dome at an angle of approximately 70°, measurements being then performed in M-mode. The excursion amplitude was measured on the vertical axis of the trace, from the baseline to the point of maximum height during inspiration. The average of three measurements was calculated.[12] DTF was assessed with a 5-7 MHz linear probe and measured at the zone of apposition of the diaphragm and the rib cage between the anterior axillary and midaxillary lines, between the eighth and tenth intercostal spaces. The two-dimensional mode was used in order to locate the best image, measurements being then performed in M-mode. Diaphragm thickness was evaluated at the end of inspiration (DTi) and at the end of expiration (DTe), DTF being calculated by the following formula and expressed as a percentage: $(DTi - DTe)/DTe \times 100$.[13] The average of three measurements was calculated.

Statistical analysis

Data were collected and analyzed with the IBM SPSS Statistics software package, version 25.0 (IBM Corporation, Armonk, NY, USA), and R software, version 4.3.0 (The R Foundation for Statistical Computing, Vienna, Austria). Qualitative variables were expressed as absolute and relative frequencies, whereas quantitative variables were expressed as medians and interquartile ranges. For quantitative variables, the data distribution types were assessed with the Shapiro-Wilk test, and the Mann-Whitney U test was used. Multivariate Poisson regression was performed to adjust for potential influences of covariates.

RESULTS

Seventy-six patients on IMV for more than 48 h were included in the study. Figure 1 shows the patient selection process. The patients with COVID-19 were younger than those without the disease (a median age of 58 [46-76] years vs. a median age of 75

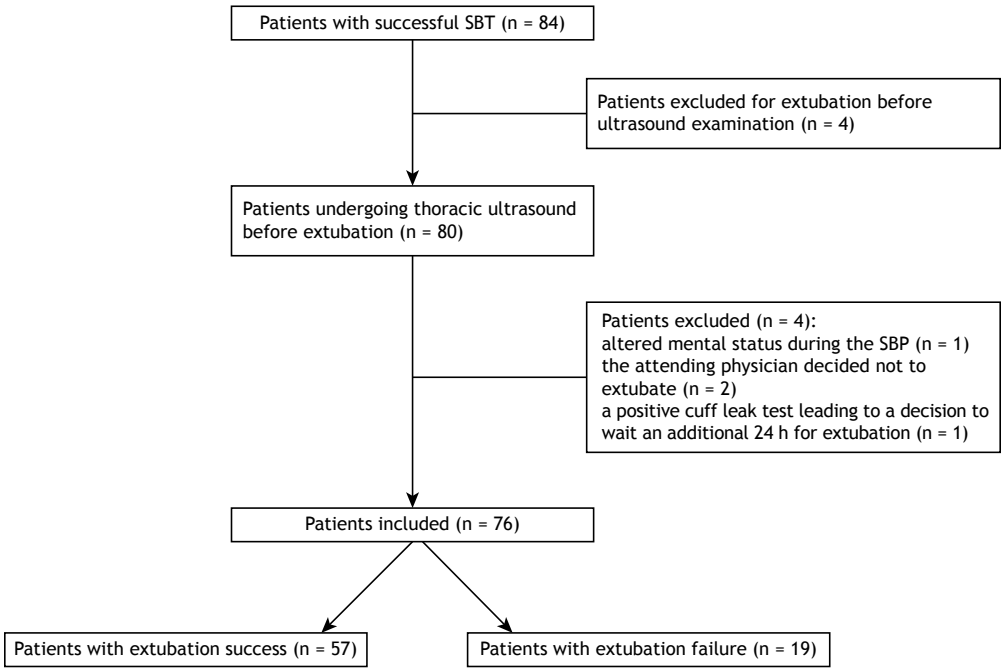

Figure 1. Flow chart of patient selection. SBT: spontaneous breathing trial.

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

Variable	Total	Non-COVID-19	COVID-19	p	
				Crude*	Adjusted**
Number of patients	76 (100%)	45 (59.2%)	31 (40.8%)		
Age, years	71 (56-82)	75 (69-85)	58 (46-76)	0.01	0.03
Male	46 (60.5%)	26 (57.8%)	20 (64.5%)	0.55	0.49
Charlson Comorbidity Index	4 (2-6)	5 (4-6)	2 (1-4)	< 0.01	0.04
APACHE II score	14 (9-20)	18 (13-22)	9 (8-14)	< 0.01	< 0.01
Pre-ICU admission length of stay, days	1 (0-4)	1 (0-5)	2 (1-4)	0.54	0.63
Duration of IMV before SBT, days	7 (4-10)	5 (3-8)	10 (7-13)	< 0.01	0.01
$PaCO_2$, mmHg	41 (37-46)	39 (36-44)	42 (40-48)	0.02	0.08
Duration of SBT, min	50 (30-60)	50 (35-60)	60 (30-69)	0.18	0.23
Use of vasopressor	74 (97.4%)	44 (97.8%)	30 (96.8%)	> 0.99	0.94
Need for RRT	21 (27.6%)	15 (33.3%)	6 (19.4%)	0.18	0.12
Systemic corticosteroid use	63 (82.9%)	32 (71.1%)	31 (100%)	0.01	0.01
SBT on PSV	40 (52.5%)	11 (24.4%)	29 (93.5%)	< 0.01	< 0.01
Extubation success within 72 h	57 (75%)	35 (77.8%)	22 (71%)	0.50	0.47
Tracheostomy	14 (18.4%)	5 (11.1%)	9 (29%)	0.04	0.04
Simple weaning	47 (61.8%)	34 (75.6%)	13 (41.9%)	< 0.01	< 0.01
Duration of IMV, days	8 (4-12)	6 (3-8)	11 (9-23)	< 0.01	< 0.01
Length of ICU stay, days	17 (12-29)	15 (10-23)	23 (16-36)	< 0.01	< 0.01
Length of hospital stay, days	35 (21-51)	32 (18-51)	38 (23-57)	< 0.01	0.03
Death during hospitalization	22 (29.3%)	6 (20%)	16 (35.6%)	0.14	0.08
Discharge from the ICU	57 (75%)	25 (80.6%)	32 (71.1%)	0.34	0.31

IMV: invasive mechanical ventilation; SBT: spontaneous breathing trial; RRT: renal replacement therapy; and PSV: pressure support ventilation. [a]Data expressed as n (%) or median (IQR). *Pearson's chi-square test or Fisher's exact test for qualitative variables and the Mann-Whitney test for quantitative variables. **Multivariate Poisson regression to adjust for potential influences of covariates.

[69-85] years; p = 0.01), had fewer comorbidities (a median Charlson Comorbidity Index of 2 [1-4] vs. a median Charlson Comorbidity Index of 5 [4-6]; p < 0.01), and were less severely ill at ICU admission (a median APACHE II score of 9 [8-14] vs. a median APACHE II score of 18 [13-22]; p < 0.01). The patients

intubated for COVID-19 spent more time on IMV until SBT (10 [7-13] days vs. 5 [3-8] days; p < 0.01) and underwent SBT more often on pressure support ventilation (29 [93.5%] vs. 11 [24.4%]; p = 0.01) than did those intubated for other reasons. There was no difference in extubation success within 72 h between the non-COVID-19 and COVID-19 groups (35 [77.8%] vs. 22 [71%]; p = 0.5). However, the non-COVID-19 population had more patients with simple weaning (34 [75.6%] vs. 13 [41.9%]; p = 0.003) and underwent fewer tracheostomies (5 [11.1%] vs. 9 [29%]; p = 0.04). On the day of the SBT and subsequent extubation, median $PaCO_2$ was slightly higher in the patients with COVID-19 than in those without the disease (42 [40-48] vs. 39 [36-44]; p = 0.02). There was no difference in mortality between the non-COVID-19 and COVID-19 patients (16 [35.6%] vs. 6 [20%]; p = 0.14). Table 1 shows the characteristics of the two populations.

Inter-rater reliability was found to be good, with an I^2 of 0.83 for the LUS, an I^2 of 0.82 for DE, and an I^2 of 0.87 for DTF. With regard to the results of ultrasound assessment (Table 2 and Figure 2), even after a multivariate analysis, *correcting for variables that showed significant differences,* the median LUS of the COVID-19 patients was significantly higher than that of the non-COVID-19 patients (23 [18-25] vs. 15 [11-18]; p < 0.01), as was the median DE (2.1 [1.7-2.4] vs. 1.7 [1.3-2.0]; p < 0.01). As can be seen in Table 2 and Figure 2, DTF was similar between the two groups of patients (30% [20-40%] vs. 30% [20-30%]; p = 0.49).

A binary logistic regression evaluating the subgroup of patients intubated for COVID-19 showed that the ultrasound scores were not accurate in predicting extubation success (Table 3).

DISCUSSION

In the present study we compared patients intubated for COVID-19 with those intubated for other reasons. The group of patients with COVID-19 was younger and had fewer comorbidities. They also had a lower severity score at ICU admission. However, they remained on IMV for a longer duration of time, resulting in longer ICU and hospital stays. Nevertheless, they did not have higher mortality rates. Socolovithc et al. reported similar findings in a study in which patients with COVID-19 required IMV three times more often than did those admitted for other reasons.[14] A systematic review including 32 studies and over 69,000 patients confirmed these findings, showing high rates of IMV use, longer lengths of stay, and elevated mortality.[15]

Lung ultrasound has been used in order to diagnose and prognosticate COVID-19 pneumonia.[8,9] However, only a few studies have examined the use of lung ultrasound in weaning from IMV. This is the first study to assess the LUS in COVID-19 patients at the time of extubation. The LUS is used as a tool to aid in weaning non-COVID-19 patients, with cutoff points of 13 or less to predict successful weaning from IMV.[11,16] In the present study, the patients with COVID-19 had a higher LUS than did those without the disease; however, they achieved similar extubation success rates, indicating that a cutoff point of 13 or less may not be applicable to these individuals. The role of LUS in weaning from IMV still needs further investigation. In assessing the ability of ultrasound scores to predict extubation success in patients with COVID-19, the LUS tended to be higher in those in whom extubation failed, although the difference was not significant. This could be explained by the small number of intubated patients with COVID-19.

The diaphragm also appears to be affected differently in this population of patients. In a study involving autopsy diaphragm specimens from 34 critically ill individuals (26 of whom had COVID-19 and 8 of whom did not have the disease), Shi et al. demonstrated that fibrosis was twice as high in those with COVID-19 than in those without the disease, suggesting that severe COVID-19-induced myopathy leads to diaphragmatic weakness and contributes to weaning failure.[17] seems to be a predictor of worse prognosis, associated with lymphocyte count.[18] Hadda et al. found that DTe decreases during hospitalization, although the study population consisted of spontaneously breathing patients.[19] Corradi et al. showed that DTF may be a predictor of failure of noninvasive support in COVID-19 patients.[20] However, the use of DTF in weaning from IMV has been poorly studied. Vetrugno et al. evaluated DTF as an indicator of weaning failure in patients with COVID-19 but found no difference between the success and failure groups.[5] In the present study, DTF was similar between the groups of patients with and without COVID-19. In addition, our subgroup analysis of patients intubated for COVID-19 showed that DTF was not a good predictor of extubation success.

Regarding the assessment of DE in COVID-19 patients, it has been shown that DE assessment within the first 15 min of SBT has good accuracy in

Table 2. Multivariate analysis of ultrasound variables in patients with and without COVID-19.[a]

Variable	Total	COVID-19	Non-COVID-19	p*	
				Crude	Adjusted
LUS	17 (13-24)	23 (18-25)	15 (11-18)	< 0.01	0.02
DE, cm	1.76 (1.42-2.22)	2.1 (1.7-2.4)	1.7 (1.3-2.0)	< 0.01	0.04
DTF, %	26 (16-35)	30 (20-30)	30 (20-40)	0.49	0.45

LUS: lung ultrasound score; DE: diaphragmatic excursion; and DTF: diaphragm thickening fraction. [a]Data expressed as median (IQR). *Mann-Whitney test, crude and adjusted for variables showing significant differences in the multivariate Poisson regression model.

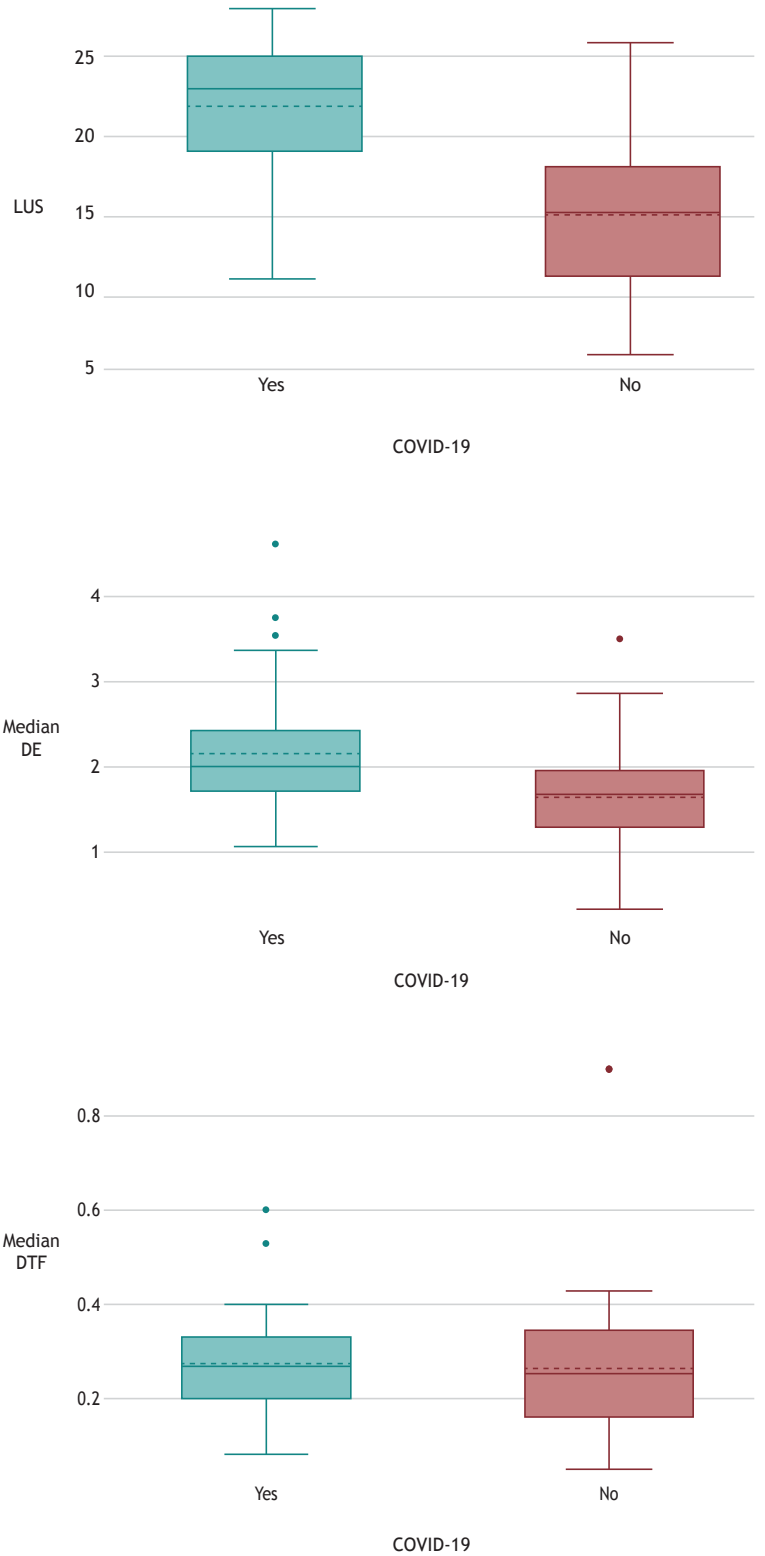

Figure 2. Box plot of ultrasound variables in patients with and without COVID-19. LUS: lung ultrasound score; DE: diaphragmatic excursion; and DTF: diaphragm thickening fraction.

predicting weaning success even when performed under positive pressure, where it may be influenced by increased lung volumes.[21,22] In the present study, DE was higher in the COVID-19 group than in the non-COVID-19 group; however, DE was not a good predictor of extubation success when evaluated

Table 3. Ultrasound evaluation of COVID-19 patients who failed or succeeded extubation within 72 h.[a]

	Total	Extubation failure	Extubation success	Crude		Adjusted*	
				OR (95% CI)	p	OR (95% CI)	p
LUS	23(19-25)	25 (24-26)	21 (18-24)	0.88 (0.68-1.08)	0.26	0.82 (0.6-1.02)	0,10
DE, cm	2.01 (1.73-2.41)	2.13 (1.75-2.39)	1.86 (1.68-2.38)	0.73 (0.31-2.53)	0.74	0.7 (0.19-2.7)	0,57
DTF, %	27 (20-33)	28 (18-34)	26 (21-32)	1 (0.93-1.08)	0.96	1.02 (0.94-1.12)	0,65

LUS: lung ultrasound score; DE: diaphragmatic excursion; and DTF: diaphragm thickening fraction. [a]Data expressed as median (IQR). *Binary logistic regression adjusted for potential influences of covariates.

exclusively in the group of patients with COVID-19. In one of the aforementioned studies,[21] pressure support ventilation during SBT was set at 5 cmH2O, whereas, in the present study, it varied.

The present study is the first to compare ultrasound scores between patients intubated for COVID-19 and those intubated for other reasons. Additionally, this is the first study to assess the LUS at the time of extubation in patients with SARS-CoV-2 pneumonia. However, the study was conducted at a single center and is a secondary analysis of an original study.

