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HIGHLIGHT

Real-world effectiveness of elexacaftor/tezacaftor/ivacaftor treatment in cystic fibrosis

Importance of tongue size in obstructive sleep apnea

High direct and indirect costs to treat tuberculosis in Brazil: how can we mitigate it?

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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Diagnosis and management of post-tuberculosis lung disease

Denise Rossato Silva[1], Fernanda Carvalho de Queiroz Mello[2], Giovanni Battista Migliori[3]

Worldwide, an estimated 10.6 million people fell ill with tuberculosis in 2021. Tuberculosis is the second leading infectious killer after COVID-19, and a total of 1.6 million people died from tuberculosis in 2021. However, tuberculosis is curable and preventable. Since 2000, approximately 74 million lives have been saved because of adequate tuberculosis diagnosis and treatment. In 2020, it was estimated that there were 155 million tuberculosis survivors still alive globally.[1]

Most tuberculosis programs focus on diagnosing and treating patients who are followed up until the end of treatment. However, monitoring and clinically and functionally evaluating after treatment is fundamental, since up to 50% of patients (> 70% of those with multidrug-resistant tuberculosis) have post- tuberculosis lung disease (PTLD), defined as "evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous (pulmonary) tuberculosis."[2,3]

Patients with PTLD may have varying degrees of functional and structural lung sequelae, such as bronchiectasis, fibrosis, and pleural thickening. Due to structural sequelae, they are at a high risk for other pulmonary infectious diseases, including those caused by bacteria, viruses, nontuberculous mycobacteria, and fungi, requiring protocols for diagnostic and prevention. They may have lung function deficits (obstruction, restriction, or mixed patterns), having a two-fold greater risk of presenting with spirometric abnormalities than the general population, and approximately 10% of these patients may have lost more than half of their lung function.[2,4,5] In addition, these patients may have persistent respiratory symptoms, such as residual cough and dyspnea, in addition to reduced exercise capacity and quality of life.[2,6] Furthermore, it has been shown that tuberculosis survivors have a long-term post-treatment mortality rate almost three times higher than the general population, with most deaths occurring in the first year after the end of treatment.[7]

In fact, tuberculosis can cause several types of sequelae besides PTLD. Tuberculosis survivors may experience cardiovascular and pericardial disorders, neurological impairments, as well as psychological and socioeconomic effects. Nightingale et al.[8] have recently published a clinical statement on post-tuberculosis health and wellbeing. The authors developed a guide for the diagnosis and management of post-tuberculosis conditions, such as PTLD, cardiac disorders, neurological disorders, and post-tuberculosis effects in children and adolescents. They described the clinical presentation, made recommendations for assessment after tuberculosis treatment, and discussed the clinical and pharmacological management of each of the post-tuberculosis conditions.

This important document joins the previously published "Clinical standards for the assessment, management and rehabilitation of post-TB lung disease,"[9] which had already highlighted the importance of a minimal basic assessment at the end of tuberculosis treatment to verify the possibility of PTLD. Only with the early recognition of disabilities can strategies be devised for a better approach and treatment/rehabilitation of PTLD cases.[10,11]

In Brazil, although there are many patients living with tuberculosis sequelae, functional and radiological assessment after the end of treatment is neither routinely performed, nor is it recommended in the Brazilian Ministry of Health "*Manual de Recomendações para o Controle da Tuberculose no Brasil* (Manual of Recommendations for Tuberculosis Control in Brazil)."[12] In this sense, the Brazilian Thoracic Society has decided to develop a specific document for the diagnosis and management of PTLD in Brazil. The elaboration of the document should be carried out during a meeting of specialists in tuberculosis to be held during the next congress of the Society in August of 2023. The document will be fundamental to emphasize that tuberculosis must be considered a leading cause of chronic lung disease and that the diagnosis and treatment of PTLD must be implemented in various programmatic settings.

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AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

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Legal action in sleep medicine: new alternatives need to be sought!

Simone Chaves Fagondes[1,2], Angela Beatriz John[1]

In this issue of the *Jornal Brasileiro de Pneumologia*, the article by Pachito et al.[1] raises the discussion of an increasingly common approach in Brazil, as well as in other countries, which is taking legal action for access to medical procedures and treatments.[2]

The evolution of knowledge in health care has introduced more sophisticated diagnostic methods and therapeutic options, and, consequently, costs have increased. However, many of these methods and treatments are not covered by the *Sistema Único de Saúde* (SUS, Brazilian Unified Health System) or private health insurance plans, which, based on the premise that health is a universal right, makes legal action an alternative, with all the complexity that this approach imposes.

From the perspective of sleep medicine, there is a great lack of public services that offer specialized care in this area. A recent study has identified the presence of 36 specialized centers in Brazil, with a great asymmetry in terms of geographic distribution, and 44% of those are concentrated in the southeastern region of the country (personal information). Regarding diagnosis, sleep laboratory beds accredited to perform tests by the SUS are a minority, totaling only 28 centers throughout Brazil (personal information). On the other hand, the use of portable polysomnograms, which are less expensive and dispense with sleep laboratories, still requires improvements in both logistics and operationalization.

In addition to diagnostic limitations, we have an even greater challenge when we address issues related to treatment. The main treatment for moderate and severe obstructive sleep apnea is the use of a device that generates CPAP in the upper airways. It is a high-cost piece of equipment that is included neither in the SUS nor in most private health insurance plans. In our daily practice at a public tertiary university hospital, we have observed actions that aim to fulfill this need at the municipal level; however, these actions are generally restricted to patients with more severe disease and are concentrated in larger cities, closer to capitals.

The magnitude of the problem, therefore, is directly related to the prevailing socioeconomic reality in our country and the limitations arising from an area of medicine that is still being consolidated, especially in the public sphere, as well as to a highly prevalent medical condition (approximately 30% of the adult population),[3] whose consequences have been widely documented in the literature.[4,5]

One of the concerns pointed out in the article by Pachito et al.[1] is the high economic costs that the growing practice of legal action in sleep medicine imposes. The study presents an additional cost estimate of 588% for diagnostic tests and of 21.7% for treatment with CPAP. These values are substantially higher when we compare the public health care system with the private health insurance plans.

The theme takes on an even more relevant and worrying role considering that the number of lawsuits identified in the manuscript seems to be underestimated. The authors performed an analysis based on information extracted from the judicial system database over a period of five years and identified only 1,462 lawsuits, that is, approximately 292 cases/year. Considering the already mentioned high prevalence of obstructive sleep apnea in a country with an estimated adult population of 159.2 million individuals,[6] the number of patients who would potentially seek public health care assistance should be much higher. Another aspect that deserves attention is the decrease in the number of lawsuits between 2017 and 2019 reported in that study.[1] This finding differs from our experience in a public hospital. In recent years, with the deepening of the socioeconomic crisis in Brazil and the consequent decrease in income, making it difficult to maintain a private health insurance plan and to acquire a CPAP device, we have observed a substantial growth in the number of patients referred to our sleep outpatient clinic.

As it was already pointed out by the authors,[1] the need for public policies that include the training of physicians to care for those patients, the dissemination of diagnostic methods, a detailed review of health care staff wages, and the establishment of partnerships is vital in order to improve the offer of CPAP treatment. It is also necessary that these patients have access to follow-up by a qualified medical team in the various regions of the country.

Definitely, legal actions regarding sleep medicine are far from being a solution. They should be an exception, and it is urgent that we seek new alternatives!

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Left upper lobe atelectasis

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

A 68-year-old man presented with complaints of persistent, severe cough and weight loss in the last six months. Chest X-rays showed opacity in the upper third of the left lung and volume loss (Figure 1).

The aforementioned chest X-ray findings are indicative of left upper lobe atelectasis. Atelectasis appears as parenchymal opacification and volume loss caused by loss of lung aeration. Atelectasis can be lobar, segmental, or subsegmental, or it can involve an entire lung, with varying imaging appearances. It can occur through different mechanisms, including passive retraction of the lung parenchyma, scar tissue formation, compression of lung tissue, surfactant deficiency, and bronchial obstruction. Obstructive atelectasis occurs when airway obstruction inhibits regional lung ventilation partially or completely. Perfusion to the area is maintained; however, gas uptake into the blood continues. Eventually, all of the gas in that segment will be absorbed and, without return of ventilation, the airway will collapse. The causes of bronchial obstruction are varied, the most common being bronchial tumors in adults and foreign bodies in children. Children are especially susceptible to resorption atelectasis in the presence of an aspirated foreign body because they have poorly developed collateral pathways for ventilation.[1-3]

The radiological signs of pulmonary atelectasis can be divided into direct signs and indirect signs. Displacement of fissures is the most important direct sign of pulmonary atelectasis. The indirect signs are basically related to the loss of lung volume and include increased lung opacity, elevation of the diaphragm, mediastinal shift, and compensatory hyperinflation of the remaining lung parenchyma. Total atelectasis caused by bronchial obstruction appears as an opaque hemithorax, with displacement of the mediastinum toward the affected side. Left upper lobe atelectasis appears as a superior and anterior displacement of the major fissure. Anterior displacement of the major fissure is more easily seen on lateral chest X-rays. Segmental atelectasis of the left upper lobe with preservation of the lingula, as seen in our patient, can result in findings similar to those of atelectasis of the right upper lobe. Although the Golden S sign was initially used in order to describe signs of right upper lobe atelectasis, it can be applicable to atelectasis involving any lung lobe. The Golden S sign represents bowing or displacement of a fissure caused by a mass (generally bronchial carcinoma) that prevents complete displacement of the fissure.[1-3]

On the basis of the aforementioned findings, a diagnosis of left upper lobe atelectasis was made. A bronchoscopy was then performed, showing a tumor obstructing the left upper lobe bronchus, the lingular segments being spared.

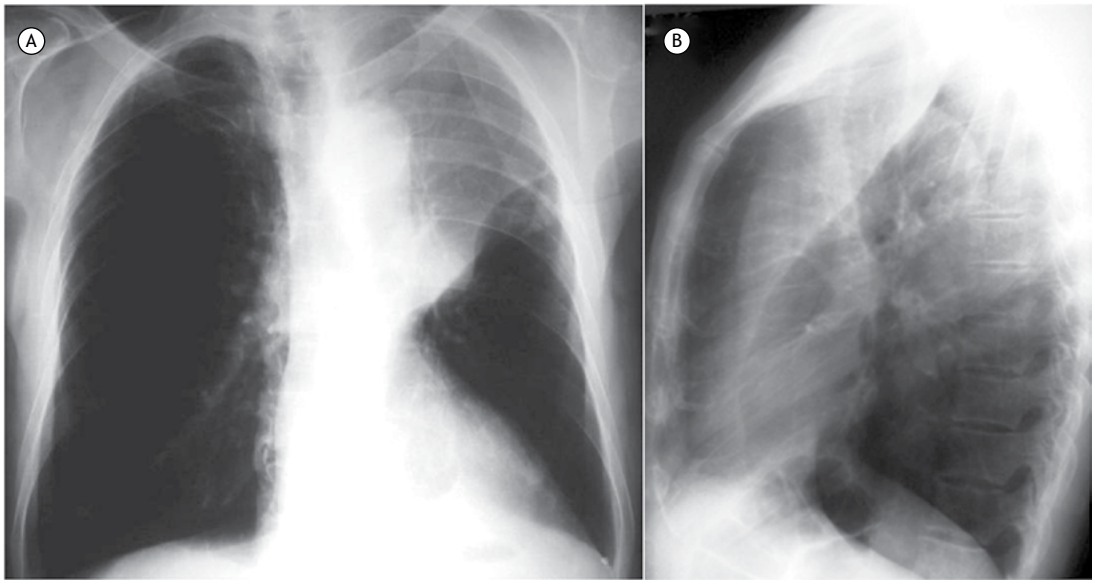

Figure 1. Posteroanterior and lateral chest X-rays (in A and in B, respectively) showing opacity and left upper lobe volume loss. Note an upward and forward shift of the major fissure and a mass in the left hilar region, preventing complete displacement of the fissure, which assumed an S shape (the Golden S sign).

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Mixed-effects model: a useful statistical tool for longitudinal and cluster studies

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PRACTICAL SCENARIO

A multicenter clustered clinical study involving patients with multimorbidity hospitalized at 82 hospitals in Switzerland evaluated the effectiveness of a hospital discharge planning tool embedded in the electronic medical records in comparison with standard discharge procedures on reducing hospital length of stay.[1] The authors analyzed the results of an interrupted time series of acute medical hospitalizations. They reported that the planning tool vs. standard procedures reduced the length of hospital stay (−0.879 h/month; 95% CI, −1.607 to −0.150 h/month vs. −0.011/month; 95% CI, −0.281 to 0.260 h/month), with no increase in hospital readmissions, in-hospital mortality, or facility discharge.

CHARACTERISTICS AND USEFULNESS OF MIXED-EFFECTS MODELS

Regression models, such as linear and logistic regression, are widely applied to evaluate relationships between an exposure (independent variable) and an outcome (dependent variable). Each type of regression model has underlying assumptions that must be met. If these assumptions are not met, a different statistical approach should be required to prevent bias. In our practical scenario, the outcome was repeatedly assessed over time and across several centers. Thus, to accommodate both repeated measures and results across different centers, the authors used a mixed-effects model to analyze the data.

Mixed-effects models include specific subtypes with different names, such as hierarchical models, multilevel models, and cross-sectional time series. Notably, the key characteristic of mixed models is that they integrate both fixed and random effects in the same analysis.

Fixed effects are exposures with specific values that do not change throughout the study, such as sex, age at baseline, race, and ethnicity, and whose relationship with the outcome is constant or fixed. When we include a variable as a fixed effect in a model, we assume that no relationship exists among the levels of this variable. For example, if we include sex as a fixed effect, the model will provide a separate estimated effect for males and females. Exposures, predictors, and interventions at baseline are usually treated as fixed effects in such studies, because we are interested in the independent effect of each of the variable levels on the outcome.

Random effects are more challenging to define and assimilate. In brief, when a variable is introduced in a statistical model as a random effect, its levels are not entirely independent. On the contrary, there is a relationship across the measurements, which adds variability.

Measurements from the same participant over time and within a cluster (in our scenario, the hospitals) are more similar than are measurements across participants not in a cluster. For this reason, to measure the effect of clusters, statistical models that incorporate random effects should be considered in the analytic approach to account for random variation within and between clustering.

In our practical scenario, the data set contained repeated measurements from the same participant, which precludes using, for example, linear or logistic regression analysis. Additionally, because the data were collected from 82 different hospitals, participants were grouped at the center level. Therefore, the authors used mixed-effects regression analysis with random effects for hospitals and patients to account for individual tendencies for each hospital and each patient. Age, sex, comorbidity index, and frailty score were inserted into the model as fixed effects.

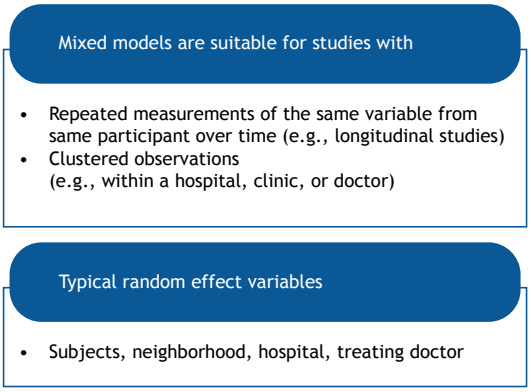

Figure 1. Examples of situations in which mixed effects models should be considered in the analysis plan and examples of variables that are often used as random effects.

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Examples of studies that require mixed-effects models are time series, longitudinal studies with multiple measurements taken over time on the same subject, and studies that involve participants from different sites or that are evaluated by different physicians (clustered measurements). In such cases, the effects of participants and centers would be considered a random effect, and they would be added to the model to take into account correlations between measurements[2] that traditional linear or logistic regression cannot address.

Choosing the appropriate statistical model to answer specific research questions considering the data set structure improves the models' fit. In addition, it enhances the interpretation of studies that could potentially be used to guide clinical decision making.

KEY POINTS

- Mixed-effects models combine fixed and random variables.
- Fixed effects do not change over time; their levels have explicit values that are not correlated. E.g., age at baseline, color of eyes, race/ethnicity.
- Random effects introduce sources of variation within or across patients.
- Mixed-effects models account for correlations across measurements; therefore, they may be used in studies with longitudinal and clustered data.
- It is important to align research questions and data configuration with the appropriate statistical model to answer and interpret study results adequately, thus guiding clinical decision making efficiently.

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The pulmonary function laboratory in the investigation of dyspnea of unknown origin

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

BACKGROUND

Chronic dyspnea (i.e., dyspnea for at least 3 months) negatively impacts the health-related quality of life of ~10% of the general population. In a sizable fraction of these individuals, the underlying cause remains unclear after detailed clinical assessment, basic pulmonary function tests, and chest imaging, characterizing dyspnea of unknown origin (DUO). The "lung doctor" is frequently called to assess these patients for diagnostic clarification, an endeavor fraught with complexities in most circumstances.

OVERVIEW

A 67-year-old, nonsmoking, sedentary woman (BMI = 34.6 kg/m^2) reported progressive exertional dyspnea after SARS-CoV-2 infection two years before (a modified Medical Research Council dyspnea score of 3-4). Her medical history was positive for systemic arterial hypertension, depression, and fibromyalgia. Extensive investigation at rest was inconclusive (Figure 1). Incremental cardiopulmonary exercise testing revealed a tachypneic breathing pattern with a consistent reduction in dynamic inspiratory capacity despite the lack of resting hyperinflation; moreover, she reported disproportionate dyspnea relative to the achieved work rate (a Borg scale score of 5/10 at 45 W, > the 95th percentile).[1] These findings raised the suspicion of inspiratory muscle weakness/fatigue[2]: although MIP and MEP were reduced, they were still within the limits of normal. Of note, however, 12-s maximal voluntary ventilation (MVV; 38 L/min) was reduced both in % of predicted (47%) and relative to the MVV estimated from FEV_1 (73 L/min). Electroneuromyography of the extremities of the upper and lower limbs was consistent with myopathy

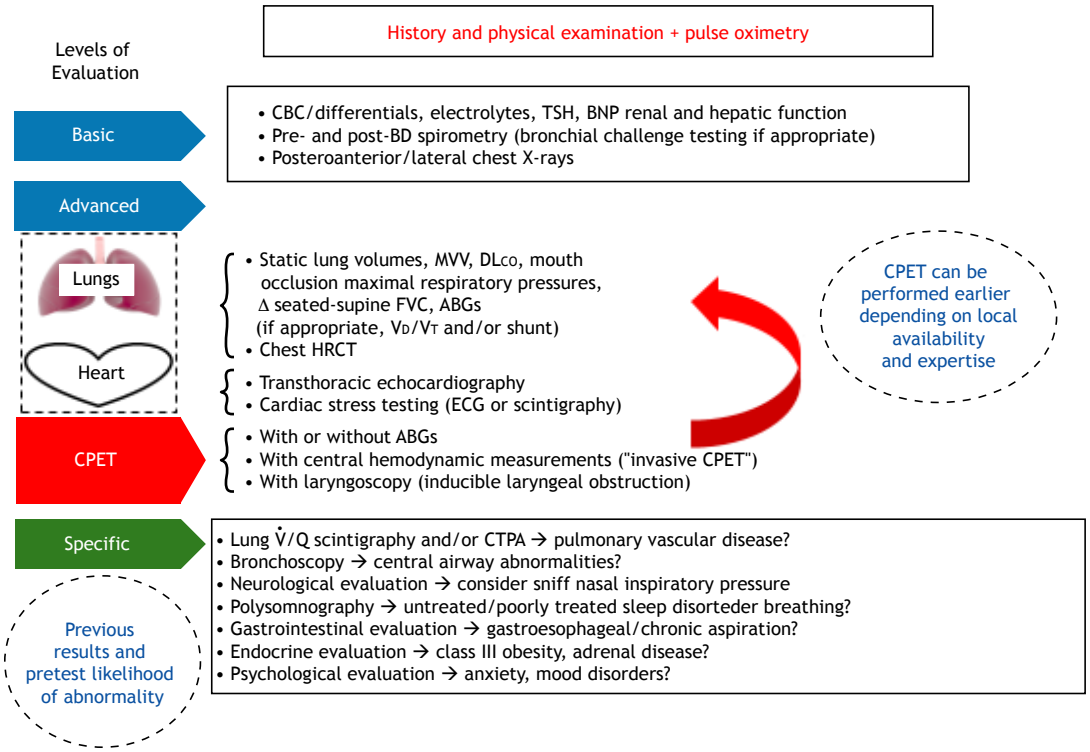

Figure 1. Suggested workup of patients with chronic dyspnea of unknown origin. The levels are based on the complexity of the tests and the epidemiology of the disease(s) that can be uncovered. Note that the sequence can be modified on the basis of clinical impression and depending on local resources and expertise. Modified with permission from Berton et al.[7] CBC: complete blood cell count; BNP: brain natriuretic peptide; BD: bronchodilator; MVV: maximal voluntary ventilation; ABGs: arterial blood gas analysis; V_D/V_T: dead space to tidal volume ratio; ECG: electrocardiography; CPET: cardiopulmonary exercise testing; V̇/Q: ventilation/perfusion; and CTPA: CT pulmonary angiography.

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with myotonic discharges. At this writing, the patient is under investigation for myotonic dystrophy versus channelopathies, potentially triggered by SARS-CoV-2 and associated with an inflammatory response.

DUO is a heterogeneous syndrome that is frequently multifactorial. Only a minority of patients with DUO (including our patient) report dyspnea in the absence of any active disease known to elicit the symptom (dyspnea without an apparent cause). More commonly, however, there is dyspnea with multiple potential causes in patients who present with cardiopulmonary or systemic diseases and who are deemed to be "optimally treated" (residual exertional dyspnea).[3] There is no uniformly accepted algorithm for the investigation of DUO (Figure 1). The value of more sophisticated pulmonary function tests—particularly those assessing the small airways[4]—remains elusive. Cardiopulmonary exercise testing is frequently useful to rule out major cardiopulmonary disease, showing the negative consequences of obesity, simple deconditioning, and, occasionally, hyperventilation/dysfunctional breathing.[5] Dynamic inspiratory capacity measurements are paramount,[6] and arterial blood gas analysis (or arterialized capillary blood gas analysis) is often required. In the present case, increased metabolic demands secondary to obesity led to normal peak oxygen uptake despite reduced peak work rate.[5] An apparently normal MIP might be misleading because 1) overactivation of the accessory inspiratory muscles during the static maneuver might not be dynamically sustained (MVV, exercise); and 2) thresholds for an abnormal test result can vary up to 50% depending on the set of reference values.[5]

CLINICAL MESSAGE

The principles of Bayesian inference considering disease prevalence locally and the pretest likelihood of abnormality should be applied to judge the best investigative steps in individual patients with DUO. By following a logical stepwise sequence (Figure 1), the pulmonologist can minimize costs and enhance the diagnostic yield while avoiding futile and potentially iatrogenic procedures.

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Legal action for access to resources inefficiently made available in health care systems in Brazil: a case study on obstructive sleep apnea

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) is a highly prevalent chronic disease, associated with morbidity and mortality. Although effective treatment for OSA is commercially available, their provision is not guaranteed by lines of care throughout Brazil, making legal action necessary. This study aimed at presenting data related to the volume of legal proceedings regarding the access to diagnosis and treatment of OSA in Brazil. **Methods:** This was a descriptive study of national scope, evaluating the period between January of 2016 and December of 2020. The number of lawsuits was analyzed according to the object of the demand (diagnosis or treatment). Projections of total expenses were carried out according to the number of lawsuits. **Results:** We identified 1,462 legal proceedings (17.6% and 82.4% related to diagnosis and treatment, respectively). The projection of expenditure for OSA diagnosis in the public and private spheres were R$575,227 and R$188,002, respectively. The projection of expenditure for OSA treatment in the public and private spheres were R$2,656,696 and R$253,050, respectively. There was a reduction in the number of lawsuits between 2017 and 2019. **Conclusions:** Legal action as a strategy for accessing diagnostic and therapeutic resources related to OSA is a recurrent practice, resulting in inefficiency and inequity. The reduction in the number of lawsuits between 2017 and 2019 might be explained by the expansion of local health care policies or by barriers in the journey of patients with OSA, such as difficulties in being referred to specialized health care and low availability of diagnostic resources.

Keywords: Sleep apnea, obstructive; Continuous positive airway pressure; Polysomnography; Health services accessibility.

INTRODUCTION

Access to health care is a right granted to the Brazilian citizen by the Federal Constitution of 1988.[1] Article 196 reads "Health is a right for all and a duty of the State, guaranteed through social and economic policies." In this sense, Brazilian National Ministry of Health/Health Minister's Office Ordinance no. GM 4,279/2010, which establishes guidelines for the organization of the Brazilian Health Care Network within the scope of the *Sistema Único de Saúde* (SUS, Unified Health Care System), aims to promote the systemic integration of health actions and services, ensuring the provision of continuous, comprehensive, responsible, humanized, and high-quality care.[2]

The process of incorporating technologies in the SUS is carried out by an agency of the Brazilian National Ministry of Health called the *Comissão Nacional de Incorporação de Tecnologias no SUS* (Conitec, Brazilian National Commission for the Incorporation of Technologies in the SUS). Conitec carries out the evaluation for incorporation of health technologies by assessing effectiveness, safety, cost-effectiveness, and budgetary impact. Technologies incorporated after the evaluation process become part of the National List of Medications or the National List of Equipment and Permanent Fundable Materials for the SUS. Together, the list of these products and services are made available to SUS users in compliance with the recommendations on specific lines of care, presented in the Brazilian Clinical Protocols of Therapeutic Guidelines.

Obstructive sleep apnea (OSA) is a highly prevalent chronic disease. OSA is characterized by partial or complete obstruction of the upper airways during sleep, contributing to fragmented, poor-quality sleep.[3] In Brazil, it is estimated that OSA affects 50 million inhabitants.[4] This condition promotes an negative impact on quality of life[5] and is associated with clinical conditions such as systemic arterial hypertension,[6] acute myocardial infarction,[7] atrial fibrillation,[8] stroke,[9] diabetes mellitus,[10] motor vehicle crashes,[11] and work-related accidents.[12] Despite the its high prevalence of OSA and the association of OSA with morbidity and mortality, assistance to patients with OSA is neither included in

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health care protocols nor guaranteed by lines of care or networks nationally established in Brazil.

Legal action is a strategy that users of health care systems in Brazil have employed as a way to gain access to incorporated diagnostic and therapeutic procedures that are not effectively available, as well as to non-incorporated technologies. According to data from the Brazilian National Council of Justice, between 2008 and 2017, there were 498,715 health-related lawsuits in the first instance.[13] Among these lawsuits, 55.6%, 47.1%, and 33.1%, respectively, were related to access to diagnostic technologies, procedures, and supplies or materials. The temporal analysis of the volume of legal actions showed an increase of approximately 130% in the number of health-related legal proceedings between 2008 to 2017.[13]

Positive airway pressure (PAP) devices are considered the most effective technology for treating moderate to severe cases of OSA. Although this technology has officially been incorporated by Conitec, with provision for dispensation by the states and the Federal District, the effective provision of the technology depends on local terms of cooperation with responsible bodies. In this scenario, legal action is expressed as a strategy for obtaining specialized assistance. This study aimed at presenting data related to the volume of legal proceedings regarding the access to diagnosis and treatment of OSA in Brazil.

METHODS

This was a descriptive study of secondary data collected nationwide between January of 2016 and December of 2020. The identification and evaluation of legal proceedings related to access to diagnosis and/or treatment of OSA were conducted in four phases (Chart 1).

During phase 1, two search strategies were developed. Search terms for the diagnosis of OSA were "Polysomnography", "Polysomnogram", "PSG", and "Sleep Apnea Diagnosis," whereas those for the treatment of OSA were "CPAP", "CEPAP", "BILEVEL", "BIPAP", and "Positive Pressure." Sources of information were first and second instances courts of justice at the national, state, and Federal District levels in Brazil.

Phase 2 involved conducting searches in the databases of the courts of justice within the period defined for the analysis. Data from lawsuits potentially related to the diagnosis and/or treatment of OSA were retrieved for further analysis and consolidation.

During phase 3, information related to legal proceedings was manually extracted and consolidated, and then entered into Microsoft Excel software spreadsheets. The compiled variables included date, court of origin, geographic region, medical board registration number of the prescribing physician, incurred monetary value, object of the demand (diagnosis or treatment), and type of device demanded.

Phase 4 involved the analysis of information obtained from the Information Technology Department of the SUS: geographic region (of the plaintiff and of the court of justice), presence of regional protocols and/or guidelines for the provision of CPAP, and registration number at the National Registry of Health Establishments of the health care facility (defendant). Data from the Federal Council of Medicine were also collected about the prescribing physicians with regard to their being registered as specialists in sleep medicine in the Brazilian Medical Association.

The number of lawsuits was presented as absolute and relative frequencies by geographic region. Data referring to the amounts incurred in the legal proceedings were presented according to the type of health care system (public or private) using measures of central tendency and dispersion. For the estimate of total expenses associated with legal proceedings, including those with no report on the expenses incurred, a projection was made by using the median value of the known expenses. Additionally, a best-case deterministic sensitivity analysis was performed, using the first quartile for the projection of total expenditure, as was a worst-case deterministic sensitivity analysis, using the third quartile for the projection of total expenditure.

RESULTS

The present study identified a total of 1,462 cases of legal proceedings related to OSA, 258 (17.6%) of which regarding diagnosis and 1,204 (82.4%) of which regarding treatment. In total, only 59.4% of the records had reported the monetary values incurred. Of these, 36.4% were related to the diagnosis and 64.4% were related to the treatment of OSA (Figure 1). Over the period analyzed, there was a downward trend in the number of lawsuits related to OSA treatment and diagnosis, with a reduction of more than 50% in the number of lawsuits in 2019 in comparison with that in 2017. The distribution of lawsuits among the geographic regions of Brazil is presented in Table 1.

The analysis of the distribution of legal proceedings by state and the Federal District showed a concentration of proceedings in São Paulo (n = 780; 53%); Minas Gerais (n = 263; 18%); Rio Grande do Sul (n = 171; 12%); Rio de Janeiro (n = 77; 5%); and the Federal District (n = 30; 2%). They accounted for 91% of the total number of cases during the study period. When considering the number of lawsuits per million

Chart 1. Steps for identifying lawsuits related to obstructive sleep apnea.

Phase 1: Search planning, and defining keywords, information sources, and study period
Phase 2: Execution of the search in pre-defined information sources
Phase 3: Data consolidation
Phase 4: Analysis of variables and comparison of information obtained from other public databases

population, the rate in the Southeast region was 1.8 times greater than that in the whole country (10.6 per million population vs. 5.7 per million population).

Of the 1,462 lawsuits, 1,383 (94%) were against governments, 70 (5%) were against private health care providers, and 9 (1%) were kept confidential. Of the lawsuits against governments, 720 (52%), 654 (47%), and. 9 (1%), respectively, were at the municipal, state, and federal levels.

Analysis of legal proceedings related to the diagnosis of OSA

The analysis of the legal proceedings related to the diagnosis of OSA showed that the state of Minas Gerais ranked first (n = 102; 40%), followed by São Paulo (n = 57; 22%), Rio Grande do Sul (n = 22; 9%), Rio de Janeiro (n = 20; 8%), and Goiás (n = 9; 3%).

Polysomnography is the diagnostic procedure for OSA and is identified in the Management System of the Table of Procedures, Medications, Orthoses, Prostheses, and Special Materials of the SUS (SIGTAP). The analysis showed that 87 legal proceedings (34%) originated from municipalities where the procedure is available in public or private health care services, whereas 171 (66%) originated from municipalities where this procedure is not offered to SUS users.

In 94 legal proceedings (36.4%), it was possible to identify the expenses associated with the requested resource. The monetary value was analyzed separately according to the type of defendant in question (public or private). Legal action was taken against the public and private sphere in 83 and 11 lawsuits, respectively. For lawsuits involving public entities, corresponding to 78 (89%) of the records, the projected expenses related to all lawsuits, calculated after the imputation of the median value for lawsuits with no reference to the expense incurred, was R$575,227 for the base case. Sensitivity analysis showed expenses ranging from R$542,747 to R$1,031,227 in the best and worst case scenarios. In the private health care system, the total expenditure was estimated at R$188,002, and sensitivity analyzes ranged from R$168,906 to R$202,330 (Table 2).

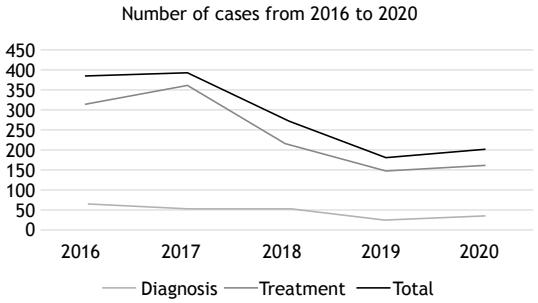

Figure 1. Number of lawsuits related to obstructive sleep apnea from 2016 to 2020.

Analysis of legal proceedings related to the treatment of OSA

Profile of the physician responsible for prescribing treatment

It was possible to identify the physician prescribing treatment in 424 lawsuits (29.0%). Of these, 104 requesting physicians (24.6%) were considered specialists in sleep medicine by the Brazilian Medical Association, whereas 320 had no specialization in that area. We were able to identify the specialties of 297 physicians. The most common ones were ear, nose, throat, in 28.3%; pulmonology, in 18.2%; and neurology, in 13.1%. There were also cardiologists (2.7%), general practitioners (2.7%), psychiatrists (1.7%), and occupational physicians (1.3%).

Types of PAP devices requested and expenses incurred

CPAP and BiPAP devices were demanded in 1,117 (95.8%) and 36 (3.0%) of the lawsuits, respectively. It was not possible to identify the type of device requested in 1.2% of cases. Approximately 64% of the lawsuits presented the amounts of expenses incurred.

The expenses associated with CPAP, both in the public and private spheres, were classified as expenses with the purchase or lease of equipment. In the public sphere, 210 of the 624 lawsuits (34%) were related to purchase, while 414 (66%) were related to leasing.

For cases involving public entities, the projected value related to the acquisition of the devices, with the imputation of the median for cases with no reference to the expense incurred, was R$1,340,781; sensitivity analyzes ranged from R$1,284,769 to R$1,443,229. Regarding equipment leasing, the total expenses incurred were estimated at R$574,525. Including the projection of the lawsuits in which the type of arrangement was not mentioned (i.e., purchase or

Table 1. Number of lawsuits related to the diagnosis and treatment of obstructive sleep apnea, stratified by geographic regions of Brazil, during the study period.

Region	Type of resource				TP	Per million population		
	Diagnosis	Treatment	Total	%		Diagnosis	Treatment	Total
Southeast	180	943	1,123	76.8	89	2.0	10.6	12.6
South	28	164	192	13.1	30	0.9	5.4	6.4
Central-west	28	63	91	6.2	17	1.7	3.8	5.5
Northeast	20	3	53	3.6	57	0.3	0.6	0.9
North	2	1	3	0.2	19	0.1	0.1	0.2
Total	258	1,204	1,462	100	212	1.2	5.7	6.9

TP: total population in millions.

leasing), according to the proportions observed in the lawsuits in which this information was present, we found a total expense of R$2,656,696, and the sensitivity analysis ranged from R$2,503,032 to R$2,937,754.

In the private health care system, the total expenditure on lawsuits related to the treatment of OSA was estimated at R$253,050, and the sensitivity analyzes ranged from R$211,191 to R$349,763 (Table 3).

DISCUSSION

Our findings demonstrate that legal action as a way of accessing diagnostic and therapeutic resources for OSA is a common practice, both in the public and private spheres. Treatment with a PAP device is considered the first line of treatment for moderate to severe cases, in addition to being considered cost-effective.[14] The absence of well-defined lines of care and national public guidelines for a highly prevalent condition, potentially treatable, and with a significantly associated burden is a demonstration of the restriction of an integral health care system, one of the basic principles of the SUS.

