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HIGHLIGHT

Effects of air temperature on the risk of death from COPD

Mobile health applications designed for self-management of chronic pulmonary diseases

Lady Windermere syndrome

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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Idiopathic bronchiectasis. What are we talking about?

Jose Daniel Gómez-Olivas[1], Grace Oscullo[1], Miguel Ángel Martínez-García[1,2]

The origin of bronchiectasis is marked by a necessary underlying pathophysiological condition: the existence of inflammation in the bronchial wall. In most patients, this consists of mixed inflammation with a predominance of neutrophils, although there is also an increase in the number of eosinophils and mononuclear cells in some individuals.[1,2] This inflammation has many origins, although in most cases it is caused by a bronchial infection by pathogenic microorganisms (usually bacteria and mycobacteria)[3,4] or by the bronchial wall's inflammatory reaction to the underlying disease (either intra or extrapulmonary) responsible for bronchiectasis[1] or in an exacerbation period.[5] Sometimes, however, the origin of this inflammation is unknown. Be that as it may, pro-inflammatory products (especially proteases and elastases) derived from both the immune cells themselves (especially neutrophils) and pathogenic microorganisms are the ultimate causes of the airway damage and typical images of lumen dilation with thickening of the bronchial wall observable on CT.[1,2] It is important to consider that the diagnosis of bronchiectasis requires this inflammatory pathophysiological substrate to be accompanied by a clinical impact on the patient, usually in the form of chronic cough with expectoration, sometimes with a purulent component, and exacerbations of an infectious profile.[5,6]

One of the peculiarities of bronchiectasis is its great clinical heterogeneity, mainly determined by dozens of possible etiologies, both local and systemic. All national and international guidelines on bronchiectasis recommend an exhaustive etiological study, particularly to diagnose potentially treatable etiologies. However, despite the performance of multiple tests, some of the causes of bronchiectasis are still not being identified reliably, giving rise to what has come to be called "idiopathic bronchiectasis."[1]

There is no precise definition of idiopathic bronchiectasis. Although from a theoretical point of view it would refer to the lack of any specific etiology, in most cases it is due to ignorance of the existing cause or an incomplete etiological analysis. The percentage of idiopathic bronchiectasis varies enormously in the different registries in the world. Thus, in the recently published data from the European Bronchiectasis registry,[7] comprising almost 17,000 patients from 28 countries, the overall percentage of idiopathic bronchiectasis was 38.1%, the overall percentage of idiopathic bronchiectasis was 38.1%, similar to those observed in the South Korean and the Australian registries (41% and 32.5%, respectively).[8,9] However, when the various European countries that have contributed with data to the European registry[7] are analyzed separately, the percentages vary enormously, from almost 60% in Poland to less than 10% in Croatia, Slovenia, Bulgaria, and North Macedonia. Broadly speaking, the percentage of idiopathic bronchiectasis was higher in Southern Europe (36.3%) and in the UK (44.5%) than in Northwest Europe (28.8%) and Central-East Europe (26.4%).[7]

Paradoxically, some countries with fewer health care resources, such as India[10] and some Latin American countries,[11] present substantially lower percentages of idiopathic bronchiectasis (22.4% and 26%, respectively). Finally, a third pattern can be seen in China, with very high relative percentage of idiopathic bronchiectasis (66% in Shangong and 46% in Guantzu).[12,13]

What could be the causes of this enormous heterogeneity in the percentages of idiopathic bronchiectasis? The explanation may be multifactorial. On the one hand, as it has already been remarked, there is no clear definition of idiopathic bronchiectasis, or, in other words, there is no agreement on the necessary etiological tests to perform before considering bronchiectasis as idiopathic due to the substantial variations in the definition used by different countries. On the other hand, it is possible that there are factors capable of causing bronchiectasis which are not generally subject to etiological tests, such as gastroesophageal reflux and long-standing mild immunodeficiencies (e.g., the quantitative or functional deficit of IgG subclasses).

One interesting conundrum is why countries such as India[10] or some areas in South America,[11] with no specific bronchiectasis guidelines, present a significantly lower percentage of idiopathic bronchiectasis than other countries with greater health care resources. This can probably be explained by the fact that idiopathic bronchiectasis is measured as a percentage, and that, in these countries, post-infectious (including post-tuberculosis) bronchiectasis clearly predominates. Something similar can be deduced from the data of the European registry,[7] in which those countries with less than 10% of idiopathic bronchiectasis are the ones that present a higher percentage of post-infectious bronchiectasis. However, it is important to reflect that post-infectious bronchiectasis (especially when attributable to childhood infections) is usually diagnosed via a process of elimination, which can lead to an underestimate of the percentage of idiopathic forms. Perhaps this problem is less noticeable in post-tuberculosis bronchiectasis, since its usual characteristics (previous pulmonary tuberculosis and bronchiectasis at the site of the pulmonary infiltrate, predominantly in the upper lobes, together with cavernous areas) tend to give rise to fewer diagnostic errors. This circumstance could explain the low rate of idiopathic bronchiectasis found in countries

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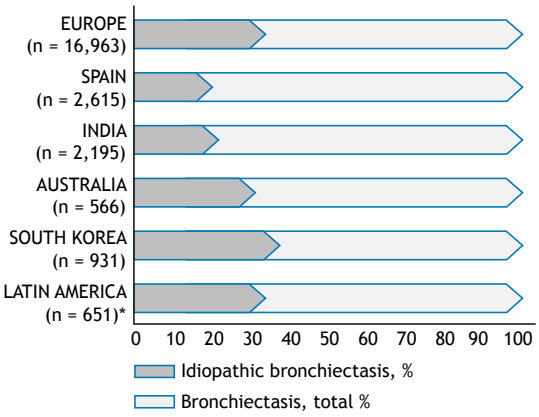