AUTHOR CONTRIBUTIONS

LCM participated in the study conception and design; the acquisition, analysis, and interpretation of data; the statistical analysis; and the drafting of the manuscript. BC and GHS participated in the acquisition of data. JMW participated in the statistical analysis. FLDN participated in the study conception and design; the acquisition, analysis, and interpretation of data; the statistical analysis; and the drafting and revision of the manuscript. PTD participated in the study conception and design; the analysis and interpretation of data; and the drafting and revision of the manuscript. AS and J-JR participated in the drafting and revision of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Recent increase in asthma mortality in Brazil: a warning sign for the public health system

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ABSTRACT

Objective: To provide an update on asthma mortality trends in Brazil and its regions between 2014 and 2021. **Methods:** This was a retrospective descriptive observational study based on asthma mortality data from the Brazilian National Ministry of Health Mortality Database for the 2014-2021 period. **Results:** In the study period, there were 18,584 asthma deaths in Brazil, with an annual increase of 2.5%, corresponding to 0.03 deaths/100,000 population (95% CI, 0.01-0.04; p = 0.01). The northeastern region of the country had the highest prevalence of asthma deaths (1.50 deaths/100,000 population), and the southern region showed the greatest variation in the study period (44%). We observed a higher proportion of deaths among females and elderly patients, and when analyzing asthma deaths by place of occurrence, we observed that 28% of all deaths occurred at home. **Conclusions:** Asthma mortality remains high and shows an increasing trend for the first time in the past decades. This constitutes an important public health concern, given the treatable nature of the disease.

Keywords: Public health; Asthma; Mortality.

INTRODUCTION

Asthma is one of the most common noncommunicable diseases, with a substantial impact on the quality of life of patients.[1] Asthma is considered a public health issue in Brazil and worldwide, and its prevalence has been rising in the past decades, demanding closer attention from health authorities and the medical community.[2,3] Epidemiological data reveal the extent of this challenge, raising the need for in-depth studies to understand the underlying factors and develop more effective strategies of prevention and treatment.[4] The prevalence of asthma has been shown to be high in many countries, including those in Latin America.[2] Asthma mortality is an important outcome to be monitored by public health systems worldwide.[3,5]

In Brazil, until 2013, studies based on data from the *Departamento de Informática do Sistema Único de Saúde* (DATASUS, Information Technology Department of the Brazilian Unified Health Care System) and the *Instituto Brasileiro de Geografia e Estatística* (IBGE, Brazilian Institute of Geography and Statistics) showed a historical reduction in asthma mortality.[6] By updating asthma mortality data in Brazil we are able to understand the dynamics of the disease and the factors that influence it; this is essential to guide public health policies and appropriate interventions aimed at improving the quality of life of asthma patients and reducing the burden of asthma morbidity and mortality.[7] The availability of open data from death certificates and ICD-10 codes allows us to perform a detailed evaluation of the trends in asthma mortality in Brazil.[8] The objective of the present study was to provide an update on asthma mortality trends in Brazil and its regions between 2014 and 2021.

METHODS

This was a retrospective descriptive observational study based on asthma mortality data from the *Sistema de Informações Sobre Mortalidade do Ministério da Saúde do Brasil* (SIM, Brazilian National Ministry of Health Mortality Database), available at https://opendatasus.saude.gov.br/, for the 2014-2021 period.[9] The study period was defined on the basis of the fact that a previous report covers the 2008-2013 period.[6] The study population consisted of all asthma deaths (ICD-10 codes J45 and J46) among individuals > 6 years of age.[7] Deaths from COVID-19 alone (ICD-10 codes B34.2 and U07.2) were not included in the analysis.

We also conducted a geographic analysis, correcting the variables for the population size as assessed by the 2022 IBGE census and selecting the population > 6 years of age. The extracted data were subdivided into Brazil and its regions (central-west, north, northeast, south, and southeast). To analyze asthma deaths exclusively, we used the SIM variable "*causabas*," which refers to the underlying cause of death. According to the SIM Procedures Manual, the underlying cause of death is understood as the disease or injury that started the succession of morbid events that directly led to death.[10]

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The mortality rate was calculated by dividing the total number of asthma deaths (stratified by country region, age group, sex, and place of occurrence) by the corresponding population (within each stratification), multiplied by 100,000.[11] The relative variation for each year was calculated in relation to the year 2014. To obtain the mean percentage of variation for each stratum, we calculated the average of the variations.

To compare prevalence rates, we employed a linear regression model. To compare proportions, we used the chi-square test. To analyze the number of years of schooling, we selected adults > 18 years of age. The significance level was set at 5%. The data were processed with R studio, version 2023.6.01 (The R Foundation for Statistical Computing, Vienna, Austria). The SIM is in the public domain, requiring no research ethics committee approval. The analysis script (in R language) is available at https://github.com/mobrant94/asthma_mortality.

RESULTS

Between 2014 and 2021, 18,584 asthma deaths were recorded in Brazil (Figure 1), with a mean prevalence of 1.16/100,000 population per year. There was an increase of 14% in asthma deaths, corresponding to 0.03 deaths/100,000 population per year (95% CI, 0.01-0.04; p = 0.01). The northeastern region showed the highest annual average (of 1.50 deaths/100,000 population), whereas the central-western region had the lowest annual average (of 0.48 deaths/100,000 population). The southern region showed the greatest variation during the study period, from 0.97 deaths/100,000 population in 2014 to 1.39 deaths/100,000 population in 2021, corresponding to an increase of 44%, which is equivalent to 0.06 deaths/100,000 population per year (95% CI, 0.01-0.09; p < 0.01). On the other hand, the northeastern region showed the lowest variation, with 1.41 deaths/100,000 population in 2014 and 1.58 deaths/100,000 population in 2021, an overall increase of 12%, corresponding to approximately 0.03 deaths/100,000 population per year (95% CI, 0.01-0.07; p = 0.01; Figure 2).

The highest proportion of deaths was observed in females (Figure 3), accounting for an annual average of 64% of total deaths (p < 0.01). In the population ≥ 60 years of age, we observed an asthma mortality prevalence that was 10 times higher than that in the 18- to 59-year age bracket (5.87 vs. 0.59 deaths/100,000 population). As for the variation in each age group, individuals < 18 years of age showed an overall reduction of 10% and an annual decrease of 0.01 deaths/100,000 population (95% CI, −0.01 to 0.01; p = 0.88). In the 18- to 59-year age bracket, a 19% increase was observed, with an annual increase of 0.02 deaths/100,000 population (95% CI, 0.01-0.04; p = 0.03). In the group of individuals ≥ 60 years of age, there was an overall reduction of 0.5% and an annual decrease of 0.03 deaths/100,000 population (95% CI, −0.13 to 0.07; p = 0.47). Proportionally, the group of individuals < 18 years of age accounted for 2% of all deaths in the study period, followed by the group of individuals in the 18- to 59-year age bracket (30%) and that of those ≥ 60 years of age, which accounted for 68% of all asthma deaths (p < 0.01; Figure 4).

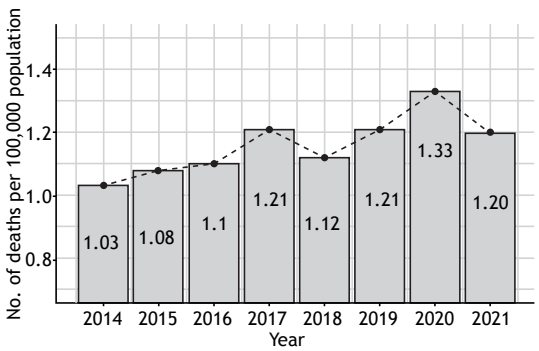

Figure 1. Overall mortality from asthma in Brazil between 2014 and 2021.

Regarding the proportion of deaths by place of occurrence (Figure 5), 59% occurred at a hospital, 28% occurred at home, 10% occurred in health facilities other than hospitals, and 3% occurred in the street or in public spaces (p < 0.01). Between 2014 and 2021, deaths occurring in health facilities other than hospitals or at home showed average increases of 86% and 23%, respectively. Additionally, we observed a significant increasing trend in both categories (p < 0.05).

Regarding deaths by place of occurrence and region (Figure 6a), the northeastern region showed the highest proportion of deaths occurring at home (35%), whereas the northern region had the lowest proportion of deaths occurring at home (22%). Regarding sex (Figure 6b), the proportion of deaths occurring at home was higher among males than among females (32% vs. 26%). When looking at the age groups (Figure 6c), we found that the group of individuals < 18 years of age accounted for 15% of all deaths occurring at home, whereas that of those ≥ 60 years of age accounted for 31% of all deaths occurring at home. Regarding the level of education (Figure 6d), the proportion of deaths occurring at home was higher among individuals who had had < 9 years of schooling than among those who had had ≥ 9 years of schooling (30% vs. 22%).

DISCUSSION

We found an increase of 14% in asthma mortality in Brazil between 2014 and 2021. Asthma mortality in Brazil remains high despite regional disparities, with an average of 6 asthma deaths/day. The group of individuals ≥ 60 years of age showed the highest mortality rate, and females showed the highest proportion. The proportion of deaths that occurred at home in Brazil was 28%.

Studies conducted before 2015 showed a progressive decrease in the number of asthma deaths in Brazil,

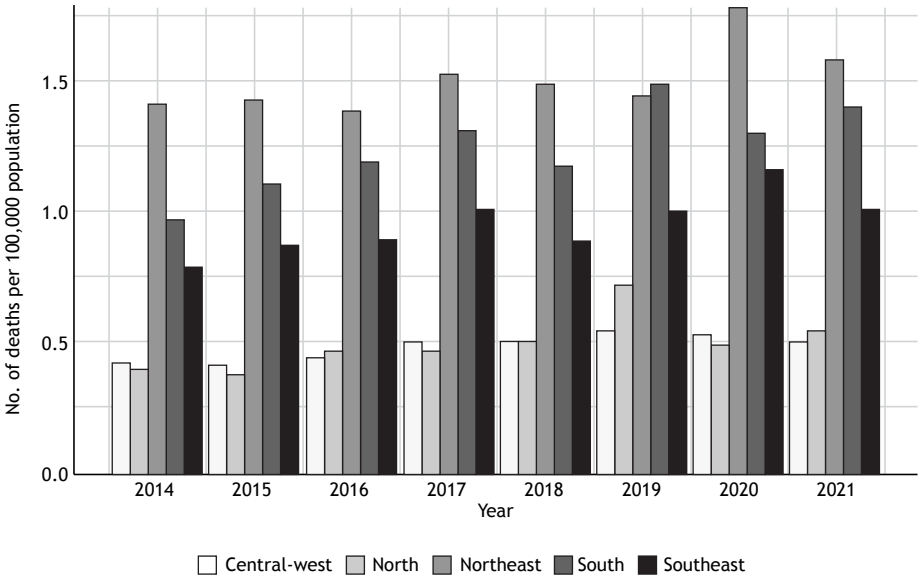

Figure 2. Asthma mortality in Brazil, by region.

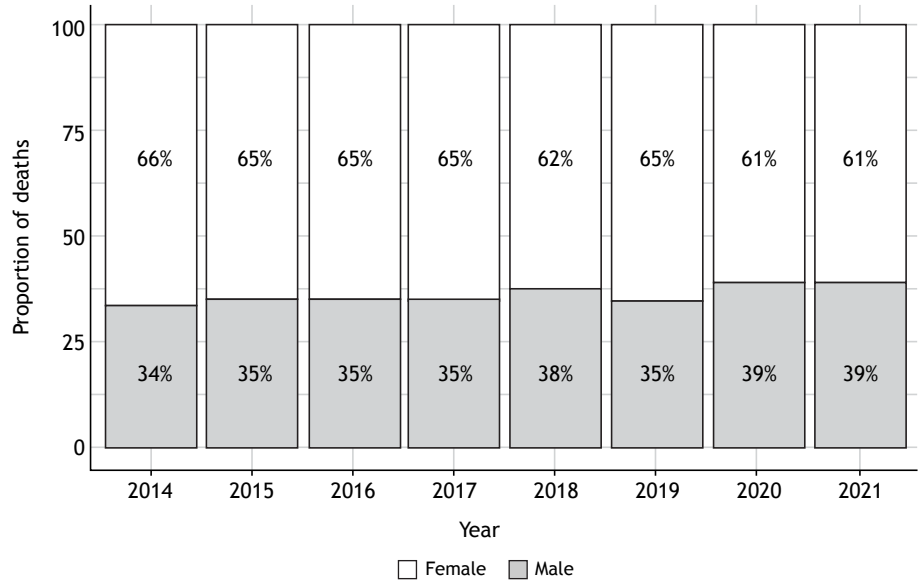

Figure 3. Proportion of asthma deaths in Brazil, by sex.

showing a reduction of 46.2% between 1980 and 2014, and of 10% between 2008 and 2013.[6,12] A decreasing mortality trend was also observed between 1980 and 2010, with an annual percentage reduction of approximately 2%.[7,13] Global data also showed a downward trend in asthma mortality, with a 57% decrease in global mortality between 1993 and 2006, and an approximate mortality rate of 0.9/100,000 population from 2006 to 2012.[14] However, our study showed an increase of asthma deaths of approximately 2.5% per year from 2014 to 2021. Estimates from the WHO corroborate our findings, showing an increasing trend in asthma mortality rates between 2014 and 2020 in Brazil, by approximately 30% (1 vs. 1.3/100,000 population).[15]

In the present study, we observed a peak in mortality in 2020, the first year of the COVID-19 pandemic. Although we excluded deaths directly related to COVID-19, this increase may reflect the indirect impacts of the pandemic, such as reduced access to health care and poor diagnosis of respiratory conditions. Furthermore, although the SIM/DATASUS is robust, it is subject to underreporting and misclassification. Our findings highlight the need for greater accuracy in death records and the management of respiratory diseases during pandemics.

We found higher asthma mortality rates in the northeastern region of Brazil. Data published between 2008 and 2013 showed that the southeastern and southern regions had higher in-hospital asthma

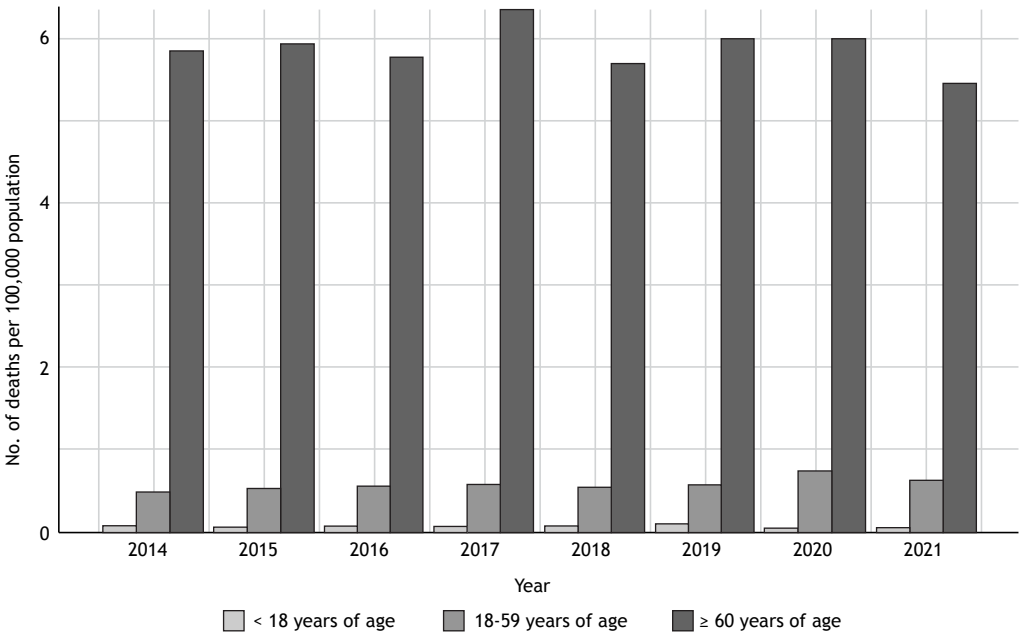

Figure 4. Asthma mortality in Brazil, by age group.

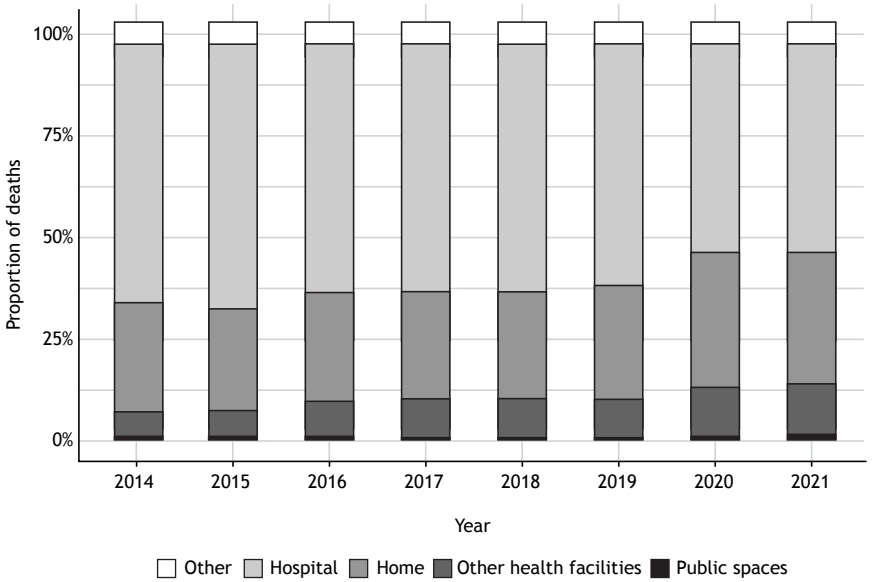

Figure 5. Proportion of asthma deaths in Brazil, by place of occurrence.

mortality rates.[6,16] On the other hand, studies evaluating overall mortality between 1998 and 2009, and in individuals ≤ 19 years of age between 1996 and 2015 in Brazil showed that the northeastern region had higher overall asthma mortality rates.[17,18] Although we did not directly assess the Human Development Index, it is important to consider that the northeastern region of Brazil historically has one of the lowest Human Development Indices, which could be indicative of disparities in access to health care and the quality of medical care.[19]

Asthma-related mortality was found to be higher in females than in males in the present study, with asthma deaths among females accounting for 64% of all asthma deaths. This finding is consistent with data from the United States.[20] However, we observed a significant increasing trend in mortality among males, which is consistent with previous studies.[15,21] Further studies are needed to find out why females are at a higher risk of death from asthma.