Legal action regarding health care has become an increasingly common practice to obtain access to health care in Brazil. In a study conducted in the state of Minas Gerais, most lawsuits were related to legalized high-cost medications, approved by the Brazilian Health Regulatory Agency, for more advanced lines of treatment for clinical conditions such as rheumatoid arthritis and ankylosing spondylitis.[15] In the same study, approximately 5% of the technologies demanded were not registered by the Brazilian Health Regulatory Agency, which denotes the emerging nature of these technologies.[15] Similar findings were found in a study conducted in the state of Rio Grande do Norte which showed a predominance of claims related to antineoplastic agents and immunomodulators.[16] Approximately 13% of the lawsuits in the state of Rio Grande do Norte involved at least one off-label drug.[17] Additionally, a systematic review of descriptive studies evaluating lawsuits in Brazil showed that the proportion of therapeutic technologies being requested that could potentially be replaceable by technologies available in the SUS ranged from 41.7% to 80.0%.[18]

The present study identified a total of 1,462 cases of legal action related to OSA, 17.6% and 82.4% of which related to the diagnosis and treatment of this condition, respectively. Data from the Brazilian National Council of Justice[19] revealed that the proportion of lawsuits requesting access to diagnosis of any condition was 55.6%, and our results showed that 17.6% were

Table 2. Expenses associated with legal proceedings regarding diagnosis of obstructive sleep apnea in Brazil during the study period.

Sphere	Lawsuits indicating costs, n	Costs indicated in the lawsuits, R$			Lawsuits, N	Total projected value, R$		
		Total	Median (IQR)	Mean		Base case	Best case scenario	Worst case scenario
Public	83	415,227	1,000 (797-3,850)	5,002.73	243	575,227	542,747	1,031,227
Private	11	140,906	11,774 (7,000-15,356)	12,809.63	15	188,002	168,906	202,330
Total	94	556,133	1,000 (899-5,975)	5,916.31	258	763,229	711,653	1,233,557

R$: Brazilian reais.

Table 3. Expenses associated with legal proceedings regarding treatment of obstructive sleep apnea in Brazil during the study period.[a]

Sphere	Lawsuits indicating costs, n	Costs indicated in the lawsuits, R$			Lawsuits, N	Total projected value, R$		
		Total	Median (IQR)	Mean		Median	Best case scenario (Q1)	Worst case scenario (Q3)
Public	624	1,589,754	1,000 (1,000-3,000)	2,708.53	1,140	2,656,696	2,503,032	2,937,754
Purchase	212	1,063,229	3,652 (2,915-5,000)	5,138.70	288	1,340,781	1,284,769	1,443,229
Lease	414	526,525	1,000 (1,000-1,000)	2,783.30	462	574,525	574,525	574,525
Unspecified	0				390	741,390	643,737	920,000
Private	21	140,619	5,000 (1,000-10,000)	2,703.59	55	253,050	211,191	349,763
Purchase	12	113,353	10,000 (5,000-12,000)	9,525.19	16	153,353	133,353	161,353
Lease	9	27,267	1,000 (1,000-4,000)	2,783.30	30	48,267	48,267	111,267
Unspecified	0				9	51,430	29,571	77,143
Total	645	1,730.373	1,000 (1,000-3,400)	2,838.66	1,204	2,909,746	2,714,223	3,287,517

R$: Brazilian reais; Q1: first quartile; and Q3: third quartile. [a]For lawsuits with no specification of the demand (purchase or lease), the proportion of purchase and lease observed in the lawsuits in which such information was available was considered, as were the summary measures of these lawsuits.

related to the diagnosis of OSA alone. Regarding treatment-related lawsuits, the Brazilian National Council of Justice reported an overall proportion of 33.1%, whereas we found a much greater proportion (82.9%) considering the treatment of OSA alone. This difference may indicate that it is more difficult to have access to OSA treatment than to treatment for other conditions. In this sense, legal action as a form of access to the diagnosis and treatment of OSA differs in relation to the prevailing demands in the national scene. The use of CPAP is considered the first line of treatment for moderate to severe OSA cases. The use of intraoral appliances as an alternative treatment for OSA, usually effective for milder cases,[20] is not covered by the SUS either, which means that the only treatment alternatives offered are airway surgical procedures.

Legal action in this scenario can, therefore, be explained by the inexistence of a line of care for these patients, the high prevalence of the disease, and the scarcity of allocated resources, such as hospital beds for polysomnography, which is necessary for diagnosis. Polysomnography is a mandatory procedure to be provided by the SUS, either in the hospital or in the outpatient clinic environment. According to SIGTAP, polysomnography costs in an outpatient clinic or in a hospital were R$125.00 and R$170.00, respectively, in 2020.[21] Considering that this is a specialized procedure that takes a long time and needs continuous technical supervision, the monetary value presented in the SIGTAP is lower than the real cost of the test, which represents a barrier to the opening and maintenance of sleep laboratories accredited by the SUS.

The median of expenditure incurred in lawsuits related to the diagnosis of OSA in the SUS was R$1,000 during the study period. According to the SIGTAP, the cost for performing a polysomnography in a hospital environment was R$170.00, that is, five users of the public health care system could have undergone to a polysomnography at that cost, which demonstrates the harmful effects of legal action on the efficiency and sustainability of the SUS.

Although there is not an official protocol or national guidelines from the Brazilian National Ministry of Health to define the line of care for patients with OSA, Conitec recommends an expense of R$3,000 for the acquisition of a CPAP device. The average amount incurred in the analyzed lawsuits involving the public health care system was R$3,652, representing a 21.7% surplus of the value recommended by the Conitec. Such discrepancies can be justified by the lack of implementing bidding processes for the acquisition of equipment and by missing opportunities to negotiate prices for high-volume purchases.

The negative impact on health care system efficiency also occurs from the perspective of private health care systems. Polysomnography is part of a set of mandatory procedures. The reference value to be paid depends on negotiations between each service provider and the paying source. The *Classificação Brasileira Hierarquizada de Procedimentos Médicos* (CBHPM, Brazilian Hierarchical Classification of Medical Procedures) table provides the reference value to be used for initial negotiations. The 2016 CBHPM projected for 2018 stipulated that polysomnography had an initial trading value of R$797.00.[22] Dividing the median of expenses incurred with lawsuits in the private sphere related to the diagnosis of OSA (R$11,774) by that initial value, it is observed that 14 private health care users could have been served by the value proposed by the CBHPM table.

Over the period analyzed, there was a reduction in the absolute number of lawsuits between 2017 and 2019. This fact could be explained by the expansion of local policies allowing access to the diagnosis and treatment of OSA in some localities that introduced administrative processes for the treatment of OSA with CPAP. Alternatively, it may reflect the presence of barriers in patient care, such as the lack of diagnosis and reduced supply of specialized services. However, these arguments are speculative since there is no organized literature review evidencing it. National public guidelines have been proven to be effective to reduce legal action. In 1999, HIV infection was a well-established case of government response to reduce legal action and address health care needs. Between 1991 and 1998, 90% of the legal proceedings were related to the HIV infection. In 1999, with the creation of a national public health program to fight the condition, such lawsuits decreased to 16.7%.[23] Other possibilities are the existing barriers during the journey of the patient with OSA, such as the difficulty of being referred to a specialist and the low availability of polysomnography. According to the Brazilian legislation, the diagnosis and treatment of OSA can be performed by any physician. In clinical practice, however, board-certified physicians in sleep medicine are more prone to diagnose and treat patients with OSA.

The methodology used to identify lawsuits is a strong point of the current study. In order to portray the national scenario of legal action related to the care of patients with OSA, research was carried out in the electronic databases of 21 Brazilian Courts of Justice, 4 Superior Courts of Justice or Federal Regional Courts, and the Federal Supreme Court, using descriptive terms for identifying lawsuits related to the topic. The period analyzed encompassed the past 5 years. The projection of total expenses was carried out, with the imputation of the median values for the lawsuits that did not report expenses incurred, as well as deterministic sensitivity analyzes of the best and worst case scenarios, imputing the values of the first and third quartiles, respectively. This procedure allowed a more complete estimate of the total expenses incurred, in addition to considering the uncertainties in relation to the assigned amounts. It is noteworthy that the median was used and that the use of means would have led to more expressive expenditure estimates.

Despite the careful methodology adopted, this study has limitations. It is not possible to rule out the possibility of the existence of legal proceedings in which nonstandard terms describing the requested technologies have been used and which, therefore, might not have been identified, leading to an underestimation of the total universe of legal proceedings related to OSA. Additionally, the identification of specialists in sleep medicine among the prescribing physicians was carried out at the time of the analysis, and not at the time of the execution of the lawsuits, which might have led to an overestimation of the proportion of cases originated by such physicians. Similarly, the identification of health care facilities where the polysomnography procedure was available was performed at the time of analysis.

Although it is public knowledge that there are municipalities that have an organized administrative process, with public sleep centers to offer diagnoses and treatments, there are no systematized public data that allow these municipalities to be evaluated and compared. The present study offers a possibility to understand the volume of legal proceedings related to access to diagnosis and treatment of OSA in Brazil. It is therefore recommended that studies in this area should be conducted.

In conclusion, the high volume of legal proceedings related to the care of patients with OSA in Brazil might be due to the lack of a national public policy that coordinates and guarantees the line of care of a prevalent, treatable condition associated with morbidity and mortality.

AUTHOR CONTRIBUTIONS

DVP: conceptualization; methodology; formal analysis; drafting of the manuscript; and approval of the final version of the manuscript. BF: conceptualization; data curation; funding acquisition; project administration; methodology; formal analysis; drafting of the manuscript; and approval of the final version of the manuscript. CA: funding acquisition; review and editing the manuscript; and approval of the final version of the manuscript. AG, CP, and PV: investigation; data curation; resources; and approval of the final version of the manuscript. ALE and LFD: conceptualization; methodology; drafting and review of the manuscript; and approval of the final version of the manuscript.

CONFLICT OF INTEREST

DVP, ALE, and LFD: consultancy activities for ResMed Brasil for this and other projects. BF: employee at ResMed Brasil during study conduction. CA: current employee at ResMed Brasil. AG, CP, and PV: consultancy activities for ResMed Brasil for this project.

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ORIGINAL ARTICLE

Tongue size matters: revisiting the Mallampati classification system in patients with obstructive sleep apnea

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ABSTRACT

Objective: The Mallampati classification system has been used to predict obstructive sleep apnea (OSA). Upper airway soft tissue structures are prone to fat deposition, and the tongue is the largest of these structures. Given that a higher Mallampati score is associated with a crowded oropharynx, we hypothesized that the Mallampati score is associated with tongue volume and an imbalance between tongue and mandible volumes. **Methods:** Adult males underwent clinical evaluation, polysomnography, and upper airway CT scans. Tongue and mandible volumes were calculated and compared by Mallampati class. **Results:** Eighty patients were included (mean age, 46.8 years). On average, the study participants were overweight (BMI, 29.3 ± 4.0 kg/m^2) and had moderate OSA (an apnea-hypopnea index of 26.2 ± 26.7 events/h). Mallampati class IV patients were older than Mallampati class II patients (53 ± 9 years vs. 40 ± 12 years; $p < 0.01$), had a larger neck circumference (43 ± 3 cm vs. 40 ± 3 cm; $p < 0.05$), had more severe OSA (51 ± 27 events/h vs. 24 ± 23 events/h; $p < 0.01$), and had a larger tongue volume (152 ± 19 cm^3 vs. 135 ± 18 cm^3; $p < 0.01$). Mallampati class IV patients also had a larger tongue volume than did Mallampati class III patients (152 ± 19 cm^3 vs. 135 ± 13 cm^3; $p < 0.05$), as well as having a higher tongue to mandible volume ratio (2.5 ± 0.5 cm^3 vs. 2.1 ± 0.4 cm^3; $p < 0.05$). The Mallampati score was associated with the apnea-hypopnea index ($r = 0.431$, $p < 0.001$), BMI ($r = 0.405$, $p < 0.001$), neck and waist circumference ($r = 0.393$, $p < 0.001$), tongue volume ($r = 0.283$, $p < 0.001$), and tongue/mandible volume ($r = 0.280$, $p = 0.012$). **Conclusions:** The Mallampati score appears to be influenced by obesity, tongue enlargement, and upper airway crowding.

Keywords: Sleep apnea, obstructive; Tongue; Obesity; Diagnostic imaging.

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repeated upper airway obstruction during sleep. OSA is highly prevalent and is associated with impaired quality of life and increased cardiovascular risk.[1-5] Obesity, advanced age, and being male are the major risk factors for OSA.[6,7] Each one of these factors is associated with soft tissue enlargement and higher upper airway collapsibility.[6] The tongue is the largest anatomical structure of the pharynx and is particularly prone to enlargement caused by fat deposition.[8] The imbalance between upper airway bone structure and soft tissue volume is thought to play a major role in the increased upper airway collapsibility of OSA patients.[9]

The Mallampati scoring system was developed to predict the risk of difficult endotracheal intubation on the basis of direct examination of the upper airway when the tongue is maximally protruded in a seated patient.[10] If the base of the tongue is disproportionately large, it overshadows the oropharynx. The Mallampati score ranges from I to IV, a higher score translating to a narrower upper airway.[10] The Mallampati score has recently been used in order to assess the risk of OSA.[11-15] However, the anatomical structures that lead to a higher Mallampati score have yet to be fully described. Given that a higher Mallampati score is associated with a crowded oropharynx, we hypothesized that the Mallampati score is associated with tongue volume and an imbalance between tongue and mandible volumes.

METHODS

The present study is part of a larger study addressing anatomical risk factors for OSA.[9] The study protocol consisted of a clinical evaluation, baseline polysomnography (PSG), and upper airway CT scans.[9] All procedures were performed within 14 days; however, in most of the study participants, CT scans were performed in the afternoon before baseline PSG.[9]

We recruited male Brazilians (either White or of Japanese descent) who were in the 18- to 70-year

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age bracket and who had been referred to the University of São Paulo *Hospital das Clínicas* sleep clinic, located in the city of São Paulo, Brazil.[9] The exclusion criteria were as follows: being female; having craniofacial abnormalities; having comorbidities such as COPD, heart failure, chronic kidney disease, and neuromuscular disease; and currently using sedatives.[9] All patients underwent clinical evaluation and physical examination, including measurements of height, weight, waist circumference, and neck circumference, as well as assessment of the Mallampati score.[9]

Patients were evaluated by PSG during natural sleep. Monitoring and evaluation included electroencephalography, electrooculography, chin and leg electromyography, electrocardiography, oximetry, measurements of airflow (with a nasal pressure cannula and an oronasal thermistor), and measurements of thoracic and abdominal movements during breathing (Alice 5; Philips Respironics, Murrysville, PA, USA), in accordance with the American Academy of Sleep Medicine guidelines.[9,16]

All patients underwent a CT scan of the upper airway (Discovery CT 750 HD; GE HealthCare Technologies Inc., Chicago, IL, USA). Image acquisition was performed during quiet tidal breathing, with patients lying supine and a neutral head position. This neutral position was defined by aligning the Frankfurt plane, a plane from the inferior margin of the orbit to the superior portion of the tragus, perpendicular to the scanner table.[17] The scans were acquired at a 2.5-mm collimation/interval and were reconstructed at a 0.625/0.625-mm thickness/interval, with 120 kV, 100 mA, and a rotation time of 0.8 s. Axial and sagittal image reconstructions were performed on an Advantage Workstation, version 4.5 (GE HealthCare Technologies Inc.) for linear and volumetric measurements.[18] Mandible volume was determined by a technique based on HU values for bone (i.e., 160-3,000 HU). To determine tongue volume, the tongue outline was identified and manually traced on each axial image.[19,20] Volumetric reconstructions were performed to determine mandible and tongue volumes. All measurements were performed by the same investigator.[9]

All patients underwent upper airway examination and assessment of the Mallampati score.[9] Patients were asked to breathe through their nose after a single swallowing and open their mouths wide with voluntary protrusion of the tongue without phonation. All evaluations were performed by the same investigator. Oropharyngeal crowding was graded in accordance with the Mallampati classification system, as follows: grade I—tonsils, pillars, and soft palate were clearly visible; grade II—the uvula, pillars, and upper pole were visible; grade III—only part of the soft palate was visible, whereas the tonsils, pillars, and base of the uvula could not be seen; and grade IV—only the hard palate was visible. At the same visit, the BMI was calculated.[9]

Clinical, polysomnographic, and anatomical variables were compared between Mallampati classes (I-IV). The Kolmogorov-Smirnov test was used in order to test whether variables had a normal distribution. One-way ANOVA with Bonferroni post-hoc analysis was used for between-group comparisons. Spearman's rank correlation was used in order to test the associations among the Mallampati score, the apnea-hypopnea index (AHI), BMI, neck circumference, waist circumference, tongue volume, and tongue/mandible volume ratio. The accuracy of the study variables in predicting moderate to severe OSA was also tested. ROC curve analysis was applied, and the AUC was used in order to test the accuracy of the study variables in detecting an AHI > 15 events/h, a cutoff showing the best balance between sensitivity and specificity being determined. Univariate and multivariate logistic regression models were built to test predictors of moderate to severe OSA (an AHI > 15 events/h). A value of $p < 0.05$ was considered significant. Variables were described as mean ± SD or median [IQR]. All statistical analyses were performed with the SPSS Statistics software package, version 17.0 (SPSS Inc., Chicago, IL, USA).

The present study was approved by the University of São Paulo School of Medicine *Hospital das Clínicas* Research Ethics Committee (Protocol no. 0230/09; SDC 3235/08/151).[9] All participating patients gave written informed consent.[9]

RESULTS

Eighty male patients were included in the study (Table 1) and divided into four groups on the basis of the Mallampati score (Table 2). In comparison with the study participants who were classified as being Mallampati class IV patients, those who were classified as being Mallampati class I patients had a lower BMI (26.7 ± 2.4 kg/m^2 vs. 30.8 ± 3.6 kg/m^2; $p < 0.01$), a smaller neck circumference (39.7 ± 2.3 cm vs. 42.7 ± 2.7 cm; $p < 0.01$), a smaller waist circumference (94.2 ± 9.1 cm vs. 106.5 ± 11.0 cm; $p < 0.01$), and less severe OSA (22.3 ± 17.8 events/h vs. 51.3 ± 27.2 events/h; $p < 0.01$). The study participants who were classified as being Mallampati class II patients were younger (40.1 ± 11.7 years of age vs. 53.3 ± 9.3 years of age; $p < 0.01$), had a smaller neck circumference (40.4 ± 3.0 cm vs. 42.7 ± 2.7 cm; $p < 0.05$), had less severe OSA (23.6 ± 22.7 events/h vs. 51.3 ± 27.2 events/h; $p < 0.01$), and had smaller tongue volume (134.8 ± 17.7 cm^3 vs. 152.3 ± 19.1 cm^3; $p < 0.01$) than did those who were classified as being Mallampati class IV patients (Figure 1). The study participants who were classified as being Mallampati class III patients had smaller tongue volume (134.5 ± 12.7 cm^3 vs. 152.3 ± 19.1 cm^3; $p < 0.05$) and lower tongue-to-mandible volume ratio (2.1 ± 0.4 cm^3 vs. 2.5 ± 0.5 cm^3; $p < 0.05$) than did those who were classified as being Mallampati class IV patients. The Mallampati score was associated with

the AHI (r = 0.431, p < 0.001), BMI (r = 0.405, p < 0.001), neck circumference (r = 0.393, p < 0.001), waist circumference (r = 0.393, p < 0.001), tongue volume (r = 0.283, p < 0.001), and tongue/mandible volume ratio (r = 0.280, p = 0.012).

Table 3 shows the accuracy of the study variables in predicting OSA, as well as the results of the univariate logistic regression analysis in which OSA (an AHI > 15 events/h) was used as the dependent variable. Table 4 presents the results of the multivariate logistic regression analysis in which OSA (an AHI > 15 events/h) was used as the dependent variable. Mallampati class III or IV (OR = 3.075; 95% CI, 1.003-9.428; p = 0.049) and being over 45 years of age (OR = 5.300; 95% CI, 1.768-15.873; p = 0.003) were independently associated with an increased risk of OSA, regardless of ethnicity.

Table 1. Demographic and anthropometric characteristics of the study participants (N = 80), as well as polysomnographic parameters.[a]

Parameter	Result
Males	80 (100%)
Brazilians of Japanese descent	40 (50%)
Age, years	46.8 ± 13.0
BMI, kg/m^2	29.3 ± 3.9
Waist circumference, cm	101 ± 10
Neck circumference, cm	41 ± 3
Comorbidities	49 (60%)
Hypertension	30 (37%)
Diabetes	13 (16%)
Dyslipidemia	16 (19%)
Epworth Sleepiness Scale score	11 ± 6
AHI, events/h	26.2 ± 26.7
Total sleep time, min	360.3 ± 64.6
Sleep efficiency, %	80 ± 9
Sleep latency, min	11 ± 12
REM sleep, %	11.5 ± 8.1
Lowest SpO_2, %	79 ± 9
Tongue volume, cm^3	141.3 ± 18.3
Tongue/mandible volume ratio	2.3 ± 0.4

AHI: apnea-hypopnea index; and REM: rapid eye movement. [a]Data expressed as n (%) or mean ± SD.

DISCUSSION

The major finding of the present study is that the Mallampati score was associated with obesity-related variables, OSA severity, tongue volume, and an imbalance between tongue and mandible volumes. Mallampati class IV patients tended to be older and more obese (having either a higher BMI or larger neck and waist circumferences) than Mallampati class I or II patients, had as well as having more severe OSA and greater tongue volume. Mallampati class IV patients also had a greater imbalance between tongue and mandible volumes than did Mallampati class III patients. These findings suggest that the Mallampati score is influenced by obesity and tongue volume.

Obesity is a major risk factor for OSA and can lead to enlargement of upper airway soft tissue structures, particularly the tongue.[8,21] Animal studies have shown that obesity leads to an increase in tongue volume through fat infiltration.[22] In an autopsy study, Nashi et al.[8] showed that tongue weight and tongue fat percentage were strongly correlated with BMI. Studies using CT and magnetic resonance imaging have shown that tongue fat infiltration and upper airway soft tissue volume are associated with obesity.[6] Schwab et al.[23] analyzed digital photographs of 318 controls and 542 patients with

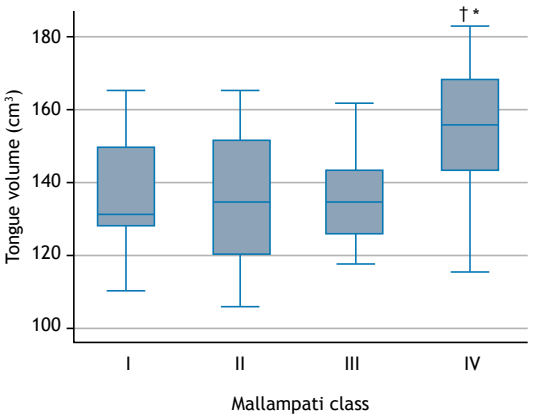

Figure 1. Tongue volume, by Mallampati class. *p < 0.01 vs. Mallampati class II. †p < 0.05 vs. Mallampati class III.

Table 2. Anthropometric variables and tongue volume, by Mallampati class.[a]

Variable	Mallampati class I	Mallampati class II	Mallampati class III	Mallampati class IV
Participants, n	17	19	18	26
Age, years	44.4 ± 14.0	40.1 ± 11.7*	46.3 ± 14.4	53.3 ± 9.3
BMI, kg/m^2	26.7 ± 2.4*	28.9 ± 4.6	29.5 ± 4.3	30.8 ± 3.6
AHI, events/h	22.3 ± 17.8*	23.6 ± 22.7*	39.8 ± 25.1	51.3 ± 27.2
Neck circumference, cm	39.7 ± 2.3*	40.4 ± 3.0†	41.6 ± 2.3	42.7 ± 2.7
Waist circumference, cm	94.2 ± 9.07*	100.1 ± 11.56	101 ± 9.61	106.5 ± 10.99
Tongue volume, cm^3	138.1 ± 17.2	134.8 ± 17.7*	134.5 ± 12.7†	152.3 ± 19.1
Tongue/mandible volume ratio, cm^3	2.2 ± 0.4	2.2 ± 0.4	2.1 ± 0.4†	2.5 ± 0.5

AHI: apnea-hypopnea index. [a]Data expressed as mean ± SD, except where otherwise indicated. *p < 0.01. †p < 0.05 vs. Mallampati class IV.

Table 3. Univariate logistic regression between obstructive sleep apnea (an apnea-hypopnea index > 15 events/h) and clinical/anthropometric variables and their accuracy in predicting obstructive sleep apnea (an apnea-hypopnea index > 15 events/h).

Variable	OR [95% CI]	p	AUC	Cutoff	Sensitivity, %	Specificity, %
BMI	1.26 [1.08-1.48]	0.003	0.729	27.86	70.37	69.23
BMI > 27.86 kg/m^2	5.34 [1.93-14.78]	< 0.001				
Mallampati classes I and II	1.75 [1.13-2.71]	0.013	0.671	3	66.67	69.23
Mallampati classes III and IV	4.5 [1.64-12.31]	0.003				
Age	1.07 [1.03-1.12]	< 0.001	0.751	45	72.2	73.1
Age > 45 years	7.06 [2.47 - 20.20]	< 0.001				
ESS score	1.12 [1.02-1.22]	0.015	0.664	10	68.5	53.9
Berlin questionnaire	4.99 [0.59-41.78]	0.137				
Neck circumference	1.74 [1.32-2.29]	0.000	0.831	40.2	77.78	76.92
Neck circumference > 40.2 cm	11.67 [3.82-35.59]	< 0.001				
Waist circumference	1.10 [1.04-1.16]	< 0.001	0.739	100	64.81	69.23
Waist circumference > 100 cm	4.14 [1.52-11.30]	0.005				

ESS: Epworth Sleepiness Scale.

Table 4. Multivariate logistic regression analysis of predictors of obstructive sleep apnea (an apnea-hypopnea index > 15 events/h).

Predictor	OR	SE	Z	p > |z|	95% CI	
Mallampati class III or IV	3.075	1.757	1.97	0.049	1.003	9.428
Age > 45 years	5.300	2.966	2.98	0.003	1.768	15.873
White	1.135	0.635	0.23	0.821	0.379	3.398
_cons	0.495	0.255	-1.36	0.173	0.180	1.360

OSA. Tongue size was larger in the patients with OSA than in the controls in unadjusted models controlled for age, sex, and race, but the difference was not significant when the models were controlled for BMI.[23,24] Weight loss leads to a reduction in tongue fat content and pharyngeal length, reinforcing the association between obesity and increased tongue volume through fat infiltration.[7]

Ahn et al. reported that the Mallampati score was associated with a higher tongue volume and a higher tongue volume/intramandibular area ratio.[25] In another study, a higher Mallampati score was associated with a larger tongue area in surgical patients ($p < 0.05$).[26] The Mallampati score has been associated with the BMI.[11,23] In the present study, the Mallampati score was associated with tongue volume and an imbalance between tongue and mandible volumes. Amra et al. evaluated anthropometric data and the Mallampati score in patients with confirmed OSA and found that those with severe OSA were more obese and had a higher Mallampati score than those with mild to moderate OSA.[11] These findings are consistent with ours, which show that the Mallampati score is associated with obesity-related variables (BMI, neck circumference, and waist circumference). Together, obesity and enlargement of upper airway soft tissue structures can lead to a higher Mallampati score.

In the present study, Mallampati classes III and IV were accurate predictors of moderate to severe OSA (i.e., an AHI > 15 events/h). In a meta-analysis, Friedman et al. showed that a higher Mallampati score was significantly associated with OSA severity.[12] Previous studies assessing predictors of OSA severity showed that the Mallampati score was the most important variable associated with OSA severity, Mallampati class IV patients having a five-fold increased risk of mild to severe OSA.[27,28] Nuckton et al.[13] found that for every 1-point increase in the Mallampati score, the odds of having OSA increased by 2.5 (95% CI, 1.2-5.0; $p = 0.01$) and the AHI increased by 5.2 events/h (95% CI, 0.2-10; $p = 0.04$), independently of variables related to airway anatomy, body habitus, symptoms, and medical history. In another study, a higher Mallampati score was associated with a higher AHI, both unadjusted and controlling for age, sex, race, and BMI.[23] Therefore, a higher Mallampati score is a risk factor for OSA.

Our study has several limitations. Because of the cross-sectional design, we cannot establish a causal relationship among the Mallampati score, tongue volume, and obesity. We included male patients only, our findings therefore being limited to men. By including male patients only, we intended to reduce the variability of the study variables. Our study population consisted of male Brazilians who were either White or of Japanese descent, our conclusions therefore being limited to these ethnicities. Future studies should

address these limitations by investigating larger samples, including other ethnicities, and exploring differential tongue and mandibular measurements in males and females. The Mallampati classification is susceptible to interobserver disagreement. In order to minimize this potential bias, the same investigator performed all of the examinations in the present study. Future studies assessing the effects of weight loss on tongue volume and the Mallampati score are warranted.

The Mallampati score was found to be associated with obesity-related variables, a larger tongue, and a greater tongue/mandible volume imbalance. The Mallampati score might be affected by the impact of obesity on tongue size and upper airway crowding.

AUTHOR CONTRIBUTIONS

RABA: data/statistical analysis and drafting of the manuscript. LLIC: data/statistical analysis. FS: data collection and data/statistical analysis. EMMSG and GLF: critical revision of the manuscript for important intellectual content. PRG: study conception/design, data/statistical analysis, and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Lymphangioleiomyomatosis: circulating levels of FGF23 and pulmonary diffusion

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ABSTRACT

Objective: Lymphangioleiomyomatosis (LAM) is a rare, destructive disease of the lungs with a limited number of determinants of disease activity, which are a critical need for clinical trials. FGF23 has been implicated in several chronic pulmonary diseases. We aimed to determine the association between serum FGF23 levels and pulmonary function in a cohort of patients with LAM. **Methods:** This was a descriptive single-center study in which subjects with LAM and controls with unreported lung disease were recruited. Serum FGF23 levels were measured in all subjects. Clinical data, including pulmonary function testing, were retrospectively obtained from electronic medical records of LAM subjects. Associations between FGF23 levels and clinical features of LAM were explored via nonparametric hypothesis testing. **Results:** The sample comprised 37 subjects with LAM and 16 controls. FGF23 levels were higher in the LAM group than in the control group. In the LAM group, FGF23 levels above the optimal cutoff point distinguished 33% of the subjects who had nondiagnostic VEGF-D levels. Lower FGF23 levels were associated with impaired DL_{CO} ($p = 0.04$), particularly for those with isolated diffusion impairment with no other spirometric abnormalities ($p = 0.04$). **Conclusions:** Our results suggest that FGF23 is associated with pulmonary diffusion abnormalities in LAM patients and elicit novel mechanisms of LAM pathogenesis. FGF23 alone or in combination with other molecules needs to be validated as a biomarker of LAM activity in future clinical research.

Keywords: Lymphangioleiomyomatosis; Fibroblast growth factor-23; Pulmonary diffusing capacity.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare cystic disease of the lungs.[1] It affects almost exclusively young women of childbearing age and occurs sporadically or in association with tuberous sclerosis complex (TSC), the latter of which affects up to 81% of women with the genetic syndrome.[2,3] LAM causes progressive destruction of the lung parenchyma due to accumulation of smooth muscle-like LAM cells that, without cytostatic medical therapy, ultimately results in respiratory failure and death in the absence of lung transplantation.

Loss-of-function mutations in the tumor suppressor genes *TSC1* or *TSC2* result in constitutive activation of the mammalian/mechanistic target of rapamycin pathway, leading to unchecked growth, motility, and survival of LAM cells amongst other abnormalities.[4] LAM cells—in addition to monocytes stimulated by *TSC2*-deficient cells—release VEGF-D,[5,6] which has been validated as a diagnostic biomarker due to its elevation in the peripheral blood of patients with LAM when compared with healthy controls.[6,7] A VEGF-D level greater than 800 pg/mL is 100% specific for LAM but has a false negative rate of about 40%, which, in the absence of other features of LAM (i.e. angiomyolipoma, chylous effusions), often necessitates a lung biopsy.[8] Independent of VEGF-D levels or evidence of pulmonary hypertension, we and others have previously demonstrated that a subgroup of patients with LAM can present with an isolated reduction in DL_{CO}.[9-11]

Abnormal bone mineral density is frequent in patients with LAM and has been associated with estrogen deficiency and pulmonary diseases.[12] FGF23, a thirty-two-kDa protein secreted by osteocytes, is essential for maintaining serum phosphate homeostasis and is dysregulated in human diseases affecting bone mineral density.[13] Accordingly, FGF23 levels positively correlate with airway inflammation in COPD and are elevated in the lungs of patients with idiopathic pulmonary fibrosis (IPF), a disease in which FGF23 reportedly has an antifibrotic and anti-inflammatory role.[14,15] We therefore hypothesized that circulating FGF23 levels would be altered in patients with LAM and be associated with impaired lung function.

METHODS

Adult (≥ 18 years of age) women with LAM and healthy, adult female controls were enrolled at Brigham

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and Women's Hospital (Boston, MA, USA) in protocols approved by the Mass General Brigham Institutional Review Board (2008P002027 and 2012P000840). Written informed consent was obtained from all participating subjects. LAM was diagnosed by established criteria.[16] Subjects with a history of smoking or who were receiving mammalian/mechanistic target of rapamycin inhibitors were excluded. Serum samples were collected from each subject via standardized protocols. Data on age and pulmonary function tests (PFTs) were collected retrospectively from medical records. PFTs were performed in a clinical laboratory according to American Thoracic Society standards.[17] FGF23 concentrations were determined by ELISA (R&D Systems, Minneapolis, MN, USA) as per the manufacturer's protocol.

Baseline age was compared between LAM and control groups by Mann-Whitney U test. Diffusion defect was defined as per American Thoracic Society criteria.[18] Isolated reduction in DL_{CO} was defined as FEV_1 and FVC greater than (i.e., normal) and DL_{CO} less than (i.e., abnormal) the fifth percentile of predicted values. A ROC curve was generated to determine if FGF23 levels were effective in identifying women with LAM versus controls. FGF23 levels below the level of detection of the ELISA test (78.1 pg/mL) were excluded, and levels above the level of detection (5,000 pg/mL at a 1:10 dilution) were assigned a value of 50,000 pg/mL for these analyses. Outliers were excluded by the extreme studentized deviate method. The AUC and corresponding 95% CI were calculated by the trapezoidal and Wilson/Brown methods, respectively. The optimal FGF23 values to differentiate between subjects with and without LAM were determined by the Youden index. The association between FGF23 and VEGF-D levels was determined by Spearman's rank correlation. All statistical analyses were carried out using Stata, version 16.1 (College Station, TX, USA).

RESULTS

We recruited 37 subjects with LAM and 16 control subjects for this analysis. Baseline characteristics of LAM subjects are displayed in Table 1. The median age in the LAM (46 years; IQR, 35-56 years) and control (43 years; IQR, 37-51 years) groups did not differ statistically (p = 0.94). Pulmonary function data for control subjects were unavailable; nonetheless, they had no self-reported history of pulmonary disease. The median interval between phlebotomy for assessment of serum FGF23 levels and PFTs was one day (IQR, 0-31 days).

Table 1. Baseline characteristics of subjects with lymphangioleiomyomatosis (N = 37).[a]

Variable	Subjects
Age, years	46 [35-56]
TSC	6 (16)
FEV_1, % predicted	88 [75-98]
FVC, % predicted	98 [90-108]
DL_{CO}, % predicted	73 [57-88]
Isolated reduction in DL_{CO}	7 (19)

TSC: tuberous sclerosis complex. [a]Values expressed as n (%) or median [IQR]. Data missing: DL_{CO} (n = 1).