Figure 1. Relative percentages of idiopathic bronchiectasis. Based on published national and international registries and large bronchiectasis databases. *Five series included: three from Brazil (n = 474; range of idiopathic bronchiectasis: 25.3-44.7%), one from Argentina (n = 108; 34.2% of idiopathic bronchiectasis), and one from Chile (n = 69; 59% of idiopathic bronchiectasis).

such as India[10] and various Latin American[11] and European countries.[7]

As regards the evolution over time of the percentage of idiopathic bronchiectasis, there are hardly any data in the literature. Only in Spain can a significant reduction in the percentage of this type of bronchiectasis be observed from the beginning of the 21st century to the present day (from 24.2% to 18.2%), maybe because Spain has bronchiectasis regulations dating back more than 15 years, including a more recent one (from 2018) with clear algorithms for performing diagnostic tests to avoid the term "idiopathic" as much as possible. Spain has also been collecting data from patient registries for 20 years. However, in view of the increase in post-infectious bronchiectasis, from 30% in the first Spanish registry (2002-2011) to 40% in the second one (2015-2019) ,[14,15] it cannot be ruled out that some idiopathic bronchiectasis has wrongly been attributed to post-infectious bronchiectasis.

In short, it is important to recognize that the term "idiopathic bronchiectasis" does not mean, in most cases, bronchiectasis with no etiology, but rather an etiology of unknown origin—in most cases derived from the lack of performance of tests needed to rule out known causes. It is absolutely essential, in this respect, to at least rule out potentially treatable causes, as well as to reach an international consensus that clearly defines general and specific tests to be performed before bronchiectasis can be considered idiopathic.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

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Questionnaires and risk scores: how to transform research projects into practical tools

Frederico Leon Arrabal Fernandes[1]

COPD is a heterogeneous, progressive disease that is potentially serious. Given the complexity of COPD and its impact on the quality of life of patients, multidisciplinary approaches and effective management strategies are needed. Questionnaires and risk scores assessing various dimensions of COPD have been translated into Portuguese and validated for use in Brazil.

The variety of questionnaires reflects the complexity of COPD and the need to understand the many different facets of the disease. Currently available COPD questionnaires include symptom questionnaires such as the modified Medical Research Council scale[1] and the COPD Assessment Test,[2] both of which have been incorporated into the GOLD classification of COPD severity,[3] as well as questionnaires assessing activities of daily living,[4,5] the impact of COPD and patient health status,[6,7] and quality of life.[8,9] Risk scores assessing COPD are varied and include screening questionnaires,[10] scores for predicting the risk of developing COPD,[11] and scores for predicting the risk of mortality or complications from acute exacerbations of COPD (AECOPD). There is a wide variety of currently available tools for COPD assessment, and a quick literature search shows that much of the research into COPD focuses on developing, translating, and adapting questionnaires.

This is no coincidence. Studies aimed at developing and validating questionnaires have proven to be a valuable opportunity to teach research methods to graduate students and enrich their training. Questionnaire development requires knowledge not only of the disease itself but also of statistics and psychometrics, contributing to the advancement of research and enriching the academic and scientific training of future researchers.[12]

COPD is a multifaceted disease, and clinical evaluation should include a history of respiratory symptoms, comorbidities, treatment adherence, and correct inhaler use. Because many of the currently available questionnaires are lengthy and complex, it can be difficult to use them in clinical practice. It is impractical to use several different questionnaires (or a single long questionnaire) in the evaluation of patients with AECOPD.

When developing a questionnaire or risk score for COPD, researchers must keep in mind the applicability of the questionnaire or score in a clinical setting. Such tools should be designed to provide relevant information to support medical decision making regarding hospitalization, the need for noninvasive ventilation, and intensive care monitoring.

Questionnaire data should aid in monitoring disease progression and evaluating treatment efficacy. More importantly, questionnaires should be objective, easy to understand, and easy to use, and the results should be easily accessible and interpretable.[12]

In this issue of the *Jornal Brasileiro de Pneumologia*, Gomes et al. report the results of a study evaluating the performance of four different risk scores in predicting outcomes during and after hospitalization for AECOPD.[13] The study was a retrospective study involving 119 patients admitted with AECOPD and evaluating various outcomes. The National Early Warning Score 2 (NEWS2) and $NEWS_{88-92\%}$ were found to be useful for outcomes such as prolonged hospitalization and use of noninvasive ventilation, although they were not as effective as the Dyspnea, Eosinopenia, Consolidation, Acidemia, and atrial Fibrillation (DECAF) and modified DECAF scores in predicting mortality. The $NEWS2_{88-92\%}$ was associated with an 8.9% reduction in the number of individuals classified as requiring close, continuous observation in comparison with the NEWS2. Although the study was a single-center study and the sample size was too small for definitive conclusions, the results suggest that the $NEWS_{88-92\%}$ is superior to the NEWS2 in this context.[13]

Not surprisingly, however, the study showed that each questionnaire performed better in assessing the specific outcome for which it was designed. The NEWS2 scores are used in order to assess the risk of clinical deterioration during hospitalization. The DECAF scores are used in order to assess the risk of mortality in patients with AECOPD. This finding is consistent with existing knowledge in the literature and underscores the importance of using appropriate tools for specific purposes.