Individuals ≥ 60 years of age showed the highest asthma mortality rates in the study period. Previous studies have also found higher asthma mortality rates in the elderly.[7,22,23] Data from the Centers for Disease Control and Prevention for the 2006-2018 period in the United States showed a higher mortality

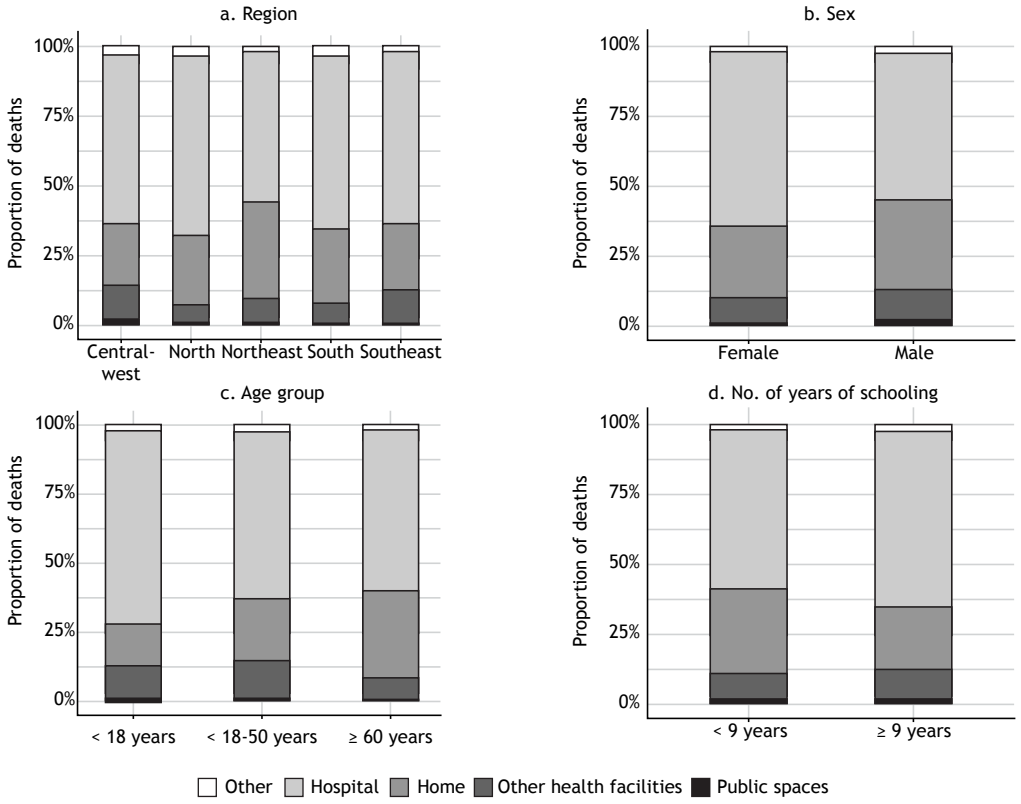

Figure 6. Proportion of asthma deaths in Brazil, by place of occurrence, in relation to region, sex, age group, and number of years of schooling.

rate among individuals > 65 years of age (29.5 per million) and a lower mortality rate among younger individuals, with a 1.6 per million rate in children in the 0- to 4-year age bracket.[24] One Brazilian study, which also used data from the DATASUS (for the 1980-2012 period), found a higher mortality rate in individuals > 75 years of age, as well as an increase in the proportion of asthma deaths in older age groups over time.[7] We acknowledge that elderly patients may have a higher asthma mortality rate because of the presence of comorbidities, highlighting the need for a protocol for the clinical management of severe asthma in elderly patients in the public health system.

The place of death occurrence is an important aspect to be considered when developing public health strategies to reduce asthma mortality. Deaths occurring at home or in a hospital setting can influence prevention strategies for asthma-related deaths by public health officials. Our study showed that approximately one third of all asthma deaths occurred at home, and the northeastern region had the highest proportion of at-home deaths (35%). In Denmark, one study showed that approximately 25% of all individuals who had a sudden death at home had asthma.[25] Regarding age groups, we showed that 15% and 31% of all at-home deaths occurred in individuals < 18 years of age and ≥ 60 years of age, respectively. The high prevalence of at-home asthma deaths in our study shows that this must be a priority concern for the public health system. Furthermore, we found that individuals who had had < 9 years of schooling had a higher proportion of deaths at home than did those who had had ≥ 9 years of schooling. Studies suggest that lower parental or individual educational levels are risk factors for mortality.[18] Factors such as region, sex, age, and educational level do not seem to be associated with the place of death occurrence.

Our study has some limitations. First, because our study involves secondary data, there is a risk of issues related to cause of death notification, such as underreporting of asthma. However, previous studies have shown that mortality records in Brazil have a data completeness of 98%.[26] Another limitation refers to the input of DATASUS data. To minimize this and ensure that the data were treated reliably, we collected and analyzed data consolidated in the SIM 12 months after the index year. On the basis of our previous experience using the DATASUS, a period of 12 months is enough for the database to present the final figures.[27] The COVID-19 pandemic period included in the study may introduce some bias, particularly regarding the difficulty in accessing health care services for non-COVID-19 conditions, which could have influenced asthma mortality patterns during the study period. Finally, these limitations are mitigated by the fact that our update on asthma mortality trends is based on official data from the Brazilian National Ministry of Health.[28]

In conclusion, asthma mortality remains high and shows an increasing trend for the first time in the past decades. This constitutes a serious public health issue, given the treatable nature of the disease. Our findings highlight the need for greater attention to asthma diagnosis and management in Brazil, particularly in the primary health care setting.

AUTHOR CONTRIBUTIONS

MB participated in the conception and design of the study; in the acquisition, analysis, and interpretation of data; and in the writing and critical review of the article. JH, MB, and SS participated in the design of the study and in the writing of the article. FF and PMP participated in the design of the study; in the interpretation of data; and in the writing and critical review of the article. All authors approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

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Recommendations for the diagnosis and treatment of alpha-1 antitrypsin deficiency

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ABSTRACT

Alpha-1 antitrypsin deficiency (AATD) is a relatively rare genetic disorder, inherited in an autosomal codominant manner, that results in reduced serum AAT concentrations, with a consequent reduction in antielastase activity in the lungs, as well as an increased risk of diseases such as pulmonary emphysema, liver cirrhosis, and necrotizing panniculitis. It results from different mutations in the *SERPINA1* gene, leading to changes in the AAT glycoprotein, which can alter its concentration, conformation, and function. Unfortunately, underdiagnosis is quite common; it is possible that only 10% of cases are diagnosed. The most common deficiency is in the Z variant, and it is estimated that more than 3 million people worldwide have combinations of alleles associated with severe AATD. Serum AAT concentrations should be determined, and allelic variants should be identified by phenotyping or genotyping. Monitoring lung function, especially through spirometry, is essential, because it provides information on the progression of the disease. Although pulmonary densitometry appears to be the most sensitive measure of emphysema progression, it should not be used in routine clinical practice to monitor patients. In general, the treatment is similar to that indicated for patients with COPD not caused by AATD. Exogenous administration of purified human serum-derived AAT is the only specific treatment approved for AATD in nonsmoking patients with severe deficiency (serum AAT concentration of < 57 mg/dL or < 11 μM), with evidence of functional loss above the physiological level.

Descriptors: alpha 1-antitrypsin; Emphysema; Pulmonary disease, chronic obstructive.

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder that was first recognized in 1963. Underdiagnosis of AATD has been widely reported in the literature.[1] It is a relatively rare genetic disorder that is inherited in an autosomal codominant manner and results in reduced serum AAT concentrations, consequently reducing antielastase activity in the lungs, as well as increasing the risk of diseases such as pulmonary emphysema, liver cirrhosis, and necrotizing panniculitis.[2,3]

The serine protease inhibitor gene (*SERPINA1*), located on chromosome 14q32.1, encodes AAT. This gene is highly pleomorphic and its variants can be related to normal or below-normal concentrations of AAT in mild, moderate, or severe forms, or even to a total lack of AAT secretion (undetectable serum concentrations), designated the null variant.[4] In most countries, the prevalence of AATD is not known, being better known in Europe and the United States.[5] There is now more information on the disorder, and tests made available by the pharmaceutical industry have facilitated the genetic diagnosis.[6,7]

Although AAT production occurs mainly in hepatocytes, it also occurs in intestinal cells, alveoli, macrophages, neutrophils, and the cornea.[3] The protein is released into the bloodstream and acts as a protector against neutrophil elastase, mainly in the lungs.[3] Its half-life is 3-5 days, and serum concentrations vary little in normal individuals, although they can be elevated during inflammatory processes.[3]

Unfortunately, it is possible that only 10% of cases of AATD are diagnosed, a high rate of underdiagnosis that precludes genetic counseling and makes appropriate treatment difficult.[8] The determination of serum concentrations of

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AAT is recommended in all patients with COPD, liver disease, necrotizing panniculitis, granulomatosis with polyangiitis, or bronchiectasis without a defined cause.[2,9] The World Health Organization (WHO) suggests that patients diagnosed with late-onset asthma be evaluated for AATD.[10]

Patients with pulmonary manifestations should be monitored according to the recommendations for COPD.[11] In some cases, such patients should be referred for specific treatment with AAT replacement.[12]

The aims of this article are to improve care for individuals with AATD; to accurately inform fellow pulmonologists about AAT and AATD; to promote active AATD case finding; to encourage the creation of treatment guidelines; to stimulate the evaluation of AAT in all diseases potentially associated with AATD; and to investigate the family members of patients with AATD, as well as individuals with suspicious findings on imaging examinations and those with clinical symptoms or functional alterations. Thus, the rates of underdiagnosis could be reduced and the possibility of appropriate care could be increased.

GENETICS

Mutations in the *SERPINA1* gene lead to different changes in the AAT glycoprotein, which can alter its concentration, conformation, and function.[5,13] More than 200 variants of the *SERPINA1* gene have been described.[14] The AAT variants initially found were classified with letters from A to Z, depending on the speed of migration of the molecule in a pH gradient after isoelectric focusing. The normal protease inhibitor (PI) of AAT is designated with the letter M, also called the M allele, and is present in 85-90% of the population.[13,15] Individuals homozygous for the M allele are designated Pi*MM homozygotes and have normal serum AAT concentrations (100-220 mg/dL). The M allele has some benign subvariants, including two M1 variants (Ala213 and Val213), as well as variants M2, M3, and M4, and there are tests that can be employed to differentiate among those.[16] Other benign alleles are E, G, and Zpratt, which encode AAT variants that do not decrease the serum concentration or function of the protein.[17,18]

The allele most commonly associated with severe AATD is Z, mainly in homozygosity (Pi*ZZ), presenting serum AAT concentrations of 10-20% of normal (20-45 mg/dL). The Z allele is found most commonly in northern and western Europe.[5,16,19] In the Z allele, glutamic acid is replaced by lysine at position 342 of the *SERPINA1* gene, and this mutation leads to the synthesis of a malformed protein, which can polymerize and accumulate in hepatocytes, potentially causing liver disease.[5,15] Subsequently, the secretory defect leads to a reduction in serum concentrations and activity, predisposing to the onset of emphysema.[5,20,21] Among the known mutations, Pi*ZZ is present in 95% of cases of severe deficiency and the Z allele can be found in one in 25 people of European ancestry. Heterozygous mutations, such as Pi*MZ, generally cause a mild to moderate reduction in AAT. Combinations of the Z allele and other pathogenic variants (e.g., Pi*SZ and $M_{Procida}$) can result in below-normal serum AAT concentrations and lung disease.[5,15] However, there are variations in the clinical expression of the disease, in which the presence of AATD alone is not sufficient to induce pulmonary emphysema. Factors such as smoking, environmental exposure, and genetic factors predispose to the onset of emphysema in these cases.[9,22] Many patients with the Pi*ZZ genotype will never develop pulmonary emphysema over the course of their lives.

Other alleles associated with severe AATD are $M_{Procida}$, $M_{Heerlen}$, M_{Malton}, S_{Iiyama}, P_{Lowell}, as well as some rarer variants and the family of null (Q0) alleles, which do not produce AAT.[5,15] Alleles such as the variants I and S, the latter being the variant most commonly found in Mediterranean Europe (mainly in the Iberian Peninsula), lead to lower serum concentrations than in the Pi*MM genotype, although still with protective value, resulting in a clinical form of AATD that is milder.[5] However, when these variants are associated with risk factors, such as smoking, they can lead to pulmonary involvement.[2,23] The so-called dysfunctional variants, including the F and Pittsburgh variants, lead to the production of AAT with abnormal function, with low binding to neutrophil elastase or altered inhibitory activity.[23,24]

The Z, S_{Iiyama}, M_{Malton}, and King alleles do not affect synthesis, although 70% of the mutant AAT is retained within the hepatocyte and 15% forms polymers that are not fully degraded and accumulate in the liver, causing chronic disease. The formation of hepatic polymers is directly related to structural alterations in the mutant protein.[25] Currently, it is known that several other alleles, although considered rare, can cause serious liver problems[12]: Pi*$M_{Palermo}$, Pi*$M_{Nichinan}$, Pi*P_{Lowell}, Pi*P_{Duarte}, Pi*$Q0_{Cardiff}$, Pi*$Y_{Barcelona}$, and Pi*$Z_{Augsburg}$.

The alleles S, I, and Queen can also form polymers, although at a slower rate, facilitating their removal and rarely causing liver injury (Chart 1). In addition, higher serum concentrations of AAT are released, generally conferring protection of the lungs in nonsmokers.[3]

EPIDEMIOLOGY

The prevalence of AATD has not yet been defined in most countries, although it is known to vary across geographic regions and racial groups and to primarily affect White individuals of European descent.[19] It is estimated that more than 3 million people worldwide have allele combinations associated with severe AATD[26] and that the Pi*ZZ genotype occurs in 1:2,000-5,000 individuals in Europe and in 1:5,000-7,000 individuals living in countries with European immigration, such as the United States and Australia.[19] Although little is known about the prevalence of the most common rare alleles, even less is known about the rare non-S and non-Z alleles.

Chart 1. Major alleles associated with alpha-1 antitrypsin deficiency.[3,15]

Allele	Clinical significance
F	Uncertain; slight reduction in activity
I	Uncertain; slight reduction in activity
S	Uncertain; slight reduction in activity
Z	Marked reduction in activity; risk of emphysema and liver disease
$M_{Procida}$	Marked reduction in activity; risk of emphysema
M_{Malton}	Marked reduction in activity; risk of emphysema and liver disease
S_{Iiyama}	Marked reduction in activity; risk of emphysema and liver disease
P_{Lowell}	Marked reduction in activity; risk of emphysema and liver disease
$M_{Heerlen}$	Marked reduction in activity; risk of emphysema
$Q0_{Granite\ Falls}$	No protein expression; risk of emphysema
$Q0_{West}$	No protein expression; risk of emphysema
$Q0_{Bellingham}$	No protein expression; risk of emphysema
$Q0_{Mattawa}$	No protein expression; risk of emphysema

A review of the Spanish Registry of AATD patients from 1998 to 2010 revealed that 56 (1.6%) of 3,511 patients with AATD had rare alleles.[27]

Registries such as that of the Alpha-1 Foundation in the United States and, more recently, that of the European Alpha-1 Research Collaboration (EARCO) are very important. Such registries allow us to understand AATD in a given location, to characterize patients, and to establish programs aimed at early diagnosis, as well as enabling the expansion of knowledge about the natural history of the disease. Between 2020 and 2022, the EARCO evaluated 1,044 individuals with AATD (defined as a serum AAT concentration < 11 μM, or 50 mg/dL) in 15 countries.[28] Among the 629 individuals (60.2%) who had the Pi*ZZ genotype, most (51.5%) were male; the mean age was 55.6 ± 13.2 years; the mean age at diagnosis was 44.7 ± 16.7 years; the mean FEV_1 was 66.9 ± 30.7%; the mean DL_{CO} was 68.0 ± 23.2%; the mean COPD Assessment Test score was 13.2 ± 9.3 points; and 190 (30.2%) had received AAT replacement therapy.

There are several ways to assess the prevalence of a genetic disease: screening newborn infants; measuring the concentration in blood stored at a blood bank; and evaluation in genetic databases or in the general population. In Sweden, 200,000 infants born between 1972 and 1974 were evaluated and the Pi*ZZ genotype was found in 127 (0.06%), or one in every 1,600.[5] Although screening neonates allows guidance to be given to avoid exposure to risk factors such as smoking and environmental or occupational pollution, ethical aspects have made such screening unfeasible. Of 20,000 blood donors in the United States in 1988, 2,850 (0.03%) were found to have the Pi*ZZ genotype.[5]

It is also possible to track AATD cases by evaluating patients with diseases caused by AATD. Among patients with COPD, it is expected that 1-4% will be found to have the Pi*ZZ genotype, which is why the WHO recommends AAT testing for all patients diagnosed with COPD.[10] Recently, the Pi*ZZ/COPD prevalence ratio in Europe was reported to be 0.12% (0.08-0.24%), with considerable differences among countries.[19] In Argentina, the prevalence of AATD among patients with COPD was found to be 0.83%.[29] In Brazil, a cross-sectional study evaluated 926 patients with COPD in five different states; the authors found that 0.8% of the patients had the Pi*ZZ genotype and that 2.80% had some variant allele, although only the S and Z variants were evaluated.[30]

In a recent study, the frequency of variant alleles was described in 30,827 individuals who might have some deficiency were evaluated—by buccal swab or by dried blood spot (DBS) sampling (collection of a blood drop on filter paper)—between 2018 and 2022 in six countries (Argentina, Brazil, Chile, Colombia, Spain, and Turkey). The prevalence was found to be 12.7% for the MS genotype, whereas it was 7.4%, 3.0%, 1.6%, and 0.8% for the MZ, ZZ, SZ, and SS genotypes, respectively.[7] In another analysis of that sample of individuals,[6] all variant alleles were evaluated and mutations were found in 9,528 (30.9%), of whom 818 (2.7%) had rare alleles (excluding all S and Z alleles). The authors stated that the identification of the range of alleles can establish a new distribution of alleles in various countries and that their findings can facilitate the selection of new alleles to include in the diagnostic panel.