Subjects with LAM had higher FGF23 levels than did controls (Figure 1A). A ROC curve assessing the efficiency of FGF23 levels in discriminating between LAM and control groups (Figure 1B) produced an AUC of 0.74 (95% CI, 0.60-0.88; p = 0.0059). The optimal cutoff point of 1,349.0 pg/mL estimated from the ROC curve correctly identified all but 2 controls, yielding a specificity of 87.50%, and 22 subjects with LAM, yielding a sensitivity of 59.46% (positive likelihood ratio of 4.76). FGF23 and VEGF-D levels were inversely correlated ($\rho = -0.37$; p = 0.03). The median FGF23 level in LAM subjects with non-diagnostic VEGF-D levels (< 800 pg/mL) was significantly higher (12,843.9 pg/mL; IQR, 3,044.2-32,096.6 pg/mL) than in those with diagnostic VEGF-D levels (1,365.6 pg/mL; IQR, 395.4-1,690.8 pg/mL; p = 0.01). Of the 22 LAM subjects with elevated FGF23 levels, 21 had VEGF-D level results available for analysis, of which 7 (33%) were below the diagnostic threshold of 800 pg/mL. Conversely, of the 27 subjects with elevated VEGF-D levels, 13 (48%) had FGF23 levels below the optimal cutoff point.

Amongst subjects with LAM, a diffusion defect was associated with lower FGF23 levels (Figure 2A). Subjects with an isolated diffusion defect also had lower FGF23 levels when compared with those with normal DL_{CO} or with accompanying PFT abnormalities (Figure 2B). FGF23 levels were not, however, associated with abnormalities in FEV_1 or FVC.

DISCUSSION

FGF23 has been associated with chronic pulmonary diseases such as COPD and IPF.[14,15] Here, we demonstrate that serum FGF23 levels differentiate LAM subjects from controls and are associated with pulmonary diffusion defects. These findings have not been previously reported, suggest underlying mechanistic differences in disease pathogenesis, and propose a potential candidate biomarker for disease activity in LAM, an unmet need in clinical trial design.

FGF23 is a phosphaturic hormone that acts on tissues via FGF receptors and Klotho, the latter of which acts as a co-receptor.[19] Prior studies have implicated FGF23 and Klotho in pulmonary disease. Plasma levels of FGF23 are increased in patients with COPD and have been associated with a frequent exacerbation phenotype.[20] In both Klotho and FGF receptor 4 knockout mouse models, airway inflammation is increased.[14,21] Furthermore, FGF23 levels are upregulated in subjects with IPF, and co-administration of FGF23 and Klotho have reduced fibrotic and inflammatory markers in TGF-β-stimulated fibroblasts.[15] The present study is, to our knowledge, the first to implicate FGF23 in LAM.

Low Klotho levels have been associated with impaired lung function, including low DL_{CO}, in patients with mild

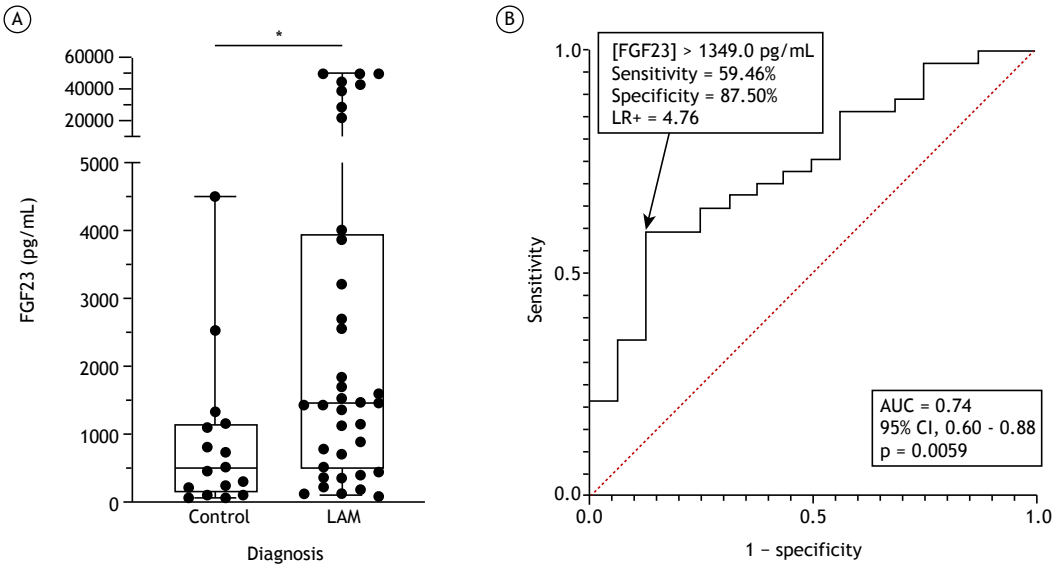

Figure 1. Circulating FGF23 levels differentiate subjects with lymphangioleiomyomatosis (LAM) from healthy controls. In A, serum FGF23 levels in control (N = 16) and LAM (N = 37) subjects. In B, ROC curve assessing the efficiency of serum FGF23 levels in discriminating subjects with LAM from controls. LR+: positive likelihood ratio. *p < 0.05.

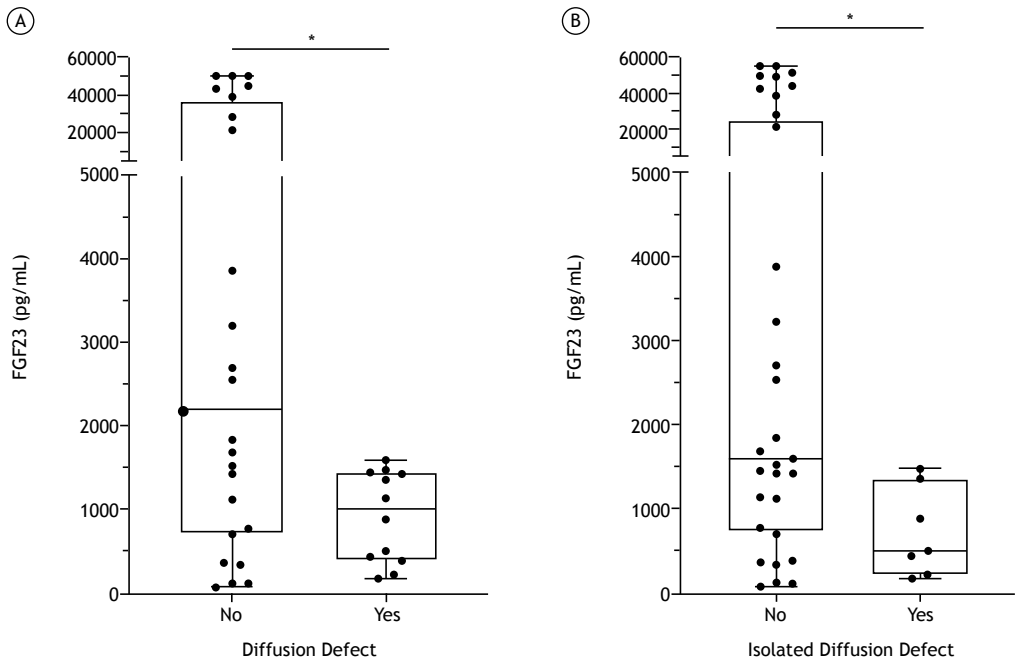

Figure 2. Circulating FGF23 levels are lower in subjects with lymphangioleiomyomatosis (LAM) and pulmonary diffusion abnormalities. In A, serum FGF23 levels in LAM subjects (N = 36) with or without a diffusion defect. In B, serum FGF23 levels in LAM subjects (N = 36) with or without an isolated diffusion defect. *p < 0.05.

nondependent parenchymal abnormalities affecting more than 5% of the lungs on CT scans, which are termed interstitial lung abnormalities.[22] In *TSC2*-deficient cells—such as LAM cells—Klotho has been demonstrated to have a cytocidal effect.[23] Klotho and FGF23 are reciprocally regulated such that patients with low Klotho levels would be expected to have high FGF23 levels.[24] In our study, patients with LAM who had a diffusion defect had lower FGF23 levels, which is distinct from the association described in patients with interstitial lung abnormalities. Given the interplay between FGF23 and Klotho in experimental models and their previously described roles in human respiratory disease, it is tempting to hypothesize that FGF23 not only is a biomarker of LAM but also may contribute to the pathogenesis of the disease. The role of FGF23 in LAM may mirror what has been described for the *MUC5B* promoter variant in IPF—both predicatively

and prognostically.[25,26] Pre-clinical studies examining the role of FGF23 and/or its cofactor Klotho in the pathogenesis and progression of LAM are needed.

Many biomarkers have been described for LAM; however, most do not associate with severity of disease. VEGF-D is a widely used biomarker in the diagnosis of LAM; however, it has a false negative rate of about 40%.[7,8] Our cohort yielded a similar performance, as 8 of the 35 LAM subjects with VEGF-D data available (23%) had levels lower than the diagnostic threshold. Reassuringly, we found that FGF23 correctly identified 7 of these 8 subjects (88%) with LAM and non-diagnostic VEGF-D levels. FGF23 and VEGF-D levels were negatively correlated in our study. A possible explanation for this observation is that FGF23 and VEGF-D may have different regulatory mechanisms and that LAM patients with high FGF23 and low VEGF-D may have a unique clinical phenotype of mild disease. Our data suggest that, once validated, FGF23 may be of diagnostic value in women with "VEGF-D-negative LAM" to obviate the need for lung biopsy.

Identification of biomarkers of LAM disease activity to support clinical trial design is a widely recognized research priority amongst experts in the field.[27-29] Prior research has demonstrated that, in addition to VEGF-D,[30] serum endostatin and vitamin D binding protein levels are correlated with DL_{CO} levels and that the latter is also associated with a progressive disease phenotype.[10,31] Our study suggests that FGF23 may also be a valuable addition to these emerging biomarkers of lung function in LAM patients, as lower levels were associated with a diffusion defect and an isolated reduction in DL_{CO}. Future research is needed to determine the performance of these biomarkers, inclusive of FGF23, potentially as part of a panel that assesses disease activity in LAM patients, which may perform better than any in isolation.

Our study has several important limitations. Although our data identified an association between FGF23, pulmonary diffusion abnormalities, and subjects with LAM, the performance of FGF23 as a potential biomarker of the disease has yet to be verified. We suggest a potential role for FGF23 in the assessment of disease activity; however, future studies will need to validate these findings in an independent cohort to establish generalizability. In addition, our sample size of patients with LAM was small, which is in part due to the extremely low prevalence of the disease. Despite this consideration, we were still able to determine statistically significant associations with important clinical implications, suggesting that the effect size of FGF23 may be substantial. In subsequent studies with larger cohorts, significant power to identify associations between FGF23 and characteristics of patients with LAM will likely boost our conclusions. Furthermore, our study lacks longitudinal assessment. It is possible that FGF23 levels be associated with progressive decline in pulmonary function; for our purposes, such levels were only determined at a single time point. It would be important to determine whether FGF23 levels predict progressive disease, because there would be important therapeutic and prognostic implications.

In summary, we found that serum FGF23 levels were associated with pulmonary diffusion abnormalities and distinguished subjects with LAM from controls. While additional studies are needed to validate our conclusions, these findings may have important implications for future translational research investigations of LAM pathogenesis and for clinical trial design, potentially as a marker of disease activity.

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AUTHOR CONTRIBUTIONS

AJE, AML, MV, HJG, IOR, EPH, and SYE-C: study design. AJE, JI, SS, SB, AML, MV, and SYE-C: data acquisition, analysis, or interpretation. AJE and SYE-C: statistical analysis. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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Elexacaftor/tezacaftor/ivacaftor—real-world clinical effectiveness and safety. A single-center Portuguese study

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ABSTRACT

Objective: To evaluate the effectiveness of treatment with elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) and to characterize its safety profile in cystic fibrosis (CF) patients in a real-world clinical setting. **Methods:** This was a prospective observational study carried out in a CF referral center in Portugal involving adult CF patients who started treatment with ELX/TEZ/IVA. Clinical characteristics of the patients were collected, and effectiveness and safety data were evaluated. **Results:** Of the 56 patients followed in the center at the time of the study, 28 were eligible for ELX/TEZ/IVA treatment in accordance with the Portuguese National Authority for Medicines and Health Products at the time of the study. Of these, 24 met the follow-up time requirement to be included in the clinical effectiveness analysis. The mean follow-up time was 167.3 ± 96.4 days. Adverse events were generally mild and self-limited. Significant improvements in lung function, BMI, sweat chloride concentration, and number of pulmonary exacerbations were observed. No significant differences in outcomes between F508del homozygous and heterozygous patients were found. The effectiveness of this new CFTR modulator combination also applied to patients with advanced lung disease. **Conclusions:** Treatment with ELX/TEZ/IVA showed effective improvement in real-world clinical practice, namely in lung function, BMI, sweat chloride concentration, and number of pulmonary exacerbations, with no safety concerns.

Keywords: Cystic fibrosis; Cystic fibrosis transmembrane conductance regulator; Membrane transport modulators; Treatment outcome.

INTRODUCTION

Cystic fibrosis (CF) is a rare genetic autosomal recessive disease caused by mutations on the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and, consequently, dysfunction of its protein, leading to multiorgan involvement, namely progressive lung disease and early death.[1] Although there are more than 2.000 *CFTR* mutations described, the most common mutation worldwide, the F508del mutation, is found in nearly 90% of CF patients, of which approximately 50% are homozygous.[2]

The emergence of new CFTR modulator therapies was a turning point in the treatment of CF. In clinical trials of CF patients with at least one F508del mutation, the new CFTR modulator combination, elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) showed significant improvement in clinical outcomes of patients, such as lung function, sweat chloride concentration, and nutritional status.[3,4] These remarkable results and its potential impact on prognosis have led to ELX/TEZ/IVA approval by the U.S. Food and Drug Administration in October of 2019 and by the European Medicines Agency in August of 2020.

Patients with advanced lung disease (FEV_1 < 40% of the predicted value) were excluded from clinical trials, leading to drug approval; however, preliminary data on these patients suggest that they present with significant clinical improvement with ELX/TEZ/IVA as well.[5,6]

In Portugal, the National Authority for Medicines and Health Products (Infarmed) approved ELX/TEZ/IVA on July 22, 2021 for CF patients ≥ 12 years of age and homozygous for the F508del mutation or heterozygous for the F508del mutation and a minimal function mutation.[7]

Real-world data regarding ELX/TEZ/IVA effectiveness are limited, and, although these new CFTR modulators have been well tolerated in clinical trials,[3-5,8] there is also scant real-world data about their adverse events of these new CFTR modulators.

In this study we aimed to identify the clinical and functional outcomes of patients who started treatment with the ELX/TEZ/IVA combination in order to evaluate its effectiveness and safety. Additionally, we intended to characterize the effects of ELX/TEZ/IVA on the CF population with advanced lung disease. The present study also compared the effects of ELX/TEZ/IVA on lung function, BMI, and sweat chloride concentration in F508del homozygous patients vs. F508del heterozygous patients with a minimal function mutation.

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METHODS

We conducted a prospective, observational, single-center study of adult CF patients at the Cystic Fibrosis Center of the Santa Maria Hospital, located in the city of Lisbon, Portugal, who started treatment with ELX/TEZ/IVA. The drug combination was administered in accordance with the general approval of the Infarmed[7] or in specific situations based on early access to a program that Infarmed approved.

All adult patients meeting the requirements of Infarmed for use of this drug combination, as stated before, and who agreed starting treatment with ELX/TEZ/IVA were eligible for inclusion. However, only patients who had at least a minimum of 12 weeks of follow-up after treatment initiation were considered for the clinical effectiveness analysis.

Clinical and functional data were collected at treatment initiation, and then at 4, 12, and 24 weeks after treatment initiation or in a medical visit out of that timeframe (for example, if an exacerbation or side effects due to treatment occurred). The relevant medical history of patients was assessed through revision of their medical records. All data were documented and processed anonymously, a written informed consent was obtained from all patients, and the institutional research ethics committee approved the study (Protocol no. 155/22).

The data collected included age; sex; BMI at baseline and 24 weeks after treatment initiation; *CFTR* genotype; date of treatment initiation; history of treatment with CFTR modulators; baseline lung function (FEV_1) and after 12 to 24 weeks of treatment; laboratory data at baseline (most recent results before ELX/TEZ/IVA treatment initiation) and during follow-up, including sweat chloride test (24 to 48 weeks after baseline), transaminases, and creatine kinase (worst value registered during monitoring every 2-4 weeks after treatment initiation); reported side effects; and occurrence of pulmonary exacerbations.

The study was carried out between March 10, 2021 and February 28, 2022, and all eligible patients evaluated in our center during that period were included in the study, forming a convenience sample.

Statistical analysis was performed with the IBM SPSS Statistics software package, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean and standard deviation, whereas categorical variables were expressed as absolute and relative frequencies. We used t-tests for independent and paired samples, as well as the Wilcoxon test. Significance was set at $p < 0.05$.

RESULTS

During the study period, 56 patients were being treated in the clinic, and 28 were eligible for ELX/TEZ/IVA therapy in accordance with the Infarmed recommendations.[7] Of these, 4 patients were excluded from the clinical effectiveness comparative analysis for not meeting the minimum 12-week follow-up period required.

Figure 1 presents the flow chart of patient recruitment, enrollment, and follow-up. Table 1 summarizes demographic and clinical characteristics of the patients.

At the time of data extraction and analysis on February 28, 2022, the mean follow-up time after treatment initiation was 167,3 ± 96,4 days. Only 9 patients (37.5%) had a history of treatment with lumacaftor/ivacaftor, which is another CFTR modulator combination previously approved in Portugal for CF homozygous F508del patients.

Of the 28 patients in the study, 20 (71.4%) reported having adverse events, mostly during the first week of treatment. Adverse events were headaches, in 12 (42.6%); cutaneous rash, in 6 (21.4%); gastrointestinal symptoms, such as epigastric pain and diarrhea, in 5 (17.6%); neurological symptoms, including vision and sensorial alterations and paresthesia, in 4 (14.3%); new-onset psychiatric disorders, namely depression, dysphoric mood, depersonalization, and bipolar syndrome, in 4 (14.3%); wheezing, in 3 (10.7%); testicular tenderness, in 2 (7.1%); and recurrent bacterial infections, namely tonsillitis, chalazion, and bartholinitis, in 3 (10.7%).

Seven patients had asymptomatic changes in blood tests. Elevated liver transaminases greater than twice the upper limit of normal were seen in 4 (14.3%), but were normalized in up to 3 months, and there was no need for treatment interruption or dose reduction in any of these patients. Creatine kinase levels were increased twice the upper limit of normal in 2, (7.1%), and elevated total bilirubin occurred in 1 (3.6%).

One patient had severe intracranial hypertension and had to be hospitalized, at which point an undiagnosed congenital malformation (Budd-Chiari syndrome) was found that led to an unfavorable clinical course and death. Apart from that patient, adverse events were generally mild and self-limited even in patients with advanced lung disease, neither requiring specific interventions nor dose adjustments of the medication.

Because of the COVID-19 pandemic, several in-person visits and lung function tests could not safely take place as expected and had to be postponed. For that reason, 2 patients were unable to have a lung function revaluation, and 7 were unable to have a sweat chloride test reassessment by the time data were collected.

Significant improvements in terms of lung function, BMI, and sweat chloride concentration were observed, as shown in Table 2. After 12-24 weeks of ELX/TEZ/IVA treatment, FEV_1 in % of predicted and in L, respectively, improved 15.23% (95% CI, 10.51-19.95; $p < 0.001$) and 0.54 L (95% CI, 0.36-0.72; $p < 0.001$). The mean increase in BMI after 24 weeks of treatment was 1.31 kg/m^2 (95% CI, 0.84-1.78; $p < 0.001$). There was also a significant mean decrease

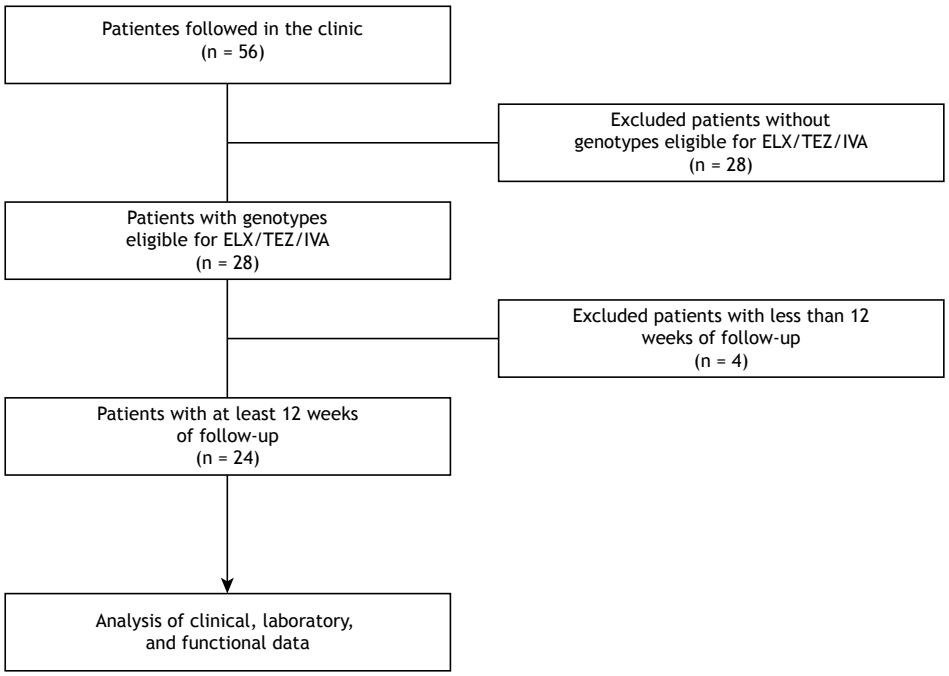

Figure 1. Flow chart of patient recruitment, enrollment, and follow-up.ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor.

Table 1. Clinical and demographic characteristics of the patients included in the study (N = 24).[a]

Characteristic	Result
Sex	
Female	11 (45.8)
Male	13 (54.2)
Age, years	26.9 ± 7.7
BMI, kg/m^2	19.3 ± 1.5
Follow-up time, days	167.3 ± 96.4
CFTR genotype	
Homozygous F508del	13 (54.2)
Heterozygous	11 (45.8)
F508del/R334W	6 (25.0)
F508del/G85E	3 (12.5)
F508del/R1066C	2 (8.3)
Prior CFTR modulator therapy	9 (37.5)
Advanced lung disease[b]	8 (33.3)

CFTR: cystic fibrosis transmembrane conductance regulator. [a]Values expressed as n (%) or mean ± SD. [b]Defined as FEV_1 < 40% of the predicted value.

in sweat chloride concentration (−35.94 mmol/L; 95% CI, −49.65 to −22.24; p < 0.001).

Although FEV_1 improvement was interestingly greater in heterozygous F508del patients when compared with homozygous F508del patients (16.36 vs. 14.10% and 0,58 L vs. 0.50 L), these differences were not statistically significant (p = 0.630 and p = 0.658, respectively; Figure 2). The same was observed for sweat chloride concentration, which had a greater decrease in the heterozygous group than in the homozygous group (−39.56 mmol/L vs −31.88 mmol/L; p = 0.570). However, both groups had the same improvement in BMI (1.31 kg/m^2).

There were 8 patients who were considered as having advanced lung disease, defined as FEV_1 < 40% of predicted, and they were demographically similar to patients with FEV_1 ≥ 40%. These patients also had significant improvements in FEV_1, both in % of predicted (13.28%; 95% CI, 3.97-22.58%; p = 0.012) and in L (0.42 L; 95% CI, 0.16-0.68 L; p = 0.006), as well as in BMI (2.13 kg/m^2; 95% CI, 1.27-2.98; p = 0,001; Table 2). Although there was also a decrease in sweat chloride concentration, that was not statistically significant (−28.83 mmol/L; 95% CI, −63.05 to +5.38; p = 0.083). Moreover, of the 3 patients in the transplantation waiting list, 1 had such a significant improvement with ELX/TEZ/IVA that the indication for lung transplantation was suspended.

Regarding pulmonary exacerbations (Table 3), there were only 3 patients who had pulmonary exacerbations after starting ELX/TEZ/IVA treatment during the study period, only 1 having advanced lung disease who needed hospitalization, compared with 29 patients in the previous year before ELX/TEZ/IVA treatment (p = 0.001), of whom 14 required hospitalization (p = 0.016).

DISCUSSION

Although we have found adverse events more frequently than in previous clinical trials,[3,4,9] most appeared in the first week of treatment and were only minor, self-limited, with no impact on treatment in contrast to what occurred in other studies, in which treatment had to be interrupted.[8] However, 1 of our

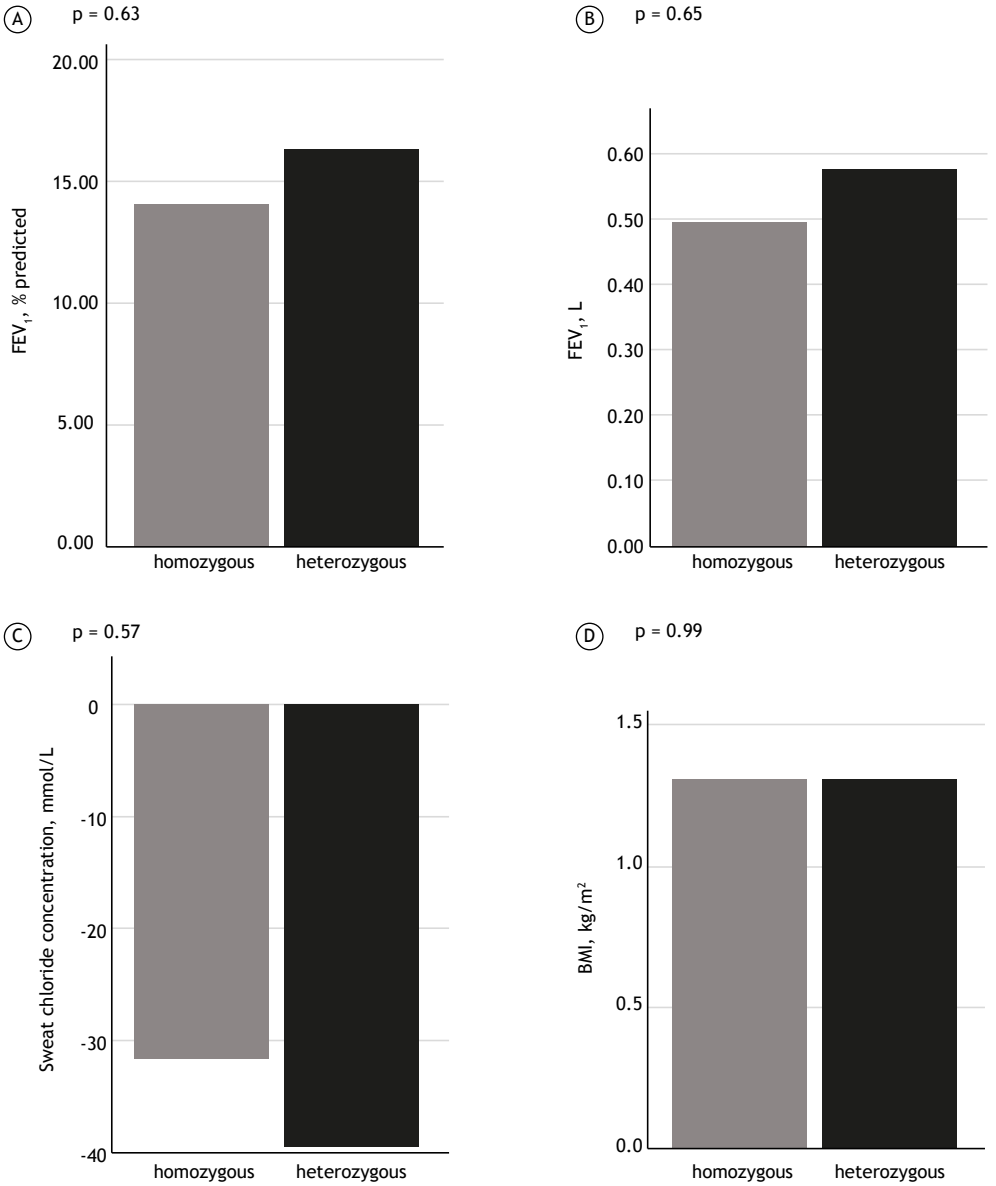

Figure 2. Differences in outcomes between F508del homozygous patients and F508del heterozygous patients with a minimal function mutation, in terms of changes after treatment initiation: in A, FEV_1, % predicted; in B, FEV_1, L; in C, sweat chloride concentration, mmol/L; and in D, BMI, kg/m^2.

patients who had a congenital cranial malformation had severe intracranial hypertension and died. There are some case reports of severe intracranial hypertension following ELX/TEZ/IVA treatment, mainly related to hypervitaminosis A toxicity,[10,11] but with good prognosis despite continuation of treatment with ELX/TEZ/IVA, supporting our belief that our patient's unknown congenital malformation was determinant for the negative outcome.

Blood test alterations have frequently been described[12,13] and the same was seen in our study; however, these changes were all asymptomatic and normalized in up to 3 months without any intervention.

Our results provided clear evidence of ELX/TEZ/IVA effectiveness on lung function in a real-world clinical setting, as shown by an improvement in FEV_1 of 15.23% of predicted and of more than 500 mL within just 12-24 weeks of treatment. Some studies suggested that improvements were larger in those naive for modulators, albeit substantial in all groups,[14] but we did not perform this analysis since only 9 patients in our study had undergone previous treatment with CFTR modulators. Likewise, we found a significant decrease in sweat chloride levels (−35.94 mmol/L) and a significant increase in BMI (1.31 kg/m^2), reflecting the CFTR functional improvement and its association with nutritional status, similarly to other studies.[14-16]

Table 2. Effects of elexacaftor/tezacaftor/ivacaftor treatment on lung function, BMI, and sweat chloride concentrations at baseline and at the end of the follow-up period of the study.

Sample or subgroup	Outcome	Baseline	End of follow-up	Mean difference	p
Overall (n = 24)	FEV_1, % predicted	50.36 (42.27-58.46)	65.60 (56.14-75.05)	15.23 (10.51-19.95)	< 0.001
	FEV_1, L	1.75 (1.41-2.10)	2.29 (1.87-2.71)	0.54 (0.36-0.72)	< 0.001
	Sweat chloride, mmol/L	71.59 (56.29-86.88)	35.65 (25.89-45.40)	−35.94 (−49.65 to −22.24)	< 0.001
	BMI, kg/m²	19.72 (18.98-20.45)	21.03 (20.23-21.82)	1.31 (0.84-1.78)	< 0.001
Homozygous (n = 13)	FEV_1, % predicted	51.82 (39.52-64.18)	65.92 (51.62-80.22)	14.10 (5.33-22.87)	0.005
	FEV_1, L	1.79 (1.27-2.31)	2.29 (1.66-2.92)	0.50 (0.18-0.82)	0.006
	Sweat chloride, mmol/L	67.88 (40.49-95.26)	36.00 (17.14-54.86)	−31.88 (−55.42 to −8.33)	0.015
	BMI, kg/m²	19.46 (18.26-20.65)	20.76 (19.51-22.03)	1.31 (0.71-1.90)	< 0.001
Heterozygous (n = 11)	FEV_1, % predicted	48.91 (36.15-61.67)	65.27 (50.23-80.32)	16.36 (10.96-21.77)	< 0.001
	FEV_1, L	1.72 (1.18-2.26)	2.30 (1.62-2.97)	0.58 (0.10-0.33)	< 0.001
	Sweat chloride, mmol/L	74.89 (53.07-96.71)	35.33 (22.60-48.07)	−39.56 (−59.84 to −19.27)	0.002
	BMI, kg/m²	20.03 (19.07-20.99)	21.34 (20.22-22.46)	1.31 (0.43-2.19)	0.008
Advanced lung disease[a] (n = 8)	FEV_1, % predicted	32.98 (27.81-38.14)	46.25 (32.31-60.19)	13.28 (3.97-22.58)	0.012
	FEV_1, L	1.07 (0.93-1.20)	1.49 (1.12-1.86)	0.42 (0.16-0.68)	0.006
	Sweat chloride, mmol/L	62.50 (33.87-91.13)	33.67 (16.02-51.31)	−28.83 (−63.05 to 5.38)	0.083
	BMI, kg/m²	18.83 (17.48-20.18)	20.96 (19.43-22.49)	2.13 (1.27-2.98)	0.001

[a]Defined as FEV_1 < 40% of the predicted value.

Table 3. Pulmonary exacerbations twelve months before elexacaftor/tezacaftor/ivacaftor treatment initiation and during the follow-up period of the study.

Sample/subgroup	Outcome	Before	During	p
Overall	Exacerbation, n	29	3	0.001
	Hospitalization, n	14	1	0.016
Advanced lung disease[a]	Exacerbation, n	9	1	0.041
	Hospitalization, n	5	1	0.068

[a]Defined as FEV_1 < 40% of the predicted value.

We also acknowledge that the mean changes were not statistically different between homozygous F508del patients and heterozygous F508del patients with a minimal function mutation, even though the rates of improvements in FEV_1 and sweat chloride concentrations were interestingly greater in the heterozygous group. These results might suggest that other patients with different mutations might also benefit from ELX/TEZ/IVA.

Pulmonary exacerbations rates were also significantly smaller after starting treatment when compared with the 12 months before ELX/TEZ/IVA therapy; nevertheless, it must be noted that the mean follow-up time of this study was approximately 6 months, which might have underestimated these results.

Regarding advanced lung disease patients, our data contradict previous studies that suggested that CFTR modulators were less effective in this group of patients and that lung damage was irreversible.[17] In fact, we found a significant improvement in FEV_1 of 13.28% of predicted over a period of 12-24 weeks of treatment, which is similar to the results reported in a recent French study by Burgel et al.[6] Of note in that study[6] is that a significant smaller proportion of patients with advanced lung disease required long-term oxygen therapy or noninvasive ventilatory support after 1-3 months of treatment with the triple CFTR modulator therapy. Likewise, an increase in nutritional status, inferred by BMI improvement, was also seen in this population as previously described. In terms of sweat chloride concentrations, our results were not as expressive, which could be related to the small sample, given the lack of results at the time of data collection, as mentioned before.

Importantly, 1 of our 3 patients in the transplantation waiting list was excluded from that list because of such a clinical improvement that transplantation was no longer indicated. This has also been reported in another study,[6] in which there was a two-fold decrease in lung transplantations. Moreover, there were no special safety concerns in this group of patients when compared with patients with less severe disease.

There are some limitations in our study that need to be noted. First, the official approval of ELX/TEZ/IVA in Portugal occurred only in July of 2021, which implied a short follow-up period. Also, the COVID-19 pandemic interfered with and prevented some in-person visits, including spirometry evaluations, in 2 patients, and sweat chloride tests, in 7 patients, who were not included in this study. It should also be noted this was an observational, non-randomized, single-center study that involved a limited number of patients in the analysis. Notwithstanding, the Cystic Fibrosis Center of the Santa Maria Hospital is the largest adult

CF center in Portugal, following about one-third of adult CF patients in the country, which allows us to contextualize our results within the national reality.

Other treatments, such as inhaled antibiotics or mucolytic agents, were not considered in this analysis, and whether they impact effectiveness of ELX/TEZ/IVA is unclear. Furthermore, we did not evaluate whether ELX/TEZ/IVA allow discontinuation of these classic baseline CF treatments, hence we have to wait for the results of studies evaluating those outcomes to understand whether ELX/TEZ/IVA would lead to significant reductions in the use of supportive therapies.

We found effective benefits of ELX/TEZ/IVA treatment in real-world clinical practice, even in patients initially not included in clinical trials, such as those with advanced lung disease, with improvements in FEV_1, BMI, sweat chloride concentrations, and number of exacerbations, and no significant differences were seen between F508del homozygous patients and F508del heterozygous patients with a minimal function mutation.

Overall, treatment with ELX/TEZ/IVA was well tolerated, and our data support the safety of ELX/TEZ/IVA, even in patients with advanced lung disease; above all, our results reflect the life change that this treatment brought to life expectancy of our CF patients.

AUTHOR CONTRIBUTIONS

PA: study conception and design. KL, CC, CL, RB, and PA: patient follow-up. KL, CC, RB, and PA: data collection. KL and CC: statistical analysis and drafting of the manuscript. All of the authors revised the manuscript and approved the final version as submitted and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

None declared.