In summary, questionnaires and risk scores play a crucial role in COPD research and clinical management. However, a balance should be struck between a comprehensive approach to COPD and the ease of use of COPD questionnaires and scores so that such tools can be effectively used in everyday life. When developing COPD questionnaires and scores, researchers and health professionals should focus on contributing significantly to advances in the treatment and quality of life of patients with COPD rather than simply using such tools as projects for the academic training of future researchers.

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Pulmonary hypertension

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A 29-year-old man presented with exertional dyspnea and syncope. He had been diagnosed with idiopathic pulmonary hypertension (PH) 7 years prior. A chest CT showed marked dilatation of the pulmonary artery trunk (Figure 1).

PH is a progressive disease of the pulmonary arteries that is characterized by marked remodeling of the pulmonary vasculature and a progressive increase in pulmonary vascular pressure, leading to right ventricular hypertrophy and remodeling. PH is defined as a mean pulmonary artery pressure greater than 20 mmHg at rest, leading to increased pulmonary vascular resistance. It may be idiopathic or arise in the setting of other clinical conditions. Diagnosis and treatment planning are made on the basis of clinical and hemodynamic criteria, pulmonary function test results, and radiological and histological findings, usually at specialized referral centers. The clinical picture is nonspecific and may include dyspnea, limitations in daily activities, retrosternal and chest pain, dizziness, cyanosis, and hemoptysis, among other findings. Death usually results from right ventricular failure. It is of note that pulmonary arterial hypertension is a subgroup of PH. This subgroup includes the idiopathic form.[1,2]

The classic imaging findings of PH can be divided into three categories: vascular, cardiac, and parenchymal. The chief vascular finding is dilatation of the pulmonary artery trunk, which should be measured in the axial plane at the level of its bifurcation and orthogonal to its long axis. A diameter equal to or greater than 29 mm should be considered abnormal. We should also consider the ratio of the diameters of the pulmonary artery and aorta, which should be measured in the same plane as that in which the aforementioned finding is measured. The pulmonary artery diameter should not be greater than the ascending aorta diameter. It should, however, be considered that main pulmonary artery dilatation may develop in pulmonary fibrosis patients in the absence of PH. Other vascular findings include a ratio of the diameters of arteries and bronchi > 1, observed in three or four lung lobes, and bronchial artery dilatation (hypertrophy). Cardiac findings include hypertrophy or dilatation of the right cavities, leading to inversion of the interventricular septum. Parenchymal findings include the presence of a mosaic attenuation pattern and the presence of centrilobular ground-glass nodules.[1,2]

Extensive clinical, laboratory, and hemodynamic studies did not determine the specific cause of this patient's PH, which was therefore classified as an idiopathic form.

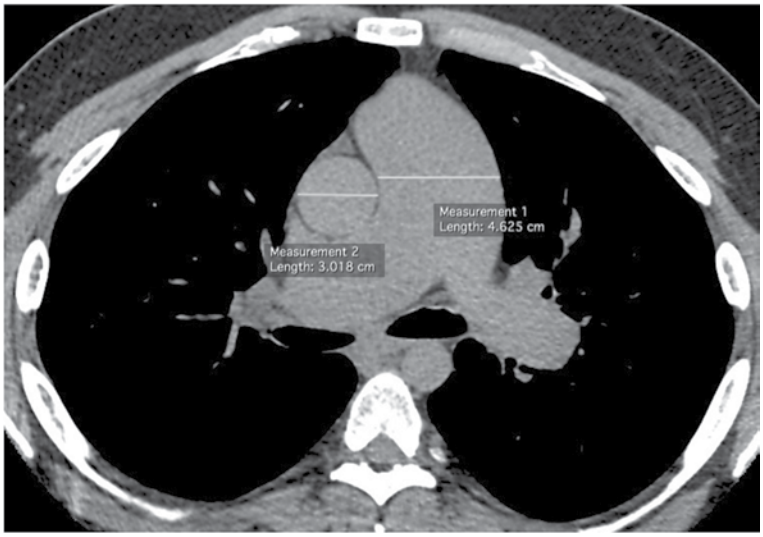

Figure 1. Axial chest CT scan with mediastinal window settings shows an increased pulmonary artery diameter (46 mm — normal up to 29 mm). Also note that this diameter is greater than the aortic diameter measured in the same plane (30 mm).

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Twelve tips to manage a research project—advice for the young investigator

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ILLUSTRATIVE SCENARIO

During the 2023 ATS-ALAT MECOR course recently held in Panama, a group of early career physicians from Latin America shared their experience on conducting research in their home countries. They expressed excitement about getting involved in research studies but were feeling anxious at the prospect of successfully carrying out both clinical and research activities. In search of guidance, they created a group to exchange experience and, inspired by the book by Hulley et al.,[1] they developed the following guide:

BEGINNER'S GUIDE TO RESEARCH PROJECT MANAGEMENT: 12 ESSENTIAL TIPS

1. Choose a familiar topic: start by selecting a topic that you enjoy and are knowledgeable about. This will make your research project more pleasurable, and likely to achieve high quality. It will also allow you to identify knowledge gaps more easily. Make sure you carry out a comprehensive review of the literature available, identifying high-quality articles which could potentially be references for your project and finalized manuscript.
2. Find a mentor, not just an advisor: look for a mentor who has experience in mentoring, shares your interest in the topic, has availability to meet regularly, and can guide you effectively.