RISK FACTORS FOR LUNG DISEASE

As demonstrated in previous studies,[3,31,32] AATD is a heterogeneous condition in which the combination of the genotype with low serum AAT concentration and risk factors are fundamental for the emergence and progression of its clinical and functional manifestations. Although smoking continues to be the main risk factor for lung disease, other factors, including predisposing familial conditions, respiratory infections, and exposure to environmental or occupational pollutants, which also increase inflammation and elastase in the airways and alveoli, have increasingly been studied and valued.[31-33]

Individuals with undetectable AAT associated with null alleles can develop emphysema, even without a history of smoking, as can those with marked deficiency (AAT concentrations < 11 μM) associated with Z alleles, homozygous Pi*ZZ genotypes, or rare variants.[3,9] However, exposure to tobacco smoke increases the number of neutrophils and macrophages in the lungs and increases the individual production of elastase per cell, accelerating the onset, severity, and progression of emphysema in these individuals. The progression of emphysema is related to the age at which smoking began, as well as to the lifetime smoking history.[9,34,35]

In a registry of patients with AATD in follow-up for 11 years in Germany, there was an association between a greater decline in FEV_1 and a shorter time since smoking cessation, occupational exposure to inhalants, and the frequency of COPD exacerbations.[36] In a study of smokers between 37 and 39 years of age with the Pi*ZZ genotype and normal spirometry results, it was observed that there could be changes in DL_{CO} and small airway disease, consistent with emphysema.[37] In a study of patients with the Pi*ZZ genotype, a high level of exposure to environmental pollution was associated with worsening gas exchange and respiratory status.[38]

Heterozygous individuals, especially those with the Pi*MZ and Pi*SZ alleles, can also develop emphysema depending on the degree of exposure to smoking; although that risk is low in nonsmokers, it is still a matter of controversy.[31,39] In a study of smokers with AATD,[31] the risk of COPD was found to be 5.2 times higher among those with the Pi*MZ genotype than among those with the Pi*MM genotype.[31] However, many studies that have demonstrated greater loss of lung function in individuals with the Pi*MZ genotype are biased by not having adjusted that loss for smoking history. When thus adjusted, the decline in FEV_1 is generally small.

One study demonstrated that the risk of developing emphysema among smokers with the Pi*SZ genotype was similar to that among smokers with the Pi*MM genotype, although those in the former group had sought medical evaluation earlier.[39] In another study, never-smokers with the Pi*SZ genotype did not present an increased risk of developing COPD, whereas smokers with the same genotype had greater airflow obstruction and former smokers with the genotype did not have a greater decline in FEV_1.[40] Currently, there is concern about individuals carrying the Pi*SZ alleles, who should be advised not to expose themselves to risk factors and to have periodic follow-up examinations.

In the last decade, with the new taxonomy and etiopathogenesis of COPD, early-life risk factors, such as prematurity, low birth weight, and exposure to smoking (in intrauterine life and infancy), as well as asthma, infections, and environmental/occupational exposures throughout life, have been given ever greater weight.[11,41] The influence of many of these risk factors for bronchopulmonary disease needs to be better studied in AATD, not only in relation to its early onset but also in relation to its progression. In COPD, especially in smokers with COPD, airflow obstruction is caused by inflammation in the small airways and loss of elastic recoil due to emphysema, changes that cannot be identified by spirometry.[11,41]

Although the role of small airway disease as a risk factor, early marker of lung involvement, prognostic factor, and treatable feature in patients with AATD was well discussed in a recent review,[42] further studies are needed. A study of 193 patients with AATD evaluated nitrogen washout, a sensitive method for identifying small airway disease, and showed that the lung clearance index *was* abnormal in 83% of the patients with the Pi*ZZ genotype, in 47% of those with other genotypes, and in 43% of the 117 patients with normal FEV_1.[43]

The Subpopulations and Intermediate Outcome Measures in COPD Study showed that smokers with the Pi*ZZ or Pi*MZ genotype had more bronchiectasis than did those with other genotypes, and that those changes were associated with a greater degree of emphysema, more small airway disease, and more severe clinical repercussions than what was seen in smokers without bronchiectasis.[44]

The relationship between asthma and AATD remains controversial, and although some studies have shown the prevalence of asthma to be higher among patients with AATD, that finding is usually concomitant with a diagnosis of COPD.[33] In principle, asthma is not a risk factor for an accelerated decline in lung function, and AAT replacement does not prevent a loss of function due to asthma.[33]

PULMONARY CLINICAL MANIFESTATIONS

The classic clinical presentation of AATD is the early onset of COPD. Considerable variability in the time to symptom onset has been described, although it rarely appears before 25 years of age. Symptoms that are more severe are more commonly seen in smokers and former smokers, which also influences the mean age at symptom onset, which is typically 32-40 years in smokers and 48-54 years in nonsmokers.[45-47]

The characteristics that distinguish AATD-related COPD in nonsmokers or smokers without occupational risk factors from COPD caused by smoking (unrelated to AATD) are the early onset of symptoms, panacinar emphysema, and a predominance of radiological changes at baseline.[5] However, the "classic" presentation of smoking-related COPD also occurs in patients with AATD and should not rule out the possibility in such patients.[47,48] It is important to emphasize that up to 37% of individuals with severe AATD have emphysema predominantly in the upper lobes.[19,49]

Among the most common symptoms of AATD,[50] dyspnea on exertion is the most prevalent (in 84% of cases), followed by wheezing associated with

respiratory infections (in 76%); wheezing without respiratory infections (in 65%); cough and phlegm (in 50%); and chronic cough (in 42%). On spirometry, obstructive ventilatory defect is a classical finding, with normal or reduced FVC. In the analysis of lung volumes, RV and TLC can be increased, with reduced DL_{CO}. A response can be seen after bronchodilator use, and concomitance with asthma can be associated with faster progression of the disease.[51] Factors associated with a rapid decline in lung function include symptom onset between 30 and 44 years of age, male gender, low BMI, low serum AAT concentrations, frequent exacerbations, reversibility by bronchodilators, and a severe reduction in functional capacity.[52,53] Although the association between AATD and bronchiectasis is known, the pathophysiology of the onset of the symptoms has yet to be well defined. Its prevalence varies greatly among studies, ranging from 26% to 52% in the studies with the largest patient samples, although the presence of bronchiectasis without emphysema should not rule out a diagnosis of AATD.[54]

EXTRAPULMONARY CLINICAL MANIFESTATIONS

Liver disease

Liver disease is the second most common manifestation of AATD in adults and the second leading cause of death in patients with the disorder.[55] Liver disease associated with AATD occurs primarily due to abnormal accumulation of mutated protein polymers within the rough surface of the endoplasmic reticulum of hepatocytes. These polymers can lead to inflammation, with consequent liver fibrosis, cirrhosis, and increased risk of hepatocellular carcinoma, especially in individuals with hepatitis B.[55] Because liver disease is highly variable and not all patients with the ZZ genotype develop the disease despite the presence of polymers in the liver, there must be other causal factors that are not yet fully understood. It has been suggested that genetic determinants of intracellular protein processing have some influence on susceptibility to liver disease in AATD.[56] Patients with genetic variants associated with the presence of hepatic polymers, such as S_{Iiyama}, M_{Duarte}, M_{Malton}, and particularly the presence of the Z allele, can develop signs of liver disease.[56]

Liver disease has a bimodal age distribution, with the first peak in early childhood and the second in individuals over 50 years of age.[57] In the neonatal period, prolonged cholestasis is the main clinical manifestation. A study that evaluated 200,000 newborns in Sweden identified the Pi*ZZ genotype in 127, of whom 73% had prolonged jaundice and 8% had severe liver disease.[58] Alterations in liver enzymes were identified in 50% of those neonates, with spontaneous resolution within months. At 18 years of age, most were healthy. Only 3% had severe progressive disease.[59] In the pediatric population, AATD accounts for 3.5% of the indications for liver transplantation.[60] In adults, liver fibrosis occurs in 20-36% of patients with the Pi*ZZ genotype, and advanced fibrosis is 10-20 times more common in such patients than in those with other genotypes.[61] Approximately 10% of patients with severe AATD develop cirrhosis, and 14.5% of such patients require liver transplantation.[60,62] Only a small percentage of patients with AATD and advanced liver fibrosis present alterations in liver enzymes, with levels varying over the years.[63]

In patients with AATD, gamma-glutamyl transferase is the most sensitive marker for the diagnosis of liver disease, with a mean concentration significantly higher than that of glutamic pyruvic transaminase.[64] Although patients with the Pi*SS genotype can have mild transaminase alterations, they do not develop hepatobiliary disease.[64] Patients with the Pi*SZ genotype show elevated liver enzymes, with a clear predisposition to fibrosis, liver cirrhosis, and hepatocellular carcinoma, although that predisposition is much lower than that observed in patients with the Pi*ZZ genotype.[57,64] Patients with the Pi*MS genotype do not show an increased risk of liver disease.[64]

Noninvasive liver evaluation through biochemical studies, transient hepatic elastography, and the determination of phenotypes/genotypes should be performed routinely in individuals with AATD.[5] Given the nature and risk of complications, liver biopsy is reserved for selected cases only. Although transient hepatic elastography is useful to rule out advanced fibrosis (stages 3 and 4), it is less effective in the early stages.[62] In patients with altered enzymes, cirrhosis, or portal hypertension, liver ultrasound every six months is indicated in order to screen for hepatocellular carcinoma.[65]

There are no currently approved therapies for liver disease other than liver transplantation in patients with advanced disease.[66] Promising strategies are being investigated, such as small RNA molecules that block polymer formation or stimulate pathways that accelerate their elimination. Fazirsiran, an RNA interference therapeutic that targets AAT and Z-AAT messenger RNA for degradation, was evaluated in a small phase 2 study of 16 patients with the Pi*ZZ genotype and was found to provide an 83% decrease in total liver Z-AAT after 24-48 weeks and improvements in histological liver abnormalities, including a reduction in the portal inflammation score in two thirds of the patients.[67]

Panniculitis

Panniculitis associated with AATD is an extremely rare disease, and its clinical manifestations include nodular, painful, red skin lesions, often with an oily discharge, affecting areas of previous trauma such as the thighs, buttocks, abdomen, and upper limbs.[68] It affects men and women with equal frequency, and the frequency also does not vary among the various phenotypes. It is much more associated with the Pi*ZZ genotype, and its pathogenesis is related to

the lack of any opposition to proteolytic activity in the subcutaneous fat tissue.[68] A number of therapies, including antibiotics, anti-inflammatory agents, and chemotherapeutics, have been tested, with varying rates of success. Treatment with AAT replacement has shown excellent results, with rapid clinical responses, and should be used in cases refractory to other therapies.[69]

Associations with other diseases

There is insufficient evidence to support a relationship between AATD and other diseases (vascular disease, inflammatory bowel disease, glomerulonephritis, and systemic vasculitis). It has been suggested that patients with the Pi*ZZ genotype are susceptible to several vascular abnormalities, including abdominal/intracranial aneurysms, arterial fibromuscular dysplasia, and venous thromboembolism, on the basis of the principle that unopposed proteolytic activity damages vessel walls in severely deficient individuals.[5,70,71] One report described the case of an individual with the Pittsburgh AAT mutation who died of severe bleeding after a viral infection.[72] There is a functional relationship between the plasma proteins AAT and antithrombin III. To elucidate this relationship, the plasma of a 14-year-old boy who died of a hemorrhagic disorder was studied, and a variant of AAT was found in which the methionine at position 358 was replaced by an arginine, converting the normal function of AAT as an elastase inhibitor to that of a thrombin inhibitor.[72] The data regarding the association between AATD and inflammatory bowel disease are conflicting and cannot be legitimized. One study evaluated children with the Pi*ZZ genotype who developed significant liver disease and associated nephropathy.[73] In patients with AATD, there appears to be an increased risk of cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA)-associated vasculitis, which is supported by plausible pathogenetic mechanisms. In the extravascular fluid, AAT plays an important role as an inhibitor of proteinase 3, a serine protease similar to neutrophil elastase and located in the primary granules of neutrophils. If left unchecked, proteinase 3 has potent tissue-destructive capacity, and AATD could therefore trigger an autoimmune response, allowing increased extracellular exposure to proteinase 3.[74]

DIAGNOSIS

When to test

A diagnosis of AATD has several immediate impacts,[75] such as the need to test family members; the opportunity to implement educational measures; early intervention regarding smoking habits; advising patients about environmental and occupational exposures; and the opportunity to consider specific AATD treatment. The WHO recommends AAT testing in all patients diagnosed with COPD or adult-onset asthma.[10] The GOLD and international AATD guidelines recommend that AATD screening be performed at least once in all individuals with COPD, regardless of age, ethnicity, or disease severity,[11] as well as in those with emphysema or asthma with fixed airway obstruction.[2,5,9,76-78] Despite global efforts to recommend AATD screening, the condition is still highly underdiagnosed.[79] In most individuals with AATD, there is a long interval between symptom onset and the diagnosis of the disorder.[80] As detailed in Chart 2, all individuals with chronic liver disease of undetermined etiology should also be screened for AATD, as should individuals with necrotizing panniculitis, C-ANCA-positive vasculitis, bronchiectasis of undetermined etiology, or a family history of any of the above.[2,5,77]

Given that AATD is inherited in an autosomal codominant manner, testing should be offered to first-degree relatives of index cases, even if those relatives are asymptomatic, because of the risk that they could have some variant allele or even AATD.[11] Family members who carry mutations benefit from genetic counseling and preventive measures, the most important of which are avoiding smoking and exposure to environmental or occupational pollutants.[76] For example, the risk of developing COPD has been shown to be 5-10 times greater for smokers who are heterozygous for the Z allele and another normal allele (i.e., with the Pi*MZ genotype) than for smokers with the Pi*MM genotype.[31] However, among nonsmokers, the risk of developing COPD is similar between those two genotypes.[79] When evaluating family members, the determination of serum AAT concentrations is not recommended as the initial test, because it does not detect the genetics of the alleles; a patient with normal or near-normal serum concentrations of AAT could mistakenly be categorized as genetically normal. Therefore, family members should always be initially evaluated by genotyping.[2] For genetic counseling purposes, the partner of an individual with the Pi*ZZ genotype or with some rare or heterozygous association should also be tested. Because the Pi*MZ phenotype is not uncommon and marriages occur by affinity, it is advisable to test the children of a couple who are both carriers of the Pi*MZ genotype, in order to identify those with a severe homozygous genotype.[9] The current guidelines do not recommend testing the general population, adolescents, or newborns.[78,81]

Diagnostic methods

Quantitative measurement of AAT

The measurement of serum AAT concentration is preferably performed by immunonephelometry, because of the high sensitivity of that method. The serum concentration can be expressed in milligrams per deciliter (mg/dL) or millimoles per liter (μmol/L or μM), with normal values of > 113 mg/dL and 20-39 μM, respectively. Values below 110 mg/dL indicate the possibility of a mutant allele (S, Z, or a rare one) and serve as a guide to continue investigating the genotype. Values ≥ 11 μmol/L are considered protective. In patients with lung or liver disease,

Chart 2. Indications for evaluation of alpha-1 antitrypsin deficiency.

- COPD or emphysema (regardless of age or ethnicity)
- Adult-onset asthma or asthma with fixed airway obstruction
- Bronchiectasis of undetermined etiology
- Chronic liver disease of undetermined etiology
- Necrotizing panniculitis
- C-ANCA positive vasculitis, including granulomatosis with polyangiitis
- First-degree relatives and partners of individuals with AATD*
- Family history of emphysema, bronchiectasis, liver disease, or panniculitis

C-ANCA: cytoplasmic antineutrophil cytoplasmic antibody; and AATD: alpha-1 antitrypsin deficiency. *AATD should be diagnosed by genotyping rather than by determination of the serum concentration of AAT.

below-normal serum AAT values should represent a warning sign for further investigation. In general, approximately 80% of serum AAT reaches the interstitial fluid and 10% reaches the epithelial lining fluid.[82] The total volume of serum AAT is second only to that of plasma albumin.

Because AAT is an acute phase protein and its concentration can be increased by 75-100% in patients with infection or inflammatory disease,[83] serum AAT concentrations should be measured when the patient is in a stable phase. That change is more evident at intermediate concentrations of AAT. It is recommended that the level of C-reactive protein be measured because a high level indicates the possibility of an ongoing infection, in which case the AAT test result should not be taken into account and the test should be repeated.[12] The concentration of AAT can also be abnormally high in the third trimester of pregnancy,[84] in very elderly individuals,[85] and in women who routinely use oral contraceptives.[86] Conversely, low AAT concentrations can be associated with hypoproteinemia and liver failure. It has been observed that the median AAT concentration decreases in the first six months of life and increases to adult concentrations by the end of the first year.[87] Data related to serum AAT levels in blood samples are available for most of the states in Brazil.

Serum AAT concentrations can also be measured by DBS sampling, which consists in collecting a drop of blood by pricking the distal region of one of the fingers with a lancet or by performing venipuncture. The blood should be distributed evenly across the five circles of a filter paper (Whatman 903; Sigma-Aldrich, Burlington, MA, USA), ensuring that the blood soaks through to the back of the card. If the blood is collected by venipuncture, 50 µL of blood can be distributed evenly across the circles with a pipette. Thereafter, the filter paper should be dried in room air for 12 h and stored in an envelope, away from humidity and light.

Qualitative measurements of AAT

AAT phenotyping

In the diagnosis of AATD, phenotyping is performed by electrophoresis with isoelectric focusing, observing the migration of the alpha-1 protein at pH 4.0-5.0. Although this differentiation method is not difficult to perform, it is quite time-consuming and requires great experience on the part of the technician because the different mutations migrate at very similar speeds due to small changes in the electrolytic dissociation constant.[88] Null (Q0) alleles do not produce alpha 1 and are not recognized on electrophoresis.

Genotyping

Genotyping identifies allele variants that occur due to mutations in the *SERPINA1* gene locus. Analysis of the DNA region using polymerase chain reaction amplification allows the identification of variants. Genetic analysis can be performed in tissue cells, in white blood cells, or in blood samples collected on filter paper (by DBS sampling).