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CT features of osteosarcoma lung metastasis: a retrospective study of 127 patients

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ABSTRACT

Objective: Osteosarcoma lung metastases have a wide variety of CT presentations, representing a challenge for radiologists. Knowledge of atypical CT patterns of lung metastasis is important to differentiate it from benign lung disease and synchronous lung cancer, as well as to determine the extent of primary disease. The objective of this study was to analyze CT features of osteosarcoma lung metastasis before and during chemotherapy. **Methods:** Two radiologists independently reviewed chest CT images of 127 patients with histopathologically confirmed osteosarcoma treated between May 10, 2012 and November 13, 2020. The images were divided into two groups for analysis: images obtained before chemotherapy and images obtained during chemotherapy (initial CT examination). **Results:** Seventy-five patients were diagnosed with synchronous or metachronous lung metastases. The most common CT findings were nodules (in 95% of the patients), distributed bilaterally (in 86%), with no predominance regarding craniocaudal distribution (in 71%). Calcification was observed in 47%. Less common findings included intravascular lesions (in 16%), cavitation (in 7%), and the halo sign (in 5%). The primary tumor size was significantly greater (i.e., > 10 cm) in patients with lung metastasis. **Conclusions:** On CT scans, osteosarcoma lung metastases typically appear as bilateral solid nodules. However, they can have atypical presentations, with calcification being the most common. Knowledge of the typical and atypical CT features of osteosarcoma lung metastasis could play a key role in improving image interpretation in these cases.

Keywords: Neoplasm metastasis/lung; Osteosarcoma; Tomography, X-ray computed.

INTRODUCTION

Osteosarcoma is the most common primary malignant bone tumor in children and young adults, with an estimated global incidence of 2-4 million cases per year.[1-5] Despite the development of multimodal therapies, such as those involving surgery, systemic therapy, and immunotherapy, the prognosis of osteosarcoma remains poor, and patient survival correlates strongly with treatment response and metastatic status.[4] The prognosis is also related to other variables, such as primary tumor location and size; patient sex and age; and histological subtype.[6-8] The lungs are the most common site of osteosarcoma metastasis, with osteosarcoma lung metastases being observed in approximately 80% of patients.[9] The 5-year survival rates in patients without and with osteosarcoma lung metastases are approximately 70% and 20%, respectively.[4,10,11]

Primary osteosarcoma involves the distal femur, proximal tibia, and proximal humerus in more than 75% of cases, other long and flat bones being affected in the remaining cases.[12] Osteosarcoma can metastasize to virtually any site or organ, mostly to the lungs, but occasionally to bone and lymph nodes. At the time of diagnosis, 18-30% of patients with osteosarcoma have metastatic disease, the lungs being the most commonly affected site.[13]

Reported risk factors for pulmonary lesions in patients with osteosarcoma include male sex, primary malignant bone tumor of the femur or tibia, and primary tumor size.[9] In addition, the number, distribution (unilateral or bilateral), and location of lung metastases may have prognostic value.[2] Thus, the correct diagnosis and characterization of these lesions has an impact on patient management.

Chest CT is the gold standard for the detection of lung metastases and may aid in distinguishing lung metastasis from benign lung disease. Radiologically, lung metastases typically appear as multiple peripheral round nodules of varying sizes in the lower lobes. However, osteosarcoma lung metastases may have atypical radiological features, which make their diagnosis challenging. On CT scans, lung metastases can have an extremely heterogeneous appearance, including calcification, hemorrhage halos around nodules, cavitation, pneumothorax, tumor embolism, an endobronchial location, solitary masses, dilated vessels within masses, and sterilized metastasis.[14,15]

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The purpose of this retrospective study was to determine the most common distribution, morphological characteristics, and chest CT features of osteosarcoma lung metastases. Epidemiological aspects and prognostic factors were also explored.

METHODS

Patients

This study was approved by the local research ethics committee, which waived the requirement for informed consent because of the retrospective nature of the study. All of the patients with osteosarcoma treated at the Brazilian National Cancer Institute between May 10, 2012 and November 13, 2020 (n = 156) were assessed for eligibility for inclusion in the study. Those who were included had an osteosarcoma diagnosis confirmed by primary tumor biopsy and had undergone chest CT examination. Those who did not undergo chest CT before chemotherapy (n = 29) were excluded. The study sample comprised 127 patients, 75 of whom had been diagnosed with synchronous or metachronous lung metastases.

Demographic data (including patient age and sex), mortality data, and clinical data (including the histological type, location, and size of the primary tumor) were collected. The lung metastases that were identified at the time of diagnosis were classified as synchronous, whereas those representing relapse despite chemotherapy for the primary tumor were classified as metachronous.[16]

CT protocol and image analysis

Although all of the patients included in the study were recruited from the same institution, some CT examinations were performed at other institutions, with different scanners. Nevertheless, the technical parameters were the same for all chest CT examinations: 1–2.5-mm slice thickness with up to 10-mm increments. Images were acquired from the lung apices to the diaphragm at the end of a deep inhalation, with the patients in the supine position. Two radiologists (one with 4 years of experience and the other with 13 years of experience) retrospectively and independently reviewed the chest CT images, with any disagreement being resolved by discussion until consensus was reached.

Images were interpreted with the aid of a digital database system (CARESTREAM Vue PACS, version 12.1.0.0365; Carestream Health, Rochester, NY, USA), lung parenchymal window settings (width, 1,200-1600 HU; level, −500 to −700 HU) and mediastinal window settings (width, 350-450 HU; level, 20-50 HU) being used. The observers performed maximum intensity projection reconstruction for accurate identification of pulmonary nodules.

CT images of primary osteosarcoma were analyzed in order to determine tumor size and location. Primary tumor sizes were classified as ≤ 5 cm, 6-10 cm, or > 10 cm.

Two groups of images were evaluated: the group of images obtained before chemotherapy and that of those obtained during chemotherapy (i.e., 3-12 months after initiation of chemotherapy).

Lung metastases were defined as lung lesions suspicious for malignancy, the number and/or dimensions of which increased progressively on serial CT examinations, as well as those found in patients undergoing metastasectomy. In accordance with the Fleischner Society glossary of terms for thoracic imaging,[17] lung metastases were classified on the basis of the following: pattern (nodule or mass); shape (smooth, lobulated, or spiculated); density (solid, nonsolid, or partially solid); presence of calcification, the halo sign, or cavitation; number of lesions (≤ 3, 4-10, or > 10); and size (as well as changes in size). The distribution of metastases in the lung parenchyma was classified on the basis of the following: laterality (unilateral or bilateral metastases); symmetry and the most affected lung (right or left lung); axial distribution (central, peripheral, or random distribution); and craniocaudal distribution (upper, middle, or lower lung).

The presence of pleural effusion and lymph node enlargement was recorded. Lung metastasis complications such as pneumothorax, vascular thrombosis, and pericardial effusion were also recorded.

RESULTS

Demographic and clinical characteristics

The study sample comprised 127 patients with osteosarcoma in the 5- to 72-year age bracket (mean age, 20 ± 12.7 years). Seventy-five (59%) of the patients (61% of whom were male; mean age, 18 ± 11.3 years) had lung metastases, and 53 (41%) of the patients (54% of whom male; mean age, 25 ± 14 years) did not.

The most common primary tumor location was the femur (in 53% of the study sample), and this location was more common in patients with lung metastasis than in those without (57% vs. 45%). Other primary tumor sites were the tibia (in 21%), humerus (in 7%), jaw (in 5%), and fibula (in 4%). Primary tumors of the foot, sacrum, scapula, clavicle, radius, ulna, sphenoid sinus, frontal bone, and retroauricular space occurred at a frequency of 1%.

The most common histological type was classic osteosarcoma (in 81%). Other histological types included high-grade osteosarcoma (in 6%), telangiectatic osteosarcoma (in 6%), small cell osteosarcoma (in 2%), parosteal osteosarcoma (in 2%), epithelioid osteosarcoma (in 1%), and giant cell osteosarcoma (in 1%). One case of osteosarcoma secondary to fibrous dysplasia was observed in a patient without lung metastasis (1%).

At admission, 10% of the primary tumors were < 6 cm in size, 27% were 6-10 cm in size, and 63% were > 10 cm in size. Primary tumor size was greater in patients with lung metastasis (> 10 cm in 81% of the cases) than in those without (< 10 cm in 36% of the cases). During the study period, death occurred more frequently in the group of patients with lung metastasis than in that of those without (77% vs. 21%).

CT findings before and during chemotherapy

Before chemotherapy

Seventy-five patients underwent CT examination before chemotherapy. Lung metastasis was observed in 72 (96%). Lesion size ranged from 0.3 cm to 7.8 cm in diameter (mean, 1.3 ± 1.5 cm), and nodules predominated, being observed in 69 patients (96%). Margins were smooth in 55 (76%) and lobulated in 17 (24%). Solid lesions predominated, being observed in 70 patients (97%; Figure 1). Semisolid nodules were observed in 2 (3%). Calcification was observed in 23 (32%; Figure 2), and cavitation was observed in 3 (4%).

Pulmonary involvement was bilateral in 58 patients (80%), with no predominance regarding the affected lung (n = 49; 68%) or craniocaudal distribution (n = 48; 66%) in most of the cases. Peripheral lesions predominated in 40 patients (55%), and no specific axial distribution was observed in 32 (45%). Fewer than 3 lesions were observed in 17 patients (23%), 4-10 lesions were observed in 25 (35%), and > 10 lesions were observed in 30 (42%).

The halo sign, which is an area of ground-glass opacity surrounding a nodule or mass, was observed in 4 patients (5%; Figure 3). Eleven patients (15%) showed intravascular lesions (Figure 4). Pleural effusion and lymph node enlargement were observed in 4 patients (5%; Figure 5). In 2 patients (3%), pneumothorax was identified as a complication of lung metastasis (Figure 3).

Of the 72 patients presenting with lung metastasis before chemotherapy, 2 were lost to follow-up. Of the remaining 70 patients, 58 died during the study period (mean survival, 18.5 ± 16 months). Pulmonary masses > 3 cm were observed only in patients who died (n = 3; 5%), and cases of patients with more than 3 lesions predominated in the nonsurviving group (n = 44; 79%). Bilateral involvement was more common among the patients who died (n = 47; 84%).

During chemotherapy

Of the 75 patients who underwent CT before treatment, 14 did not undergo follow-up CT examination. On follow-up CT scans, lung metastases ranged from 0.3 cm to 14 cm in diameter (mean, 2.6 ± 2.9 cm), and nodules predominated, being observed in 57 patients (93%). Smooth margins were observed in 36 patients (59%). Most of the lesions were solid (n = 58; 95%). Semisolid nodules were observed in 3 patients (5%). Calcifications were observed in 22 (36%), and cavitations were observed in 4 (6%).

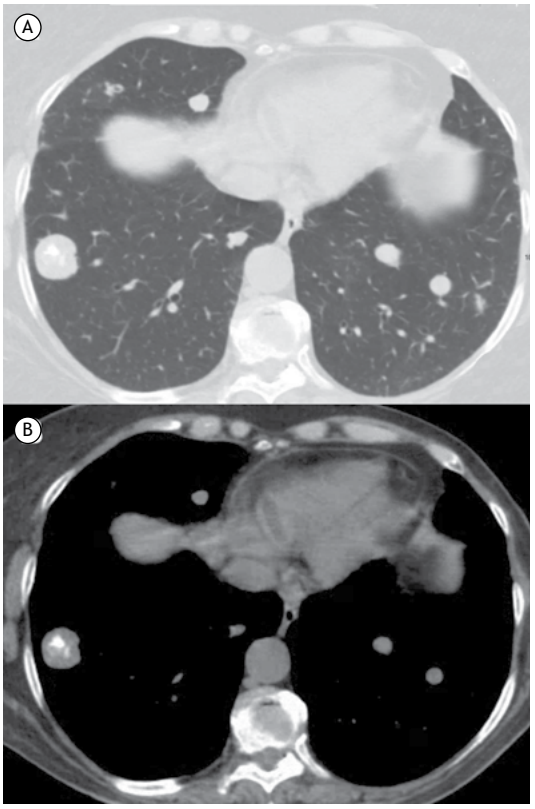

Figure 1. A 72-year-old woman with primary osteosarcoma of the femur. In A and B, CT scans showing multiple nodules of various sizes in both lungs, with the largest nodule being on the right side and showing inner calcification. The patient died 9 months after treatment initiation.

Pulmonary involvement was bilateral in 57 patients (93%), with no predominance regarding the affected lung (n = 42; 69%) or craniocaudal distribution (n = 46; 75%) in most of the cases. Peripheral lesions predominated in 28 patients (46%), and no specific axial distribution was observed in 32 (52%). Fewer than 3 lesions were observed in 5 patients (8%), 4-10 lesions were observed in 20 (33%), and > 10 lesions were observed in 36 (59%).

The halo sign was observed in 1 patient (2%). Eleven patients (8%) had intravascular lesions, and 1 (2%) had an endobronchial lesion (Figure 5). Complications occurred in 2 patients: pneumothorax, in 1 (2%); and central line–associated thrombosis, in 1 (2%). Table 1 summarizes the main CT features of metastatic lung lesions.

The lesions were stable from baseline in 6 patients (10%), and decreased in size or disappeared in 11 (18%). In 44 patients (72%), the lesions progressed over time, with lesion growth or new lesion appearance (Figure 4), the mean size having increased from 1.3 cm at baseline to 2.6 cm. Changes in morphological patterns occurred in 17 patients (71%); in 14 of those patients, smooth lesions became lobulated.

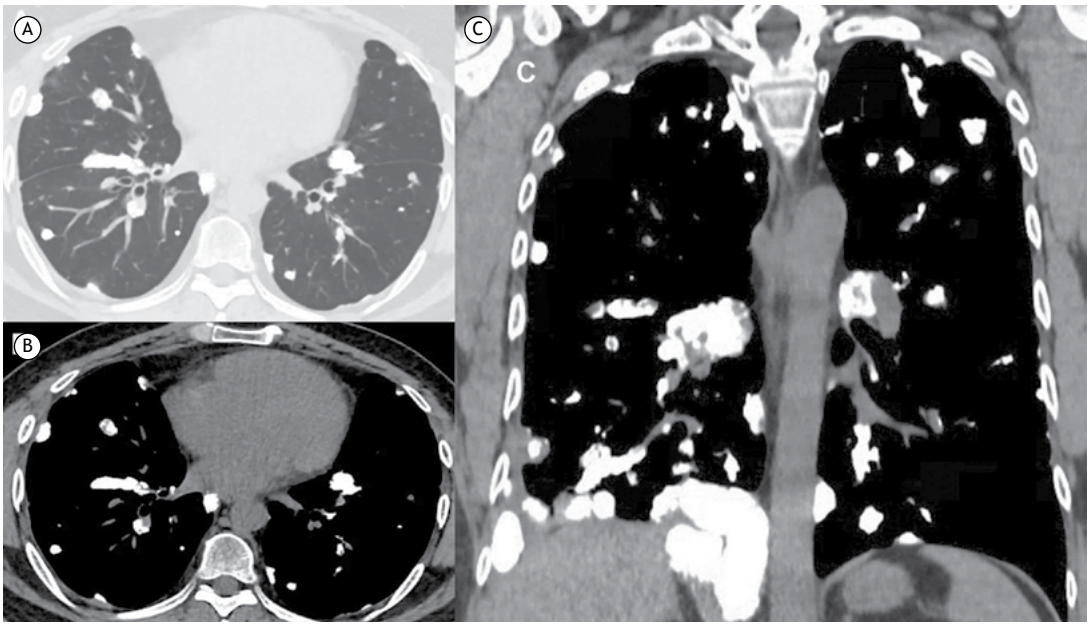

Figure 2. A 44-year-old man with primary osteosarcoma of the femur. In A, B, and C, CT scans showing multiple calcified nodules and masses in both lungs.

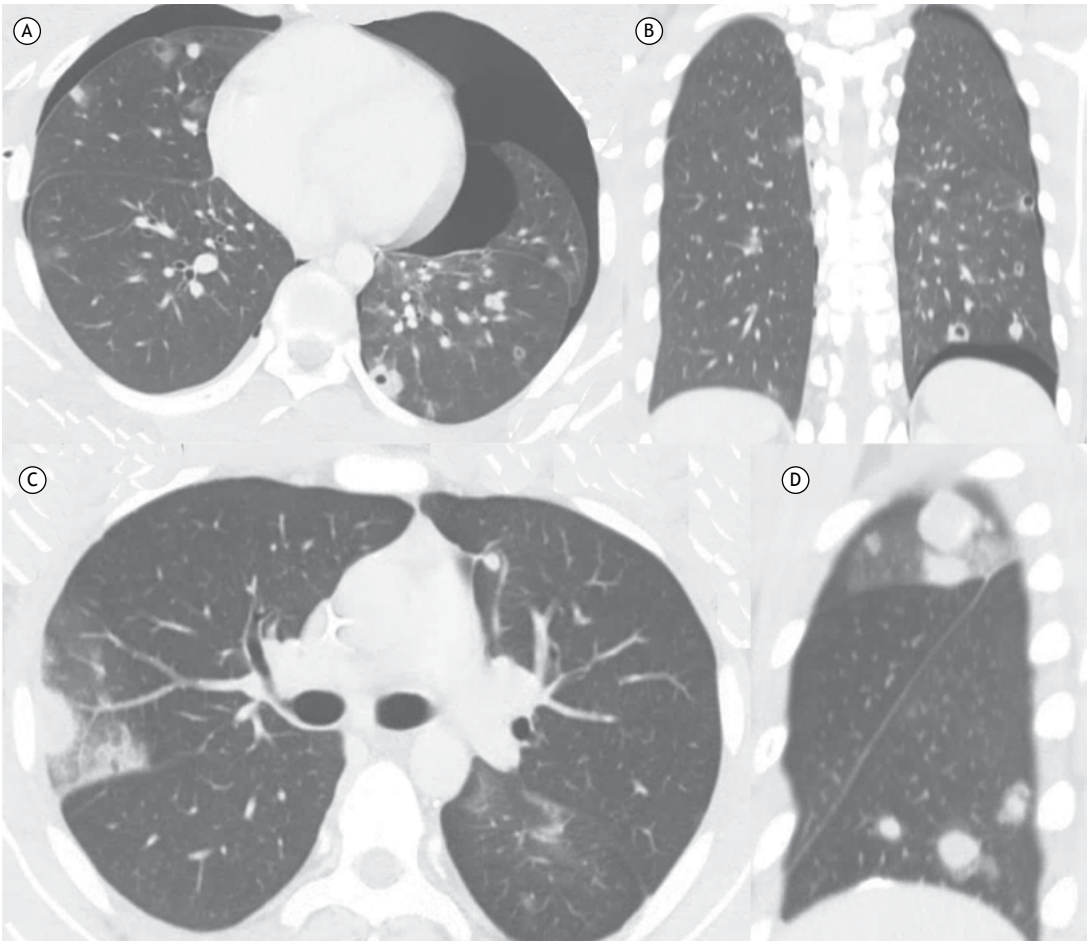

Figure 3. A 16-year-old boy with primary osteosarcoma of the femur. In A and B, CT scans performed at the time of diagnosis, showing multiple cavitary lung lesions with bilateral pneumothorax. In C and D, CT scans performed 5 months after initiation of chemotherapy, showing growth of the nodules, which are surrounded by ground-glass halos (indicating hemorrhagic pulmonary metastases).

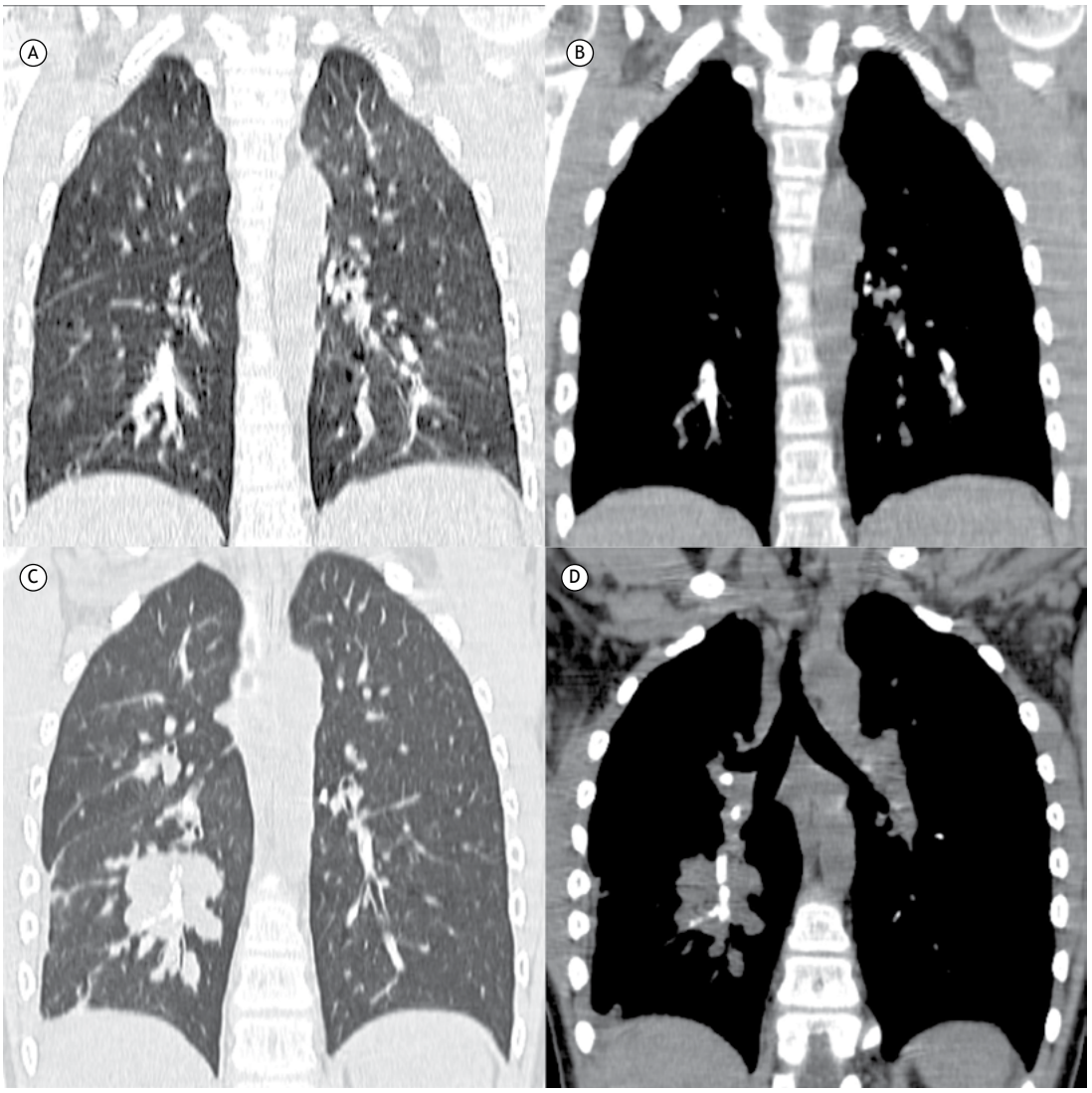

Figure 4. A 7-year-old boy with primary osteosarcoma of the femur. In A and B, CT scans showing calcified intravascular lung metastasis, which was confirmed by biopsy. In C and D, CT scans acquired 6 months later, showing progression of the lung lesions, with mass formation on the right.

DISCUSSION

In our study, patient age ranged from 5 years to 72 years. The incidence of osteosarcoma was highest in males in the second decade of life, and the most common primary tumor sites were the femur and the tibia, findings that are consistent with the literature.[1,3,4,18,19]

The lung is the most common site of osteosarcoma metastasis.[20] Risk factors for osteosarcoma lung metastasis include male sex, primary malignant bone tumor of the femur or tibia, and primary tumor size.[9] In our study, 59% of the patients had lung metastases. Of those, 61% were male. The most common primary tumor sites were the femur and the tibia (in 52% and 22%, respectively). The primary tumor size was > 10 cm in 81% of the cases.

Patients with osteosarcoma lung metastases have a dismal prognosis, with an estimated 5-year survival rate of 20%.[4,10] Our findings of worse prognosis and lower mean survival in patients with lung metastasis than in those without (26 ± 25 months vs. 64 ± 33 months) are consistent with the literature.[4,10]

Chest CT is a recommended component of the initial evaluation of patients with osteosarcoma, because of the high prevalence of lung metastasis and its significant impact on prognosis.[3,4,9,21] Recognition of the most common morphological CT characteristics of osteosarcoma lung metastasis is of fundamental importance, especially for small lesions, which are difficult to characterize and biopsy.[22] In the present study, there was a predominance of solid nodules (in 96% of the patients) with smooth margins (in 68%), distributed peripherally (in 55%) and bilaterally (in

80%). These findings are consistent with the typical radiological appearance of lung metastases.[14,22,23]

Cicarese et al.[2] found that 61.6% of their patients had calcification and the lesions increased in size and progressively calcified over time. Brader et al.[24] described that, in their population, the osteoid matrix produced by the osteosarcoma cell may form bone and lead to calcification in pulmonary nodules. In our study, calcification was observed in less than 50% of our patients. The fact that this imaging pattern was less common in our study may be attributable to the fact that we evaluated CT images obtained within 12 months of chemotherapy initiation. The literature contains little information regarding atypical presentations of lung metastases. In a retrospective analysis of CT and pathological findings for resected osteosarcoma lung metastases, the masses were not nodular in 14.1% of cases, and the presence of striae, consolidation, pleural/cavitary lesions, ground-glass opacity, irregular shapes, and the halo sign varied widely.[2] Cavitation was present in only a few of our patients (7%) and was associated with pneumothorax in 2. Hemorrhagic metastases, which are characterized by nodular opacities with ground-glass halos and which reflect fragile new blood vessels and, consequently, vessel rupture,[25] were observed in 4% of our patients.

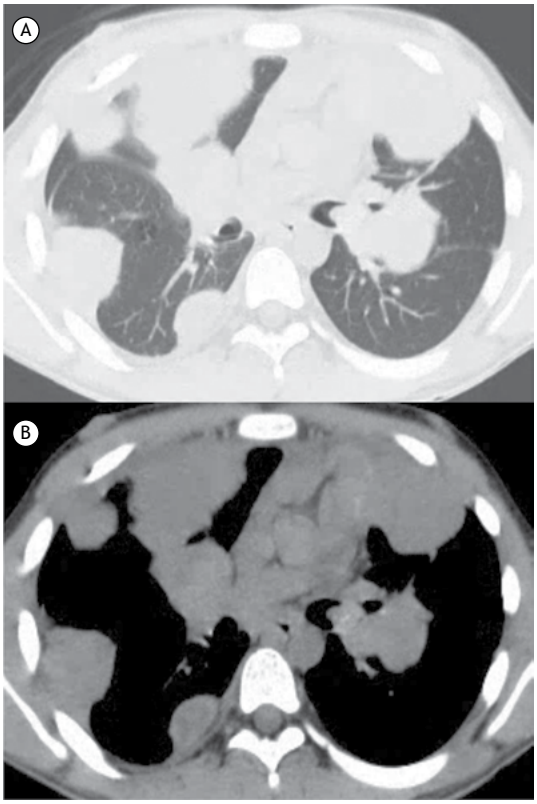

Figure 5. A 15-year-old boy with primary osteosarcoma of the femur. In A and B, CT scans showing multiple irregularly shaped masses in both lungs, with invasion of the left main bronchus.

Another atypical presentation of osteosarcoma lung metastasis was intravascular lesion (in 16%), which has rarely been reported in the literature. Intravascular metastasis usually affects small or medium-sized pulmonary arteries, a radiological diagnosis therefore being difficult.[26] Intravascular tumor embolism should be differentiated from pulmonary thromboembolism because they are managed differently.

Endobronchial metastasis is also a rare form of pulmonary involvement in osteosarcoma, being found in only 1 patient in our study. It can occur as secondary metastasis or as direct metastasis to the tracheobronchial tree from an extrapulmonary lesion.[25,27,28] Pleural effusion and lymph node involvement were also uncommon in our study. We found no reports on the incidence of pleural effusion in patients with osteosarcoma and one report on the incidence of lymph node involvement in such patients, the reported incidence being < 3%.[15]

In a follow-up study of osteosarcoma lung metastases, disease progression was observed in 59.4% of cases.[2] We observed disease progression in a larger proportion of patients (72%) and changes in morphological patterns in 17 patients (71%); in 14 of those patients, smooth lesions became lobulated.

Smaller numbers of metastatic lung lesions have been related to better survival and may reflect a low disease burden or favorable tumor biology.[11]

Table 1. CT features of osteosarcoma lung metastasis before and during chemotherapy.[a]

CT feature	Before chemotherapy (n = 72)	During chemotherapy (n = 61)
Nodule	69 (96%)	57 (93%)
with calcification	23 (32%)	22 (36%)
with cavitation	3 (4%)	4 (6%)
with the halo sign	4 (5%)	1 (2%)
Intravascular lesion	11 (15%)	11 (8%)
Endobronchial lesion	0 (0%)	1 (2%)
Pleural effusion	4 (5%)	6 (10%)
Lymph node enlargement	4 (5%)	5 (8%)
Pneumothorax	2 (3%)	1 (2%)
Vascular thrombosis	0 (0%)	1 (2%)

[a]Data expressed as n (%).

Furthermore, the number of pulmonary nodules detected on baseline CT scans is believed to have greater prognostic significance than does lesion size.[2,21] In our study, many of the patients who died during the study period had > 10 lesions on CT scans obtained before chemotherapy. All 3 patients with pulmonary masses on initial CT scans died. However, because this is a small number of patients, we were unable to assess the impact of this parameter on patient survival.

The present study has some limitations. It was a retrospective study, and the CT techniques varied widely because the examinations were performed on different scanners. Moreover, because we did not have full clinical and disease progression data for all patients, it was difficult to establish clinical and radiological correlations.

In conclusion, the most common CT findings in our patients were solid nodules with smooth margins, predominantly distributed peripherally and bilaterally. Nevertheless, lung metastases can have atypical presentations, with calcification being the most common. Given that the detection of lung metastases and their number and size at the time of diagnosis have a strong impact on the prognosis of patients with osteosarcoma, clinicians must be able to recognize the common and uncommon imaging presentations of lung lesions in these patients.

AUTHOR CONTRIBUTIONS

JAMS: data collection; editing and review of the manuscript. EM: data analysis; supervision; editing and review of the manuscript. VBA: data analysis; editing and review of the manuscript. MMB: conception and design of the study; editing and review of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Ambulatory oxygen therapy in lung transplantation candidates with idiopathic pulmonary fibrosis referred for pulmonary rehabilitation

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ABSTRACT

Objective: To determine independent factors related to the use of oxygen and the oxygen flow rate in idiopathic pulmonary fibrosis (IPF) patients placed on a lung transplant waitlist and undergoing pulmonary rehabilitation (PR). **Methods:** This was a retrospective quasi-experimental study presenting functional capacity and health-related quality of life (HRQoL) data from lung transplant candidates with IPF referred for PR and receiving ambulatory oxygen therapy. The patients were divided into three groups on the basis of the oxygen flow rate: 0 L/min (the control group), 1-3 L/min, and 4-5 L/min. Data on functional capacity were collected by means of the six-minute walk test, and data on HRQoL were collected by means of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), being collected before and after 36 sessions of PR including aerobic and strength exercises. **Results:** The six-minute walk distance improved in all three groups (0 L/min: Δ 61 m, $p < 0.001$; 1-3 L/min: Δ 58 m, $p = 0.014$; and 4-5 L/min: Δ 35 m, $p = 0.031$). Regarding HRQoL, SF-36 physical functioning domain scores improved in all three groups, and the groups of patients receiving ambulatory oxygen therapy had improvements in other SF-36 domains, including role-physical (1-3 L/min: $p = 0.016$; 4-5 L/min: $p = 0.040$), general health (4-5 L/min: $p = 0.013$), social functioning (1-3 L/min: $p = 0.044$), and mental health (1-3 L/min: $p = 0.046$). **Conclusions:** The use of ambulatory oxygen therapy during PR in lung transplant candidates with IPF and significant hypoxemia on exertion appears to improve functional capacity and HRQoL.

Keywords: Oxygen; Exercise therapy; Idiopathic pulmonary fibrosis; Rehabilitation; Quality of life.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an irreversible fibrotic lung disease characterized by progressive fibrosing interstitial pneumonia of unknown cause whose natural history is variable and often unpredictable.[1,2] The pathophysiology of IPF is probably related to repeated microinjury to the pulmonary epithelium that is followed by wound repair processes.[3] This results in a restrictive ventilatory pattern and impaired gas exchange, leading to exertional hypoxemia and functional limitation in many cases.[4] As pulmonary fibrosis advances, exertional breathlessness is triggered by simple daily activities and is the strongest determinant of health-related quality of life (HRQoL) in these patients.[5,6] In addition, oxygen desaturation contributes to exercise intolerance in patients with interstitial lung disease.[7]

In this context, the management of oxygen therapy in patients with IPF is still controversial.[7-9] The 2011 IPF guidelines did not provide guidance on the use of oxygen therapy in patients with exertional hypoxia alone.[2] However, the 2015 British Thoracic Society guidelines state that ambulatory oxygen should not be routinely used in patients who are not hypoxic at rest.[10] Visca et al. evaluated ambulatory oxygen therapy for patients with IPF and obtained significant results regarding important outcomes, such as the six-minute walk distance (6MWD), HRQoL, perception of dyspnea, and ability to walk.[7]

SpO_2 should be taken into consideration because of its association with scores that predict desaturation during the six-minute walk test (6MWT).[8] In a systematic review, Bell et al.[9] investigated the impact of oxygen therapy in patients with IPF and found that it had no beneficial effect on dyspnea, functional capacity, or quality of life. Therefore, there is no robust evidence to recommend the use of ambulatory oxygen therapy in patients with IPF. There is an ongoing clinical trial that is currently in the data collection phase; however, the trial will not quantify the amount of oxygen provided, and it will exclusively compare patients receiving oxygen therapy with those not receiving it.[11] The objective of the present study was to determine independent factors related to the use of ambulatory oxygen therapy and the oxygen flow rate

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in IPF patients placed on a lung transplant waitlist and undergoing pulmonary rehabilitation (PR).

METHODS

Study sample

This was a retrospective quasi-experimental study of IPF patients undergoing PR while on a waiting list for lung transplantation between January of 2018 and March of 2020. The study was carried out in the Department of Pulmonary Rehabilitation of the Santa Casa de Misericórdia de Porto Alegre, located in the city of Porto Alegre, Brazil, and was approved by the local research ethics committee (Protocol no. 04453412.7.0000.5335).

IPF was diagnosed by a multidisciplinary team before PR, on the basis of HRCT and/or surgical lung biopsy findings or the affected lung showing a usual interstitial pneumonia pattern, in accordance with the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/*Asociación Latinoamericana de Tórax* guidelines.[2] Forty-five patients were included in the study and were divided into three groups on the basis of the oxygen flow rate that was used during PR and that was determined on the basis of DL_{CO} and oxygen saturation: 0 L/min (the control group), 1-3 L/min, and 4-5 L/min. Patients with clinically significant resting hypoxemia (resting SpO_2 ≤ 88%) were prescribed long-term oxygen therapy. The oxygen flow rate was increased as needed during exercise, in order to maintain SpO_2 at > 92%. None of the patients in the control group required oxygen therapy to maintain SpO_2 at > 92%.[12]

Data were retrospectively reviewed from patient medical records, including pre- and post-PR data (when available). Completion of a PR program was defined as participation in at least 36 sessions[12,13] and all post-PR evaluations, including a 6MWT and an HRQoL questionnaire.[14,15]

PR program

The PR program consisted of medical appointments with the PR team every two months and included psychiatric evaluation, nutritional counseling, social assistance, and monthly educational lectures.[12] The physical training component of the program was administered by two physical therapists, with three sessions per week for a total of 36 sessions. During physical training, patients performed a warm-up, followed by muscle strengthening and aerobic exercises. The warm-up consisted of breathing exercises (respiratory cycle) and arm raising. Muscle strengthening was based on arm and leg exercises performed with an initial load of 30% of a one-repetition maximum test, with a set of ten repetitions per exercise. The load was increased by 0.5 kg every seven sessions depending on exercise tolerance.[12] Aerobic exercises were performed on a treadmill at 70% of the speed achieved during the 6MWT, the speed being progressively increased every 6 min for a total of 30 min of exercise. The speed was increased by 0.3 km/h every seven sessions. The modified Borg scale was used for measuring dyspnea and leg fatigue, and the exercises were interrupted if patients reported dyspnea or leg fatigue, as assessed by a modified Borg scale score > 4.