Figure 1. Tips to research project management: choose a knowledgeable topic, find a mentor and a team, understand your institution and the ethics committee, plan your research, make a reasonable schedule, consult a statistician, and disseminate the results.

3. Understand your institution: identify what resources are available in your department or explore alternatives such as public databases and collaborations with other research groups.
4. Plan your research: develop a feasible research protocol that describes the research question and hypothesis, study design, study population, the intervention or exposure, and expected outcomes. Write out the research plan following your institution's guidelines. Be reasonable!
5. Develop a comprehensive statistical analysis plan: make sure you understand your study design, variables, and the appropriate statistical tests and processes. Whenever possible, consult and work with a statistician prior to data collection and throughout the study.
6. Make ethics a priority: ensure that your project addresses ethical aspects, including risks, benefits, and compliance with research guidelines.
7. Consult the Research Ethics Committee: engage with your institution's Ethics Committee or Scientific Council to understand their requirements and to receive valuable guidance. Some offer free consultations that can save you a lot of wasted time going back and forth with the project.
8. Create a manual of procedures: develop a manual of procedures that describes, in detail, how the research will be conducted, data collection procedures, and data storage processes. Test data collection forms to ensure they are appropriate for the study.
9. Set a realistic schedule: make sure to create a schedule that accommodates unexpected delays and that the duration of each step is feasible in your environment. Research often encounters unforeseen obstacles.
10. Ensure data collection uniformity: train your data collection team using a standardized procedure plan to ensure consistency.
11. Expect the unexpected: keep your focus when unforeseen situations or delays arise during planning and execution. These are common in research. Stay calm and carry on.
12. Disseminate research results: the work is only half done after data are collected. The final step is documenting your findings for an oral presentation, a poster at conferences, or an original manuscript for publication.

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

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BACKGROUND

Interstitial lung disease (ILD) encompasses a large and heterogeneous group of diffuse parenchymal disorders which are typically associated with low lung compliance and impaired gas exchange. A comprehensive evaluation of pulmonary function (spirometry, "static" lung volumes, DLco, oxygenation) is recommended in the initial assessment and follow-up in all patients with suspected or confirmed ILD.[1]

OVERVIEW

A 78-year-old never smoking woman reported a 12-year history of dry cough which had been unsuccessfully treated as secondary to gastroesophageal reflux disease. She also complained of progressive dyspnea (mMRC = 2) over the past few months. Physical examination revealed fine, Velcro-like crackles over the lower lung fields. Spirometry showed normal FEV_1 and FVC with an FEV_1/FVC ratio above normal (113% of the predicted value);

Assessing dysfunction at rest

- Spirometry may suggest a restrictive ventilatory defect: ↓ FVC plus ↔ or ↑ FEV_1/FVC
- ↑ mid-expiratory flows may unravel incipient/mild restriction
- ↓ TLC confirms restriction; however, ↓ FRC and ↓ RV may coexist with still-preserved TLC
- (F)VC might be preserved despite extensive fibrosis if TLC and RV decrease in tandem
- Although all "static" lung volumes are typically reduced, RV may be relatively preserved, resulting in a high RV/TLC ("complex restriction")
- DLco might be reduced even when lung volumes are still within normal limits
  - o A severely reduced DLco (< 40%) and a low IC are strong predictors of disabling dyspnea

Assessing dysfunction on exercise

- The 6MWT is helpful in quantifying functional impairment and the severity of exertional hypoxemia
- Longitudinal interpretation of changes in the 6MWT distance should carefully consider known confounders, e.g., O_2 flows, walking aids, variations in body weight, locus of symptom limitation
- Continuous monitoring of SpO_2 might provide a better metrics of the overall burden of exertional hypoxemia than end-exercise SpO_2
- CPET might be helpful in exposing excessive ventilation for the metabolic demand and mechanical constraints in patients with "out-of-proportion" dyspnea
- Cycling-based CPET, however, usually underestimates the severity of exertional hypoxemia compared with walking (treadmill)

Uncovering evidence of, or risk factors for, disease progression

- Absolute decline in FVC ≥ 5% pred within 1 yr (e.g., from 50% to 45% pred)
- Absolute decline in Hb-corrected DLco ≥ 10% pred within 1 yr
- Any form of pulmonary fibrosis with one of the following in the past 2 years should be considered for lung transplant referral: relative decline in FVC ≥ 10% (e.g., from 60% to 54% pred); relative decline in DLco ≥ 15%; relative decline in FVC ≥ 5% in combination with worsening of respiratory symptoms or radiographic progression
- Other criteria for referral to lung transplant include: FVC < 80% pred, DLco < 40% pred, or increasing supplemental O_2 requirements at rest/exercise

Identifying prognostic factors at rest and exercise

- Evaluation of changes over time (6-12 months) usually provide more accurate prognostic information than baseline values alone
- FVC and DLco consistently remain in different multidimensional indexes to predict mortality in IPF, e.g., the GAP index (**G**ender, **A**ge, and **P**hysiology variables)
- Absolute decline in FVC > 10% pred, though smaller declines (5-10% pred) have also been associated with worse prognosis in IPF
- Low walking distance (< 207-350 m) and desaturation during the 6MWT
- Low peak $\dot{V}O_2$ (< 61% pred or ≤ 13.8 mL/kg/min) and high $\dot{V}E/\dot{V}co_2$ nadir (> 34 L/L) during CPET