A new AAT genotyping method in which cells are collected from the oral mucosa (by swab), developed by Progenika Biopharma (Derio, Spain) and widely used in Brazil since 2018, allows the simultaneous identification of the 14 most common variants.[89] The collection of cells from the cheek mucosa by swab is minimally invasive, is rapid, and does not require drying time; the specimen remains stable for two months in room air and can be transported by regular mail.[90] The nondetection of any of the 14 mutations on the test is reported as "variant not detected", which translates to a 99% chance that the subject has the MM genotype.[91]

Genetic sequencing

If no mutant allele is detected and the blood concentration is below 50 mg/dL or if there is discordance between the serum AAT concentration and the genotype, genetic sequencing is necessary.[2,9]

Algorithm for diagnosing AATD

There are two approaches to the diagnosis of AATD (Figure 1): one begins with the serum concentration of AAT (the conventional approach); and the other begins with phenotyping or genotyping (the alternative approach). In Brazil, measurement in blood samples in more widely available and it is therefore more common to begin with the assessment of serum AAT concentrations. If the serum AAT concentration assessed by nephelometry is below 113 mg/dL, there is a possibility of AATD and genotyping should be requested. If the decision is made to start with genotyping, one alternative is the Progenika Biopharma test with buccal swab collection, which allows the simultaneously identification of the 14 most common

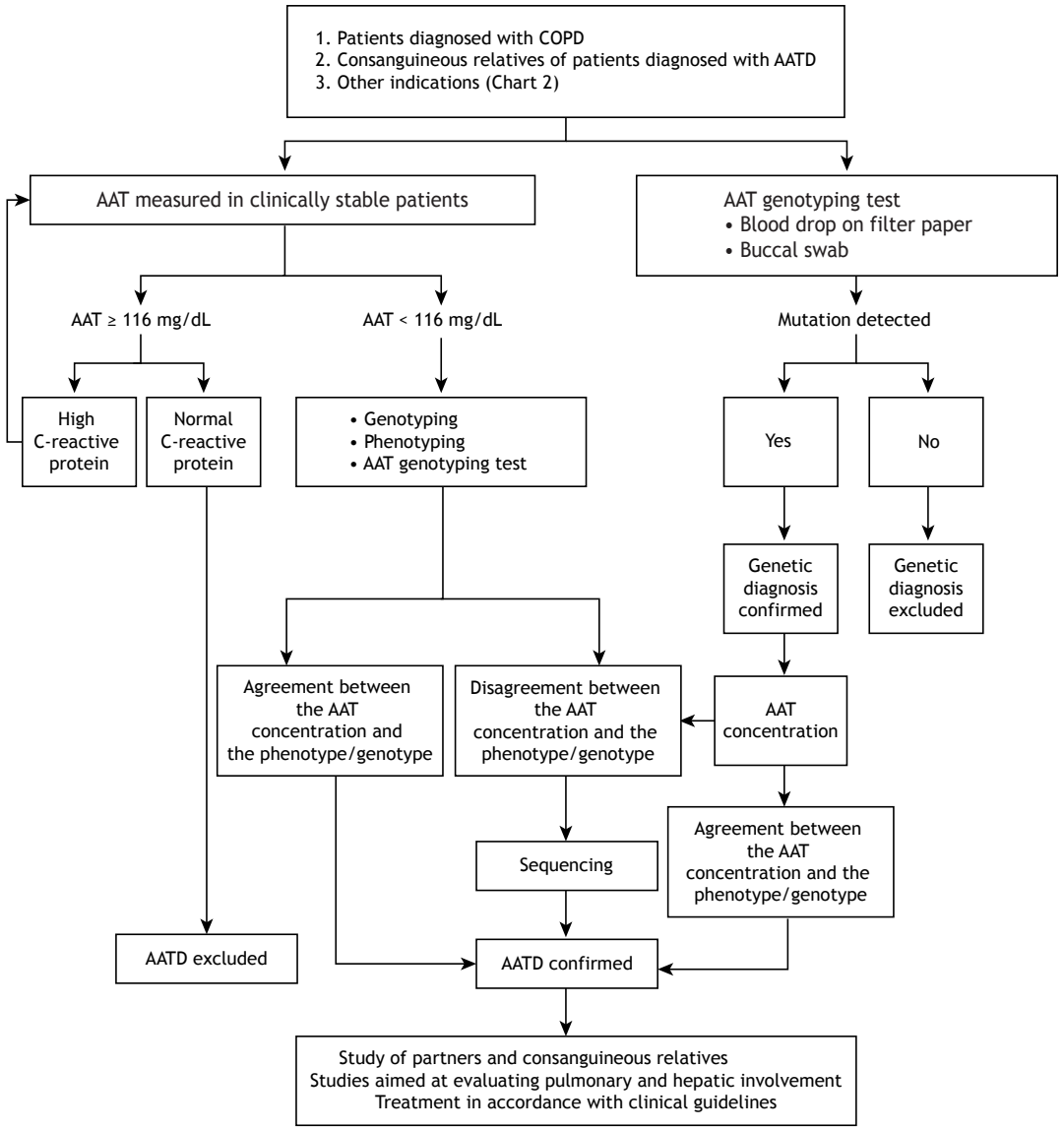

Figure 1. Diagnostic algorithm for alpha-1 antitrypsin deficiency (AATD). In cases of patients diagnosed with AATD, investigate partners to assess the risk of the disease in offspring. Measurement of AAT in serum should be performed by nephelometry. For other techniques, apply a conversion factor. If there is high clinical suspicion of AATD, measure the AAT concentration when the patient is in a stable clinical condition.

variants (Chart 3). In this approach, if any variant allele is present, it is necessary to determine the serum AAT concentration. In either approach, gene sequencing (the most sensitive confirmatory test) may be necessary if the results of the serum screening and genotyping/phenotyping are discordant.

Filter paper collection (DBS sampling) has the advantage of being a simple technique, as well as allowing easy storage and transport of the samples to a central laboratory for the measurement of serum concentration and genotyping/phenotyping. However, the disadvantage is that there are very few laboratories in Brazil that handle the analysis of DBS samples.[12]

MONITORING OF ASYMPTOMATIC PATIENTS

It is not uncommon for low serum concentrations of AAT not to result in functional or anatomical changes that manifest as respiratory symptoms. This poses a clinical challenge: how should we manage asymptomatic cases of AATD? Although the proportion of individuals with AATD who develop lung disease is still unknown, studies indicate that up to 50% of nonsmokers with AATD maintain normal lung function throughout life.[9]

The first step is an adequate assessment of the symptoms. In patients with progressive lung disease and a gradual loss of function, the symptoms may be underestimated. To avoid discomfort, the patient might reduce their activities of daily living, attributing their

Chart 3. Allelic variants of the serine protease inhibitor gene, detected through genotyping.

Variant	Associated allele(s)	Predicted AAT activity
c.187C>T	Pi*I	Reduced (mild)
c.194T>C	$Pi*M_{Procida}$	Reduced (severe)
c.226_228delTTC	$Pi*M_{Malton}$, $Pi*M_{Palermo}$, $Pi*M_{Nichinan}$	Reduced (severe)
c.230C>T	PPS_{Iiyama}	Reduced (severe)
c.552delC	$Pi*Q0_{Granite\ Falls}$	None (absent)
c.646+1G>T	$Pi*Q0_{West}$	None (absent)
c.721A>T	$Pi*Q0_{Bellingham}$	None (absent)
c.739C>T	PI*F	Reduced (mild)
c.839A>T	$Pi*P_{Lowell}$, $Pi*P_{Duarte}$, $Pi*Q0_{Cardiff}$, $Pi*Y_{Barcelona}$	Reduced (mild)
c.863A>T	Pi*S	Reduced (mild)
c.1096G>A	Pi*Z	Reduced (severe)
c.1130dupT	$Pi*Q0_{Mattawa}$, $Pi*Q0_{Ourem}$	None (absent)
c.1158dupC	$Pi*Q0_{Clayton}$, $Pi*Q0_{Saarbruecken}$	None (absent)
c.1178C>T	$Pi*M_{Heerlen}$	Reduced (severe)

AAT: alpha-1 antitrypsin.

symptoms to aging or a sedentary lifestyle. Objective questionnaires such as the Medical Research Council dyspnea scale, COPD Assessment Test or London Chest Activity of Daily Living scale can help identify limitations in patients who do not objectively report symptoms during the history taking.[92]

Patients should be advised to avoid exposure to factors that can increase the risk of emphysema. All smokers should receive smoking cessation counseling and treatment. In addition, it is important to assess and provide guidance on environmental and occupational exposure to smoke and toxic fumes, because eliminating such exposure could slow the progression of lung disease in patients with AATD.[93]

It is essential to monitor patients with AATD for the appearance of pulmonary emphysema and liver disease. All patients with severe AATD should undergo pulmonary function tests, unenhanced chest CT, and liver evaluation. Evaluation of liver involvement is especially important in patients with the ZZ, SZ, or rare genotypes that can be risk factors, such as M_{Malton} and S_{Iiyama}.[2] Such patients should undergo periodic evaluations (depending on the clinical presentation), with a physical examination focused on signs of liver disease, liver ultrasound or elastography, and laboratory tests to determine the levels of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, gamma-glutamyl transferase, albumin, and bilirubin, as well as coagulation tests.[13] In patients with AATD, liver fibrosis can be silent and hepatocellular carcinoma occurs in 3%,[94] the risk factors being male sex, age over 50 years, lifestyle, and persistently elevated liver function values.[12]

The best frequency of monitoring to detect the onset or progression of lung disease in patients with AATD has yet to be established and depends on serum AAT concentration and pathogenicity of the mutation presented. Generally, in patients without respiratory symptoms and with normal baseline spirometry findings (i.e., $FEV_1 \geq 80\%$ of predicted), spirometry is repeated every 12 months or every 6-12 months if the symptoms change. If possible, it is important to measure volumes, flows, and DL_{CO} at the beginning of follow-up. In comparison with the decline in FEV_1, the change in DL_{CO} occurs earlier and is more intense. It is essential that an asymptomatic patient with a mutation be advised to seek medical assistance if they notice dyspnea, especially on exertion, or any other significant lung impairment, such as pneumonia. An unexplained reduction in post-bronchodilator FEV_1 to below the lower limit of normal is a sign to consider starting specific treatment.[2]

Monitoring of asymptomatic patients with AATD should be personalized. The pathogenicity of the specific mutation and serum concentrations are factors to be considered when establishing the frequency of monitoring. Genetic counseling and lifestyle guidelines to avoid potentially harmful exposures are the most important measures in this context. It is essential to consider a multidisciplinary approach, involving pulmonologists, hepatologists, geneticists, and other specialists, to ensure the best quality of life and prognosis for these patients.

GENERAL OR NONSPECIFIC TREATMENT

Treatment for AATD includes behavioral and pharmacological therapy for smoking cessation, together with guidance on the importance of avoiding exposure to irritants (tobacco smoke, dust, smoke, pollutants or aerosolized chemicals). Other therapies are similar to those indicated for patients with COPD not caused by AATD: anti-influenza and anti-pneumococcal vaccination; pharmacological treatment, as recommended by the GOLD,[11] including the use of slow-release bronchodilators (muscarinic antagonists and β_2 agonists) and inhaled corticosteroids (in special situations); pulmonary rehabilitation; and nutritional support. Exacerbations should be treated, and when they become recurrent, the use

of prophylactic antibiotics, inhaled corticosteroids, or both is indicated. Patients who meet the relevant blood gas criteria should be referred for supplemental oxygen therapy.[75]

Surgical treatment is also indicated for some patients with AATD and pulmonary emphysema. The results are limited and not necessarily promising. In very well-selected cases, lung volume reduction surgery has produced positive results (functional improvement and better quality of life).[95]

At major centers worldwide, AATD is one of the main indications for lung transplantation. It has been well documented that lung transplantation results in improved quality of life and survival in patients with AATD.[96,97]

SPECIFIC TREATMENT

Patients who are receiving optimized COPD treatment should also undergo AAT replacement therapy, which should be personalized.[11] It is recognized that there are patients with severe mutations in whom lung function and clinical status remain stable.

Several studies have shown that health professionals have limited knowledge about AATD and its diagnosis, as well as that there is significant inequality in access to specialized care and treatment.[9] The Organic Health Laws of the Brazilian Unified Health Care System provide for the right to the promotion, protection. and recovery of health for every citizen, although it is very difficult to provide care for rare diseases and AATD is no exception.

Although there have been recent improvements in awareness of AATD and in the understanding of its treatment, there are still challenges related to improving diagnosis, providing optimal general treatment, and improving access to the specific treatment, intravenous AAT therapy, which is the only available pharmacological intervention that can slow the progression of the disease.[98] Interpreting genetic variants and their importance, understanding the role of patient and family screening, and the management of the disease all require expertise and seem to be best developed at reference centers that have the capacity to provide appropriate care and treatment, including intravenous AAT replacement therapy.[1,9]

Intravenous replacement therapy with purified AAT is the mainstay of treatment for AATD, although lung volume reduction surgery and lung transplantation are of real value in selected cases. To avoid or reduce the destruction of lung parenchyma by AATD is the primary goal of AAT replacement therapy,[99] given that intravenous augmentation by infusion of combined human alpha-1 trypsin inhibitor is the most direct, efficient, and unique means of increasing AAT concentrations in the blood and lung interstitium and of preventing the progression of emphysema to a more severe form.[100]

There are several guidelines and scientific articles with recommendations on the treatment of AATD in adults (Chart 4). In Europe and the United States, various studies have emphasized the need for careful diagnosis and access to intravenous AAT replacement therapy in patients with severe AATD. However, there is still a need to improve the biomarkers of emphysema progression and of the response to replacement therapy. Studies on the rate of decline in lung density indicate that this tool is useful in helping to assess the results of replacement therapy. With regard to specific therapy, research on personalized replacement, with individualized selection of the therapeutic regimen, is essential.[9]

Some guidelines, such as those developed in Belgium,[101] Portugal,[13] Poland,[102] and Canada,[103] have introduced the drop in FEV_1 (% of predicted) after bronchodilator use as a criterion for initiating treatment in patients with AATD, although the drop in FEV_1 currently has less sensitivity than does the decrease in lung density. There seems to be a consensus that intravenous AAT replacement therapy is indicated in nonsmokers or former smokers over 18 years of age with a genetic variant consistent with severe AATD, a low serum AAT concentration (< 11 µmol/L or < 57 mg/dL), and evidence of airflow limitation on pulmonary function testing.[5,11,13,101-103] Identifying an accelerated decline in lung function on the basis of the drop in FEV_1 in serial functional assessments is a more sensitive method than is the identification of isolated airflow obstruction, because the former can indirectly indicate lung tissue destruction due to enzymatic imbalance. Serum AAT concentrations above 11 µmol/L or 57 mg/dL are considered protective and should be used as a parameter to determine the effectiveness of replacement therapy.[104]

Some patients present emphysema on chest CT without airflow limitation on spirometry, demonstrating that chest CT is more sensitive, at least initially, than is a functional assessment. In patients suspected of having developed emphysema, annual spirometry should be used in order to monitor lung function. A real loss of lung function is defined on the basis of the change over a three-year period, a decline in FEV_1 ≥ 100 mL/year being considered excessive and an indication for the initiation of specific therapy.[5,11,13,101]

The "Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency" study and its open-label extension, designated the RAPID and RAPID-OLE studies, respectively,[105,106] were the largest clinical trials of intravenous AAT replacement therapy ever conducted. The RAPID study was a placebo-controlled trial in which patients were randomly assigned to receive, on a weekly basis, either intravenous AAT (60 mg • kg^{-1}) or placebo, for 24 months.[105] The RAPID-OLE study began at that point: patients who had been receiving the placebo began to receive the AAT replacement, while those who were already receiving AAT replacement continued to receive it.[106] In the RAPID study, at the end of the

Chart 4. Criteria for specific treatment of alpha-1 antitrypsin deficiency.

Guideline or summary of product characteristics (country/institution of origin)	Criteria and recommendations
Argentina	Age > 18 years, nonsmoking patients with an AAT < 50 mg • dL^{-1}, emphysema on CT, or pulmonary function with an FEV_1 < 80% of predicted
	No discontinuation of AAT replacement even if FEV_1 falls below 25% of predicted
	Not recommended in patients with the Pi*MZ genotype or in most patients with the Pi*SZ genotype unless they have an AAT < 50 mg • dL^{-1} and meet the other criteria
Belgium	Nonsmoking patients with an AAT < 50 mg • dL^{-1} and FEV_1 30-60% of predicted and a decline in FEV_1 (% of predicted) > 0.5% per year
	Patients with an FEV_1 60-80% of predicted if the decline is > 1% per year
Canada	Nonsmoking patients with COPD (FEV_1 25-80% of predicted) attributable to emphysema and serum AAT < 11 µM
United States	Severe AATD in individuals with an FEV_1 < 65% of predicted
	In patients with a FEV_1 > 65% of predicted, discussion of benefits and costs
Spain	Age > 18 years, nonsmoking patients with an AAT < 50 mg • dL^{-1}, emphysema on CT or pulmonary function with an FEV_1 < 80% of predicted
	No discontinuation of AAT replacement even if FEV_1 falls below 25% of predicted
Portugal	Age > 18 years, COPD attributed to emphysema caused by AATD, serum AAT < 57 mg • dL^{-1}, FEV_1 30-70% of predicted, or if the FEV_1 is > 70% of predicted, a decline in FEV_1 > 120 mL • $year^{-1}$
	Case-by-case decision in other cases and no discontinuation of AAT replacement in case of deterioration of lung function
Poland	Severe AATD, emphysema, nonsmoking patients with an AAT < 11 µM, FEV_1 30-65% of predicted or a decline in FEV_1 > 50 mL • $year^{-1}$
BRAZIL/BTA	Age > 18 years, nonsmoking patients, preferably treated at reference centers, with severe deficiency (serum AAT < 57 mg • dL^{-1} or < 11 µM), with proven functional loss above the physiological level (even in patients with normal lung function or with mild, moderate, or severe airflow obstruction)
	For patients with an FEV_1 > 80% of predicted, excessive functional loss defined as > 100 mL/year over a three-year period
	No discontinuation of the specific treatment even if FEV1 falls below 25% of predicted

AAT: alpha-1 antitrypsin; AATD: alpha-1 antitrypsin deficiency; BTA: Brazilian Thoracic Association. Adapted from Miravitlles et al.[33]

24-month period, there was a reduction in grams of lung tissue per liter of lung volume (g/L) of 2.90 g/L in the group receiving AAT replacement, compared with 4.38 g/L in the placebo group, a statistically significant difference. In the RAPID-OLE study, at the end of a second 24-month period (i.e., at 48 months after the start of the trial), those who continued to receive AAT replacement had lost 5.03 g/L, whereas those who had received placebo for 24 months and the received AAT replacement for 24 months had lost 6.32 g/L. During the RAPID study (between day 1 and month 24), the annual loss of lung tissue, measured in TLC, was 33% greater in patients who were receiving placebo. During the RAPID-OLE study (between month 24 and month 48), the rate of loss in those who started receiving AAT replacement after month 24 decreased and, by month 48, was equal to that of those who received AAT replacement from the beginning, although their lung density was still lower than was that of those who had received AAT replacement from the beginning of the trial. Therefore, the efficacy of AAT treatment was maintained throughout the 48-month trial period in the group receiving AAT replacement. The two studies clearly showed two important points[105,106]: during the first 24 months, AAT replacement protected the lungs from excessive loss of lung tissue; and, by the end of month 48, the group that had previously received placebo and started receiving AAT replacement had a loss rate equal to that of the group that had received AAT replacement from the beginning of the study, but it did not return to the previous value, indicating that the loss was permanent. These two studies leave no doubt about the effectiveness of specific treatment with intravenous AAT replacement and increase the certainty that the therapy truly slows the progression of lung destruction.