Pulmonary function tests and HRQoL assessment

Pulmonary function tests were performed in accordance with the American Thoracic Society/European Respiratory Society and Brazilian Thoracic Association technical procedures and acceptability and reproducibility criteria.[16-18] All pulmonary function tests were performed in our pulmonary function laboratory, which is certified by the Brazilian Thoracic Association. The same physical therapists administered the pulmonary function tests and the 6MWT, in accordance with the American Thoracic Society recommendations.[14] For the 6MWT, patients were asked to walk down a 30-m corridor (delimited by traffic cones) for 6 min, verbal encouragement being given every minute. Data on HR, blood pressure, and effort perception (as assessed by the modified Borg scale) were obtained before and after the test. Patients were constantly monitored by pulse oximetry so that SpO_2 was maintained at ≥ 88% during the test. When patients presented with an SpO_2 of < 88%, oxygen was provided in an attempt to maintain exertion and encourage patients to tolerate dyspnea. The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) was used in order to evaluate HRQoL.[15]

Statistical analysis

Data were presented as absolute and relative frequencies, mean ± SD, or median (IQR). The normal distribution of the data was evaluated with the Kolmogorov-Smirnov test. Comparisons of proportions were made with the chi-square test for categorical variables. A paired t-test was used in order to compare pre- and post-PR variables in the patients who completed the program. The nonparametric Mann-Whitney and Wilcoxon tests (for unequal variance) were used for between-group comparisons.

For within-group differences, the effect size was calculated in accordance with Cohen,[19] by dividing the difference between the mean values at baseline and at follow-up by the pooled SD of both values. Effect sizes were classified as small (0.2), medium (0.5), or large (0.8).

All statistical analyses were performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). A value of $p < 0.05$ was considered significant for all analyses.

RESULTS

A total of 45 patients met the inclusion criteria and were therefore included in the study. Of those, 15 received an oxygen flow rate of 0 L/min, constituting

the control group. Of the remaining 30 patients, 15 received an oxygen flow rate of 1-3 L/min and 15 received an oxygen flow rate of 4-5 L/min. There were no significant differences among the groups regarding most of the baseline characteristics (Table 1). Most (60.5%) of the patients were male (n = 26), and the mean age was 60 ± 10 years. There were significant differences among the groups regarding lung function outcomes such as the FEV_1/FVC ratio (p < 0.001) and DL_{CO} (p = 0.003), with worse parameters in patients with greater need for oxygen.

Table 2 shows the results of the 6MWT. The 6MWD improved in all three groups (0 L/min: Δ 61 m, p < 0.001; 1-3 L/min: Δ 58 m, p = 0.014; and 4-5 L/min: Δ 35 m, p = 0.031). The control group had an improvement in dyspnea sensation (p = 0.002) and leg fatigue (p = 0.004). Additionally, HR values were significantly different in the 4-5 L/min group (p = 0.014).

With regard to HRQoL, SF-36 physical functioning domain scores improved in all three groups (0 L/min: p = 0.018; 1-3 L/min: p = 0.021; and 4-5 L/min: p = 0.024). As can be seen in Table 3, the groups of patients who received ambulatory oxygen therapy had improvements in other SF-36 domains, including role-physical (1-3 L/min: p = 0.016; 4-5 L/min: p = 0.040), general health (4-5 L/min: p = 0.013), social functioning (1-3 L/min: p = 0.044), and mental health (1-3 L/min: p = 0.046).

DISCUSSION

In the present study we found that the use of ambulatory oxygen during a PR program is associated with improved HRQoL in lung transplant candidates with IPF. Functional capacity and the 6MWD were found to have improved in all three groups, a finding that suggests that oxygen therapy alone does not affect these outcomes. Similar findings regarding the 6MWD have been reported in studies involving PR. Dowman et al.[20] reported that PR probably improves the 6MWD by 40.07 m in patients with interstitial lung disease. In the present study, the 6MWD improved by approximately 37.25 m in patients with IPF.

With regard to the baseline characteristics of the patients investigated in the present study, DL_{CO} was lower in those who received ambulatory oxygen therapy than in those who did not (the control group). Pulmonary interstitial compromise may be associated with a greater need for oxygen during exercise. In a previous study, multivariate analysis showed that resting SpO_2 and DL_{CO} ≤ 40% were predictive of desaturation during the 6MWT.[8] Thus, our findings are important in that, despite lower DL_{CO} in the groups of patients receiving ambulatory oxygen therapy, the 6MWD increased by 58 m in those who received an oxygen flow rate of 1-3 L/min and by 35 m in those who received an oxygen flow rate of 4-5 L/min, with greater exercise tolerance. The fact that patients in all three groups presented with desaturation after the 6MWT might be due to low DL_{CO} at baseline. An increase in the 6MWD is important because a reduced 6MWD is strongly and independently associated with increased mortality in patients with IPF. In addition, the 6MWD is a better predictor of 6-month mortality than is FVC.[21,22]

The findings of the present study are consistent with the literature. Visca et al.[7] investigated IPF patients receiving oxygen therapy through cylinders for use at home for 15 days and found positive results regarding the 6MWD, the sensation of breathlessness, and the ability to walk.[7] Bell et al.[9] reported that oxygen therapy during exercise had no beneficial effect on functional capacity. It is of note that, in our study, the group of patients who received the highest oxygen flow rates had submaximal HR values, showing better exercise tolerance. This finding is consistent with those of Dowman et al.,[23] whose study involved the use of

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

Variable	Total sample	Oxygen flow rate			p
		0 L/min	1-3 L/min	4-5 L/min	
	(N = 45)	(n = 15)	(n = 15)	(n = 15)	
Male sex	26 (60.5)	7 (50.0)	7 (50.0)	12 (80.0)	0.099
Age, years	60 ± 10	56 ± 913	65 ± 4	62 ± 7	0.387
BMI, kg/m^2	26.8 ± 4.71	26.4 ± 5.69	28.6 ± 4.78	26.6 ± 3.67	0.726
FEV_1, % predicted	55 ± 15	53 ± 17	52 ± 10	57 ± 16	0.700
FVC, % predicted	50 ± 14	48 ± 14	46 ± 7	54 ± 17	0.547
FEV_1/FVC ratio	0.97 ± 0.13	1.09 ± 0.08	0.95 ± 0.09	0.85 ± 0.07	< 0.001
DL_{CO}, % predicted	36 ± 13	50 ± 12	34 ± 7	27 ± 4	0.003
PASP, mmHg	44.2 ± 14.7	44.3 ± 11.6	42.8 ± 17.1	45.6 ± 14.6	0.821
6MWD, m	407 ± 97	422 ± 82	415 ± 118	387 ± 92	0.498
Hypertension	12 (26.7)	5 (33.3)	2 (13.3)	5 (33.3)	1.000
Diabetes mellitus	5 (11.1)	2 (13.3)	1 (6.7)	2 (13.3)	1.000
Osteopenia	2 (5.0)	-	-	2 (13.3)	0.108
Former smoker	18 (40.0)	6 (40.0)	2 (13.3)	10 (66.7)	0.140
Smoking, years	20 [9-31]	13 [8-21]	5 [1-5]	30 [18-38]	0.060

[a]Data presented as n (%), mean ± SD, or median [IQR]. PASP: pulmonary artery systolic pressure; and 6MWD: six-minute walk distance.

Table 2. Exercise performance and dyspnea before and after pulmonary rehabilitation in the study participants (N = 45), by oxygen flow rate.[a]

Variable	Before PR	After PR	p
0 L/min			
6MWD, m	422 ± 82	483 ± 78	< 0.001
HR, bpm	125 ± 21	126 ± 15	0.987
SpO_2, %	80 ± 6	82 ± 6	0.586
Dyspnea, modified Borg scale score	4 ± 2	3 ± 1	0.002
Leg fatigue, modified Borg scale score	3 ± 3	1 ± 1	0.004
1-3 L/min			
6MWD, m	415 ± 118	473 ± 80	0.014
HR, bpm	121 ± 18	121 ± 19	10.000
SpO_2, %	80 ± 12	84 ± 5	0.264
Dyspnea, modified Borg scale score	4 ± 3	3 ± 1	0.267
Leg fatigue, modified Borg scale score	2 ± 2	2 ± 3	0.695
4-5 L/min			
6MWD, m	386 ± 92	421 ± 99	0.031
HR, bpm	123 ± 22	139 ± 20	0.014
SpO_2, %	81 ± 8	79 ± 7	0.368
Dyspnea, modified Borg scale score	4 ± 3	4 ± 2	0.578
Leg fatigue, modified Borg scale score	2 ± 2	2 ± 1	0.325

[a]Data presented as mean ± SD. PR: pulmonary rehabilitation; and 6MWD: six-minute walk distance.

Table 3. Health-related quality of life before and after pulmonary rehabilitation in the study participants (N = 45), by oxygen flow rate.[a]

Variable	Before PR	After PR	p
0 L/min			
Physical functioning	30 [16.2-40]	37.5 [30-68.7]	0.018
Role-physical	25 [0-68.7]	12.5 [0-93.7]	0.762
Bodily pain	52 [71-51]	62.5 [43.5-96]	0.476
General health	44.5 [31.7-69.5]	47 [17.5-75.7]	0.724
Vitality	47.5 [40-62.5]	55 [41.2-68.7]	0.373
Social functioning	75 [62.5-96.7]	75 [53.2-87.3]	0.765
Role-emotional	66 [8.2-66.9]	83.3 [33-100]	0.291
Mental health	72 [52-87]	76 [69-92]	0.306
1-3 L/min			
Physical functioning	35 [20-45]	52.5 [33.7-72.5]	0.021
Role-physical	12.5 [0-50]	62.5 [0-81.2]	0.016
Bodily pain	67 [58.5-90]	64 [50.7-85.5]	0.541
General health	54.5 [35.7-77]	52 [37-65.7]	0.929
Vitality	75 [47.5-76.2]	70 [55-85]	0.092
Social functioning	62.7 [21.8-78.2]	81.2 [50-100]	0.044
Role-emotional	16.5 [0-100]	66.6 [33-100]	0.109
Mental health	84 [67-92]	84 [75-92]	0.046
4-5 L/min			
Physical functioning	12.5 [6.25-32.5]	25 [10-40]	0.024
Role-physical	0 [0-0]	25 [0-50]	0.040
Bodily pain	71 [52-100]	60 [41-71]	0.407
General health	45 [30-60]	65 [42-77]	0.013
Vitality	55 [25-80]	70 [25-90]	0.261
Social functioning	62.5 [50-100]	75 [62.5-87.5]	0.683
Role-emotional	0 [0-33]	33.3 [0-33.3]	0.171
Mental health	80 [56-88]	72 [56-84]	0.423

[a]Data presented as median [IQR]. PR: pulmonary rehabilitation.

supplemental oxygen vs. compressed air during a test performed on a cycle ergometer, with patients showing better exercise tolerance, improved saturation, and improved dyspnea.

Regarding HRQoL, SF-36 physical functioning domain scores improved in all three groups in the present study. This improvement is related to improved functional capacity as assessed by the 6MWT. However, the groups of patients receiving ambulatory oxygen therapy also had improvements in other SF-36 domains, including social functioning (in those who received an oxygen flow rate of 1-3 L/min), mental health (in those who received an oxygen flow rate of 1-3 L/min), and general health (in those who received an oxygen flow rate of 4-5 L/min). It is of note that, despite worse initial lung function, the group of patients receiving higher oxygen flow rates had improvements in physical aspects of HRQoL and in perceived general health. PR itself has been reported to have positive effects on HRQoL.[20] In a study of patients with interstitial lung disease, long-term oxygen therapy was found to improve HRQoL, with improvements in five SF-36 domains.[9] However, the results of the aforementioned study[9] were not reproduced in a study by Sharp et al.[24] Neither study investigated the use of oxygen therapy during exercise.[9,24]

Our study has limitations. Because of the single-center quasi-experimental design and the small sample size, the study is prone to the effects of confounding factors and to type II errors. In addition, we found significant differences among the groups regarding baseline lung function and DL_{CO}, which could have influenced our results.

Improving quality of life is clinically significant because physical activity improves functional capacity and has an impact on the decline in lung function. The results of the present study show that the combined use of ambulatory oxygen therapy and PR in lung transplant candidates with IPF and significant exertional hypoxemia increases functional capacity and HRQoL.

AUTHOR CONTRIBUTIONS

AM, RDMP, SA, and GW: conceptualization; methodology; investigation; data curation; and drafting of the manuscript. GMH, EC, JF, and SCM: investigation; data curation; drafting of the manuscript; and reviewing and editing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Migration and medical screening for tuberculosis

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ABSTRACT

Vulnerable populations, such as migrants and refugees, have an increased risk of tuberculosis disease, especially in the first years after arrival in the host country. The presence of migrants and refugees in Brazil exponentially grew over the period between 2011 and 2020, and approximately 1.3 million migrants from the Global South were estimated to be residing in Brazil, most of whom from Venezuela and Haiti. Tuberculosis control programs for migrants can be divided into pre- and post-migration screening strategies. Pre-migration screening aims to identify cases of tuberculosis infection (TBI) and can be carried out in the country of origin (pre-entry) or in the destination country (at entry). Pre-migration screening can also detect migrants at an increased risk of developing tuberculosis in the future. High-risk migrants are then followed up in post-migration screening. In Brazil, migrants are considered a priority group for the active search for tuberculosis cases. However, there is no recommendation or plan regarding screening for TBI in migrants and refugees. Ensuring prevention, diagnosis, and treatment for TBI and tuberculosis disease in migrant populations is an important aspect of tuberculosis control and elimination. In this review article, we address epidemiological aspects and access to health care for migrants in Brazil. In addition, the migration medical screening for tuberculosis was reviewed.

Keywords: Tuberculosis/diagnosis; Tuberculosis/therapy; Tuberculosis/prevention & control; Transients and migrants.

INTRODUCTION

Tuberculosis is a major public health concern in many countries, and remains a top killer worldwide.[1] Vulnerable population, such as migrants and refugees, have an increased risk of developing tuberculosis, especially in the first years after arrival in the host country.[2-5] The tuberculosis incidence rate in the country of origin usually influences the risk of tuberculosis infection (TBI) and tuberculosis disease (TBD), although tuberculosis may be equally or more prevalent in the destination country.[6-8] However, social and behavioral determinants on arrival, such as discrimination and economic adversity, can contribute to the increase in the risk of tuberculosis during the migration process.[3,9] Ensuring prevention, diagnosis, and treatment for TBI and TBD in migrant populations is an important aspect of tuberculosis control and elimination.[10,11] In this review article, we address epidemiological aspects and access to health care for migrants in Brazil. In addition, the migration medical screening for tuberculosis was reviewed.

EPIDEMIOLOGY

The presence of migrants and refugees exponentially grew over the period between 2011 and 2020 in Brazil. In that decade, there was the arrival of new migratory flows coming from different regions of the Global South, and, in recent years, there has been the consolidation of Latin American immigrants, mostly Haitians and Venezuelans, who made up the main nationalities in the country.[12]

The consolidation of Brazil as an emerging power, member of the BRICS (Brazil, Russia, India, China, and South Africa) and organizer of major world events (2014 World Cup and 2016 Olympics), as well as the appreciation of the national currency against the dollar and low unemployment rates, were determining factors for the international image of the country as a place of opportunities and made the migratory networks of the Global South begin to strengthen towards Brazil. Thus, migrants from different origins from the Global South, such as Haitians, Senegalese, Congolese, Guineans, Bengalis, Ghanaians, Pakistanis, among others, began to arrive at Brazilian borders.[13]

Some events have accelerated migration flows to Brazil, as is the case of the two main nationalities in the country today, Haitians and Venezuelans. The flow of Haitian immigration to Brazil began after the earthquake in Haiti on January 12, 2010, and the consequent humanitarian crises. Also, in 2012, hurricanes Isaac and Sandy hit the country, destroying its agricultural production. On the other hand, the economic and social crisis in Venezuela,

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starting in the middle of that decade, intensified the Venezuelan flow to Brazil, especially after 2016.[12]

According to data from the Brazilian demographic census, there were 592,570 migrants residing in Brazil on July 31, 2010, and the two main nationalities were Portuguese and Japanese. Among the twenty most important nationalities, there were eight other nationalities from countries in the northern hemisphere (Italy, Spain, the USA, Germany, France, South Korea, Scotland, and Poland). Between 2011 and 2020, it was estimated that approximately 1.3 million migrants were residing in Brazil, most of whom were Venezuelans and Haitians. In that period, among the top ten countries of birth of migrants, only the USA and France are located in the Global North.[12]

With regard to refugees, at the end of 2020, 4.6 million people having a refugee status were living in the Americas. Venezuelans (73.7%), Haitians (18.6%), and Cubans (5.6%) together represented 97.9% of the total requests over the last decade.[12]

The number of new cases of tuberculosis in migrants in Brazil in the years 2018, 2019, 2020, 2021, and 2022 was 568, 543, 477, 452, and 422, respectively. Of the total number of tuberculosis cases, 0.6% occurred in migrants; higher rates were found in Roraima (19.83%), the Federal District (3.87%), Santa Catarina (1.30%), and São Paulo (1.12%). Most migrants with tuberculosis were men older than > 15 years of age. About 4-5% of cases occurred in the 0-14 age group. The most common form was pulmonary tuberculosis (in 81.2%), followed by extrapulmonary tuberculosis (in 13.3%) and pulmonary plus extrapulmonary tuberculosis (in 5.5%).[14]

ACCESS TO HEALTH

Migrants/refugees have intrinsic vulnerabilities that can lead to inequalities in access to health. Some of the main barriers to migrants' access to health are: cultural differences, socioeconomic status, language difficulties, lack of documentation, lack of medical history, social isolation, lack of information about access to health care, racism, and xenophobia.[15,16] In addition, they may encounter restrictions on the care of foreigners in the local public health care system.[16]

Brazilian legislation is in line with the recommendations of international agencies regarding access to health of migrants and refugees. Law 8,666/1990 regulates the *Sistema Único de Saúde* (SUS, Brazilian Unified Health System), and Law 13,445/2018 regulates migration in the country guaranteeing the right to health for migrants in Brazilian territory regardless of their migratory status. In fact, because Brazil is the only country in South America with a free, universal public health system, and various migrants enter the country for health treatments. However, there is no specific public policy for migrants, with the exception of the municipal law 16,478/2016, which establishes a health policy for the migrant population in the city of São Paulo.[17] Even so, due to family health care programs, community agent programs, and the universal nature of the SUS, migrants end up receiving medical assistance in some cases such as tuberculosis.[12]

A study with Haitian migrants in Brazil showed that the main difficulties encountered in accessing health care were the language barrier, cultural issues (conflicts with traditional Haitian medicine), problems with schedules (need to miss work to seek care), and delay in care.[15] Other obstacles encountered by migrants were episodes of non-attendance at emergency services, lack of medication, or lack of information on how to obtain them.[18] On the other hand, health care teams also face challenges in caring for migrants, such as difficulties with the migrant language and location of patients due to their frequent change of residence or fear of revealing their address in the case of refugees.[15,19]

MIGRATION MEDICAL SCREENING FOR TUBERCULOSIS

The WHO recommends the use of chest X-ray (CXR) for tuberculosis screening among migrants from countries with a high tuberculosis incidence and the use of tuberculin skin test (TST) or IFN-γ release assays (IGRA) for TBI screening.[20-22] Systematic screening of migrants using CXR at arrival in the destination country and that of migrants from settings with a tuberculosis high burden using TST and/or IGRA have been suggested by the European Centre for Disease Prevention and Control.[23] In Brazil, since 2015, data on tuberculosis in migrants have been inserted into the *Sistema de Informação de Agravos de Notificação* (Brazilian Case Registry Database). According to the Brazilian Ministry of Health, migrants are considered a priority group for the active search for tuberculosis cases, and tuberculosis should be investigated in migrants with a cough of any duration.[24] However, there is no recommendation or plan regarding screening for TBI in migrants and refugees.

Tuberculosis control programs for migrants can be divided into pre-migration and post-migration screening strategies.[25,26] Pre-migration screening aims to identify cases of TBI and can be carried out in the country of origin (pre-entry) or in the destination country (at entry). This screening usually includes symptom assessment, CXR, and sputum smear and/or culture.[6,27-29] Pre-migration screening can also detect migrants at an increased risk of developing tuberculosis in the future. Pre-entry or at-entry TBI screening is important since between 3% and 30% have already been infected before entry.[30] One study in the Netherlands showed a prevalence of TBI of 20% among migrants.[31] In Brazil, the proportion of TBI among migrants varies between 23.5% and 46.1%, depending on the study location.[32] In fact, the first 2-5 years after arrival in the destination country is the period with the highest risk of developing TBD, which justifies pre-entry or at-entry tuberculosis preventive treatment in many cases.[6,23,33,34]

Migrants with CXR abnormalities, history of tuberculosis (treated or not), or history of a close contact

with a patient with TBI identified during pre-migration screening are considered to be high-risk migrants and are then followed up in post-migration screening.[25]

Systematic screening for tuberculosis is recommended in several countries; however, procedures vary from country to country. In a study conducted in 2016,[35] 36 national tuberculosis programs, representative of European countries with low and intermediate tuberculosis incidence, completed a questionnaire about screening and management practices among refugees. Among these, 31 (86.1%) and 19 (52.8%) reported screening for TBD and TBI, respectively. In another recent study,[27] a survey was conducted involving 1,055 respondents from 80 countries and territories. The participants agreed with regard to tuberculosis surveillance and infection control practices. However, they disagreed about diagnosis and management of TBD and TBI, especially with regard to which TBI regimens and indications for hospitalization should be adopted.

TUBERCULOSIS SCREENING PLAN FOR MIGRANTS/REFUGEES SUGGESTED FOR USE IN BRAZIL

Chart 1 lists the main items to be observed for the development of a TBD/TBI screening plan for migrants, adapted for use in Brazil. This list is based on recommendations from the European Respiratory Society and the European Region of the International Union Against Tuberculosis and Lung Disease.[10] Figure 1 shows a flow chart suggesting how to evaluate TBD/TBI in migrants/refugees.

There is a consensus that ensuring access to health care services and health education, as well as providing culturally appropriate tuberculosis services, are key components of TBD and TBI screening programs for migrants and refugees.[23,33,36] In this sense, a group of researchers in Brazil developed an educational booklet as a tool to support prevention and treatment of tuberculosis for migrants and refugees, under the auspices of the Pan American Health Organization. The purpose of the booklet is to facilitate knowledge about ways to prevent and treat tuberculosis using simple language and being accessible to adults and children. The material was prepared in three languages: Portuguese, Spanish, and Warao (language of an indigenous people in Venezuela) and was distributed in four Brazilian cities.[37]

RESEARCH QUESTIONS

In addition to implementing a screening plan for tuberculosis for migrants, it is important to promote research on migration-related issues.[9] Chart 2 shows suggestions for research questions regarding TBD and TBI in migrants/refugees.

FINAL CONSIDERATIONS

The increasing population of migrants and refugees in Brazil has required effective prevention, diagnosis, and treatment of TBI and TBD, particularly during the COVID-19 pandemic and in the post-pandemic phase.[38] The WHO recommends systematic screening of migrants originated from settings with a high burden

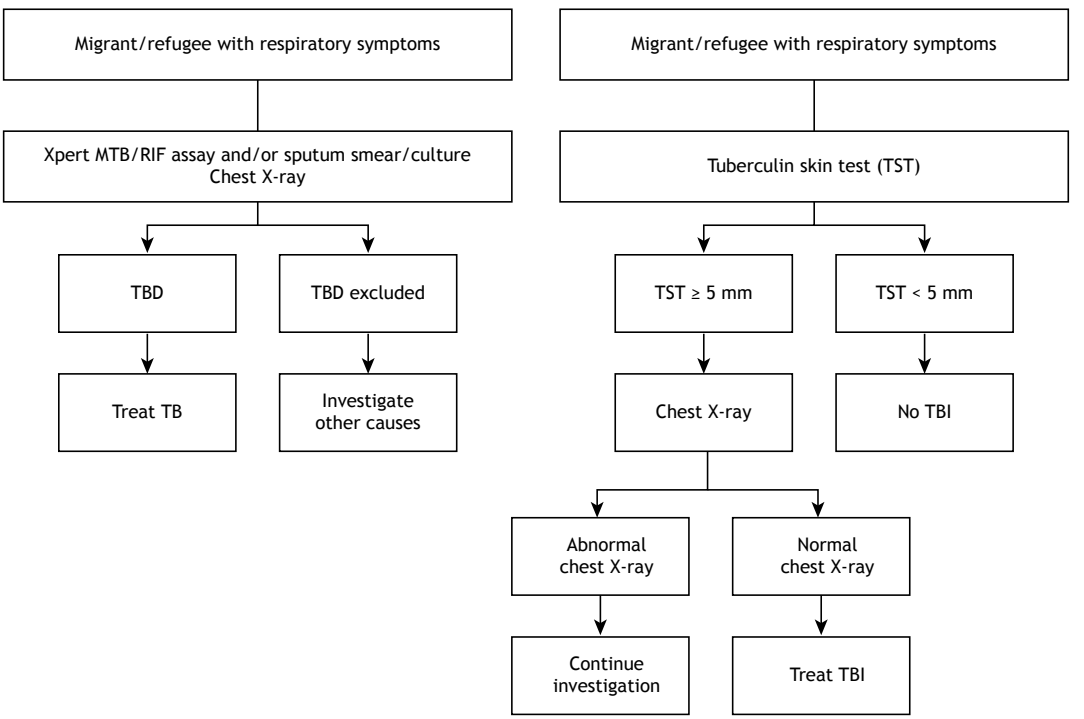

Figure 1. Flow chart suggesting how to evaluate tuberculosis infection and tuberculosis disease in migrants/refugees. TB: tuberculosis; TBD: tuberculosis disease; and TBI: tuberculosis infection.

Chart 1. Tuberculosis screening plan for migrants/refugees, adapted for use in Brazil.

• Adapt the guidelines of the "Manual of Recommendations for Control of Tuberculosis in Brazil"[24] for migrants/refugees to ensure adequate tuberculosis prevention, diagnosis, and treatment
• Ensure screening for TBD among migrants/refugees coming from countries with middle or high tuberculosis incidence
• Ensure post-migration screening for high-risk migrants
• Promote universal access to TBD/TBI services
• Provide culturally appropriate TBD/TBI services
• Provide surveillance, monitoring, and evaluation of TBD/TBI services for migrants/refugees
• Ensure health education in TBD/TBI
• Provide operational research in prevention, diagnosis, and treatment for TBD/TBI

TBD: tuberculosis disease; and TBI: tuberculosis infection.

Chart 2. Suggestions of research questions regarding tuberculosis disease and tuberculosis infection in migrants/refugees.

• TBI prevalence in different migrant risk groups
• Comparison between TBI and TBD registry data to determine reactivation rates
• Risk factors for TBD and TBI
• Transmission dynamics (migrant-to-migrant and migrant-to-native population)
• Risk factors for poor outcomes
• Barriers to accessing health care services
• Reasons for non-adherence to treatment
• Identification of socioeconomic vulnerabilities
• Feasibility of TBI testing and treatment (pre- and post-migration)

TBD: tuberculosis disease; and TBI: tuberculosis infection.

of tuberculosis. Pre-migration screening must be integrated into post-migration follow-up of high-risk migrants to ensure adequate tuberculosis control.

AUTHOR CONTRIBUTIONS

DRS: conceptualization, methodology, project administration, and drafting of the manuscript. FCQM, FDCJ, RC, and LD: conceptualization, methodology, and drafting and revision of the manuscript. GBM: conceptualization, methodology, and drafting of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Update on pulmonary arteriovenous malformations

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ABSTRACT

This review aimed to provide an overview of pulmonary arteriovenous malformations, including the major clinical and radiological presentations, investigation, and treatment algorithm of the condition. The primary etiology of pulmonary arteriovenous malformations is hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, with mutations in the *ENG* gene on chromosome 9 (HHT type 1) or in the *ACVRL1/ALK1* complex (HHT type 2). Epistaxis should always be evaluated when repeated, when associated with anemia, and in some cases of hypoxemia. In the investigation, contrast echocardiography and chest CT are essential for evaluating this condition. Embolization is the best treatment choice, especially for correction in cases of hypoxemia or to avoid systemic infections. Finally, disease management was addressed in special conditions such as pregnancy. CT follow-up should be performed every 3-5 years, depending on the size of the afferent and efferent vessels, and antibiotic prophylactic care should always be oriented. Ultimately, knowledge of the disease by health professionals is a crucial point for the early diagnosis of these patients in clinical practice, which can potentially modify the natural course of the disease.

Keywords: Telangiectasia, hereditary hemorrhagic; Arteriovenous malformations; Lung.

INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are abnormal communications between the pulmonary artery and veins.[1] These alterations can be related to hereditary diseases, such as hereditary hemorrhagic telangiectasia (HHT, also known as Osler-Weber-Rendu syndrome),[2,3] or be classified as idiopathic if no specific etiology is discovered.[1] There are different clinical presentations, such as hypoxemia, hemorrhages, and complications from distant embolization, including stroke and brain abscesses.[4]

PAVM was first described in 1864 by the British pathologist Henry Gawen Sutton.[5] Subsequently, Benjamin Guy Babington published a series of cases of epistaxis occurring in five generations of the same family.[6] In 1896, epistaxis was distinguished from hemophilia by the French doctor Henri Jules Louis Marie Rendu,[7] who reported the presence of skin lesions in a patient's mother and brother. Five years later, William Osler established that that was a hereditary disease, describing three cases of individuals with epistaxis and skin lesions and making it clear that it was not related to hemophilia.[8] In 1907, Frederick Parkes Weber described a series of cases after noticing lesions on the fingers and under the nails that were similar to those described by Osler and invited him to see his patients.[9] In 1909, Hanes coined the term HHT; however, the eponym Rendu-Osler-Weber is still widely known and accepted.[6,10]

The prevalence of PAVMs in the general population remains unclear. In a study performed using thoracic CT for lung cancer screening, it was estimated that the detection rate of PAVMs by CT was 0.038%, with a prevalence of 38 per 100,000 population, that is, 1 case in 2,600 individuals.[11] Usually, pulmonary fistulas are characterized by their anatomy; approximately 85% are simple, directly connecting an artery to the pulmonary vein.[12] Some patients could have a complex fistula with multiple arterial feeder vessels that connect with more than one pulmonary segment. In a small proportion of cases, pulmonary fistulas may be multiple, with widespread involvement of lung segments. In more rare cases, microscopic lesions are usually suspected in patients with hypoxemia, as revealed by an echocardiogram with bubbles suggestive of an intrapulmonary shunt and by the absence of CT findings of PAVMs.[13] Treatment becomes more difficult in patients with multiple complex fistulas, especially with microscopic lesions.

PAVM rupture is a rare complication, except in pregnancy, which can be responsible for up to 1% of cases among women with PAVMs.[4] The treatment of PAVMs was proposed more than 60 years ago; even in patients without many symptoms, intervention should be considered to avoid the risks of serious and potentially fatal complications.[14] Furthermore, the evolution of treatment using percutaneous techniques has decreased the risks of postoperative complications inherent to lobectomy, the length of hospital stay has become shorter, and

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more patients can be treated, even in some situations during pregnancy.[15]

This review aimed to provide an overview of this rare but potentially fatal disease. Clinical presentation findings can help identify these patients, and available diagnostic tools can be used. This study focused on familiarizing more health professionals, especially pulmonologists, with the early identification of cases of PAVMs to reduce the risk of serious or even fatal complications in these patients.

ETIOLOGIES

HHT is an autosomal dominant disorder with a high penetrance and great variability in clinical presentation. Its pathogenesis results from an anomalous sequence in the *ENG* gene on chromosome 9, which produces an endoglin protein, or a mutation in the *ACVRL1/ALK1* gene on chromosome 12.[16] The mutation in the *ENG* gene determines HHT type 1, whereas the mutation in the *ACVRL1/ALK1* gene predisposes to HHT type 2. These mutations result in the dysregulation of the TGF-β pathway, which is responsible for angiogenesis. In the context of tissue inflammation, this dysregulation can alter the vascular endothelium and predispose patients to the formation of fistulous sacs. A third disease-causing mutation has been described in the *SMAD4* gene.[17]

These genotypic alterations imply phenotypic alterations. Patients with HHT type 1 are more likely to have pulmonary and cerebral arteriovenous malformations, whereas patients with HHT type 2 have a higher prevalence of hepatic malformations and pulmonary arterial hypertension (PAH).[18] Nevertheless, a mutation in *SMAD4*, in addition to the characteristic presentation of HHT, could simultaneously cause symptoms such as familial polyposis syndrome.[17] Molecular diagnosis can identify which allele is responsible for HHT, although this is unavailable in clinical practice. In the future, it may be an important tool for the clinical characterization, prognostic analysis, and treatment of these patients.[19]

A first-degree relative of patients with PAVMs and HHT has a 1 in 4 risk of developing PAVM. The risk increases to 1 in 2 if the relative has already been diagnosed with HHT. Currently, three main tests (for *ENG*, *ACVRL1*, and *SMAD4*) are performed for the genetic investigation of HHT. However, other genes still need to be identified. Among these three genes, *ENG* and *SMAD4* are the most prevalent in patients with PAVMs, and a smaller proportion of cases have an impairment in the *ACVRL1/ALK1* gene complex.[20]

In contrast, patients without HHT usually present with a single PAVM of varying etiology, particularly thoracic surgery, trauma, actinomycosis, schistosomiasis, and liver cirrhosis with hepatopulmonary syndrome or hepatocellular carcinoma.[13,20] Another relevant etiology of non-HHT PAVM is the correction of cyanotic congenital heart disease with cavopulmonary anastomosis.[21] The major explanation for this occurrence is the absence of hepatic flow in the pulmonary territory, which induces a reduction in hepatic factors that are responsible for inhibiting the development of pulmonary fistulas.[21]

DIAGNOSIS

Clinical manifestations

Patients with HHT have epistaxis as their main clinical manifestation, usually starting at around 10 years of age and becoming more severe with aging, occurring spontaneously or recurrently.[22] Skin telangiectasias are common and usually multiple, commonly involving the lips, tongue, palate, fingers, face, and conjunctiva.[22] Neurological symptoms such as migraine with aura, brain abscess, seizure, stroke, or transient ischemic attack have been described in these patients and may occur due to the presence of cerebrovascular abnormalities; however, most of these findings are consequences of PAVMs that allow the passage of emboli unfiltered by the pulmonary capillary network to the cerebral circulation.[2]

The clinical manifestations in the gastrointestinal (GI) tract are usually upper or lower digestive tract bleeding, which occurs owing to the presence of arteriovenous malformations, telangiectasias, or angiodysplasias that may occur in the stomach, duodenum, small intestine, or colon. Anemia from chronic blood loss has been described, although uncommon, and may require iron supplementation or multiple blood transfusions.[23] These patients may present with abdominal pain due to mesenteric ischemia caused by stealing blood flow from the hepatic artery to the hepatic or portal veins.[24] GI arteriovenous fistulas promote communication between the hepatic artery and the portal vein, increasing the blood flow and causing portal hypertension and hepatic encephalopathy. Liver involvement occurs in 40-75% of patients, but most of these liver malformations are minor with no clinical repercussions.[2] Among hepatic impairments, the most common are hepatic arteriovenous malformations, which manifest as high-output heart failure through the left-to-right shunt.[22]

In the initial investigation of brain arteriovenous malformation, MRI should be performed. Liver malformations could be investigated at diagnosis using Doppler ultrasound, multiphase contrast CT, or contrast abdominal MRI.[25]

Cyanosis and digital clubbing may be present in hypoxemic patients with PAVMs; cyanosis is often masked by anemia, and the severity of digital clubbing does not appear to be predictable unless the right-to-left shunt is severe.[2] Patients with PAVMs occasionally present with orthodeoxia due to the basal predominance of arteriovenous malformations, but it is usually asymptomatic. Platypnea (dyspnea when one is upright) is uncommon.[26]

PAVM is the major pulmonary manifestation of HHT[13] and is present in 50% of these patients.[27] PAVMs are characterized by an artery connected directly to a vein

by aberrant communication, with saccular or fistulous connections. In most cases, the afferent artery is a branch of the pulmonary artery, and the efferent vein is a branch of the pulmonary vein, with rare cases involving branches of the systemic circulation responsible for the nutrition or drainage of the arteriovenous fistula.[13] These alterations are usually congenital and do not change in size in adulthood, except in the presence of pulmonary hemodynamic changes, such as puberty or pregnancy.[13] There is a predominance in women, and the most prevalent location of PAVMs is the lower lobes in patients with and without HHT.[28]

Most PAVMs are asymptomatic, but their presence can result in serious complications, especially if the artery diameter is > 3 mm.[12,29] The right-to-left shunt allows the occurrence of paradoxical embolic events that can lead to stroke, acute myocardial infarction, and brain or peripheral abscesses.[12,30] These events occur due to the loss of the filtering function of the capillary network and depend on the area and number of pulmonary fistulas.[12]

Other respiratory manifestations in individuals with HHT include hemoptysis or hemothorax, pulmonary thromboembolism, and pulmonary hypertension (PH). Hemoptysis and hemothorax can occur in cases of wall necrosis and fistula rupture.[2] In the presence of hemoptysis without PAVMs, bronchial telangiectasias should be suspected.[12] Despite the high risk of bleeding, these patients have an increased prevalence of pulmonary thromboembolism, especially in the presence of low iron levels and high factor VIII levels.[24]

Diagnostic criteria for HHT

Rendu-Osler-Weber syndrome, or HHT, can be diagnosed using a probability score defined and presented in 2000 by the Scientific Advisory Board of the HHT Foundation International, designated the Curaçao criteria.[31] These criteria facilitate the recognition of clinical findings that are less common than epistaxis, which is the main manifestation of the disease in affected individuals,[23] and allow early recognition in individuals with less classic but potentially serious manifestations, such as PAVMs.