Caveats and Pitfalls

- The bulk of the evidence derives from studies with patients with IPF
- The value of PFTs in the differential diagnosis of ILDs is limited, though IPF is typically associated with more severe hypoxemia than other prevalent ILDs, such as sarcoidosis and most connective tissue disease-lLDs
- Obstruction, alone or combined with restriction, might be seen in some ILDs, e.g., lymphangioleiomyomatosis. chronic eosinophilic pneumonia, hypersensitivity pneumonitis, sarcoidosis, and connective tissue disease-lLDs
- ↓ DLco (corrected for hemoglobin) in the presence of normal or near normal lung volumes should raise the suspicion of pulmonary vascular disease or combined pulmonary fibrosis and emphysema in subjects with a smoking history

Figure 1. Key physiological abnormalities in patients with interstitial lung diseases (ILDs) that underpin clinical complaints and represent risk factors for poor clinical outcomes. Some caveats and limitations of pulmonary function tests (PFTs) in this context are described in the bottom. FRC: functional residual capacity; IC: inspiratory capacity; 6MWT: six-minute walk test; CPET: cardiopulmonary exercise testing; pred: predicted; yr: year; Hb: hemoglobin; $\dot{V}O_2$: oxygen consumption; $\dot{V}E$: ventilation; and $\dot{V}co_2$: carbon dioxide production.

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conversely, TLC, RV, and DLCO were all reduced (67%, 57%, and 43% predicted, respectively). Chest HRCT indicated "probable" usual interstitial pneumonia. In this context, idiopathic pulmonary fibrosis was diagnosed after careful exclusion of other conditions associated with usual interstitial pneumonia.

Pulmonary function tests (PFTs) might provide ancillary information for ILD diagnosis, being instrumental to grade severity, gauge progression, and help in treatment choices (Figure 1). The typical spirometric findings of reduced FVC with a normal or increased FEV_1/FVC ratio might not be present in the initial stages of the disease. As this pattern is not always related to restriction, confirmation with measurements of lung volumes is usually required (i.e., TLC < lower limit of normal).[2] A common mistake is the assumption that a preserved FVC rules out restriction: a sizeable fraction of patients with early/mild ILD—as in the present case—shows low TLC but preserved (F)VC, provided RV decreases in tandem with TLC.[3] Not infrequently in mild disease, FVC is still preserved, but the mid-expiratory flows are supranormal, indicating increased lung elastic recoil. Despite spirometric values within normal range and normal-to-mildly reduced TLC, patients with mild fibrosis usually present with impaired gas transfer at rest (low DLCO), leading to an excessive ventilation to the metabolic demand during cardiopulmonary exercise testing.[4] Lower baseline FVC and DLCO, and oxygen desaturation during the six-minute walk test are known predictors of poor survival.[1] Recent data indicate that a severely reduced DLCO (< 40% predicted) signals multiple interconnected mechanisms (hypoxemia, low O_2 delivery, hemodynamic abnormalities, greater mechanical constraints) that jointly conspire to decrease exercise tolerance in these patients.[5] Repeated measurements of FVC and DLCO should be used in conjunction with the burden of respiratory symptoms and chest imaging to establish whether there is, or not, disease progression (Figure 1).

CLINICAL MESSAGE

"Full" PFTs (i.e., not only spirometry) associated with the six-minute walk test and, in selected cases, cardiopulmonary exercise testing, are important to ILD management across the spectrum of disease severity. Longitudinal assessment with the patient serving as the control of him/herself is paramount, paying particular attention to (F)VC in association with DLCO and exertional hypoxemia.

AUTHOR CONTRIBUTIONS

All authors contributed to conceptualization, writing, reviewing, and editing.

CONFLICTS OF INTEREST

None declared.

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Management of bronchiolitis and recurrent wheezing in preschoolers

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Wheezing is very common during the preschool years, with nearly 50% of children having at least one episode of wheezing. Preschool wheezing should be considered an umbrella term for distinctive diseases or phenotypes. Despite many efforts, there is a large gap in knowledge regarding preschool wheezing. This paper aims to review the main clinical definitions and updated clinical recommendations for wheezing in preschoolers.

The diagnosis of bronchiolitis is clinical, and the physician should recognize signs and symptoms of respiratory infection and wheezing in young infants. Peak incidence occurs between 3 and 6 months of age. In recent guidelines,[1] the definition includes only young infants. Although the same physiology can occur in toddlers (> 12 months), many clinical trials have excluded these children.[1] Acute bronchiolitis management is largely supportive, focusing on maintaining oxygenation. Supplementation should be recommended if their oxygen saturation is persistently lower than 92%.[2] Upper airway suctioning is not routinely recommended. Evidence suggests no benefits from bronchodilator or steroid use in young infants with a first episode of wheezing. Evidence for hypertonic saline is limited and not clearly defined. For infants with severe disease, the available data suggest an important role for high-flow nasal oxygen and noninvasive positive airway pressure ventilation to prevent respiratory failure.[1]

Respiratory syncytial virus (RSV) is a leading cause of respiratory disease in infants, especially in prematurely born infants. The use of RSV passive immunization targeting protection during the first 12 months of life may substantially reduce RSV burden. The WHO encouraged the use of preventive interventions for RSV.[3] Palivizumab is currently the most widely used prophylaxis for preventing RSV disease in infants. New monoclonal antibodies, such as nirsevimab, as well as maternal immunization, have been developed, which may protect infants during an entire RSV season with a single dose.[3]