For more than 30 years, there has been evidence of the biochemical efficacy of intravenous AAT replacement therapy, with increased concentrations in serum and in the lungs, including the epithelial lining fluid. In 1989, US Food and Drug Administration approved AAT purified from human plasma for intravenous administration, at a dose of 60 mg/kg, administered weekly.[107] Its administration is contraindicated in patients with selective IgA deficiencies, because of the possibility of severe anaphylaxis. In the 13 years

that intravenous AAT replacement therapy has been employed at the Hospital Regional da Asa Norte in Brasília, in 8-12 patients per week, there has never been an anaphylactic reaction. Although the incidence of severe IgA deficiency (< 7 mg/dL) is very low (< 1%) in the general population, we recommend measuring the total IgA concentration before starting replacement therapy, given that all commercial preparations for AAT replacement therapy contain some IgA and patients with severe deficiency are at risk of anaphylaxis after infusion of pooled human AAT. The AAT should preferably be administered at reference centers and by trained staff.[1,9,108] There is insufficient evidence to recommend the use of biweekly or monthly applications, although that is left to the discretion of the reference centers, according to the condition of the patient. The ongoing ProlAstin-c Randomized Therapy with Alpha-1 augmentation trial is evaluating weekly AAT replacement in three arms—60 mg/kg, 120 mg/kg, and placebo—with the hypothesis that the 120 mg/kg dose would provide a higher level of protection (> 20 µmol) and less lung tissue loss over three years.[109]

It is known that AAT can exert effects beyond protease inhibition, having antibacterial effects by inhibiting pro-inflammatory responses induced by bacterial endotoxins *in vitro* and *in vivo*.[110] Treatment with AAT replacement is associated with a reduction in the concentration of leukotriene B4, one of the most important mediators of neutrophil recruitment and activation, with a central role in airway inflammation.[111]

Treatment with AAT replacement has an indefinite duration, is costly, and requires careful consideration. The data supporting the clinical efficacy of intravenous AAT replacement are robust and include randomized trials that evaluated outcomes such as serum AAT concentrations, lung function, and lung density on chest CT.[3,9,105,106,111-113]

Supported by robust data in the literature, we recommend AAT replacement for any patient over 18 years of age with severe AATD; that is, serum concentrations below the protective level (< 57 mg • dL^{-1} or serum AAT < 11 µM), with proven functional loss above the physiological level (even if lung function is still normal or if there is mild, moderate or severe airflow obstruction). For patients with an FEV_1 > 80% of predicted, functional loss is considered excessive if it is > 100 mL/year in annual assessments over a three-year period. Short-term variations may occur due to test-retest variability. The specific treatment should not be discontinued even if the FEV_1 falls below 25% of the predicted value. There is no consensus on AAT replacement in patients with the Pi*SZ genotype, even in those with serum AAT concentrations < 11 µM or < 57 mg • dL^{-1}. It is possible that the EARCO data will answer this question.

During the period of intravenous AAT replacement, routine monitoring of serum AAT concentrations is not recommended.[9] Lung function should be monitored annually, except in patients with a suspected decline above the physiological level, in whom functional assessment should be performed as needed. The objective of monitoring lung function is to assess its decline and estimate the prognosis. It is interesting to use questionnaires to assess quality of life, assess COPD, and monitor exacerbations.[9,105] Despite the cost, AAT replacement is a specific treatment that will slow the destruction of the lung parenchyma, consequently increasing survival,[108] and should therefore be offered to all those who need it.

In addition to the Pi*ZZ, Pi*Q0, and Pi*SZ alleles (when accompanied by serum concentrations below the protective level), other genetic variants can lead to low AAT concentrations and the development of emphysema requiring AAT replacement: $Pi*M_{Procida}$, $Pi*M_{Malton}$, $Pi*M_{Palermo}$, $Pi*M_{Nichinan}$, $Pi*S_{Iiyama}$, Pi*Z, and $Pi*M_{Heerlen}$. Several variants can also cause severe liver disease[12]: $Pi*M_{Malton}$, $Pi*M_{Palermo}$, $Pi*M_{Nichinan}$, $Pi*S_{Iiyama}$, $Pi*P_{Lowell}$, $Pi*P_{Duarte}$, $Pi*Q0_{Cardiff}$, $Pi*Y_{Barcelona}$, Pi*Z, $Pi*Z_{Augsburg}$. All patients with genetic variants that can cause severe liver disease should also receive specialized hepatology care.

RECOMMENDATIONS

All adults with persistent post-bronchodilator airflow obstruction on spirometry should be tested for AATD. In addition, testing outcome measures include emphysema in individuals under 45 years of age, emphysema in a nonsmoker or smoker with a minimal smoking history, emphysema that is predominantly in the basal regions on chest CT, a family history of emphysema or liver disease, current or previous panniculitis, and current or previous unexplained chronic liver disease.[3,9,11]

Given that AATD is inherited in an autosomal codominant manner, first-degree relatives (parents, siblings, children, and partners) of the index case should be tested, even if they are asymptomatic, because there is a risk that they will present some variant of AAT.[11] If the variant identified in a relative is not severe, it is not necessary to measure the serum concentration of AAT, although it should always be measured in relatives carrying severe mutations.[76] The risk of developing COPD is 5-10 times greater in smokers who are Pi*MZ heterozygotes than in smokers with the Pi*MM genotype.[31] However, among nonsmokers, the risk of developing COPD is comparable between those two genotypes. The same applies to heterozygous carriers of any rare severe variant.[79]

Individuals who are heterozygous for Pi*SZ, for two very rare variants, or for Pi*Z and another rare variant should be monitored and advised to avoid risk factors for COPD. In symptomatic individuals with an AAT test showing no variants, genetic sequencing should be requested, because they might be carriers of a null variant, in which case, serum AAT will be undetectable.[2]

An individual with the Pi*MZ genotype or with the Pi*M genotype in combination with a rare allele requires special attention, because if their partner also has the Pi*MZ genotype, the couple could produce a child with the Pi*ZZ genotype.[9] In such cases, the person with the Pi*MZ or with the Pi*M genotype and a rare allele should be advised that if they have a child, the genotype of that child should be assessed and if homozygous for severe deficiency, the child should be advised not to smoke and to avoid other risk factors.

After genotyping and serum measurements have been performed on the family members of the index case, a meeting should be held with the entire family to explain what AAT is, where it is produced, its action, what normal and variant alleles are, and the possible consequences for individuals with AATD who are carrying variants, as well as the risk factors for lung lesions. These meetings can be held virtually; the purpose is to clarify, guide, and, above all, reassure the family.

To avoid stigmatization of AATD carriers, it is necessary to guide the individual to lead a healthy life, to not feel limited, and to not fear the future. In relation to the discovery of children with variants that may predispose to lung lesions, parents should be advised not to smoke, to educate children not to smoke or expose themselves to risk factors, and to explain the genetics of AATD only after they are old enough to understand the facts. Parents should guide children to have as normal a life as possible so that they do not feel limited.

Current guidelines do not recommend testing the general population, adolescents, or newborns.[78,81] Genotyping adolescent and young smokers and advising them to quit smoking could be an important preventive measure. Although that measure has never been implemented in any country, it could be cost-effective.

Finally, it is possible to group individuals with AATD into a database and monitor them, which allows us to understand the natural history of the disorder, provide earlier interventions, personalize treatments, and provide family genetic counseling. The international EARCO database currently includes anonymized data provided by researchers in 24 European countries and the Americas (Argentina, Colombia, Costa Rica, and Canada). Data storage partnerships with the EARCO can be established only by individual hospitals and not by a group of centers representing a country or a medical society. Although patient data are considered the property of the hospital and the principal investigator, they can be shared if authorization is obtained from the hospital coordinator of the research group.

When AAT replacement is indicated, it should follow the criteria described in this document.[1,9,108,114] Experience with lung volume reduction surgery in patients with AATD is limited. Lung and liver transplantation are reserved for severe and terminal cases of AATD.[96] After liver transplantation, AATD is corrected because the phenotype-normal donor liver produces and secretes AAT.

AUTHOR CONTRIBUTIONS

All authors contributed to study conception and design, as well as drafting of the manuscript. PHTF, JRBJ, and MM contributed to critical revision of the manuscript for important intellectual content and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Short-term effects of elexacaftor/tezacaftor/ivacaftor in pediatric cystic fibrosis patients in Brazil: a case series

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TO THE EDITOR:

Cystic fibrosis (CF) is a chronic autosomal recessive disorder, with an estimated incidence of approximately 1 in 7,000 live births.[1] It results from genetic mutations on chromosome 7, affecting the CF transmembrane conductance regulator (CFTR) protein.[2] A deeper understanding of the molecular consequences of mutations in the *CFTR* gene has led to the development of small-molecule modulators, such as the triple combination of elexacaftor, tezacaftor, and ivacaftor (ETI), which enhance CFTR activity and improve organ function in patients with CF.[3] CFTR modulators are transforming the lives of CF patients, with short- and long-term clinical improvements.[4,5] Real-life studies in Brazil have detailed the remarkable effects that ETI therapy has on adult CF patients.[6] Nevertheless, to our knowledge, this is the first case series showcasing the short-term effects of ETI therapy on pediatric patients in Brazil, all of whom were monitored at a CF referral center in southern Brazil. Written informed consent was obtained from the patients for publication of the details of their medical case and any accompanying images.

The first case report shows remarkable short-term lung function improvements in a 12-year-old Caucasian female with homozygous *F508del* mutation in the *CFTR* gene. She had pancreatic insufficiency, no liver impairment, bronchiectasis (a Brody score of 78; Figure 1A), and chronic *Pseudomonas aeruginosa* colonization. On January 18, 2023, her BMI was 15.2 kg/m^2 (her z-score was −1.31), and spirometry revealed impaired lung function: an FVC of 1.52 L (60%), an FEV_1 of 1.11 L (50%), an FEV_1/FVC ratio of 73%, and an $FEF_{25-75\%}$ of 0.88 L/min (31%). On April 5, 2023, she was started on treatment with ETI, being reevaluated on May 24, 2023. Although she reported significant improvement in respiratory and gastrointestinal symptoms, she still had pancreatic insufficiency, with no change in fecal elastase levels. She also showed a slight increase in her BMI, to 16.4 kg/m^2 (her z-score was −0.79), which does not indicate a notable improvement in nutritional status. Spirometry results showed normal lung function: an FVC of 2.55 L (95%), an FEV_1 of 2.05 L (86%), an FEV_1/FVC ratio of 88%, and an $FEF_{25-75\%}$ of 1.96 L/min (64%). Treatment with ETI effectively reversed lung function decline, with FEV_1 increasing by more than 35%. Figure 1B depicts FEV_1 improvement from the year before initiation of ETI therapy. Oscillometry showed improvements in lower airway obstruction (Figure 1C). At 12 months after initiation of ETI therapy, a CT scan showed a remarkable improvement in bronchiectasis (a Brody score of 18; Figure 1A).

The second case report shows complete regression of nasal polyps in a 10-year-old Caucasian male with a heterozygous *CFTR* gene mutation (*F508del*/*R1162X*). He had pancreatic insufficiency, no liver impairment, normal lung function, and no bronchiectasis (a Brody score of 24). He had a history of nasal obstruction and polyps, which required surgical removal—performed on August 4, 2021 and subsequently on August 1, 2022. During a follow-up evaluation performed on January 18, 2023, a CT scan showed that nasal polyps had reappeared (Figure 1D). His BMI was 15.3 kg/m^2 (his z-score was −0.92). Spirometry results showed normal lung function: an FVC of 2.60 L (101%), an FEV_1 of 2.27 L (104%), an FEV_1/FVC ratio of 94%, and an $FEF_{25-75\%}$ of 2.78 L/min (112%). The patient was started on treatment with ETI on April 22, 2023 and underwent a follow-up evaluation on May 25, 2023. Spirometry results continued to show normal lung function: an FVC of 2.73 L (105%), an FEV_1 of 2.47 L (112%), an FEV_1/FVC ratio of 91%, and an $FEF_{25-75\%}$ of 3.25 L/min (130%). He reported a substantial improvement in nasal obstruction and congestion, the absence of nasal polyposis being confirmed by a CT scan performed on June 23, 2023. Remarkably, within a few weeks of ETI initiation, the nasal polyps had completely regressed (Figure 1D).

The third case report describes significant clinical improvements in a 14-year-old Caucasian female with heterozygous *N1303K*/*1078del* mutations in the *CFTR* gene. Notably, these mutations have yet to be approved for triple combination therapy with ETI in some countries. She had pancreatic insufficiency, no liver impairment, bronchiectasis (a Brody score of 36), and chronic *Burkholderia cepacia* complex colonization. On March 8, 2023 she presented with a BMI of 20 kg/m^2 (her z-score was 0.15), and spirometry showed a slight decrease in lung function: an FVC of 2.25 L (80%), an FEV_1 of 1.99 L (79%), an FEV_1/FVC ratio of 88%, and an $FEF_{25-75\%}$ of 3.15 L/min (98%). She was started on treatment with ETI on July 6, 2023 (provided by the family), and a follow-up evaluation performed on August 9, 2023 revealed significant respiratory symptom improvement (as reported by the patient). Spirometry showed normal lung function: an FVC of 2.74 L (95%), an FEV_1 of 2.44 L (94%), an FEV_1/FVC ratio of 89%, and an $FEF_{25-75\%}$ of 3.67 L/min (111%). Treatment with ETI effectively reversed lung function decline, resulting in substantial spirometry increases: in FVC by 0.49 L (15%), in FEV_1 by 0.45 L (15%), in FEV_1/FVC by 1%, and in $FEF_{25-75\%}$ by 0.52 L/min (13%).

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◄ Voltar ao sumário

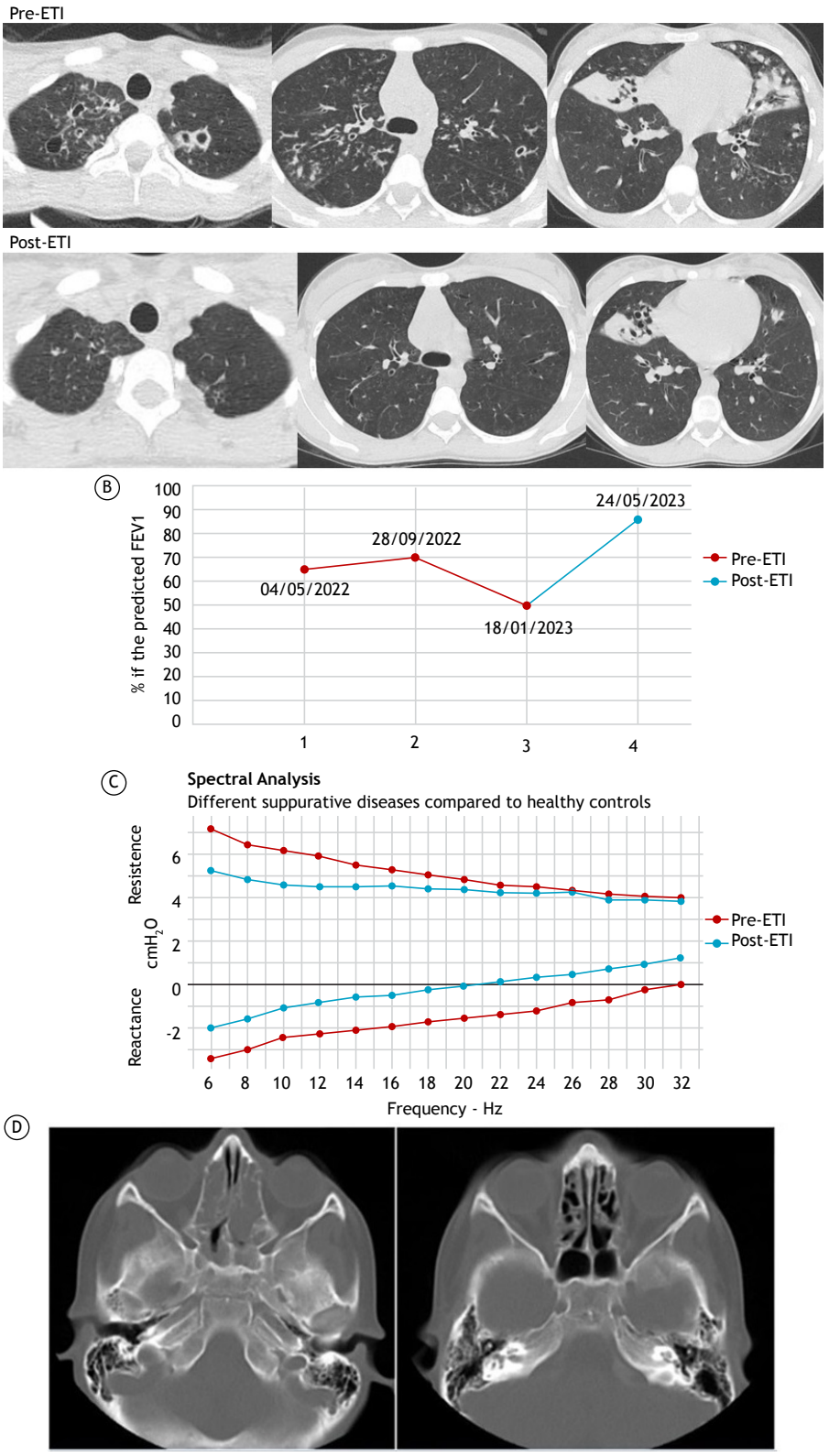

Figure 1. Short-term effects of the triple combination of elexacaftor, tezacaftor, and ivacaftor (ETI) on pediatric cystic fibrosis patients in Brazil. In A, B, and C, bronchiectasis, lung function, and oscillometry in a 12-year-old Caucasian female diagnosed with a homozygous *F508del* cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutation. In A, note significant improvement in bronchiectasis, as indicated by a decrease in the Brody score (from 78 before initiation of ETI therapy [left] to 18 at 12 months after initiation of ETI therapy [right]). In B, note an increase in FEV_1

after initiation of ETI therapy. In C, note a reduction in resistance and reactance between the measurements taken before and after initiation of ETI therapy. In D, a CT scan of the nose and sinuses of a 10-year-old Caucasian male diagnosed with heterozygous *F508del*/*R1162X CFTR* gene mutation. Note bilateral soft tissue density polyps before initiation of ETI therapy (left). At 8 weeks after initiation of ETI therapy, the nasal polyps had completely regressed (right).