Based on those criteria,[31] the diagnosis can be definitive (when three criteria are present); possible, (if two criteria are present); or suspected (if less than two criteria are present). The criteria are as follows: 1) presence of epistaxis (spontaneous and on more than one occasion); 2) presence of visceral lesions (GI telangiectasia, or pulmonary, hepatic, cerebral, or spinal vascular malformation); 3) presence of mucocutaneous telangiectasia in a typical location; and 4) first-degree family history (or presence of the genetic mutation). In families with individuals with HHT, the diagnosis can be made from the findings of two sites with visceral lesions.[31] These criteria have a positive predictive value of 100% and a negative predictive value of 97% in comparison with genetic testing.[32]

Despite the genetic knowledge of the molecular pathways damaged to generate the disease, there is great heterogeneity in the locus of these genes, which makes it difficult for the diagnosis to be established by molecular criteria in the general population, although they may be useful in individuals with possible/suspicious diagnosis.[31]

COMPLEMENTARY EXAMINATIONS

Transthoracic contrast echocardiography

Transthoracic contrast echocardiography (TTCE) is an important diagnostic modality. It is considered positive if bubbles are detected in the left atrium after the infusion of saline solution with microbubbles in the peripheral vein.[33] The passage of bubbles after the third beat suggests PAVMs, differently from intracardiac shunts. In this case, the test is considered positive when the passage occurs up to the third beat. Also, healthy people may have some degree of shunting.[25]

TTCE can predict the size of and need for therapeutic intervention for PAVMs.[12] In addition, the risk of cerebrovascular events can be evaluated based on the estimated pulmonary shunt calculation, in which the finding of 30 microbubbles on the TTCE is not related to the increased prevalence of central nervous system events, whereas that of more than 100 microbubbles is a strong independent predictor of brain abscess and cerebrovascular events.[12,13,34] Finally, TTCE performed using infused saline with microbubbles is capable of diagnosing microscopic lesions when there is a positive finding of shunt on the test but an absence of arteriovenous fistulas on CT of the chest and abdomen.[12]

Chest radiography

Chest radiography is simple and easy and results in low radiation exposure. However, there is low sensitivity for identifying small PAVMs.[35] The most common finding on chest radiography is a pulmonary nodule.[36] Nevertheless, when the fistulous sac is large, it can be confused with a pulmonary mass (Figure 1). Chest radiography may be useful for follow-up.

Chest CT

The presence of chest CT radiological findings consistent with PAVMs is the gold standard for the diagnosis of these malformations.[20] The most common radiological presentation is the presence of well-defined peripheral nodules. The use of intravenous contrast is not mandatory, but it can allow better definition of PAVM angioarchitecture to plan endovascular therapy.[12] Differential diagnoses of PAVMs (Chart 1) based on radiological findings are true pulmonary artery aneurysms or true aneurysms secondary to syphilis, connective tissue diseases, Behçet's disease, Takayasu's arteritis, chronic thromboembolic pulmonary hypertension, idiopathic PH, or hepatopulmonary syndrome; false aneurysms secondary to tuberculosis,

or septic embolism; and even nonvascular changes such as bronchocele or tumors.[36]

Morphological classification is based on radiological findings from chest CT or angiography and is relevant in planning endovascular interventions.[12,20] Simple PAVMs are those in which only one supplying artery is connected to one or more of the draining veins. Complex PAVMs are lesions in which two or more supplying arteries are connected to multiple drainage veins by a septate aneurysmal sac. The latter are rarer, corresponding to 20% of the cases. Complex PAVMs radiologically present as ground-glass areas connected by nourishing and draining vessels.[13] Diffuse fistulas are characterized by the involvement of an entire lung segment and may even affect the entire lung.[37]

Other examinations

Chest magnetic resonance angiography is an accurate method for detecting PAVMs and analyzing fistula patency, which are important in embolization therapy planning.[38]

Despite not being routinely used for the diagnosis of pulmonary arteriovenous fistulas (sensitivity = 60%), catheter angiography can be used for therapeutic programming because of its accurate assessment of the distribution of nourishing and drainage vessels of the PAVM.[13] Angiography is also relevant for guiding embolization.

Screening for PAVMs should be performed for all individuals older than 16 years of age with a suspected or established diagnosis of HHT. Chest radiography cannot exclude the presence of PAVM, even in asymptomatic patients with normal oxygen saturation, since it has a low sensitivity for detecting small PAVMs.[20] However, chest radiography can sometimes reveal alterations.

The use of TTCE for screening is not a consensus in the literature.[13,20] It is a safe and noninvasive test with a low rate of false negatives and high sensitivity[13]; however, it is operator-dependent and not available in all centers.[20] In specialized services, it is recommended that TTCE be a part of the screening algorithm (Figure 2). Chest CT can exclude pulmonary fistulas in the absence of compatible radiological findings. Repeat chest CT is

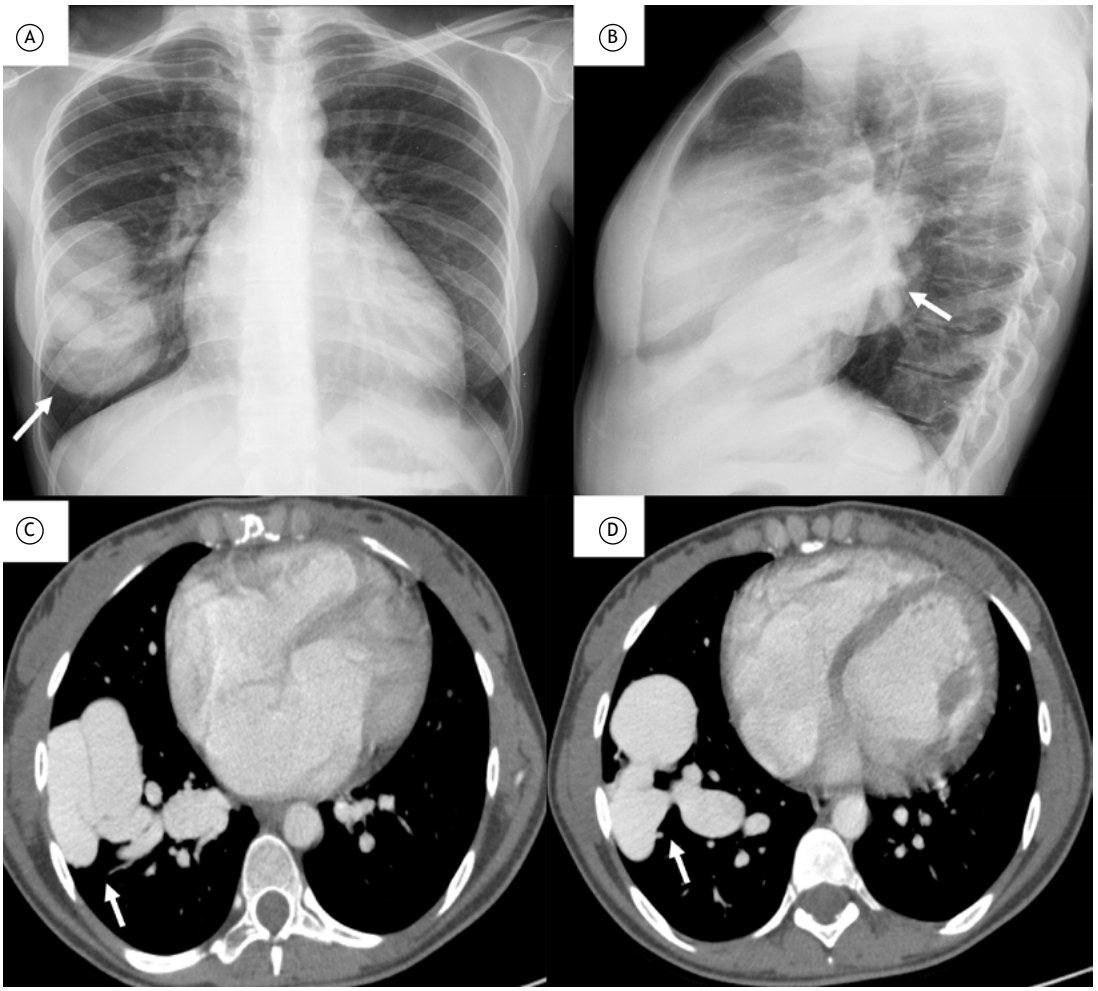


Figure 1. In A and B, chest radiographs showing a large pulmonary arteriovenous malformation/fistulous sac (white arrows). In C and D, CT scans demonstrating a large arteriovenous malformation (white arrow).

Chart 1. Differential diagnoses.

Vascular		
Pulmonary aneurysmal disease	True aneurysms	Idiopathic Secondary to syphilis; connective tissue diseases; Behçet's disease; Takayasu's arteritis; CTEPH; IPH; hepatopulmonary syndrome
	False aneurysms	Secondary to tuberculosis; pneumonia; septic emboli; connective tissue diseases
Pulmonary varices	Congenital	
	Acquired	Associated with mitral valve disease Secondary to chronic tuberculosis or sarcoidosis
Pulmonary artery collaterals	Associated with IPH and CTEPH	
Nonvascular		
Bronchocele	Congenital Acquired	Congenital bronchial atresia Foreign body; endobronchial tumor; bronchiectasis of any cause
Tumors	Primary carcinoid Metastases	

Adapted from Boussel et al.[38] CTEPH: chronic thromboembolic pulmonary hypertension; and IPH: idiopathic pulmonary hypertension.

not routinely indicated due to high radiation exposure, and screening with TTCE is recommended every 5-10 years, or after pregnancy, which can increase the risk of PAVM rupture.[12] An investigation algorithm option may be through SpO_2 in a patient with suspected or confirmed HHT. When SpO_2 > 95%, we should start with TTCE; if positive, perform chest CT. When SpO_2 ≤ 95%, the initial option is chest CT, which may or may not confirm the presence of PAVMs (Figure 2).

TREATMENT MANAGEMENT

Epistaxis and GI bleeding

Epistaxis is the main symptom presented by patients with HHT, and it is also very impacting on daily activities of patients with the disease. This results in social isolation and difficulties in work and travel.[39] Initial treatment recommends the use of medications that promote humidification of the nasal mucosa.[33] Another alternative is surgical treatment.[33] However, the Second International Guidelines for the Diagnosis and Management of HHT[25] propose the use of systemic medications to reduce bleeding. In 2014, two randomized clinical trials[40,41] demonstrated the benefits of tranexamic acid, which is an oral antifibrinolytic agent that has been shown to reduce nosebleeds, although it does not increase hemoglobin levels. Thus, tranexamic acid has become the first choice when the use of other medications is unable to control the bleeding.[42]

Recently, animal models have shown that VEGF leads to telangiectasias and arteriovenous malformations, and the normalization of its levels inhibits the formation of abnormal vascular structures.[43] These findings have stimulated the development of systemic antiangiogenic agents that directly or indirectly inhibit VEGF to treat epistaxis and GI bleeding in HHT. Two drugs with potential use in patients are bevacizumab (Avastin; Genentech, San Francisco, CA, USA) and thalidomide (Thalomid; Celgene, Summit, NJ, USA).[44] The latter has immunomodulatory effects and potentially inhibits VEGF; some adverse effects, such as neuropathy, have limited its long-term use.[45] Bevacizumab exhibits antiangiogenic action, showing the greatest potential for the treatment of HHT. With promising results and low adverse event rates, bevacizumab has the potential to treat both epistaxis and GI bleeding. Argon plasma coagulation could also be a therapeutic option in emergencies for this type of bleeding.[42]

Iron deficiency and anemia

Iron replacement therapy is recommended when there is deficiency, as well as in situations where there is impairment in iron absorption, such as in inflammatory bowel disease. Iron levels should be monitored after the initiation of oral therapy. After normalization, this therapy must be discontinued.[20]

PAVM embolization

Embolization is the standard of care for PAVMs,[12,46] with substantial improvement in oxygenation and reduction in the risk of embolic events.[3,47] When all arteries are obliterated, the sac regresses within 6 months after the procedure. However, if not all supplying arteries are embolized, the fistulous sac may not regress, indicating the possibility of recanalization.[48,49]

Persistence of blood flow after embolization is present in up to 25% of cases, and this can occur by recanalization or reperfusion.[12] In the former, flow occurs through an already embolized fistula. Although controversial, it is believed that the risk of complications is lower in this situation, which is present in 88-91% of cases.[50,51] In the latter, there is rupture of an accessory artery. In both situations, the preferred treatment is new embolization. The results were better for recanalization than for reperfusion.[50]

Ideally, embolization should be performed before any complications due to the presence of fistulas.[37]

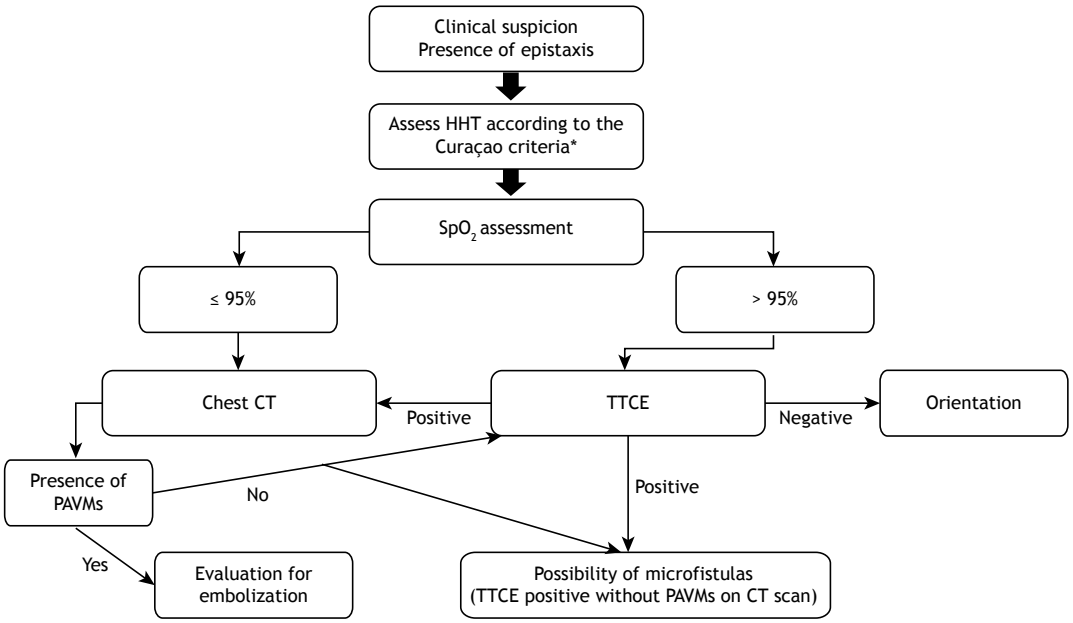


Figure 2. Investigation algorithm. HHT: hereditary hemorrhagic telangiectasia; PAVMs: pulmonary arteriovenous malformations; and TTCE: transthoracic contrast echocardiography. Adapted from Saboo et al.[13] *Shovlin et al.[31]

Several devices are available, such as fibered steel coils (Figure 3), fibered platinum coils (Nester embolization coils), fibered microcoils, hydrophilic coils, and self-expandable nitinol plugs (Amplatzer vascular plugs). The anchoring technique is used for coils and consists of locking the spring within a small collateral branch of the main supply artery immediately upstream of the arteriovenous malformation, allowing for optimal occlusion of the cross-section and preventing further accidental mobilization of the device and distal migration into the left circulation.[35] However, coils cannot be relocated in the event of unsatisfactory deployment on a vessel. In contrast, Amplatzer plugs are anchored in the candidate vessel without the need to occlude adjacent normal vessels (Figure 4).[52] Sometimes, both coils and Amplatzer plugs can be used (Figure 5). One study comparing the use of coils vs. Amplatzer plugs showed that the coils had a higher rate of recanalization.[52]

Surgery

The performance of lobectomy or segmentectomy is restricted to cases with complex or multiple PAVMs when catheter embolization is not possible.[26] Lung transplantation is also performed in selected cases, because the survival of these patients, despite the hypoxemia and infectious risks related to the disease, is greater in many cases than in transplanted individuals.[53]

Anticoagulation and antiplatelet therapy

Although HHT is a bleeding disorder, there is no protection against thromboembolic events.[42] In fact, these patients may have an increased risk of embolic events due to iron deficiency and consequently increased levels of factor VIII.[54,55] According to current guidelines, the use of (prophylactic or therapeutic) anticoagulant medications or antiplatelet agents is rare and recommended when arterial or venous embolic events occur. However, the risk of bleeding should be considered. These medications are tolerated by most patients, and there should not be an absolute contraindication to their use. Furthermore, patients should be closely monitored.[56] One exception is the concomitant use of two antiplatelet medications or the combination of antiplatelets and anticoagulants, which should be avoided.[42]

Antibiotic prophylaxis

Although controversial, some procedures that involve transient bacteremia and the use of prophylactic antibiotics are recommended in the general population. However, prophylactic antibiotic therapy is mandatory in patients with PAVMs.[20,26] Based on recommendations, prophylactic medication should be administered 1-2 h before a dental or surgical procedure, and another dose should be taken after the procedure. Amoxicillin/clavulanic acid is the preferred agent,[57] and metronidazole or clindamycin may be used in patients who cannot receive β-lactams.[58] In other procedures such as endoscopy, prophylactic antibiotics are recommended to avoid brain abscesses.[20] Prophylaxis is recommended if TTCE is positive, even in the absence of CT findings suggestive of PAVM.[59]

General measures

Long-term oxygen therapy is used to improve hypoxemia, especially when the alveolar-capillary membrane is compromised. However, in PAVMs, there is a direct shunt in which the use of oxygen is controversial, and the indication is more based

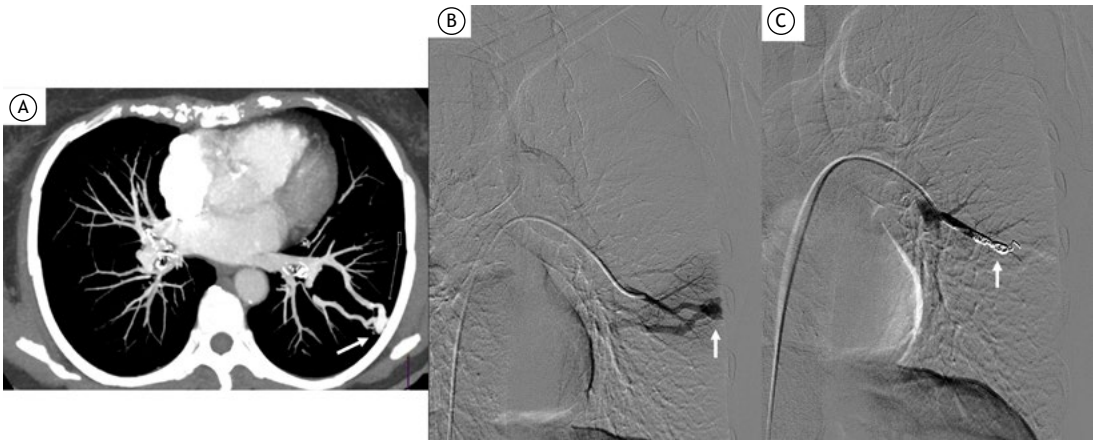


Figure 3. In A, a CT scan demonstrating peripheral pulmonary arteriovenous malformations (white arrow). In B, localization of the malformation by pulmonary angiography (white arrow). In C, embolization with coils (white arrow).

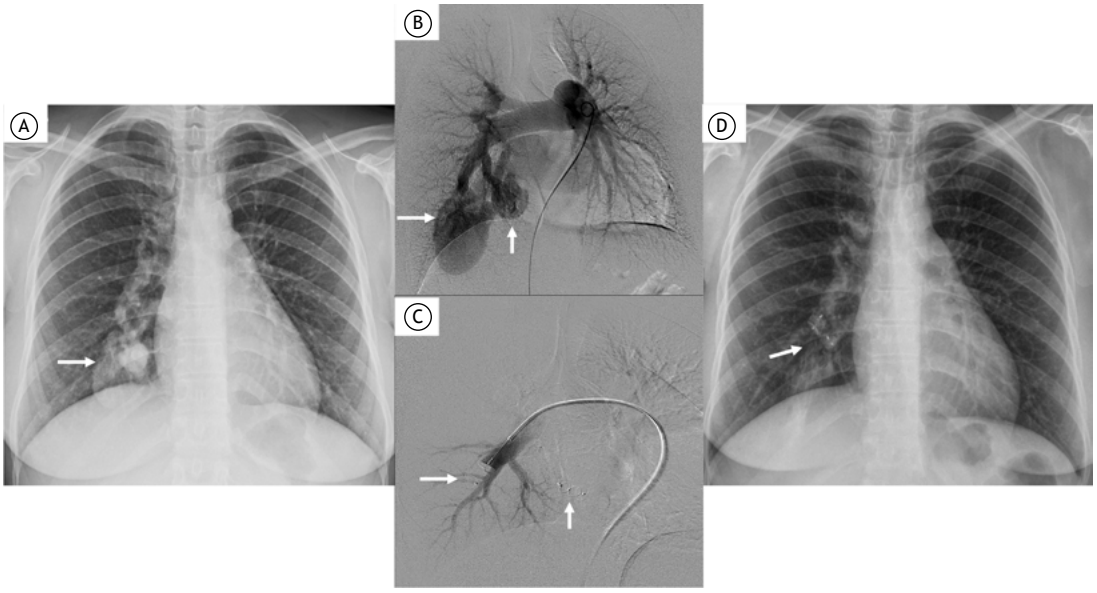


Figure 4. In A, a chest radiograph showing pulmonary arteriovenous malformations (white arrow) before embolization. In B, localization of the malformations by pulmonary angiography (white arrows). In C, embolization with Amplatzer vascular plugs (white arrows). In D, a chest radiograph after embolization (white arrow).

on symptoms than on SpO_2. In travels, there is no evidence that using supplemental oxygen modifies the risk of complications. Long-term oxygen therapy may be indicated in patients with comorbidities such as heart disease or neurological disorders. There is no formal indication for phlebotomy.[20]

FOLLOW-UP

Follow-up of patients with HHT should be performed every 5 years in those whose initial evaluation is negative for the presence of a shunt.[12]

The guidelines recommend follow-up every 3-5 years in patients with small fistulas (diameter < 3 mm). However, two recent studies have demonstrated that the growth of these fistulas is slow and infrequent,[60,61] and they recommend follow-up CT every 5 years (Figure 6).

In cases treated with embolization, the initial recommendation is to repeat CT 6-12 months after treatment. Thereafter, CT can be repeated every 3-5 years.[33] In patients with complex PAVM, follow-up can be performed earlier; in those with simple fistulas with no sign of shunt, control can be repeated after a longer time.[12] Treatment is considered successful when there is 70% regression of the drainage vein or of the fistulous sac within 3-6 months.[12,50,51] It is worth mentioning that TTCE remains positive in 80-90% of successfully treated patients.[35,62]

When cerebral malformations are diagnosed, treatment with embolization should be considered. In cases of GI bleeding, both endoscopy and colonoscopy can be used if there is major bleeding. Liver transplantation is a perspective in specific situations, such as refractory high-output cardiac failure, biliary ischemia, or complicated portal hypertension.[25]

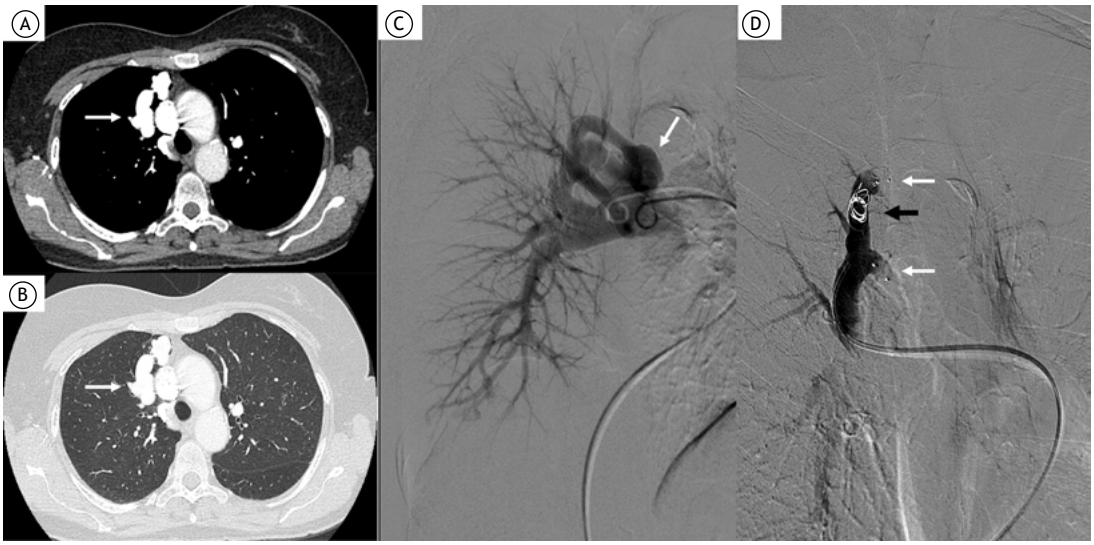


Figure 5. Combined coils and Amplatzer embolization In A and B, respectively, CT scans of the chest with mediastinal and lung window settings showing the pulmonary malformation (white arrows). In C, localization of the malformation by pulmonary angiography (white arrow). In D, embolization with coils (black arrow) and Amplatzer vascular plug (white arrow).

Recently, initial studies have recommended the use of MRI for the follow-up of patients who underwent embolization.[63,64] This choice involves excessive exposure to radiation and the use of contrast CT.[65] Nonetheless, MRI equipment and trained personnel should be available for its routine use.

FUTURE PERSPECTIVES

In addition to the abovementioned VEGF inhibitors, other antiangiogenic medications are being studied. Antiangiogenic therapies using tyrosine kinase inhibitors can also act by inhibiting VEGF, and consequently, decrease the formation of telangiectasias and arteriovenous malformations.[66] Among these medications, two were tested in murine models, sorafenib and a pazopanib analog, both of which improved hemoglobin levels and reduced GI bleeding but did not prevent skin telangiectasia.[67]

Nintedanib, a tyrosine kinase inhibitor that targets PDGF, FGF, and VEGF receptors, was used in a patient with HHT and idiopathic pulmonary fibrosis, with a reduction in nasal bleeding, showing potential for use in patients with HHT.[68]

Another potential therapy is anti-ANGPT2 antibodies and PI3-kinase inhibitors, which would act on genes encoding components of the BMP9/BMP10 signaling pathway. Tacrolimus and sirolimus have the potential for future use in patients with HHT.[66]

SPECIAL SITUATIONS

Diffuse PAVMs and microscopic arteriovenous connections

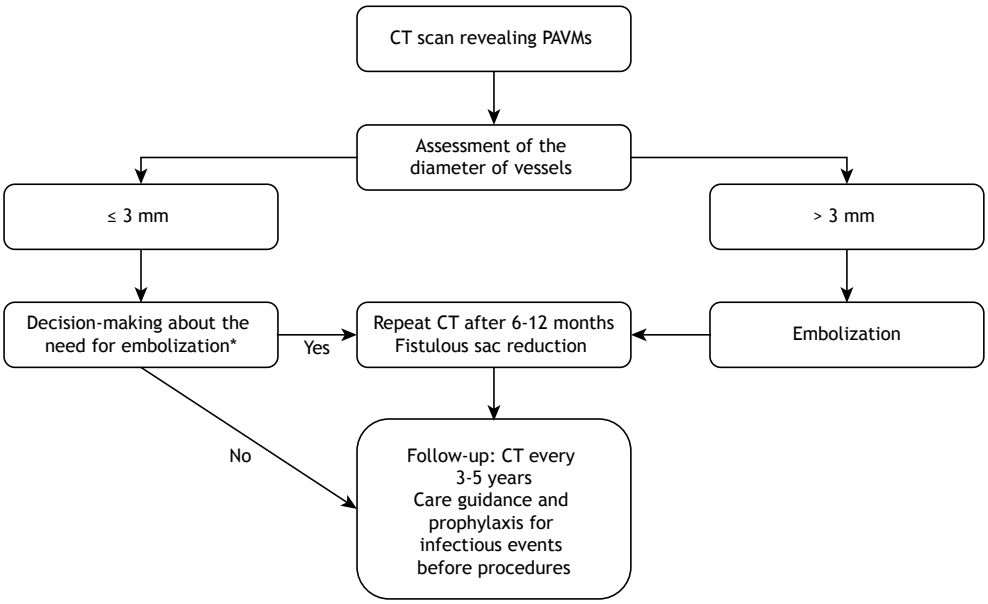
Diffuse pulmonary fistulas affect several segments or subsegments.[13] These are considered complex subtypes of PAVMs.[12] These patients are at an increased risk of hypoxemia and central nervous system complications.[13] One of the most important difficulties in these cases is embolization. Some authors have performed this procedure in patients with diffuse fistulas, treating those with the largest caliber (> 3 mm), while leaving the others untreated. A decrease in neurological complications was observed, but there was no improvement in hypoxemia.[37,69]

Microscopic arteriovenous connections are difficult to manage. This situation can occur when there are hypoxemia and right-to-left shunt on TTCE, but normal results on CT scans.[13] In the evolution phase of this type of alteration, CT scans can reveal images such as nodular ground-glass opacities after the connection between the precapillary pulmonary artery and the postcapillary venules and definitive formation of a PAVM, which is composed of an aneurysmal connection between the dilated drainage vein and the supplying pulmonary artery with concomitant disappearance of the ground-glass lesion.[13]

Diffuse PAVMs remain a diagnostic and treatment challenge. The evaluation of lung transplantation remains controversial for these patients, because survival tends to be long and long-term outcomes are still uncertain.[69] In these cases, an individual decision should be made, and an experienced transplant team should define the treatment of choice.[53]

PREGNANCY

HHT is a rare disease, and there are few data in the literature regarding pregnancy-related care. Dupuis et al.[70] estimated that the spontaneous abortion rate was between 14.4-20.0% and the prematurity rate was up to 13.8%; the data do not differ from those found in



*Discussion with the interventional radiology team

Figure 6. Follow-up recommendations. PAVMs: pulmonary arteriovenous malformations. Adapted from Lee et al.[62] and Kawai et al.[63]

the general population. However, in the same study, the maternal mortality rate was 1.2% in those with HHT, and the rate of serious complications was between 2.7-6.8%, both of which are higher than are those in the control population.[70] Therefore, all pregnancies in HHT patients are at high risk due to the prevalence of severe complications.[15] These complications can occur near the 26th week of pregnancy and have PAVMs as the main etiology.[70]

During pregnancy, there is a reduction in systemic vascular resistance and an increase in cardiac output by 40%, especially due to the effects of estrogen and relaxin during the second and third trimesters of gestation.[71] These vascular changes (Figure 7) can be particularly important in patients with HHT, because they can increase the shunt in anomalous vessels.[70] Most gestational complications occur during this period with more significant hemodynamic changes, corroborating the hypothesis that these complications are related to physiological alterations. However, they are not associated with specific vascular effects in HHT patients.[15]

The most common complications are hemothorax, hemoptysis, hypoxemia, cerebral abscess, or cerebral ischemia. There may be an increase in the frequency of epistaxis and emergence of new telangiectasias. Although rare, hepatobiliary necrosis and cholangitis have been reported in these patients. Complications during childbirth, such as uterine bleeding, occur in 5% of deliveries.[72]

Regarding the management of these patients, a cohort study with prospective and retrospective components and analysis of family data carried out between 1999 and 2005 with data from 262 pregnancies in 111 women with HHT and PAVMs conducted by Shovlin et al.,[15] revealed that these events are more common in women who were unaware of their diagnosis of HHT before pregnancy, raising the hypothesis that counseling about gestational risks is important to reduce complications. The health care service responsible for the care of these patients must also be prepared to recognize warning signs and refer complex cases to more experienced centers.[15]

Screening and treatment of PAVMs should be performed before pregnancy. Women diagnosed with HHT or hypoxemia without a defined etiology should be investigated for pulmonary artery malformation. If the patient has never been screened before, prompt investigation reduces the complications during pregnancy.[12]

The literature regarding the treatment of arteriovenous fistulas during pregnancy is controversial, especially if the patient is asymptomatic, due to the high ionizing load of the imaging techniques and the risks of the endovascular embolization procedure.[12,73] Nevertheless, according to the Second International Guidelines for the Diagnosis and Management of HHT,[25] due to the high risk of complications during pregnancy, the recommendation is to perform embolization in the second trimester of pregnancy (Figure 7).