RECURRENT WHEEZING OR REACTIVE AIRWAYS

Viral respiratory infections have been identified as the most frequent trigger of recurrent wheezing episodes in infants and toddlers, typically rhinovirus and RSV infections. Recurrent wheezing associated with infections can subsequently progress to asthma. The variable expression of early-life wheezing phenotypes may hinder the assessment and understanding of these diagnoses. Recognizing different phenotypic characteristics may help to manage recurrent wheezing in a preschool child (Figure 1). Considering the established efficacy of inhaled corticosteroids (ICs) in the management of asthma, multiple trials have studied the role of ICs in preschool children with recurrent viral wheezing. The use of IC was associated with more episode-free days, fewer exacerbations, and less frequent use of other medications.[4]

Several trials have also examined the role of the azithromycin for the treatment of wheezing episodes. The role of azithromycin in young children with recurrent wheezing remains uncertain, with the greatest evidence for its role leaning toward the prevention of subsequent episodes.[5] Results of clinical trials[1] showed that prevention is recognized as an important intervention to reduce disease burden, and the use of immunomodulation to improve protection is also gaining importance. In this respect, OM-85 is recognized as the most studied immunomodulatory agent currently available, whose efficacy makes it a valuable tool.[6] In particular, the combined use of OM-85 and vaccination was recognized as an effective approach to improve prevention strategies in order to reduce the burden of recurrent respiratory infections associated with wheezing episodes.[6]

CHILDHOOD ASTHMA AND OTHER POSSIBLE ETIOLOGIES

Asthma is the most common chronic respiratory condition in childhood worldwide, and children with the disease typically present with wheezing, shortness of breath, and cough. Asthma is triggered by a variety of factors, such as respiratory infections.[7] Asthma diagnosis in young children can be based on symptoms, presence of risk factors, or therapeutic response to treatment. In young children with a history of wheezing, a diagnosis of asthma is more likely if they present with wheezing or coughing that occurs with exercise or in the absence of respiratory infection; a history of other allergic diseases (eczema, food allergy, or allergic rhinitis); atopy or asthma in first-degree relatives; and clinical improvement within 2 months of IC treatment.[4] Wheezing episodes in young children with risk factors for asthma should be managed with inhaled short-acting β_2 agonists for relief of symptoms. To control asthma in young children, the use of regular daily low-dose ICs is suggested as the initial treatment.[4] Wheezing in preschool children can also be associated with other complex diseases, such as lung bronchiectasis, airway abnormality, and chronic infections. Patients with

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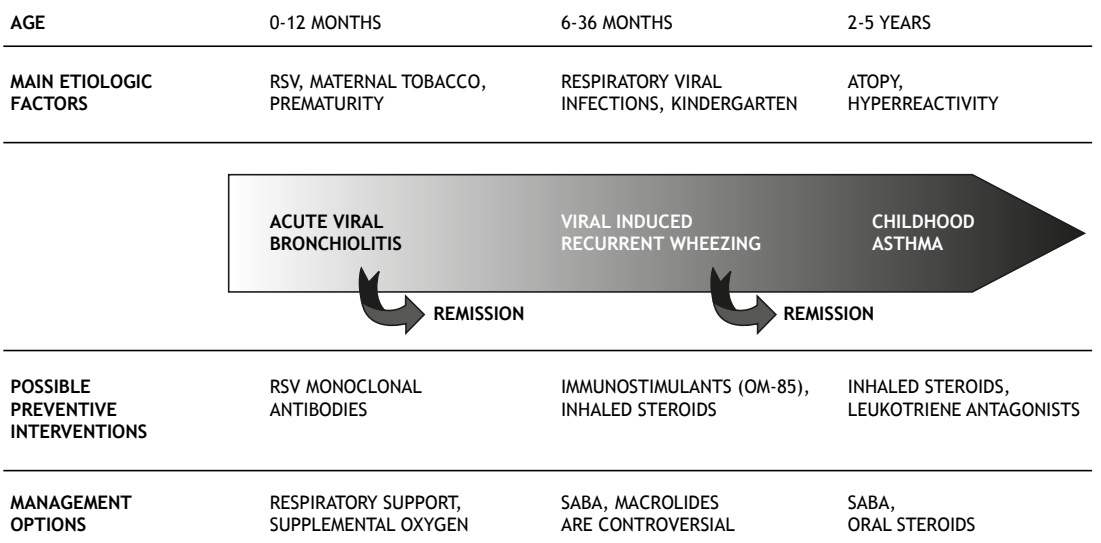

Figure 1. Common forms of wheezing in preschool children according to age and etiological agent, followed by intervention and treatment recommendations. RSV: respiratory syncytial virus; and SABA: short-acting β_2 agonists.

severe or persistent symptoms should undergo ancillary tests. Chest imaging (low-dose CT) and sweat testing may be important steps in differential diagnosis. In conclusion, wheezing in preschoolers requires careful attention and constant monitoring to ensure respiratory well-being and healthy development.

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AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

One-year follow-up of children hospitalized with COVID-19: a prospective cohort study

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ABSTRACT

Objective: Currently, little is known about the long-term outcomes of COVID-19 in the pediatric population. The aim of this study was to investigate the long-term clinical outcomes of pediatric patients hospitalized with COVID-19. **Methods:** This was a prospective cohort study involving unvaccinated children and adolescents admitted to a tertiary hospital in southern Brazil with a COVID-19 diagnosis. Data were collected from electronic medical records for one year after the diagnosis. **Results:** A total of 66 children were included: the median age was 2.9 years; 63.6% were male; and 48.5% were under 2 years of age. Over 70% had at least one comorbidity prior to the COVID-19 diagnosis. During the one-year follow-up period, 59.1% of the children revisited the emergency department, 50% required readmission, and 15.2% died. Younger children with longer hospital stays were found to be at greater risk of readmission. Having cancer and impaired functionality were found to increase the risk of death within one year. **Conclusions:** Our findings indicate that most children hospitalized with COVID-19 have comorbidities. Younger age at admission and a longer hospital stay seem to be risk factors for readmission. In addition, the presence of cancer and impaired functionality are apparently associated with the poor outcome of death within the first year after the diagnosis of COVID-19.