In conclusion, this case series represents the first study of the short-term effects of ETI therapy on pediatric CF patients in Brazil. The cases reported here show the positive impact of ETI on different clinical parameters, including reduced patient-reported symptoms, improved lung function, and complete nasal polyp regression. Moreover, none of the patients experienced any adverse effects of ETI, a finding that corroborates the positive safety profile of ETI.[5] The findings of the present study are consistent with those of a study showing improvements in the lung function of adult CF patients in Brazil[6] and provide initial documentation of nasal polyp regression in a pediatric patient. Furthermore, the clinical benefits observed in a patient with the *N1303K* mutation are consistent with previous in vitro and clinical data,[7,8] showing significant benefits from triple combination therapy with ETI in CF patients with this mutation.

AUTHOR CONTRIBUTIONS

MAB: conception and design of the study; and drafting of the article. FMV and ME: conception and design of the study; and acquisition of data. MVFD: conception and design of the study; and final approval of the version to be submitted. LAP: conception and design of the study; acquisition of data; and final approval of the version to be submitted.

CONFLICTS OF INTEREST

MAB and MVFD declare no conflict of interest. FMV, ME, and LAP disclose that they have received honoraria from Vertex Pharmaceuticals Incorporated due to previous sponsored lectures.

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Acid sphingomyelinase deficiency with homozygous p.Arg610del genotype in an elderly patient: a rare case report

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TO THE EDITOR:

Acid sphingomyelinase deficiency (ASMD; alternatively known as Niemann-Pick disease types A, B, and A/B) is an ultra-rare lysosomal storage multisystemic disorder caused by pathogenic variants of the sphingomyelin phosphodiesterase 1 (*SMPD1*) gene with over 250 variants described in ASMD patients. The global prevalence is estimated at approximately 1:100,000–1,000,000 births.[1] Niemann-Pick types A and B are pan-ethnic, but it is well-documented that type A-causing *SMPD1* variants occur more frequently among individuals of Ashkenazi Jewish ancestry than in the general population. The true incidence of type B disease in many countries remains unknown, frequently underdiagnosed by clinicians.[2] Clinical manifestations and disease severity can vary according to the subtype of disease, and predominant genetic alteration. The pathophysiology of the disease is yet to be completely understood, but initial accumulation of lysosomal sphingomyelin leads to inflammatory changes and apoptosis, mitochondrial defects with impaired cellular respiration, and changes in nuclear transport.[1] The disease spectrum ranges from infants with ASMD type A, who have a short life expectancy and rapidly progressive neurodegeneration, to more chronic and variable ASMD types A/B and B, which have a more slowly progressive visceral and/or neurovisceral disease.[3]

The most common symptoms in chronic progressive disease are splenomegaly, hepatomegaly, interstitial lung disease with frequent respiratory infections, high total cholesterol and triglyceride levels—which may lead to cardiac disease—liver fibrosis, cytopenias, including thrombocytopenia with bleeding episodes, and osteopenia or osteoporosis. However, the occurrence of such clinical manifestations is heterogeneous. Historically, the diagnosis of ASMD is challenging, and the disease is certainly underestimated. When there is a suspicion of ASMD, it is important to conduct an enzyme assay to assess ASM activity. The diagnosis is confirmed by showing that ASM activity is deficient or markedly reduced in leukocytes, fibroblasts, or dried blood spots. Assessment of mutations in the *SMPD1* gene should be performed to confirm the diagnosis of ASMD in subjects with ASM activity below the normal reference values.[1,3]

We present here a case of a 77-year-old man, White, who was admitted to our outpatient clinic with dyspnea and hypoxemia after adrenalectomy. He had adrenal macronodular hyperplasia with Cushing's syndrome and ischemic heart disease with hypertriglyceridemia. He was a former smoker. Additionally, he underwent splenectomy due to splenomegaly 30 years prior. At clinical evaluation, he had dyspnea on exertion, oxygen saturation of 92% on room air, and fine crackles in the lower lobes. Chest CT showed diffuse septal thickening with mild areas of emphysema predominantly in the upper lung lobes (Figures 1A, 1B, and 1C) and a remaining spleen was identified (Figure 1D). Pulmonary function tests demonstrated a proportional reduction in FEV_1 and FVC (FVC = 76% of predicted), normal TLC values (83% of predicted), and a severe reduction in DL_{CO} (41% of predicted). Laboratory tests were unremarkable, including negative results for autoantibodies such as antinuclear antibody, rheumatoid factor, anti-Ro/SSA, and La/SSB. Liver enzymes were normal, and there was no thrombocytopenia. The ASM activity level measured was 0.37 µmol/L/h (normal value > 1.02), and genetic testing confirmed the homozygous *p.Arg610del* mutation, establishing the diagnosis of ASMD.

This is a rare case report of an elderly patient with ASMD with the *p.Arg610del* variant in homozygosity and adrenal macronodular hyperplasia. Gene sequencing is recommended for ASMD patients, because genotyping may predict the disease course, chronic visceral manifestations, and particularly, the likelihood of neurodegeneration and/or type A disease.[1,4] The *p.Arg610del* pathogenic variant is associated with the absence of neurodegenerative disease in both homozygous and compound heterozygous patients. Patients who are homozygous for this "neuroprotective" variant have a milder disease course, normal growth, and normal bone development in comparison with those who are *p.Arg610del* heterozygous and those with other genotypes.[4] This mutation has been described to be associated with an attenuated phenotype of ASMD type B disease, being one of the most common associated variants.[5,6] In our case, the diagnosis was late, there were no neurological manifestations or severe pulmonary involvement, and the patient remained stable over the years, with no clinical complications.

ASMD is an autosomal recessive disease that results from the reduced activity of ASM due to loss-of-function variants in *SMPD1*. Over 250 *SMPD1* variants have been described worldwide, resulting in different clinical phenotypes. ASMD is a chronic condition in which the main therapy is management of complications and symptoms.[1] Olipudase alfa, an enzyme replacement

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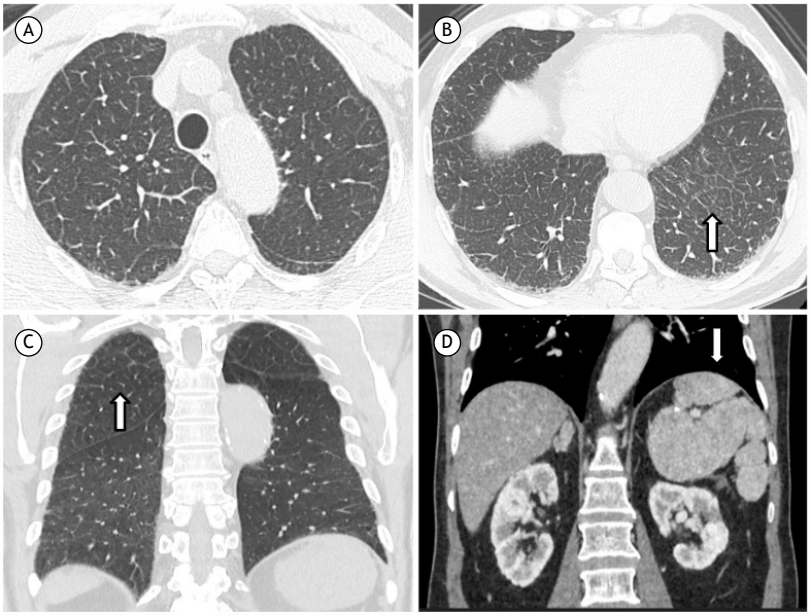

Figure 1. Chest CT shows diffuse septal thickening (arrows) and mild areas of emphysema predominantly in the upper lung lobes in A and B (axial reconstruction) and C (coronal reconstruction). In D, coronal reconstruction shows the remaining spleen (arrow).

therapy, is a promising drug for ASMD, and recent studies and series have demonstrated improvement in sphingomyelin storage, organomegaly, interstitial lung disease, and DL_{CO}, showing a safe profile after two years.[7,8] Patients with ASMD eligible to receive olipudase alfa should be evaluated individually for the potential benefits on respiratory symptoms and pulmonary function tests, spleen and liver volume, platelet count, serum lipid profile, growth in children, and quality of life.[1] In this case, the patient remained clinically and functionally stable during follow-up, with no other systemic manifestations, therefore, with no indication for olipudase alfa replacement.

AUTHOR CONTRIBUTIONS

All the authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

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Long COVID: a cross-sectional study of respiratory muscle strength, lung function, and persistent symptoms at one year after hospital discharge

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TO THE EDITOR:

Currently, the severity of and mortality associated with COVID-19 have been decreasing. However, there are a large number of survivors, who can have prolonged and varied symptoms, a condition known as post-acute COVID-19 syndrome, or "long COVID", defined as the persistence of symptoms (not explained by another diagnosis) at 12 weeks after infection, whether those symptoms developed during or after the period of infection.[1-3]

The severity of the acute illness, measured by the number of symptoms, severity score, or hospital admission, can influence the risk of long COVID, greater severity translating to a higher risk. Fatigue, dyspnea, chest pain, and impaired quality of life are among the most commonly reported late symptoms of SARS-CoV-2 infection. The predilection of the virus for lung tissue is evident, with considerable consequences for the respiratory system in cases that require hospitalization.[4] Approximately 94% of hospitalized patients have persistent lung parenchymal findings on chest CT scans at hospital discharge, and data from previous coronavirus infections (with the original severe acute respiratory syndrome coronavirus or the Middle East respiratory syndrome coronavirus) have suggested that there is substantial fibrotic post-COVID-19 sequelae, with systemic and biopsychosocial repercussions.[5]

The objective of this study was to assess respiratory muscle strength, lung function, and persistent symptoms in individuals hospitalized with COVID-19, at one year after discharge.

This was a cross-sectional study with a quantitative approach to data, conducted in the semi-intensive care unit of a reference hospital for infectious diseases and in the Cardiorespiratory Physiotherapy Laboratory of the Federal University of Ceará, both in the city of Fortaleza, Brazil. Participants were recruited between August and September of 2020. Persistent symptoms, respiratory muscle strength, and lung function were assessed at one year after hospital discharge. This study was approved by the Human Research Ethics Committee of the Federal University of Ceará (Reference no. 38197020.1.0000.5044), in accordance with Brazilian National Health Council Resolution no. 466/12.

We included individuals who were at least 18 years of age and had a clinical condition consistent with COVID-19 and a positive laboratory test result for SARS-CoV-2 infection, according to the diagnostic criteria established by the Brazilian National Ministry of Health.[6] Those who were transferred to other (internal or external) hospital units during their hospital stay were excluded, as were those who were not discharged from the follow-up unit and those with previous neurological impairment.

In the first stage of data collection, we collected demographic and clinical characteristics of the patients during hospitalization, such as age, gender, BMI, previous comorbidities, and lifestyle habits (smoking and drinking), as well as the diagnosis, history, and hospitalization of the individual. In the second stage, at one year after hospital discharge, the patients were invited to complete a self-report questionnaire designed to collect information on the appearance of symptoms after COVID-19. Participants also underwent an assessment of respiratory muscle strength and lung function with manometry and spirometry, respectively.

The study sample included 50 participants, the majority (64%) of whom were male. The mean age was 54.86 ± 17.87 years, and the mean BMI was 28.85 ± 4.85 kg/m^2. Of the 50 participants, 29 (58%) had preexisting comorbidities, cardiovascular and metabolic diseases being the most common, collectively accounting for 18%, and 23 (46%) were alcohol drinkers. The average length of hospital stay was 11 ± 8.8 days. Admission to the ICU was required in 10 cases (20%), and the mean ICU stay was 6.22 ± 8.04 days. Alterations were seen on CT scans in all 50 cases. Twenty-nine individuals (58%) required oxygen at admission and 8 (16%) were submitted to invasive mechanical ventilation. These data are shown in Table 1.

The most recurrent persistent symptoms were respiratory, reported by 78% of the participants, with fatigue on slight exertion being the most prevalent (in

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Table 1. Demographic, anthropometric, and clinical characteristics of the study participants.

Variable	(N = 50)
Age (years), mean ± SD	54.86 ± 17.87
Weight (kg), mean ± SD	78.7 ± 15.47
Height (m), mean ± SD	1.65 ± 0.09
BMI (kg/m^2), mean ± SD	28.85 ± 4.85
Gender, n (%)	
Male	32 (64)
Comorbidities, n (%)	
Cardiovascular and metabolic	09 (18)
Cardiovascular	07 (14)
Metabolic	04 (08)
Respiratory	04 (08)
Infectious	02 (04)
Neurological	02 (04)
Alcohol-related	23 (46)
Hospital stay (days), mean ± SD	11 ± 8.8
ICU admission required, n (%)	10 (20)
ICU stay (days), mean ± SD	6.22 ± 8.04
Oxygen required at admission, n (%)	29 (58)
High-flow therapy, n (%)	04 (08)
Mechanical ventilation required, n (%)	08 (16)
Days on mechanical ventilation, mean ± SD	13.25 ± 6.06
Use of an NBA for more than 24 h, n (%)	06 (12)
Change on CT, n (%)	
< 50%	41 (82)
≥ 50%	9 (18)

NBA: neuromuscular blocking agent.

32%). At one year after hospital discharge (Table 2), the mean FVC was 3.27 ± 0.88, which was only 59.78% of predicted.

The findings related to the assessment of respiratory muscle strength and lung function revealed that all of the study participants had MIP and MEP values within the normal ranges. However, in the population studied, FVC was below the predicted values. At one year after the acute infection, the persistent symptoms most commonly reported were respiratory symptoms, with fatigue on slight exertion being the most commonly reported; musculoskeletal symptoms, such as fatigue and muscle weakness; and noticeable neurological symptoms, mainly memory loss.

Patients who have been infected with Sars-CoV-2, whether or not they required hospitalization, can develop long COVID, characterized by persistent COVID-19 symptoms that last more than four weeks after infection and are not explained by any alternative diagnosis. Of those who require hospitalization, at least 34% of survivors report persistent severe symptoms and organ dysfunction after discharge. These symptoms might, in part, be a consequence of the cytokine storm experienced in the acute phase of the infection.[7,8] These long-lasting syndromes occur among patients with severe symptoms, but have also been reported regardless of the severity of the acute phase, hospitalization, and oxygen support.[9]

Recent studies have reported a prevalence of pulmonary function abnormalities after the acute phase of COVID-19. Although SARS-CoV-2 infection has repercussions on all systems, the lungs are the main organs affected, and damage can occur due to inflammatory mechanisms and direct action of the virus, leading to diffuse alveolar damage and pulmonary vascular thrombosis.[10] In our study sample, the mean FVC was lower than predicted. These results are consistent with those of a study evaluating 186 COVID-19 survivors, in which FVC was significantly lower among the patients with persistent dyspnea, and a restrictive ventilatory pattern was observed in 47%.[9]

This study was carried out at a regional reference hospital for the treatment of COVID-19 and provides relevant findings on the manifestations of COVID-19, specifically persistent symptoms related to respiratory muscle strength and lung function, even after a long period of acute infection, enabling a comprehensive reflection on the impacts of the disease, through patient accounts. A limitation of this study is the small sample size, given the difficult-to-control conditions of the second wave of the COVID-19 pandemic.

In conclusion, patients hospitalized with COVID-19 seem to present FVC results below the predicted values one year after discharge. Among such patients, the most common persistent symptom appears to be fatigue on slight exertion.

Table 2. Persistent symptoms, muscle strength, and lung function at 1 year after COVID-19.

Variable	(N = 50)
Cardiac symptoms, n (%)	
Palpitation and hypertension	8 (16.0)
Palpitation	5 (10.0)
Hypertension	5 (10.0)
Respiratory symptoms, n (%)	
Fatigue on slight exertion	16 (32.0)
Fatigue on medium exertion	9 (18.0)
Fatigue on heavy exertion	8 (16.0)
Persistent cough	6 (12.0)
Musculoskeletal symptoms, n (%)	
Muscle fatigue/weakness	12 (24.0)
Muscle/joint pain	10 (20.0)
Muscle pain, fatigue, and weakness	5 (10.0)
Dermatological symptoms, n (%)	
Dermatitis	11 (22.0)
Hair loss	10 (20.0)
Hair loss and dermatitis	2 (4.0)
Neurological symptoms, n (%)	
Memory loss	14 (28.0)
Memory loss and concentration deficit	9 (18.0)
Limb paresthesia	5 (10.0)
Loss of smell and/or taste	2 (4.0)
Psychological/emotional symptoms, n (%)	
Anxiety	9 (18.0)
Anxiety and depression	8 (16.0)
Irritability/stress	7 (14.0)
Pulmonary variables	
Manometry, mean ± SD	
MIP (cm/H_2O)	112.80 ± 36.91
MIP (% of predicted)	103.46 ± 33.19
MEP (cm/H_2O)	113.00 ± 32.67
MEP (% of predicted)	95.94 ± 25.4
Spirometry, mean ± SD	
FVC (L)	3.27 ± 0.88
FVC (% of predicted)	59.78 ± 16.89
FEV_1 (L)	2.6 ± 0.88
FEV_1 (% of predicted)	85.84 ± 31.84

MIP: maximal inspiratory pressure; and MEP: maximal expiratory pressure.