In relation to cerebrovascular malformations, screening with cranial MRI is unnecessary, except in patients with a positive family history or in the presence of specific symptoms. In relation to spinal vascular malformations, screening is controversial in the literature due to its low incidence,[72] and some authors suggest screening if regional anesthesia has been programmed.[15]

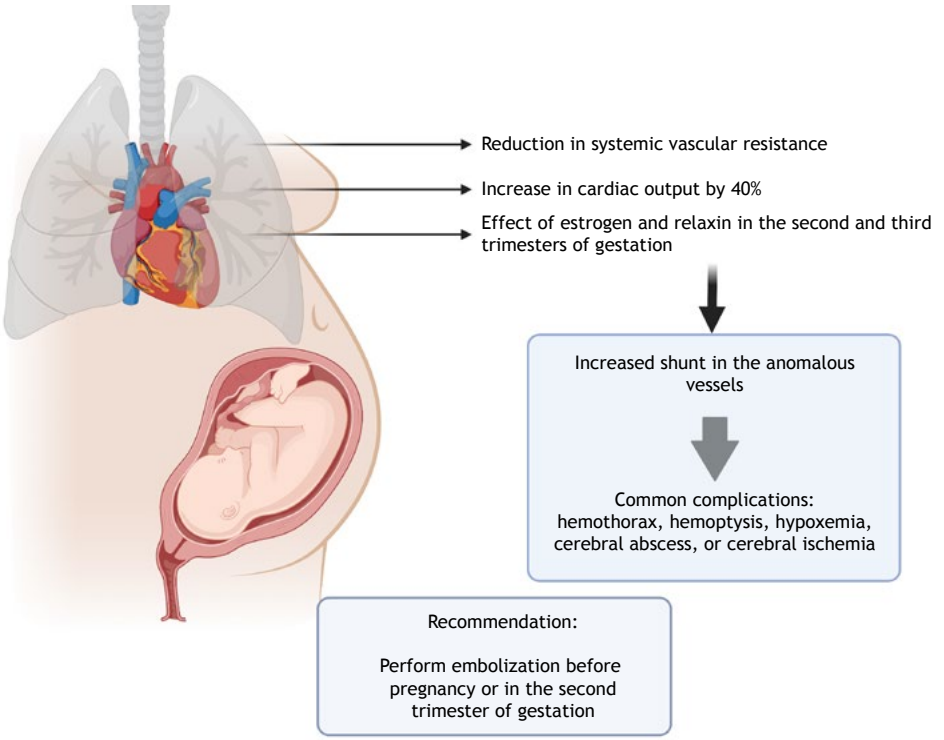


Figure 7. Pathophysiological mechanism in pregnancy and treatment recommendation. Created with BioRender.com (2022). Adapted from Geisthoff et al.,[41] de Gussem et al.,[72] and Bari et al.[73]

General care during childbirth also includes the administration of antibiotics due to the risk of septic embolism in cases of transient bacteremia, as well as avoidance of prolonged childbirth in cases where the presence of cerebral arteriovenous malformations has not been excluded.[15]

PH

PH can occur in these patients, with an estimated prevalence of 13%.[74] Most cases of PH are due to hepatic arteriovenous malformations in addition to anemia, generating postcapillary PH due to increased blood flow in the pulmonary artery territory in association with left ventricular failure because of high output.[2] Precapillary PH has a low prevalence. This is more common in the presence of endoglin or ALK1 receptor mutations and is characterized by the remodeling of the pulmonary arteries, similarly to what occurs in idiopathic PAH, resulting in elevated pulmonary vascular resistance.[18]

The coexistence of PH and PAVM may initially be protective due to the reduction in pressure in the pulmonary artery; however, as the disease progresses, the increase in pressure in the pulmonary artery can lead to the rupture of the fistulous tract.[13]

Differentiation between the presentations of PH depends on the right heart catheterization findings.[18] If PH is associated with hepatic arteriovenous malformations, high cardiac output, high pulmonary artery occlusion pressure, and normal pulmonary vascular resistance can distinguish high output heart failure in patients with PAH.[2] The initial treatment is diuretics, and the correction of anemia helps reduce the overload of the right ventricle.[2]

There have been no studies on drug treatment of patients with PAH-HHT. Initially, the management of these patients should be the same as that of those with PAH without HHT. However, there are only case reports available in the literature, one of which demonstrated the benefit of using bosentan (an endothelin receptor antagonist), with improvement in hemodynamic parameters, exercise capacity, and brain natriuretic peptide levels.[75] In another study, sildenafil was initiated.[76] The most crucial step in deciding on the initial treatment with specific medications is distinguishing between PH associated with hepatic vascular malformations and PAH.[2]

Secondary to chemotherapy (trastuzumab)

Trastuzumab is a new chemotherapeutic agent used to treat HER2-positive breast cancer that does not respond to previous lines of treatment.[77] A case report described the appearance of skin telangiectasia and PH after the use of this medication. The emtansine component of trastuzumab may explain the occurrence of mucocutaneous telangiectasia and vasculopathy of distal small vessels, eventually leading to PAH. These findings resolved after drug discontinuation.[78]

FINAL CONSIDERATIONS

Early identification of PAVM cases is of paramount importance for the prognosis of patients with this

alteration. Although rare, the consequences of these malformations can be catastrophic and lead to fatal situations. Performing embolization has the potential to protect patients from complications. Embolization has the advantage of preserving lung parenchyma when compared with surgical resection.[79]

The association between PAVMs and HHT is common; in this case, the finding of recurrent epistaxis can be an important warning sign in the history of these patients and deserves care in clinical evaluation.[80]

Identifying and treating patients with PAVM remains a challenge, but there have been advances in imaging tests and embolization techniques. In the future, we will be able to see fewer patients being diagnosed only when they present with a major complication, such as hemothorax, bleeding from the central nervous system, or infectious complications such as abscesses.

When there is a clinical suspicion of PAVMs or HHT, referral to a center specializing in treating this type of pathology can be helpful for better management of these patients.

AUTHOR CONTRIBUTIONS

WSF and MTF: study design and conception. WSF and FRO: drafting and revision of the manuscript. MTF: revision of the manuscript. WSF, FRO, and MTF: revision and approval of the final version.

CONFLICTS OF INTEREST

None declared.

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Brazilian guidelines for the pharmacological treatment of the pulmonary symptoms of cystic fibrosis. Official document of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association)

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ABSTRACT

Cystic fibrosis (CF) is a genetic disease that results in dysfunction of the CF transmembrane conductance regulator (CFTR) protein, which is a chloride and bicarbonate channel expressed in the apical portion of epithelial cells of various organs. Dysfunction of that protein results in diverse clinical manifestations, primarily involving the respiratory and gastrointestinal systems, impairing quality of life and reducing life expectancy. Although CF is still an incurable pathology, the therapeutic and prognostic perspectives are now totally different and much more favorable. The purpose of these guidelines is to define evidence-based recommendations regarding the use of pharmacological agents in the treatment of the pulmonary symptoms of CF in Brazil. Questions in the Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest (PICO) format were employed to address aspects related to the use of modulators of this protein (ivacaftor, lumacaftor+ivacaftor, and tezacaftor+ivacaftor), use of dornase alfa, eradication therapy and chronic suppression of *Pseudomonas aeruginosa*, and eradication of methicillin-resistant *Staphylococcus aureus* and *Burkholderia cepacia* complex. To formulate the PICO questions, a group of Brazilian specialists was assembled and a systematic review was carried out on the themes, with meta-analysis when applicable. The results obtained were analyzed in terms of the strength of the evidence compiled, the recommendations being devised by employing the GRADE approach. We believe that these guidelines represent a major advance to be incorporated into the approach to patients with CF, mainly aiming to favor the management of the disease, and could become an auxiliary tool in the definition of public policies related to CF.

Keywords: Cystic fibrosis; GRADE approach; Cystic fibrosis/drug treatment; Clinical practice guide.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease that results in dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is a chloride and bicarbonate channel expressed in the apical membrane of epithelial cells in various organs of the human body.[1] Dysfunction of the CFTR protein results in multisystemic manifestations, impairing quality of life and reducing life expectancy.[2]

Although CF is still an incurable pathology, the therapeutic perspective is currently more favorable due to the discovery of CFTR modulators.[3,4] Historically, treatments for individuals with CF were developed to overcome deficiencies or to modify basic aspects of the pathophysiology of the disease.[5-8]

The emergence of CFTR modulators has prompted systematic reviews on the evidence for their beneficial effects on health outcomes for individuals with CF.[3,4,9,10]

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When these guidelines were first being devised, the CFTR modulators approved by the Brazilian *Agência Nacional de Vigilância Sanitária* (ANVISA, National Health Regulatory Agency) were ivacaftor[11] and two drug combinations: lumacaftor+ivacaftor[12]; and tezacaftor+ivacaftor.[13,14] At the end of 2020, ivacaftor was incorporated into the Brazilian Unified Health Care System for use in individuals with CF ≥ 6 years of age and with genetic regulation (gating) mutations. In 2022, the Brazilian National Health Regulatory Agency approved triple therapy (elexacaftor+tezacaftor+ivacaftor), which proved to be highly effective for individuals with CF carrying the *F508del* genetic mutation, even for those who are heterozygous for that mutation.[15,16] Because that drug combination was approved so recently, it was not evaluated in these guidelines.

One of classical treatments for CF, dornase alfa,[17] has long been incorporated into the Brazilian Unified Health Care System. However, questions persist regarding its true impact on relevant outcomes, such as mortality and the frequency of pulmonary exacerbations.[18-20]

Management strategies for respiratory infections in CF are quite heterogeneous. An evaluation of the evidence supporting eradication regimens for pathogens such as *Pseudomonas aeruginosa*,[21] methicillin-resistant *Staphylococcus aureus* (MRSA),[22] and strains of the *Burkholderia cepacia* complex[23] could help clarify positions on the risks and benefits of such regimens. Another common practice in the treatment of individuals with CF is suppression therapy for chronic *P. aeruginosa* infection with inhaled antibiotic therapy. Given the impact of this treatment, which imposes long periods of nebulization,[24] the topic was also addressed in the guidelines presented here.

The aim of this special article is to carry out a systematic review and meta-analysis of data from the literature involving aspects of the treatment of individuals with CF regarding the use of CFTR modulators and dornase alfa, as well as strategies for the eradication and suppression of pathogens commonly associated with respiratory infections in such individuals.

METHODS

The steps for developing the guidelines followed the model proposed and approved by the Brazilian Thoracic Association, which employs the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach,[25] together with questions in the **P**atients of interest, **I**ntervention to be studied, **C**omparison of interventions, and **O**utcome of interest (PICO) format.[26] On May 15, 2019, a virtual meeting, involving four coordinators (two CF specialists and two methodologists), one patient, and a committee of experts, was held for the approval

Chart 1. Questions and respective outcomes selected for the preparation of the guidelines.

Question	Critical outcomes	Important outcomes
1. Should we recommend treatment with ivacaftor in patients with CF who carry class III (gating) or class IV (conduction) mutations in the *CFTR* gene?	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
2. Should we recommend treatment with lumacaftor+ivacaftor in CF patients homozygous for the *F508del* mutation?	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
3. Should we recommend treatment with tezacaftor+ivacaftor in CF patients homozygous for *F508del* or heterozygous for *F508del* and with residual function mutations?	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
4. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection?	Mortality Adverse events Time free from *P. aeruginosa* infection	Eradication of *P. aeruginosa* Lung function Exacerbations BMI variation
5. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
6. Should we recommend antimicrobial eradication treatment in CF patients with MRSA colonization of the airways?	Mortality Eradication of MRSA Adverse events Quality of life	Lung function Exacerbations
7. Should we recommend nebulized dornase alfa for CF patients ≥ 6 years of age?	Mortality Quality of life Adverse events	Lung function Exacerbations BMI variation
8. Should we recommend antimicrobial eradication treatment in CF patients with airway colonization by *Burkholderia cepacia* complex strains?	Mortality Eradication of *B. cepacia* Quality of life Adverse events	Lung function Exacerbations BMI variation

CF: cystic fibrosis; and MRSA: methicillin-resistant *Staphylococcus aureus*.

of the methodology used. The experts formulated PICO questions about the pharmacological treatment of patients with CF. A vote was then taken to select the eight most relevant questions. The outcomes of interest for each question were defined *a priori* and classified as critical or important (Chart 1).

The search for articles and the meta-analysis were carried out by a team of experienced methodologists, hired for the purpose of devising these guidelines. The project was registered on the International Prospective Register of Systematic Reviews (PROSPERO) platform (Protocol no. CRD42020173901). The searches were carried out in the MEDLINE and EMBASE databases. Clinical trials, case-control studies and cohort studies were included, with keywords pre-established by the specialist coordinators, with no date or language restrictions (Chart S1).

We first evaluated the articles on the basis of their titles and abstracts. Two methodologists, working independently, then performed a qualitative analysis of the full texts and selected articles to be included. Their selections were subsequently validated by the specialist coordinators. The reasons for inclusion or exclusion are presented in the supplementary material (Figures S1 to S8).

When appropriate, data on pharmacological interventions were pooled and meta-analyses were performed independently by the team of methodologists. For each of the eight PICO questions, the quality of evidence of each of the studies included in the meta-analyses was assessed by employing the GRADE approach, through the use of evidence tables, with the GRADEpro Guideline Development Tool (McMaster University, Hamilton, ON, Canada).

For any given study, the quality of evidence depends on the design, the implementation, and the risks of bias. As detailed in Charts 2 and 3, the quality of evidence can be classified as high, moderate, low, or very low.[25]

In December of 2021, a working group met to review the evidence and make recommendations for each question according to the GRADE approach. The recommendations were classified as strong or conditional, according to degree of certainty regarding the strength and quality of the evidence. We use the term "recommend" for strong recommendations and "suggest" for conditional recommendations. Chart 4 shows the proposed interpretations of those recommendations,[26,27] which are detailed in Tables S1 to S8.

Chart 2. Interpretation of the quality of evidence employing the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

GRADE quality of evidence	Implications	Examples
High (⊕⊕⊕⊕)	Future research is unlikely to change the level of confidence in the estimated effect; we are confident that we can expect a very similar effect in the population for which the recommendation is intended.	Randomized trials without serious limitations Well-executed observational studies with very large effect sizes
Moderate (⊕⊕⊕◯)	Future research is likely to have a major impact on the level of confidence in the estimated effect and could change this estimate.	Randomized trials with serious limitations Well-executed observational studies with large effect sizes
Low (⊕⊕◯◯)	Future research is likely to have a major impact on the level of confidence in the estimated effect and is likely to change that estimate.	Randomized trials with very serious limitations Observational studies without special strengths or serious limitations
Very low (⊕◯◯◯)	Any estimate of an effect is very uncertain.	Randomized trials with very serious limitations and inconsistent results Observational studies with serious limitations Nonsystematic clinical observational studies (e.g., case series or case reports)

Adapted from Guyatt et al.[27] GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Chart 3. Factors that can affect the quality of evidence.[a]

Quality of evidence	Situations that can lower the grade	Situations that can raise the grade
• High • Moderate • Low • Very low	• Risk of bias • Indirect evidence • Inconsistency • Imprecision • Publication bias	• Strong association, no plausible confounding factors • Evidence of a dose-response relationship • Known plausible confounding factors that reduce the effects

Adapted from Guyatt et al.[27] [a]Quality can be lowered by one or two degrees when a risk of bias, indirect evidence, inconsistency, imprecision, or publication bias is identified. However, it can be raised when there is a strong association without identification of plausible confounding factors or when there is evidence of a dose-response relationship.

Chart 4. Implications of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Target audience	Strong GRADE recommendation		Conditional GRADE recommendation	
	We recommend	We do not recommend	We suggest	We do not suggest
Patients	Most individuals would want the intervention to be indicated, and only a small number would not accept this recommendation.	Most individuals would not want the intervention to be indicated, and only a small number would accept this recommendation.	Most individuals would like the intervention to be indicated, although a considerable number would not accept this recommendation.	Most individuals would not want the intervention to be indicated, although a considerable number would accept this recommendation.
Health professionals	Most patients should receive the recommended intervention.		The professional must recognize that different choices can be appropriate for each patient and should help patients make a decision consistent with their values and preferences.	
Policy makers	The recommendation can be adopted as health policy in most situations.		Substantial debate and stakeholder involvement is required.	

Adapted from Abou Alaiwa et al. and Accurso et al.[28,29]

Question 1. Should we recommend treatment with ivacaftor in CF patients with class III (gating) or class IV (conduction) mutations in the *CFTR* gene?

Ivacaftor is a CFTR modulator. It acts as a CFTR potentiator, aimed at treating the dysfunction underlying this genetic alteration. It regulates the opening of the chlorine channel present in the cell membrane, restoring healthy mucus rheology in the airways.

In 2012, the US Food and Drug Administration approved the use of ivacaftor for CF patients ≥ 12 years of age.[11] It is the first drug approved for CF whose therapeutic action targets the basic problem of the disease, characterized by CFTR protein dysfunction. Various clinical trials were subsequently carried out, the results of which allowed the use of the drug to be extended to patients ≥ 6 years of age.

Evidence

Among the studies analyzed, there were 28 on the use of ivacaftor, for a variety of outcomes,[12,28-54] as shown in Figure S1 and Chart S2. Of those 28 studies, 8 were randomized controlled trials (RCTs).[11,29,32-34,36,44,45] Although not all investigated the same sets of outcomes, the articles collectively demonstrated a beneficial therapeutic effect of ivacaftor in patients with class III (gating) or class IV (conduction) mutations.

A detailed description of the findings can be found in the Supplementary Material (Question S1). The quality of evidence of the selected articles for this question is summarized in Tables S1A and S1B.

In 2020, Volkova et al.[55] evaluated disease progression (real-life study) in CF patients treated with ivacaftor for 5 years. Patients enrolled in US and UK CF registries, which maintain a high degree of data integrity, were evaluated. The authors analyzed 635 cases versus 1,875 controls in the US registry and 247 cases versus 1,230 controls in the UK registry. They observed that, at the end of the 5-year follow-up period, the ivacaftor group patients had better lung function and better nutritional status, as well as a lower frequency of exacerbations and hospitalizations, when compared with their baseline values and with the values obtained for the standard therapy without ivacaftor (control) group.[55]

Recommendation

For patients with CF and at least one class III (gating) or class IV (conduction) mutation, we suggest the use of ivacaftor (conditional recommendation, very low quality of evidence).

Comments

The results obtained in real-life studies of the use of ivacaftor are similar to those obtained in clinical studies, indicating that it has a positive effect as a modifying drug in the natural progression of CF. The very low quality of the evidence found is due to the high heterogeneity of the studies evaluated, given that our systematic review included clinical trials and observational studies. The studies evaluated included only patients ≥ 6 years of age, and it is not possible to extrapolate the recommendation to any younger age group.

Question 2. Should we recommend treatment with lumacaftor+ivacaftor in CF patients homozygous for the *F508del* mutation?

Lumacaftor and ivacaftor are both CFTR modulators. Lumacaftor is a CFTR corrector, which acts in the processing of the protein, correcting its format and consequently increasing in its quantity on the cell membrane.[4]

Combination therapy was evaluated in CF patients aged 6 years or older who were homozygous for the *F508del* class II mutation. The results indicated a reduction in the number of pulmonary exacerbations, a slight increase in FEV_1, improved nutritional status, better quality of life, and a reduction in sweat chloride levels.[12,56-60]

In view of the benefits it presents, the use of lumacaftor+ivacaftor has been approved by various international agencies, including the Brazilian ANVISA.

In addition, that combination has been shown to have an acceptable safety profile, satisfactory patient adherence (the majority of patients completing the prescribed therapeutic regimen), and a low incidence of relevant adverse events.[13,58-60]

Evidence

Using the methodology described, we selected 16 articles.[12,56-69] All of those articles were later included for reading, review, and synthesis of evidence (Figure S2 and Chart S3).

Of the 15 studies selected, only 2 were RCTs.[12,57] Although not all investigated the same sets of outcomes, they collectively demonstrated that lumacaftor+ivacaftor has a beneficial therapeutic effect in patients homozygous for the *F508del* mutation.

A detailed description of the findings can be found in the Supplementary Material (Question S2). For each of the articles, the quality of evidence for this question is summarized in Tables S2A and S2B.

Recommendation

For CF patients with the *F508del* mutation, we do not suggest the use of lumacaftor+ivacaftor (conditional recommendation, very low quality of evidence).

Comments

The combination of a CFTR corrector and a CFTR potentiator can benefit patients homozygous for *F508del*, representing a differential in the treatment of approximately 45% of individuals with CF and that mutation. However, in the present systematic review, we identified no significant results regarding clinical outcomes that were considered critical. The positive findings obtained for the outcomes that were considered important were only marginal. Some patients may benefit from treatment. However, given the very low quality of evidence for most of the outcomes assessed, we do not suggest the use of lumacaftor+ivacaftor for the treatment of CF patients homozygous for the *F508del* mutation. It is important to emphasize that new classes/combinations of modulators, such as tezacaftor+ivacaftor[13] and, more recently, the triple combination (elexacaftor+tezacaftor+ivacaftor),[15] have been approved and have been shown to have better efficacy and safety profiles in this population.

Question 3. Should we recommend treatment with tezacaftor+ivacaftor in CF patients homozygous for *F508del* or heterozygous for *F508del* and with residual function mutations?

Tezacaftor is a CFTR corrector that binds to the protein, improving its processing and trafficking through the cell to the cell membrane.[9]

The use of tezacaftor+ivacaftor was evaluated in phase III studies involving CF patients ≥ 12 years of age who were homozygous for the *F508del* mutation,[13] as well as for patients who were heterozygous for the *F508del* mutation and had a residual function mutation.[14] In those studies, the use of tezacaftor+ivacaftor was found to provide a significant improvement in lung function, a reduction in the number of exacerbations, and nutritional gain, with an adequate safety profile. Similar results were obtained in patients between 6 and 11 years of age.[70-72] Therefore, tezacaftor+ivacaftor was approved for use in patients in several countries, including Brazil.

Evidence

As shown in Figure S3 and Chart S4, 5 articles were selected by using the methodology described: 4 RCTs and 1 observational study.[13,14,70-72] All of the studies assessed more than one outcome, including BMI, quality of life, adverse events, occurrence of exacerbations, lung function, and mortality.[13,14,70-72]

For each of the articles, the quality of evidence for this question is summarized in Table S3. A detailed description of the findings can be found in the Supplementary Material (Question S3).

Recommendation

For CF patients homozygous for *F508del* or heterozygous for *F508del* and with a residual function mutation, we suggest using tezacaftor+ivacaftor (conditional recommendation, very low quality of evidence).

Comments

The use of tezacaftor+ivacaftor was evaluated in CF patients ≥ 6 years of age who were homozygous for *F508del* or heterozygous for *F508del* and with a residual function mutation. The main effect of the drug was on lung function. The gain in FEV_1, albeit modest, seems significant when considered in the context of a disease that leads to a progressive decline in lung function. It is important to point out that the clinical benefits obtained in patients with a residual function mutation seem to be greater than those found in patients homozygous for *F508del*. In all of the studies evaluated, there was no difference between the control and tezacaftor+ivacaftor groups in terms of the occurrence of adverse events. Most of the adverse events observed were mild and did not lead to discontinuation of the treatment. In addition, many of the events reported (such as increased pulmonary secretion and increased coughing) can be attributed to the disease itself, which attests to the adequate safety profile of the drug.[13,14,70-72]

Question 4. Should we recommend eradicating *P. aeruginosa* infection in individuals with CF?

Respiratory tract infections are common in individuals with CF, who are more susceptible to infection with certain microorganisms, including *P. aeruginosa*. Infection with this pathogen is considered a major predictor of morbidity and mortality from CF,[73] as well as of a severe loss of lung function.[74] Since the

1990s, CF referral centers have used regimens for early eradication of *P. aeruginosa*, aiming to delay the progression to chronic infection and its unfavorable outcomes.

Evidence

Using the methodology described, we selected 17 articles, conducted between 1980 and 2019 and published between 1991 and 2020,[75-91] of which 10 were observational studies[75-80,82,83,86,87] and 7 were RCTs.[81,84,85,88-91] The number of individuals included in the studies ranged from 11 to 304, and 12 of the studies had a sample size of less than 200 (Figure S4 and Chart S5).

For each of the articles, the quality of evidence for this question is summarized in Table S4. A detailed description of the findings can be found in the Supplementary Material (Question S4).

Recommendation

For individuals with CF, we do not have sufficient evidence to recommend or not recommend the use of *P. aeruginosa* eradication therapy.

Comments

The association between *P. aeruginosa* infection and poor CF outcomes is well established. In addition, eradication therapy has already been incorporated into the routine of referral centers, making it difficult to carry out new studies on the subject. The literature review made it possible to include a limited number of studies, most of which were observational in nature and, in general, had small sample sizes. Such characteristics can lead to inconsistent results, making it impossible to make an appropriate recommendation on the subject. Despite being a practice recommended in several national and international guidelines, further studies are needed to determine the efficacy and safety of *P. aeruginosa* eradication therapy, especially in the era of CFTR modulator use.

Question 5. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection?

Through complex mechanisms, *P. aeruginosa* adapts to and can remain in the airways of CF patients for long periods. Chronic infection in CF is defined as detection of the pathogen in more than 50% of respiratory secretion samples over a 12-month period.[92] Chronic infection with *P. aeruginosa* can affect up to 60% of patients in adult life and is associated with progression of lung disease and higher mortality.[21,93,94] Inhaled antimicrobials are widely used for the suppression of *P. aeruginosa* in patients with chronic infection, and their use is aimed at reducing the consequences of the presence of the pathogen in the airways. Inhaled drug options for such treatment classically include colistimethate, tobramycin, and, more recently, aztreonam.[93]

Evidence

Using the methodology described, we selected 25 studies carried out between 1995 and 2008.[94-118] Five were observational studies[101-103,109,117] and the others were classified as RCTs. Samples sizes were over 200 in 9 of the studies, of which 2 included more than 500 individuals (Figure S5 and Chart S6).

For each of the articles, the quality of evidence for this question is summarized in Table S5. A detailed description of the findings can be found in the Supplementary Material (Question S5).

Recommendation

For CF patients with chronic *P. aeruginosa* colonization, we suggest chronic suppression therapy with inhaled antibiotics (conditional recommendation, very low quality of evidence).

Comments

Although not all of the studies analyzed exactly the same sets of outcomes, as a whole, they point in favor of the use of inhalation treatment of patients with chronic *P. aeruginosa* colonization, because such treatment can result in functional improvement, better quality of life, and lower mortality in those patients. It should be borne in mind that, despite the potential benefits, there is heterogeneity among the studies evaluated, resulting in a low quality of evidence.

Question 6. Should we recommend antimicrobial eradication treatment in CF patients with MRSA colonization of the airways?

Chronic MRSA infection is associated with worse clinical outcomes in CF patients.[119] There are various antimicrobial regimens for eradicating this pathogen, including combinations of oral, topical, and inhaled drugs. There is also great variability regarding treatment time, and some authors argue that combined treatment is more effective than is monotherapy.[120,121] However, there is still no consensus in the literature and it is questionable whether there is robust scientific evidence that MRSA eradication is beneficial for CF patients.[122,123]

Evidence

Using the methodology described, we selected 8 studies (Figure S6 and Chart S7).[120-127] Of those, only 2 are RCTs[123,126] and the other 6 are observational studies.[120-122,124,125,127]

For each of the articles, the quality of evidence for this question is summarized in Tables S6A and S6B. A detailed description of the findings can be found in the Supplementary Material (Question S6).

Recommendation

For CF patients, we do not have enough evidence to recommend or not recommend the use of MRSA eradication therapy.

Comments

Although all of the studies assessed the eradication rate, they employed different treatment protocols, as well as different means of assessing eradication (short- vs. long-term follow-up). All of the studies evaluated had sample sizes of less than 70 individuals. It is possible that further studies, especially studies with larger patient samples, will result in a change in the confidence level of this recommendation.

Question 7. Should we recommend nebulized dornase alfa for CF patients ≥ 6 years of age?

In CF patients, chronic inflammation and infection results in extracellular DNA from leukocytes being constantly released into the airways and accumulating in lung secretions.[18] Consequently, there is an increase in the viscosity and adhesion of mucus. Dornase alfa is an enzyme capable of cleaving the extracellular DNA contained in mucus, reducing its viscosity and promoting greater clearance of secretions.[128]

Dornase alfa is administered by inhalation, at the usual dose of 2.5 mg once a day, and should be used in conjunction with other airway clearance techniques.[17,128]

In phase I and II studies, the use of nebulized dornase alfa in CF patients proved to be safe and led to an increase in FEV_1 in the short term, together with improvements in symptoms and quality of life.[129,130] Subsequent studies demonstrated the maintenance of benefits in the long term, with sustained improvement in FEV_1, a reduced risk of exacerbations, and a good safety profile.[128]

Evidence

We selected 32 studies,[17,131-161] 18 of which were RCTs that compared the use of dornase alfa with placebo,[17,131-135,140-142,144,145,149,151-154,159,160] and 14 were observational studies,[136-139,143,146-148,150,155-158,161] as illustrated in Figure S7 and Chart S8.

For each of the articles, the quality of evidence for this question is summarized in Tables S7A and S7B. A detailed description of the findings can be found in the Supplementary Material (Question S7).

Recommendation

For CF patients, we suggest the use of inhaled dornase alfa (conditional recommendation, very low quality of evidence).

Comments

The differences in mortality rates between the intervention and placebo groups were not significant, because few patients died. Two RCTs evaluated adverse effects[17,149] and found no significant differences in terms of the frequency of adverse events. One RCT and two observational studies[131,155,156] assessing quality of life demonstrated improvements in the intervention groups.

Nine RCTs,[17,131,141,142,144,149,152,154,160] evaluated collectively, showed that FEV_1 values were 5% higher among patients receiving dornase alfa than among those receiving a placebo. Although that is a modest improvement, FEV_1 is a proxy for mortality in population studies. In addition, 2 RCTs[17,152] demonstrated that the rate of exacerbations was 7% lower in the intervention groups than in the placebo groups. This outcome is important, because a reduction in exacerbations is associated with favorable lung function outcomes and, indirectly, with lower mortality.

The search of the literature for these guidelines did not include studies involving children under 6 years of age. Therefore, it is not possible to extrapolate this recommendation to any younger age group.

Question 8. Should we recommend antimicrobial eradication treatment in CF patients with airway colonization by *B. cepacia* complex strains?

The *B. cepacia* complex comprises 22 species,[162] the most common of which in CF are *B. multivorans* and *B. cenocepacia*. The clinical picture is quite variable, ranging from chronic, oligosymptomatic infection to severe cases, with necrotizing pneumonia, respiratory failure, and sepsis (cepacia syndrome).[163] The *B. cepacia* complex has a peculiar bacterial resistance profile, which makes the choice of antibiotic treatment difficult, and a combination of antimicrobial drugs is commonly suggested, preferably guided by antimicrobial susceptibility testing.[164]

Evidence

Using the methodology described, we selected 3 studies,[23,165,166] as illustrated in Figure S8 and Chart S9. Only 1 study was characterized as an RCT.[165]

For each of the articles, the quality of evidence for this question is summarized in Tables S8A and S8B. A detailed description of the findings can be found in the Supplementary Material (Question S8).

Recommendation

For CF patients, we do not have enough evidence to recommend or not recommend the use of eradication therapy for *B. cepacia* complex.

Comments

None of the selected studies showed any benefits of eradication therapy for *B. cepacia* complex when evaluating the many critical outcomes considered important in the methodology of these guidelines. Only a few studies on the subject were found in the literature. Most of those studies had low methodological quality, and there was considerable heterogeneity among them. The eradication regimens described were not standardized. The higher rates of adverse events found with the use of inhaled aztreonam cannot be extrapolated to other therapeutic regimens, especially because that antibiotic is not commonly recommended for this type of infection. Therefore,

our guideline committee decided that it is not possible to make a recommendation either for or against this therapy, given the scarcity of published information. Further studies are needed in order to evaluate this issue in greater detail.

FINAL CONSIDERATIONS

A summary of the recommendations for the pharmacological treatment of respiratory disease in CF is presented in Chart 5.

It is up to the prescribers to determine which treatments are appropriate for a given patient or group of patients, and that it is up to them to help patients and their families make consistent and well-founded decisions, consistent with the strength of the recommendations and the quality of existing evidence. Cost analyses and pharmacoeconomic aspects were not considered in these recommendations.

Although there is still no drug with curative capacity in CF, the present guidelines suggest several interventions with potential benefits for the treatment of the disease. Some drugs, such as dornase alfa, and strategies to control chronic infection by *P. aeruginosa* have been approved for more than a decade and are considered standard therapy in the management of CF. However, those interventions work to control the consequences of the disease, such as increased mucus viscosity and recurrent infectious exacerbations. More recently, a new class of drugs, CFTR modulators, has initiated a new phase in the treatment of CF by acting on the underlying cause of the disease.[9] Substantial gains in lung function and reduction in exacerbation rates were found when ivacaftor was used in patients with class III mutations[11] and when tezacaftor+ivacaftor was used in patients with residual function mutations.[14] However, despite the statistically significant benefits, such results were not achieved in CF patients homozygous for the *F508del* mutation who were treated with lumacaftor+ivacaftor[12] or tezacaftor+ivacaftor.[13] These data indicate the need for an adequate assessment of the benefits of each treatment according to the population evaluated. Treatment with CFTR modulators can be considered a targeted therapy, and CFTR modulators are chosen according to the action of different drugs on specific groups of CFTR mutations. A new triple combination of CFTR modulators (elexacaftor+tezacaftor+ivacaftor) appears to be an effective and safe option for patients with at least one *F508del* allele.[15,16]

In view of the many advances in the management of CF in recent years, it is recommended that even proven effective treatments, such as dornase alfa and chronic *P. aeruginosa* suppression therapy, be reassessed in the future, given the greater access to CFTR modulators in eligible patients.

Regarding the other interventions evaluated, the expert panel was not able to issue an evidence-based recommendation because of the low quality of the evidence obtained for the eradication of *P. aeruginosa*, MRSA, and *B. cepacia* complex. More studies on the topic are needed in order to make a

Chart 5. Summary of recommendations for pulmonary pharmacological treatment in cystic fibrosis.

Question	Recommendation	Grade of recommendation	Quality of evidence
1. Should we recommend treatment with ivacaftor in patients with CF who carry class III (gating) or class IV (conduction) mutations in the *CFTR* gene?	We suggest the use	Conditional	Very low
2. Should we recommend treatment with lumacaftor+ivacaftor in CF patients homozygous for the *F508del* mutation?	We do not suggest the use	Conditional	Very low
3. Should we recommend treatment with tezacaftor+ivacaftor in CF patients homozygous for *F508del* or heterozygous for *F508del* and with residual function mutations?	We suggest the use	Conditional	Very low
4. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection?	No recommendation		
5. Should we recommend treatment with inhaled antimicrobials in patients with CF and chronic *P. aeruginosa* infection	We suggest the use	Conditional	Very low
6. Should we recommend antimicrobial eradication treatment in CF patients with MRSA colonization of the airways?	No recommendation		
7. Should we recommend nebulized dornase alfa for CF patients ≥ 6 years of age?	We suggest the use	Conditional	Very low
8. Should we recommend antimicrobial eradication treatment in CF patients with airway colonization by *Burkholderia cepacia* complex strains?	No recommendation		

CF: cystic fibrosis; and MRSA: methicillin-resistant *Staphylococcus aureus*.

formal recommendation. However, clinical physicians must evaluate the particularities of each patient and recognize the possible benefits of these therapies in selected cases.

It should be borne in mind that these guidelines sought to answer questions regarding only eight of the main pharmacological interventions for the treatment of the respiratory consequences of CF. Other therapies, such as nebulization with hypertonic saline and long-term use of macrolides, were not evaluated in these guidelines. That does not mean that such therapies do not present clinical benefits or that they cannot be used according to their own eligibility criteria. Nonpharmacological care, including vaccination, physical activity, respiratory physiotherapy, and pulmonary rehabilitation, is also essential in the management of CF. Finally, because CF is a multisystemic disease, the patient must be cared for in a multidisciplinary way, involving gastrointestinal, endocrinological, and otolaryngological aspects that were not within the scope of these guidelines.[7]

It is important to clarify that the very low quality of evidence for some recommendations does not mean that they should not be considered or implemented. In these guidelines, it was decided that RCT and observational studies should be included, with the aim of better evaluating the effect of some therapies approved many years ago for CF. This strategy allows the evaluation of a large sample of patients with high external validity. However, it increases the uncertainty of the results because of the biases inherent to the different study designs. It is important to emphasize that the consistent finding of results in RCT and observational studies favors the clinical applicability of these interventions for a greater proportion of patients with CF. In addition, our recommendations are in line with those of other international guidelines.[8]

We believe that these guidelines constitute an important tool to be incorporated into the approach to patients with CF, mainly aiming to favor its management, as well as helping define public policies related to the disease.

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AUTHOR CONTRIBUTIONS

All of the authors actively participated in the process of devising these guidelines and were involved in the formulation of the questions, the choice of outcomes to be evaluated, and the reviewing of the obtained results. All of the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Pharmacological approach to iatrogenic bleeding during bronchoscopy: what do we know so far and where do we go from here?

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TO THE EDITOR:

Massive bleeding and mortality are exceedingly rare and occur mostly in therapeutic bronchoscopy.[1] In the diagnostic setting, endobronchial and especially transbronchial biopsies, as well as lung cryobiopsies, are the most problematic procedures.[1] Bleeding severity classification is crucial for management decisions.