Keywords: COVID-19; Pediatrics; Physical functional performance.

INTRODUCTION

The new coronavirus was first identified in November 2019 in the city of Wuhan, China, after a series of unspecified pneumonia cases occurred in the city. Since then, SARS-CoV-2 infection, which can lead to COVID-19, has been widely studied worldwide.[1]

It is known that the rates of contamination are lower and the symptoms of COVID-19 are milder in the pediatric population than in the adult population.[2,3] In addition, the rates of hospitalization for COVID-19 are lower in the pediatric population,[4] and most children hospitalized for COVID-19, on wards or in ICUs, have had preexisting comorbidities.[2,3]

Because of the milder presentation of the disease and lower hospitalization rates, COVID-19-related mortality is also significantly lower in the pediatric population.[5] In a multicenter study, conducted mostly in the United States, mortality rates of approximately 1.8% were reported.[6] A study conducted with a Brazilian national COVID-19 database showed that 7.6% of children hospitalized for COVID-19 died during their hospital stay.[7] Among pediatric patients, mortality rates are higher for those under 2 years of age and for those between 12 and 19 years, as well as for those with preexisting comorbidities.[6,7]

After hospital discharge, adult and pediatric patients may still have COVID-19 symptoms, a phenomenon known as long COVID or post-acute sequelae of COVID-19.[8] Studies show that, among children and adolescents with COVID-19, requiring ICU admission and having more comorbidities are associated with presenting more symptoms in the long term, the most common symptoms being fatigue, exercise intolerance, and dyspnea.[9,10] However, few studies have addressed the long-term clinical outcomes in children who were hospitalized with COVID-19.

A recent multicenter study conducted in the United States showed that 11% of pediatric patients hospitalized with COVID-19 were readmitted to the hospital within four months after discharge.[10] However, there have been few studies evaluating readmissions and late mortality

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among pediatric patients hospitalized with a diagnosis of COVID-19. Therefore, the aim of this study was to investigate the long-term clinical outcomes of pediatric patients hospitalized with COVID-19.

METHODS

This was a prospective cohort study involving unvaccinated children diagnosed with COVID-19 and admitted to the *Hospital de Clínicas de Porto Alegre* (HCPA) between March 2020 and July 2021. Patients were followed by monitoring of their electronic medical records for one year after the diagnosis. This research was approved by the HCPA Research Ethics Committee (Reference no. 57286822000005327), and the study protocol was in accordance with the ethical precepts on research involving humans outlined in Brazilian National Health Council Resolution no. 466/2012.

Sociodemographic data and laboratory test results were collected from electronic medical records. Data regarding hospital admission, including the date of admission, nutritional status, prematurity, signs and symptoms of the disease, and presence of comorbidities, were collected, as were the results of laboratory tests, such as arterial blood gases and C-reactive protein. During hospitalization, the need for ventilatory support—such as oxygen therapy, high-flow nasal cannula use, and noninvasive/invasive ventilation—and for admission to the pediatric ICU (PICU) were recorded. After hospital discharge, follow-up was carried out by reviewing electronic medical records, and information on emergency room visits, hospital admissions, and death was recorded for one year after the diagnosis of COVID-19. All patients admitted to the HCPA Department of Pediatrics with a diagnosis of COVID-19, as confirmed by a positive RT-PCR for SARS-CoV-2,[11,12] were included in the study.

For each of the children included in the study, the level of functionality was assessed in the first 24 h after hospital admission by applying the Functional Status Scale (FSS), which has been translated and validated for use in the pediatric population of Brazil.[13] The FSS assesses six domains of functionality, and the total score ranges from 6 to 30 points, a higher score indicating worse functionality.[13-15] The individuals were stratified into two groups for analysis: those with an FSS score ≤ 9 (preserved functioning or mild dysfunction); and those with an FSS score ≥ 10 points (moderate, severe, or very severe dysfunction).

Variables are expressed as absolute values and percentages or as medians and interquartile ranges. To assess the normality of continuous variables, the Shapiro-Wilk test was used. Univariate and multivariate Cox regression analyses were performed, the dependent variable being death within the first year after diagnosis. We also performed univariate and multivariate Poisson regression analyses with robust variance, in which the dependent variable was hospital readmission within one year. Data were stored in Microsoft Office Excel and analyzed with the Predictive Analytics Software package, version 18.0 (SPSS Inc., Chicago, IL, USA). The level of statistical significance adopted was 5% ($p < 0.05$).

RESULTS

The study included 66 unvaccinated children diagnosed with COVID-19: 42 (63.6%) were male; 32 (48.5%) were under 2 years of age; and the median age was 2.9 years (IQR, 0.4-9.5 years). The most common symptoms were fever (in 75.8%), cough (in 50.0%), hypoxemia (in 40.9%), rhinorrhea (in 37.9%), and diarrhea (in 25.8%). Of the 66 children evaluated, 48 (72.7%) had at least one comorbidity prior to being diagnosed with COVID-19. The most common comorbidities were cancer (in 21.2%) and respiratory disease (in 19.7%). More than 18% of the children in the sample had been born prematurely. The median length of hospital stay was 10 days (IQR, 6.0-24.5 days). Ventilatory support was required for 27 patients (40.9%), and 23 patients (34.8%) were admitted to the PICU. Table 1 shows the characteristics of the patients.