AUTHOR CONTRIBUTIONS

ERNR: contributions to the study conception/design, drafting of the manuscript, data collection, and critical revision of the manuscript. TRR: contributions to data collection, drafting of the manuscript, and tabulation of the data. BGS: contributions to data collection and tabulation of the data; RFC: contributions to data collection, drafting of the manuscript, and tabulation of the data; SSVG: contributions to drafting of the manuscript, statistical analysis, and critical revision of the manuscript; ICS: contributions to drafting of the manuscript, and proofreading of the English; DGBM: contributions to drafting and critical revision of the manuscript; NGC: contributions to the study conception/design, drafting of the manuscript, data collection, tabulation of the data, and critical revision of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Revitalizing Brazil's contribution to the International Society for Heart and Lung Transplantation Lung Transplant Database

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TO THE EDITOR:

The International Society for Heart and Lung Transplantation (ISHLT) is a professional, multidisciplinary, nonprofit organization dedicated to improving the care of patients with advanced heart or lung disease through transplantation, mechanical support, and innovative therapies by means of research and education. Currently, with more than 3,000 members across over 50 countries, the ISHLT mission is built on three pillars: education, research, and publications.[1] The registration of transplant data is part of the institutional mission.

Since its inception in 1983, more than 220,000 lung, heart, and heart-lung transplants have been submitted to the ISHLT registry, involving approximately 260 lung transplant centers and 481 heart transplant centers across 47 countries. The goal of the ISHLT Registry is to improve the care of patients with terminal lung or heart diseases.[2] It has succeeded in recruiting members from various regions and has catalyzed clinical and scientific improvements and collaborations. However, challenges in data reporting have been observed in Brazil. Initially, the responsibility for providing data was of the participating centers, which, due to the voluntary nature of participation, resulted in heterogeneous commitment. The lack of human resources for data reporting, prevalent in most hospitals in the country, significantly impacted the way data were reported. Additionally, there were no penalties for failing to send data, causing some centers to cease reporting over time.

In 2021, the ISHLT Registry was halted for regulations concerning data sharing and improvements in evaluated standards. Both data fields and the upload process were updated. In 2024, information will be shared only between the ISHLT Registry and national and regional registries, no longer between hospitals or institutions.

Considering that Brazil is the country with the highest number of organ transplants in Latin America, it is natural that our transplant society—the *Associação Brasileira de Transplante de Órgãos* (ABTO, Brazilian Association of Organ Transplantation)—has a transplant registry. This registry is the *Registro Brasileiro de Transplantes* (RBT, Brazilian Transplant Registry). Established since 1996, it is the official registry of all transplants performed in the country, including lungs, kidneys, liver, heart, pancreas, bone marrow, cornea, bones, and muscle tissues.[3] Therefore, to maintain Brazil's participation in the new ISHLT registry format, it is reasonable that the ABTO be the national association of choice for representation.

The RBT also includes sections on pediatric transplants, waiting list times, and organ donations. The publication is made quarterly with partial data, and annually with complete data. These publications are crucial for decision making in organ transplant programs in the country. Lung transplant centers participate voluntarily, contributing with mandatory variables (date of birth, gender, ethnicity, ABO group, underlying diseases, and current status) and optional variables (serology, need for pre-transplant cardiopulmonary support, need for ventilatory support, single or bilateral transplant, retransplantation, and donor conditions such as days of orotracheal intubation, cold ischemia time, Pao_2/Fio_2 ratio, donor serology, and prioritization). In 2023, 78 lung transplants were performed in three states (Rio Grande do Sul, Rio de Janeiro, and São Paulo) in Brazil, corresponding to 0.4 transplants per million population. This number is lower than the 106 performed in 2022, the year post-pandemic recovery from SARS-CoV-2, and also lower than the 120 transplants performed in 2018. Of the 78 transplants, 15 and 63 were unilateral and bilateral, respectively. One-year, three-year, five-year, and ten-year survival rates were 70%, 54%, 44%, and 22% for unilateral transplants and 68%, 58%, 52%, and 38% for bilateral transplants.[4] Figure 1 shows the evolution of lung transplants in Brazil by year until 2023.

It is evident that we must always strive to improve the national lung transplant database. Such an initiative will make information about our reality clearer and more significant, promoting higher quality programs and new discussions about funding transplant centers in public and private health care systems. The leaderships of the ABTO and the ISHLT have already signed a data-sharing agreement. Thus, transplant centers will continue to fill in their own data online in the RBT in Portuguese.

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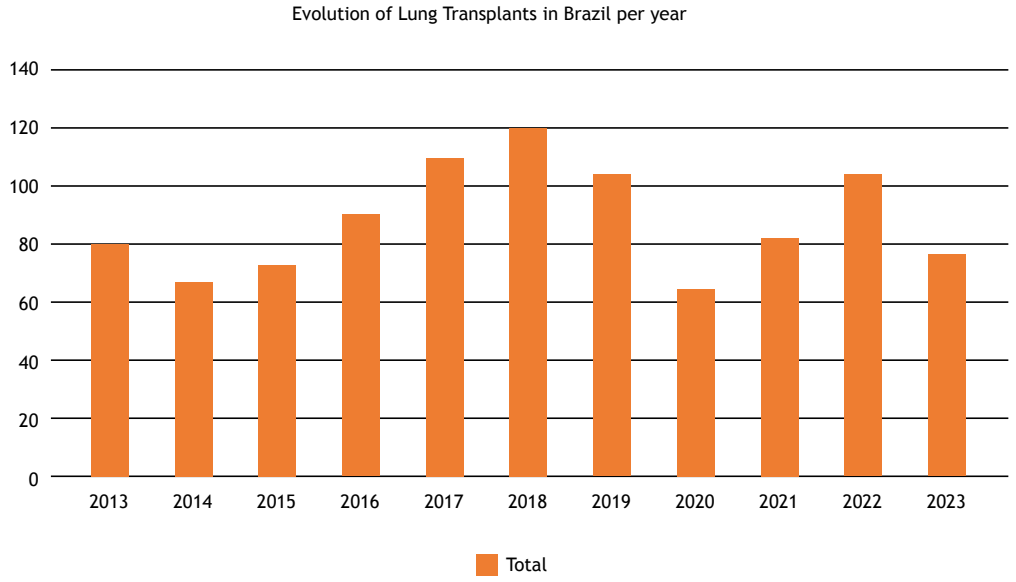

Figure 1. Evolution of lung transplants in Brazil per year.

Once a year, the ABTO will transfer all data, translated into English, to the ISHLT Registry, securely and anonymously, with no patient or hospital identification, within the strictness of data protection laws. This ensures the opportunity to participate in the global database actively so that we will have international outcome standards to compare with ours. Finally, it opens the opportunity for education and research, focusing on national needs.

To make this possible, the RBT has been upgraded to version 2.0. This is particularly important to comply with legal data protection standardizations, confidentiality, privacy, and information integrity. During the modernization of our registry, new variables were included with the same codifications as the ISHLT Registry, which will facilitate the data export process. The progressive incorporation of new variables is the plan for the future.[5]

To achieve success in this project, it is essential that all centers proactively engage, aiming to contribute and improve the national and international registries. The benefits resulting from this collaboration will bring advantages for both our patients and all of us.

AUTHOR CONTRIBUTIONS

DCM: writing-original draft and writing-review and editing; FPR: writing-original draft and writing-review and editing; FAA: conceptualization, methodology, and supervision; LBPH: conceptualization, methodology, supervision, writing-review and editing; and PMPF: project administration, supervision, validation, and writing-review and editing.

CONFLICTS OF INTEREST

None declared.

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Bubbles in my heart—systemic air embolism after CT-guided transthoracic biopsy of a pulmonary nodule

Felipe Marques da Costa[1], Augusto Kreling Medeiros[2], Felipe Roth Vargas[3]

A 70-year-old male former smoker with a history of hypertension was admitted for elective CT-guided transthoracic biopsy (CTTB) of a suspicious pulmonary nodule. He was asymptomatic, and the physical examination was unremarkable. Unenhanced CT images from the periprocedural period are shown in Figure 1. The patient was diagnosed with a systemic air embolism (SAE), after which he was placed in the Trendelenburg position and received oxygen therapy for 3 days, being discharged without complications (Figure 1).

Although it is potentially fatal complication, CTTB-related SAE is rare, occurring in less than 0.1% of cases.[1-3] The pathophysiology involves two primary mechanisms[3]: the entry of air into the pulmonary vein through the biopsy needle when atmospheric pressure exceeds pulmonary venous pressure; and the formation of a bronchovenous fistula. These events can lead to catastrophic outcomes such as myocardial infarction and stroke.[1]

Risk factors for SAE include a lesion being located in a lower lung lobe, a pulmonary nodule with a subsolid composition, pneumothorax, hemorrhage, and a lesion being located above the level of the left atrium.[2] Preventive measures, such as placing the patient in a biopsy side-down position, have significantly reduced the incidence of this complication.[1] Immediate postprocedural management involves administering oxygen to achieve an SpO_2 near 100%, placing the patient in the Trendelenburg position, and applying hyperbaric oxygen therapy if available.[3]

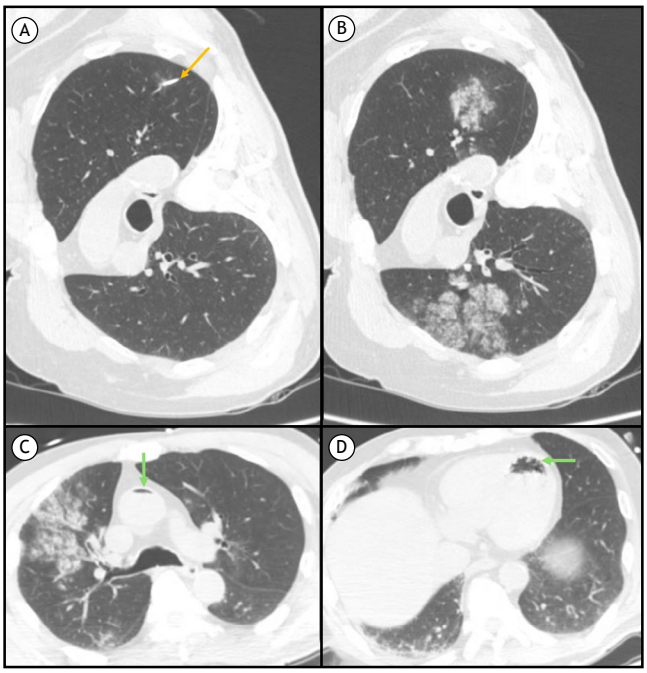

Figure 1. Axial CT slices. Slices A and B were acquired in the right lateral position. (A) The needle tip is within the lung nodule (orange arrow). (B) A few minutes after the needle biopsy, hemorrhage was observed surrounding the nodule in the left lung, as well as in the right lung, presumably due to contralateral aspiration favored by the right lateral position. Slices C and D were acquired in the supine position, at 15 m after the biopsy, and show a small amount of air in the ascending aorta, as well as air within the left ventricle (green arrows).

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◄ Voltar ao sumário
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Pulmonary hemorrhage in a patient with Marfan syndrome

Matheus de Almeida Costa[1], Miriam Menna Barreto[1], Edson Marchiori[1]

A 47-year-old woman was diagnosed with Marfan syndrome 10 years previously. At diagnosis, she was noted to have joint hyperextensibility (Figure 1A); aortic dilatation and dissection (Figures 1B and 1C); and aortic valve involvement. She underwent surgical correction and progressed well. She had been taking an oral anticoagulant (warfarin) since then. She presented to our service with a ~1-week history of cough with hemoptysis and hematuria. A chest CT scan showed bilateral ground-glass opacities (Figure 1D). Alveolar hemorrhage secondary to warfarin-induced coagulopathy was suspected and subsequently confirmed by bronchoscopy. The prothrombin time/international normalized ratio was 7.1. It was reversed with two units of fresh frozen plasma and intravenous vitamin K. Respiratory support was provided, and the patient was discharged from the hospital 20 days later in asymptomatic condition.

Marfan syndrome is an inherited connective tissue disorder that may affect various systems, including the cardiovascular, musculoskeletal, ocular, and pulmonary systems. Common cardiovascular manifestations, most of which are substantial contributors to mortality, include the following: aortic root dilatation with or without aortic valve insufficiency; aortic dissection; aortic aneurysm; and pulmonary artery dilatation. Pulmonary manifestations include paraseptal emphysema with upper lobe bullae and spontaneous pneumothorax. Patients with Marfan syndrome and cardiovascular alterations are frequently treated with warfarin for anticoagulation, which makes them susceptible to pulmonary hemorrhage, as seen in our patient.[1-3]

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

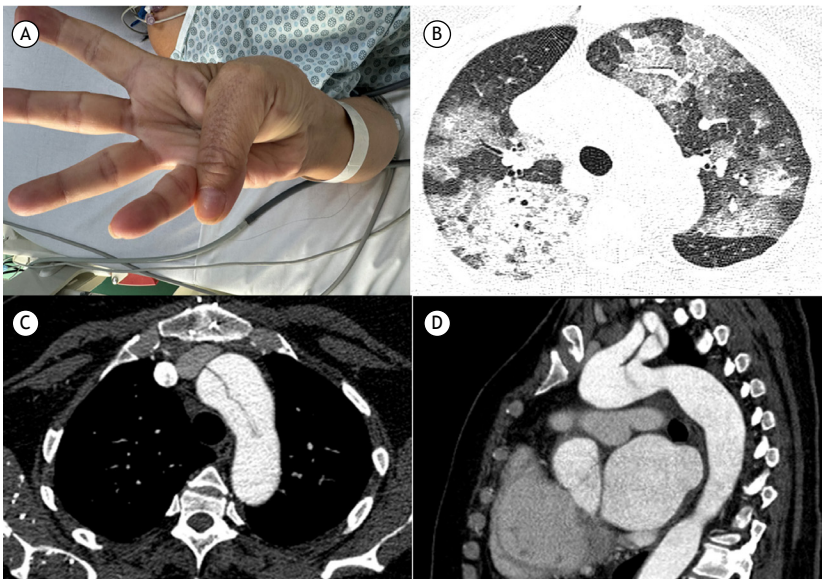

Figure 1. In A, clinical photograph showing hyperextensibility of the thumb. Note that the distal phalanx of the thumb extends beyond the ulnar border of the hand. In B, axial chest CT image (lung window) showing bilateral areas of ground-glass attenuation and interlobular septal thickening (a crazy-paving pattern). In C and D, respectively, axial and sagittal reconstructions (mediastinal window) showing areas of aortic dilatation and aortic stenosis, particularly in the ascending portion, as well as aortic dissection.

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EDITAL DE SELEÇÃO

Brasília, 25 de junho de 2024

No período entre 01 de julho e 15 de setembro de 2024 estarão abertas as inscrições para candidatos ao cargo de Vice-Editor do Jornal Brasileiro de Pneumologia, com atuação no biênio 2025-2026. O Vice-Editor eleito assumirá a posição de Editor-Chefe em 2027, permanecendo na função por quatro anos (2027-2030) e, no biênio seguinte (2031-2032), assume novamente a função de Vice-Editor para auxiliar o novo Editor-Chefe.

Os interessados ao posto deverão ter experiência prévia como editor de periódicos de circulação internacional e enviar à administração da SBPT, em Brasília, suas propostas de gestão e Curriculum Vitae na plataforma Lattes.

As propostas dos candidatos deverão abranger os campos administrativo, científico e orçamentário, e deverão ser apresentadas em relação ao período de dois anos como Vice-Editor e aos quatro anos previstos para o futuro mandato como Editor-Chefe.

Os candidatos deverão conhecer as normas relativas à seleção do Vice-Editor e o funcionamento do Jornal Brasileiro de Pneumologia, descritas em seu regulamento, que pode ser obtido por meio de contato com a secretaria do JBP em Brasília.

Dra. Margareth Maria Pretti Dalcolmo
Presidente da SBPT

Dra. Marcia Margaret Menezes Pizzichini
Editora-Chefe do Jornal Brasileiro de Pneumologia

◄ Voltar ao sumário

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

After being approved by the Editorial Board, all articles will be evaluated by qualified reviewers, and anonymity will be preserved throughout the review process.

Articles that fail to present merit, have significant errors in methodology or are not in accordance with the editorial policy of the journal will be directly rejected by the Editorial Board, with no recourse. Articles may be written in Portuguese, Spanish or English. In the online version of the Journal (www.jornaldepneumologia.com.br, ISSN-1806-3756), all articles will be made available in Spanish or Portuguese, as well as in English. Authors may submit color figures. However, the cost of printing figures in color, as well as any related costs, will be borne by the authors.

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The *Jornal Brasileiro de Pneumologia* upholds the World Health Organization (WHO) and International Committee of Medical Journal Editors (ICMJE) policies regarding the registration of clinical trials, recognizing the importance of these initiatives for the registration and international, open-access dissemination of information on clinical trials. Therefore, as of 2007, the Journal only accepts clinical trials that have been given an identification number by one of the clinical trials registries meeting the criteria established by the WHO and the ICMJE. This identification number must be included at the end of the abstract.

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An individual may be considered an author of an article submitted for publication only if having made a significant intellectual contribution to its execution. It is implicit that the author has participated in at least one of the following phases: 1) conception and planning of the study, as well as the interpretation of the findings; 2) writing or revision of all preliminary drafts, or both, as well as the final revision; and 3) approval of the final version.

Simple data collection or cataloging does not constitute authorship. Likewise, authorship should not be conferred upon technicians performing routine tasks, referring physicians, doctors who interpret routine exams or department heads who are not directly involved in the research. The contributions made by such individuals may be recognized in the acknowledgements.

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

SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.

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