Bleeding severity can be characterized according to the volume of fluid aspirated: it is usually accepted that bleeding < 50 mL is minor, bleeding of 50-100 mL is moderate, and bleeding > 100 mL is severe. Also, bleeding severity can be classified according to the intervention required to control the bleeding: moderate bleeding is defined as bleeding that requires wedging of the biopsied segment and/or endobronchial drug administration; and severe bleeding is defined as bleeding that requires additional interventions, such as temporary bronchial blocker placement or blood products administration. The latter proposal is less influenced by blood dilution with bronchial secretions and instilled products, and it is often considered easier and more reproducible.[2]

In a recently performed survey among respiratory specialists, nearly half of them were less than confident in managing acute bleeding and nearly all of them would be interested in further training.[3] Challenges in the management of iatrogenic hemorrhage are often related to insufficiently diverse clinical team training, since a systematic and multidisciplinary approach is required. In addition, availability of suitable resources such as rigid bronchoscopy, which can be safer and more efficient than flexible bronchoscopy, varies from institution to institution. Moreover, standardized recommendations are missing, including those regarding patients' hemorrhagic risk factors. Patients with uremia, thrombocytopenia, HIV/AIDS, solid organ transplant, hematological disorders, and severe pulmonary hypertension are reported to have an increased bleeding risk.[1,4] However, evidence is still lacking when several risk factors are present, and such evidence is crucial in an older population with a complex comorbid profile.[4] Regardless of careful evaluation for potential indicators of bleeding risk, about two thirds of patients with significant bleeding have normal coagulation and no identifiable risk factors.[2]

A lack of recommendations persists for drug discontinuation and pre-procedure management. Current data do not indicate a heightened risk of bleeding with the use of aspirin alone. For instance, Herth et al.[5] concluded that the use of this drug was not linked to increased probability of bleeding, and their proposal was to continue aspirin before bronchoscopy. Nonetheless, the absence of more data accentuates the need for careful decision making. Pathak et al.,[6] who summarized the literature, recommend discontinuing P2Y12-ADP receptor inhibitors 5-7 days before the procedure, discontinuing warfarin 5 days before the procedure, and monitoring the international normalized ratio. Some direct oral anticoagulants require to be discontinued for more than 48 h (Chart 1).[6] Larger studies are needed on several recent drugs, and there is a literature demand for validation of whether these practices are reliable.

Levels of systemic drug absorption through the endobronchial route remain mostly unevaluated. It is thought that more distal administration into the airway may lead to higher plasmatic absorption.

Endobronchial instillation of ice-cold saline is one of the oldest and most common practices. It can promote hemostasis by inducing vasoconstriction and by vascular tamponade. However, hypothermia may be paradoxically associated with an increased risk of bleeding, and there are no guidelines on recommended maximum safe doses.[7] After repeated instillation of 5-10 mL without a favorable outcome, other measures should be taken.

Some of the most relevant adrenoreceptors in the lungs are the beta2-adrenoreceptors, expressed on the airway smooth muscle whose activation causes bronchodilation, and the alpha1-adrenoreceptors, present on the small- and medium-sized pulmonary arteries whose stimulation leads to vasoconstriction. Examples of adrenergic drugs that selectively bind to alpha1-adrenoreceptors are phenylephrine and oxymetazoline. Adrenergic drugs can also be nonselective and bind to a combination of adrenergic receptors, such as adrenaline.[8] Vasoconstrictor drugs are widely employed, and, indeed, adrenaline has been the most extensively studied and widely used drug in this setting. However, adrenaline dosage and dilution vary widely in the literature, and adverse effects can arise with doses as low as 100 µg. The British Thoracic Society guidelines for bronchoscopy propose the instillation of 5-10 mL of adrenaline diluted to 1:10,000 (500-1,000 µg).[2] Life-threatening arrhythmia is one of the most troubling adverse effects, and it has been reported after the instillation of 5 mL of adrenaline diluted to 1:20,000 (200 µg).[1] Other side effects such as cerebral hemorrhage, hypertension, or myocardium ischemia may develop.[1] Adrenaline diluted in ice-cold saline is often used, mainly when potentially safer drugs are unavailable. Patient history should be carefully reviewed, and adrenaline

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Chart 1. Management of patients on anticoagulant therapy undergoing bronchoscopy.

Mechanism of action	Drug	Withhold time (prior to procedure)	Restart time (after procedure)	Reversal agent
Vitamin K-dependent antagonist	Warfarin[a]	Withhold drug 5 days prior to procedure, monitor INR	Restart drug 12-24 h after procedure	Vitamin K, four-factor PCC, three-factor PCC, or activated PCC
Direct thrombin inhibitor	Dabigatran	Withhold drug 1-2 days prior to procedure if CrCl ≥ 50 mL·min^{-1}; withhold drug 3-5 days prior to procedure if CrCl < 50 mL·min^{-1}	Restart drug 24 h after procedure if hemorrhagic risk is low; restart drug 48-72 h after procedure if hemorrhagic risk is high	Idarucizumab
Direct factor Xa inhibitor	Apixaban Edoxaban Rivaroxaban	Withhold drug 1-2 days prior to procedure; withhold apixaban 3 days prior to procedure if hemorrhagic risk is high	Restart drug 24 h after procedure if hemorrhagic risk is low; restart drug 48-72 h after procedure if hemorrhagic risk is high	Three- or four-factor PCC or activated PCC
Parenteral anticoagulant agent	Unfractionated heparin	Withhold drug 4-6 h prior to procedure	Restart drug 24 h after procedure	Protamine sulfate
	Enoxaparin Dalteparin	Withhold drug 24 h prior to procedure		

INR: international normalized ratio; PCC: prothrombin complex concentrate; and CrCl: creatinine clearance. [a]If spontaneous INR > 1.4 and/or platelets < 25,000, high-hemorrhagic-risk procedures are contraindicated. According to patient thrombotic risk and procedure hemorrhagic risk, consider bridging with enoxaparin.

use should be considered accordingly. Phenylephrine 0.5% and xylometazoline 0.1% have been increasingly employed as vasoconstrictor drugs to treat the nasal mucosa, despite lacking formal validation. In our center, the authors adopted the use of xylometazoline 0.1% (3 drops in 5-10 mL of ice-cold saline; maximum of 6 drops in two administrations).

Another drug that has become increasingly widespread is tranexamic acid (TXA), a synthetic antifibrinolytic agent that is a reversible competitive inhibitor to the lysine receptor found on plasminogen. The binding of this receptor prevents plasmin from binding to and stabilizing the fibrin matrix.[9] Some authors underline the risk of TXA causing thrombotic events, as described for the intravenous route.[7] However, the efficacy of TXA in controlling bleeding from mucosal tissue has led to its endobronchial use.[9] Non-standardized but upright results have been reported with endobronchial administration of 20 mL of diluted TXA (TXA 500 mg/5 mL in 15 mL of ice-cold saline) up to a maximum of 3 doses, with a 1.5-min period of observation for hemostasis between administrations.[9] Lack of formal validation also applies to aminocaproic acid. The suggestion of 2 ampules of aminocaproic acid (each ampule 2.5 g/10 mL) in 50 mL of ice-cold saline, 5-10 mL in each administration, is commonly found.[10]

When these therapeutic options have been exhausted and a major hemorrhage is present, the approach will be determined by several variables, including the procedural protocols of the working place. Resuscitation equipment and qualified clinical staff are imperative. Structured knowledge of the best approach when preventive measures fail is critical. In addition, standardization and pharmacological validation of endobronchial drug administration are key for favorable outcomes.

AUTHOR CONTRIBUTIONS

AA, VC, and LF: study conception and design. AA, VC, DN, LF, and PD: data acquisition, analysis, and interpretation. AA, VC, DN, and LF: drafting of the manuscript. PD: critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Long-term follow-up and mortality of patients with chest wall diseases on noninvasive ventilation

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TO THE EDITOR:

Chest wall diseases (CWDs) are characterized by decreased compliance of the chest wall and impaired ventilatory mechanics,[1,2] leading to chronic hypercapnic respiratory failure (CHRF). Patients with kyphoscoliosis and post-tuberculosis sequelae (TbS) have a higher risk of CHRF, depending on the degree of deformity and the age of onset.[3] The clinical presentation of CWDs is usually nonspecific, with a restrictive lung pattern, and sleep-disordered breathing frequently occurs with sleep hypoventilation preceding diurnal respiratory failure.[4]

Noninvasive ventilation (NIV) is commonly used to treat CWDs that result in CHRF combined with hypoventilation symptoms (fatigue, morning headache, hypersomnolence, tiredness, or dyspnea) or with the development of related complications. NIV improves hypoventilation symptoms, arterial blood gases (ABG), and pulmonary function test (PFT) results, and it prolongs survival.[5-8] Data on the benefits of short-term NIV are mostly available from uncontrolled trials or studies with larger and more consistent samples of patients with neuromuscular disorders. In a meta-analysis, no significant difference between volume- and pressure-cycled NIV was found in terms of survival.[2] Long-term oxygen therapy (LTOT) alone was associated with worse survival of CWD patients when compared with NIV.[7,8]

The expected survival for patients with CHRF due to kyphoscoliosis and TbS are 8 and 3 years, respectively. Factors such as female sex, younger age, higher BMI, higher Pao_2, and lower $Paco_2$ appear to be favorable independent prognostic factors in CWD patients treated with NIV or LTOT.[9]

The present study aimed to characterize and evaluate the survival of patients with CWD under follow-up after starting NIV. The primary outcome was survival time since NIV treatment initiation.

The authors conducted a retrospective descriptive analysis involving adult patients with CWD on home NIV who were followed up at a pulmonology outpatient clinic between January of 2010 and January of 2022.

Clinical data with information about treatment and mortality were collected from the medical records of the patients. PFT and polysomnography results (at baseline) and ABG analysis (at baseline and during NIV treatment) were also obtained. Comorbidities were classified using the Charlson Comorbidity Index (CCI), which predicts mortality using a score that assigns weights (1, 2, 3, or 6) to each condition that a patient has.[10]

Statistical analysis was performed using the IBM SPSS Statistics software package, version 28 (IBM Corporation, Armonk, NY, USA). Statistical significance was set at $p < 0.05$. Categorical and quantitative variables were described as absolute and relative frequencies or as means ± standard deviations. Comparisons between survivors and nonsurvivors were performed with t-tests for independent samples for continuous variables and with chi-squared tests for categorical variables. To analyze the overall sample and to compare survivors according to their diagnosis we used the Mantel-Cox, Breslow, and Tarone-Ware tests. The Cox proportional hazards model was employed to adjust the variables. The selection of independent variables for the multivariate Cox model was based on statistical significance and on curves that presented proportional risks in the univariate analysis.

During the 12-year study period, 39 CWD patients on NIV were followed. The mean age was 60.2 ± 16.4 years, and there was a predominance of females (51.3%) and nonsmokers (82.1%). In this cohort of patients with CWD and CHRF, idiopathic kyphoscoliosis (66.7%) and acquired abnormalities of the thoracic cage, mainly TbS (33.3%), were diagnosed. The mean CCI was 2.1 ± 1.1, considering that CWD is a chronic pulmonary disease. Descriptive summary statistics and comparisons between survivors and nonsurvivors are displayed in Table 1.

A restrictive lung pattern and a simultaneous diagnosis of obstructive sleep apnea were found in 51.3% and in 23.1% of the overall sample, respectively. At baseline (prior to NIV treatment), ABG analysis revealed CHRF (Pao_2 = 61.1 ± 9.7 mmHg; and $Paco_2$ = 59.5 ± 13.0 mmHg). After NIV initiation, both Pao_2 (an increase of 14.8 ± 14.5 mmHg) and $Paco_2$ (a decrease of 15.1 ± 11.7 mmHg) improved.

NIV was initiated in the presence of hypoventilation symptoms plus CHRF and in that of acute hypercapnic respiratory failure in 53.8% and in 46.2% of the sample, respectively. Patients with hypoventilation due to other respiratory diseases were excluded from the study. Most of the patients underwent pressure-targeted mode of NIV (87.2%) and wore facial masks (79.5%). LTOT was simultaneously used with NIV in 66.7% of the patients, with a mean flow rate of 1.8 ± 0.8 L/min.

In our sample, the 12-year and 5-year mortality rates were 46% and 15%, respectively. Mortality rates were higher in patients with TbS than in those with kyphoscoliosis (54% vs. 42%). The median survival time since NIV initiation was 146.0 ± 19.4 months, and no differences were found between the groups of diagnosis.

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Table 1. Descriptive statistics and comparison between survivors and nonsurvivors.[a]

Variable	Group		p	Total
	Survivor (n = 21)	Nonsurvivor (n = 18)		(N = 39)
Demographics				
Female sex	9 (42.9)	11 (61.1)	0.26	20 (51.3)
Age at follow-up initiation, years	58.3 ± 15.2	62.4 ± 17.8	0.22	60.2 ± 16.4
Smoking status				
Current smoker	1 (4.8)	0 (0.0)	0.64	1 (2.6)
Former smoker	3 (14.3)	3 (16.7)		6 (15.4)
Never smoker	17 (81.0)	15 (83.3)		32 (82.1)
BMI, kg/m^2	25.4 ± 5.3	24.7 ± 6.1	0.35	25.1 ± 5.6
Diagnosis				
Kyphoscoliosis	15 (71.4)	11 (61.1)	0.46	26 (66.7)
Tuberculosis sequelae	6 (28.6)	7 (38.9)		13 (33.3)
Comorbidity				
CCI	1.8 ± 0.9	2.5 ± 1.2	0.03	2.1 ± 1.1
PFT at baseline				
Normal pattern	3 (14.3)	0 (0.0)	0.20	3 (7.7)
Restrictive pattern	11 (52.4)	9 (50.0)		20 (51.3)
Mixed pattern	7 (33.3)	9 (50.0)		16 (41.0)
FVC, % predicted	49.6 ± 18.1	38.0 ± 11.6	0.01	43.9 ± 16.2
FEV_1, % predicted	43.4 ± 15.5	34.2 ± 10.9	0.02	38.9 ± 14.1
TLC, % predicted	62.0 ± 18.1	63.4 ± 9.2	0.43	62.6 ± 14.4
MIP, % predicted	42.5 ± 16.5	39.0 ± 18.4	0.35	41.2 ± 16.7
Polysomnography at baseline				
Respiratory disturbance index	19.9 ± 10.6	6.6 ± 1.6	0.01	16.9 ± 10.9
Minimum saturation, %	81.1 ± 6.8	81.2 ± 14.5	0.50	81.2 ± 9.8
Arterial blood gases				
Pao_2 at baseline, mmHg,	61.4 ± 10.6	60.7 ± 9.0	0.41	61.1 ± 9.7
Pao_2 after NIV initiation, mmHg	73.6 ± 12.7	69.9 ± 10.6	0.18	71.9 ± 11.7
$Paco_2$ at baseline, mmHg	54.9 ± 6.0	74.1 ± 11.5	0.01	64.0 ± 13.2
$Paco_2$ after NIV initiation, mmHg	46.2 ± 8.6	50.2 ± 8.5	0.08	48.1 ± 8.7
NIV				
Age at initiation, years	62.5 ± 10.8	65.4 ± 17.5	0.27	63.8 ± 14.2
Symptoms at initiation				
Hypoventilation and chronic hypercapnia	10 (47.6)	11 (61.1)	0.40	21 (53.8)
AHRF	11 (52.4)	7 (38.9)		18 (46.2)
Pressure-targeted mode	19 (90.5)	15 (83.3)	0.65	34 (87.2)
Facial mask	16 (76.2)	15 (83.3)	0.70	31 (79.5)
Nasal mask	5 (23.8)	3 (16.7)		8 (20.5)
LTOT + NIV				
LTOT	12 (57.1)	14 (77.8)	0.17	26 (66.7)
Flow rate, L/min	1.8 ± 0.6	1.7 ± 0.9	0.35	1.8 ± 0.8

CCI: Charlson Comorbidity Index; PFT: pulmonary function test; NIV: noninvasive ventilation; AHRF: acute hypercapnic respiratory failure; and LTOT: long-term oxygen therapy. [a]Values expressed as n (%) or mean ± SD.

Nonsurvivors presented with more comorbidities, lower FVC and FEV_1 in % of predicted values, lower respiratory disturbance index, and higher $Paco_2$ at baseline than did survivors. Older and female patients using LTOT showed a trend toward higher mortality, but the difference was not statistically significant.

Univariate Cox analysis identified the following variables as significant predictors of mortality: CCI (hazard ratio [HR] = 1.70; p = 0.02), Pao_2 after NIV initiation (HR = 0.95; p = 0.05) and $Paco_2$ at baseline (HR = 1.03; p = 0.01). No significant differences were found regarding demographic variables, diagnosis, PFT results, polysomnography results, NIV mode, mask use, and LTOT use. In the multivariate Cox analysis, lower Pao_2 after NIV initiation (HR = 0.93; p = 0.01) and higher $Paco_2$ at baseline (HR = 1.07; p = 0.01) were associated with mortality.

This retrospective study helps support the benefits of long-term NIV on morbidity and mortality in patients with CWD. This study showed a median survival time

of 12 and 13 years, respectively, for patients with kyphoscoliosis and TbS who were treated with NIV; therefore, survival was extended in 4 and 10 years, respectively, when compared with previous evidence.[9]

Some of the potential strengths of the design of this study were the homogeneity of the cohort and the long follow-up period. To the best of our knowledge, this is the largest cohort of CWD patients on NIV reported by a Portuguese center. This study has limitations, such as the small sample size, and the effects of NIV on quality of life and lung function were not evaluated. The data presented herein reflect the clinical expertise of a single institution and may not be fully representative of practices elsewhere.

In conclusion, the findings of the present study suggest that patients with CWD on NIV may have their risk of mortality reduced, which can be predicted based on $Paco_2$ at diagnosis and on Pao_2 after NIV initiation.

AUTHOR CONTRIBUTIONS

JAB: study conception and design; data collection; statistical analysis; and drafting and review of the manuscript. CR and FF: critical review of the manuscript. All of the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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A new trigger for an old problem-neurogenic pulmonary edema related to intrathecal chemotherapy with pemetrexed

Elaine Aparecida Forgiarini[1], Milena Tenorio Cerezoli[2], Augusto Kreling Medeiros[3], Marcos Aurélio Fonseca Magalhães Filho[1], Felipe Marques da Costa[2]

TO THE EDITOR:

Neurogenic pulmonary edema (NPE) is a noncardiogenic edema defined as acute respiratory distress triggered by a central nervous system (CNS) insult. The most common causes are head trauma, intracranial hemorrhages, and seizures.[1-4] Here, we present the first case of NPE related to intrathecal pemetrexed treatment.

A 34-year-old female undergoing systemic treatment for metastatic EGFR-mutated non-small cell lung cancer (NSCLC) with osimertinib presented to the hospital with symptoms of meningeal progression. In this context, an electively Ommaya catheter was inserted into the third ventricle for intrathecal treatment, and the patient started receiving intravenous infusion of dexamethasone (8 mg/day). After the procedure, SpO_2 on room air, RR, and HR were 97%, 16 breaths/min, and 85 bpm, respectively. The fluid balance remained close to zero, and no blood transfusion was necessary.

Five days later, intrathecal pemetrexed was administered via an Ommaya catheter (pemetrexed 50 mg plus dexamethasone 5 mg dissolved in 0.9% sodium chloride solution to prepare a 5-mL solution). Approximately 16 h after infusion, the patient complained of shortness of breath, cough, and tachycardia. Pulmonary auscultation showed crackles at the lung bases. HR and SpO_2 were 150 bpm and 80% on room air, respectively. Blood pressure was 140/90 mmHg. No sign of intracranial hypertension was observed. Oxygen supplementation was started with a non-rebreathing mask (10 L/min).

Bedside chest X-ray (CXR) showed bilateral lung opacities in the middle and lower fields and possible right pleural effusion (Figure 1A), and a chest CT confirmed extensive bilateral ground-glass opacities, relatively symmetrical, sometimes tending to consolidate, along with septal thickening and small right pleural effusion (Figure 1C). The CT also ruled out thromboembolism. Although there was no previous CXR for comparison, the patient had performed a thoracic spine MRI a few days before (Figure 1D), which revealed that the lungs had no diffuse abnormalities, reinforcing the hyperacute scenario. There were no clinical signs of infection. Serum electrolytes, procalcitonin, renal function, troponin, NT-proBNP (< 125 pg/mL), blood count, and echocardiogram were unremarkable. A bronchoscopy was performed, and the BAL fluid analysis ruled out infection.

The patient was referred to the ICU; non-invasive ventilation (NIV) was initiated in a bilevel ventilation mode (V_T = 6 mL/kg) in 120-min sessions every 8 h, and the patient was weaned from oxygen therapy 5 days later. No antibiotics were used. Control CXR (Figure 1B) and CT after two weeks (Figures 1E and 1F) revealed a significant reduction of lung opacities (Figure 1B). Despite the resolution of respiratory symptoms, the patient was referred to exclusive palliative care and died 60 days later.

The clinical scenario was an acute episode of tachycardia and respiratory distress in a young female after intrathecal pemetrexed for treating metastatic NSCLC. Although diffuse lung disease is not specific in imaging, the CXR findings combined with the quick onset of symptoms and a relatively rapid resolution of the pulmonary impairment favored a diagnosis of acute lung edema with a potential causative factor (intrathecal pemetrexed). The main differential diagnoses were ruled out, including cardiogenic and nephrogenic edema, infection, and aspiration. Pemetrexed pneumonitis is also a differential hypothesis, but the short time interval between drug infusion and onset of symptoms is unfavorable to the usual period of pneumonitis initiation (weeks/months). Low-dose intrathecal pemetrexed also advises against pneumonitis. It was hypothesized, therefore, a neurogenic mechanism for the pulmonary edema as the major cause of the clinical aspects.

Pemetrexed is an anticancer chemotherapy drug used in the treatment of locally advanced or metastatic NSCLC cancer and its intrathecal administration can be performed in patients with meningeal progression. In a clinical trial,[5] intrathecal pemetrexed was administered in 30 patients; the median survival time was 9.0 months (95% CI, 6.6–11.4 months). The most common adverse events were myelosuppression, which occurred in 30% of patients, and neurotoxicity. No pulmonary events were reported.[5]

NPE was first described in 1908 and defined as an increase in pulmonary interstitial and alveolar fluid due to a severe sympathetic discharge after acute CNS involvement.[4] Determining the actual prevalence of NPE is challenging due to the complex diagnosis. Several different CNS triggers have been identified, including infectious diseases (most common), cerebral bleeding, traumatic brain injury, epilepsy, stroke, and others.[6]

The pathogenesis of NPE is poorly understood but is thought to be the consequence of a massive sympathetic discharge secondary to a medulla oblongata injury. This sympathetic storm leads to systemic vasoconstriction,

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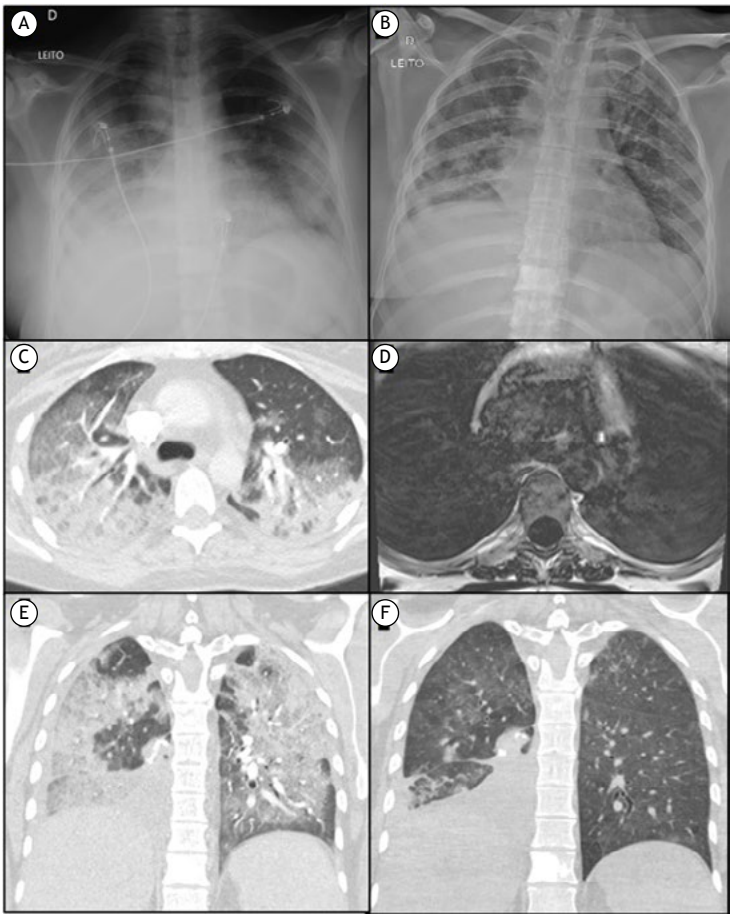

Figure 1. In A, bedside chest X-ray (CXR) demonstrating bilateral lung opacities in the middle and lower fields and possible right pleural effusion. In B, bedside CXR taken two weeks later showed significant improvement of lung opacities. In C, axial CT scan confirming lung involvement and extensive ground-glass opacities, sometimes tending to consolidate, along with septal thickening. In D, a spine MRI performed a few days prior to chest CT reliably ruled out previous lung diffuse abnormalities. Coronal CT scans confirmed significant improvement that were depicted in the control CXR (baseline CT scan in E vs. control CT scan taken two weeks later in F).

an increase in pulmonary blood volume, the rise of pulmonary capillary permeability, and subsequent accumulation of fluid in the alveolar space (pulmonary edema).[7,8]

NPE presents within minutes to hours of a CNS injury. However, more rapid or delayed onset has been described. Dyspnea is the most common symptom. Tachycardia is sometimes seen concomitantly with Takotsubo syndrome, which has a similar mechanism.[9] Physical examination generally reveals tachypnea and basilar crackles. CXRs typically show bilateral alveolar opacities and normal heart size.[6] The diagnosis of NPE include acute CNS involvement, Pao_2/FIO_2 ratio < 200 mmHg, bilateral opacities on chest imaging, no evidence of left atrial hypertension, and absence of other causes (infection, ARDS, aspiration).[10]

The management of NPE consists of addressing the underlying neurological cause and supportive therapy for the pulmonary edema,[5] based on supplemental oxygen therapy and NIV (including CPAP). In extreme cases, intubation with a certain level of PEEP.[6] The role of diuretics is still controversial, and there is no clear recommendation. Although most cases resolve within 48-72 h, the development of NPE is associated with poor long-term outcomes.[6]

This case report highlights the role of intrathecal pemetrexed treatment as a trigger for NPE. To our knowledge, this is the first description in the literature. Medical practitioners should be aware of the importance of early diagnosis and proper management.

Author contributions

FMC, EAF, and AKM: conception, planning, study design, and data collection. EAF, AKM, MAFMF, and FMC: drafting and writing the final version of the manuscript. FMC, MTC, and MAFMF: critical review of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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A rare combination: thrombotic and non-thrombotic pulmonary embolism

Felipe Marques da Costa[1], Milena Tenorio Cerezoli[1], Augusto Kreling Medeiros[1]

A 40-year-old man undergoing systemic treatment for metastatic distal rectal cancer presented with a two-week history of mild chest pain and shortness of breath. He underwent PET/CT as part of routine tumor assessment.

CT revealed multiple lesions consistent with metastasis and filling defects in bilateral pulmonary arteries. Fused PET/CT images revealed segments of filling defects with absolutely no FDG uptake, in contrast to others with high FDG avidity (Figure 1). This is in line with current knowledge in the literature that suggests that venous thromboemboli do not show FDG hypermetabolism. Conversely, tumor thrombi usually exhibit high FDG uptake.[1,2] Based on that, FDG-PET/CT can be a useful diagnostic imaging tool.

A diagnosis of combined thrombotic and non-thrombotic pulmonary embolism was made. The patient received anticoagulation therapy and a new line of systemic oncologic treatment.

Venous thromboembolism (VTE) is the third most frequent acute cardiovascular syndrome[3] and occurs in up to 10% of cancer patients.[4] Pulmonary intravascular tumor emboli are seen in about 25% of autopsies of patients with solid malignancies, although the diagnosis is rarely made before death. Because tumor embolism and VTE are difficult to distinguish, the treatment should target the underlying malignant disease and VTE at the same time.[5]

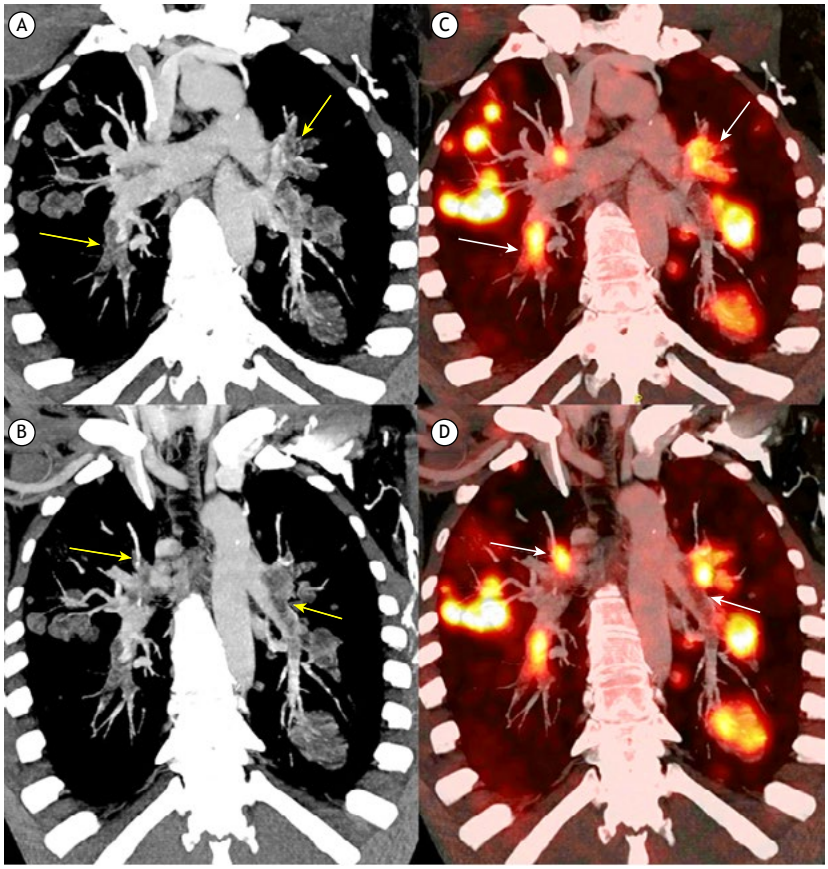

Figure 1. In A and B, coronal oblique maximum intensity projection CT reformations show the extent of the intravascular filling defects (yellow arrows). While the more expansive and nodular defects are easily seen as tumor lesions, those confined to the intravascular space are more difficult to differentiate from non-tumor thromboembolism. In C and D, coronal oblique fused PET/CT images demonstrate the extent of FDG hypermetabolism (white arrows). The fused images can separate the filling defects that have no FDG avidity and are therefore non-tumor lesions from those that show significant hypermetabolism indicating intravascular tumor embolism.

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AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

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Does virtual professional support improve the effectiveness of home pulmonary rehabilitation?

Johnnatas Mikael Lopes[1], Achilles de Souza Andrade[2], Bruno da Silva Brito[3], Rafael Limeira Cavalcanti[4]

When reading the article by Şahın et al.[1] (Effects of a home-based pulmonary rehabilitation program with and without telecoaching on health-related outcomes in COVID-19 survivors: a randomized controlled clinical study) published in this issue of the *Jornal Brasileiro de Pneumologia*, we identified elements that could have explored the results better with great clinical implications.

Starting from the central question of the research, the results in Table 3[1] showed that there were no major effects on the investigated outcomes between the groups. However, there was an exclusive effect of time, in which case it would be applied to the two groups indifferently, or there would be an effect of time-group interaction, in which case one of the groups would have a different behavior over time.

Let's exemplify: The FVC reveals only the major effect of time, when both groups increased their indicator, but in a large magnitude (Cohen's d > 0.8), which was not highlighted by the researchers. The same occurs with the six-minute walk distance outcome; the study group has a d = 2.30 and the control group has a d = 2.07. This shows the great clinical effect of pulmonary rehabilitation on FVC in these individuals.

The modified Medical Research Council scale outcome has a time-group interaction that needs to be analyzed first. It was observed that the study group evolved better over time than did the control group, with a magnitude of d = 4.51 in the intragroup analysis and d = 2.10 in the intergroup analysis, that is, telecoaching clinically enhanced this outcome. This also occurred with the social aspects when comparing the study and the control groups (d = 5.88 vs. d = 2.14), a clinical effect almost two times greater (d = 1.83). The isolated interpretation of the partial eta only allows measuring the explanatory power of the built model and not the specific effects of the factors that Cohen's d allows for balanced groups.[1]

These interesting findings reveal inconsistencies identified in the measures of the standard deviations of the groups presented in Table 3 and the distribution of the groups in Figure 2 in the study by Şahın et al.[1] Table 3[1] shows that the standard deviations of the study and control groups were the same both before and after the intervention for almost all outcomes.

This is minimally odd for interventions when individual variability follows distinct progressions. In figure 2,[1] on the other hand, the outcomes six-minute walk distance, modified Medical Research Council scale score, and perceived dyspnea and fatigue reveal distinct variability, which may lead to the invalidation of the application of factorial ANOVA.[2] It is suggested that the authors make explicit the real variability of the outcomes in order to obtain accurate values for the measures of clinical effect.

Finally, we recommend a data analysis using a generalizable mixed model in order to minimize independence biases of residues of repeated measures and the heterogeneity of variance that are apparent in the published results.[3]

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Authors' Reply

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We thank the authors for their interest in our study comparing the effects of a home-based pulmonary rehabilitation program with and without telecoaching on health-related outcomes in COVID-19 survivors.[1] We are grateful for the valuable comments on our manuscript and are happy to respond to their comments as follows.

Firstly, since our assumptions meet the general linear models, we used two-way ANOVA for repeated measures from general linear models in our study. While building the model, we set it up in factorial design. Therefore, we tried to reduce the heterogeneity for the variances as much as possible.[2]

Then, we would like to underline that the values in Table 3[1] in our study are presented as the standard error of mean, not standard deviation. This misunderstanding can cause the effect size values calculated by the authors to be confusing for the readers. Considering that the standard error of mean is calculated with the formula (standard deviation/√n), they have been specified as too large. Therefore, we calculated the Cohen's effect size values of our main results with the formula d = (X1 − X2)/standard deviation for both groups (ds = d_{study}; dc = $d_{control}$).[3] We interpreted our results with the effect size values to summarize their clinical significance.

After the rehabilitation program, the effect size of the change in FVC was moderate in the study group but higher than in the control group (ds = 0.56; dc = 0.48). As we mentioned in our study, the most important clinical gain in the study group was in the daily life dyspnea score (ds = 1.30; dc = 0.43). Large effect size was obtained in the six-minute walk distance in both groups, being relatively higher in the study group (ds = 0.90; dc = 0.82). Exertional dyspnea and fatigue scores improved only in the study group, and their effect sizes were found to be d = 0.70 and d = 0.64, respectively. While the effect size calculated for our results regarding the gains in muscle strength was d > 0.5 for deltoid and quadriceps femoris muscles in the study group, the effect size obtained for biceps muscle strength in the control group was higher than in the study group (d > 0.5).

The effect size of the change in the Saint George's Respiratory Questionnaire activity score was higher in the study group (ds = 0.62; dc = 0.56), and the effect size of the change in the impact (ds = 0.73; dc = 0.88), and of the total score (ds = 0.84; dc = 0.90) was higher in the control group. The highest effect size in the Medical Outcomes Study 36-item Short-Form Health Survey in the study group was in the social functioning domain (ds = 1.28; dc = 0.46). Although there was a small decrease in anxiety and depression scores in both groups, it was concluded that the effect size for these values was d < 0.50.

As a result, as emphasized in our study, although there were different gains on different variables in both groups, improvements in daily life dyspnea and social functioning were higher and had a larger effect size in the study group than in the control group.

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Abstracts

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

Chapter in a Book

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

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

Electronic publications

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

Homepages/URLs

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

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Referências:

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

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Chegou: EGURINEL® (pirfenidona)

O primeiro similar de pirfenidona do Brasil!

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

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

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

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