Premature birth was significantly more common among the patients under 2 years of age ($p = 0.008$). However, C-reactive protein levels were significantly higher among the patients over 2 years of age ($p = 0.000$), who also had significantly more comorbidities ($p = 0.004$), mainly cancer.

By the end of the one-year follow-up period, 39 (59.1%) of the children had revisited the HCPA Emergency Department and 33 (50.0%) had been readmitted to the hospital. Of the 33 readmissions, 4 (12.1%) were caused by a new SARS-CoV-2 infection and 27 (81.8%) were caused by complications of an underlying disease (preexisting comorbidity): cancer, in 36%; metabolic disorders, in 18%; neurological disorders, in 18%; respiratory diseases, in 15%; cardiovascular diseases, in 9%; and gastrointestinal disorders, in 6%. Of the 33 children who required readmission, only 6 (18.2%) were previously healthy. Of those 6 children, 4 were readmitted for respiratory problems, due to acute viral bronchiolitis in all four cases. One child was readmitted eight times during the one-year follow-up period because of sequelae and respiratory complications, requiring mechanical ventilation and failing ventilator weaning repeatedly, which led to the need for a tracheostomy during the fourth hospital stay. Readmission for nonrespiratory causes was identified in two children: one had a urinary tract infection, and the other had gastrointestinal symptoms.

By the end of the one-year follow-up period, 10 (15.2%) of the children had died. All of the deaths were in children who had had at least one preexisting comorbidity at the initial hospital admission, the most common comorbidity being cancer, which was present in 8 of those 10. Two deaths (20%) were due to acute respiratory distress syndrome caused by COVID-19, and seven (70%) were due to progression of the underlying disease: four due to ventilatory failure

Table 1. Characteristics of children hospitalized with COVID-19, overall and by age.[a]

Characteristic	Total (N = 66)	< 2 years of age (n = 32)	≥ 2 years of age (n = 34)	p
Male	42 (63.6)	20 (62.5)	22 (64.7)	0.835
White	56 (84.8)	27 (84.4)	29 (85.3)	0.918
Age (years)	2.9 [0.4-9.5]	0.4 [0.2-1.2]	9.2 [6.0-11.2]	0.000
Hospital stay (days)	10.0 [6.0-24.7]	8.0 [5.0-31.0]	12.5 [7.0-25.2]	0.277
Comorbidities	48 (72.7)	18 (56.2)	30 (88.2)	0.004
Respiratory disease	13 (19.7)	4(12.5))	9 (26.5)	0.157
Cancer	14 (21.2)	4 (12.5)	10 (29.4)	0.96
Prematurity	12 (18.2)	10 (31.2)	2 (5.9)	0.008
Asymptomatic	6 (9.1)	3 (9.7)	3 (9.7)	0.968
Fever	50 (75.8)	23 (71.9)	27 (79.4)	0.479
Cough	33 (50.0)	16 (50.0)	17 (50.0)	1.000
Hypoxemia	27 (40.9)	10 (33.3)	17 (56.7)	0.072
Rhinorrhea	25 (37.9)	13 (40.6)	12 (35.3)	0.658
Diarrhea	17 (25.8)	10 (31.2)	7 (20.6)	0.326
C-reactive protein (mg/L)	23.5 (3.5-77.8)	2 (1-17)	63 (28-139)	0.000
Ventilatory support required	27 (40.9)	14 (43.8)	13 (38.2)	0.651
PICU admission	23 (34.8)	8 (25)	15 (44.1)	0.106
IMV required	12 (18.2)	5 (15.6)	7 (20.6)	0.604
FSS score	8 (6-10)	7 (6-10)	8 (6.2-10)	0.922
Adequate functionality	46 (69.7)	22 (68.8)	24 (70.6)	0.872
Death during first hospitalization	5 (7.5)	2 (3.0)	3 (4.5)	0.97
Readmission	33 (50.0)	19 (59.4)	14 (41.2)	0.143
Death within one year	10 (15.2)	2 (6.2)	8 (23.5)	0.052

PICU: pediatric ICU; IMV: invasive mechanical ventilation; and FSS: Functional Status Scale. [a]Values expressed as n (%) or as median [IQR].

and three due to septic shock. One death (10%) was associated with septic shock after bone marrow transplantation. Five deaths (50%) occurred during the first hospitalization after the COVID-19 diagnosis (3 children had cancer, 1 had a respiratory disease, and 1 had a metabolic disorder). The five other deaths occurred during readmissions (4 children had cancer, and 1 had a metabolic disorder).

Table 2 shows the results of the univariate and multivariate linear regression analyses in which the dependent variable was readmission within one year. In the multivariate analysis, the dependent variable was found to be significantly associated with age ($\beta = 0.589$; $p = 0.036$) and with the length of hospital stay during the first admission ($\beta = 1.004$; $p = 0.007$).

Table 3 shows the results of the univariate and multivariate linear regression analyses in which the dependent variable was death within the first year after diagnosis. In the multivariate analysis, the dependent variable was found to be significantly associated with the FSS score ($\beta = 1.235$, $p = 0.001$) and with a diagnosis of cancer ($\beta = 33.516$, $p < 0.001$).

DISCUSSION

In the present study, pediatric patients hospitalized with COVID-19 were evaluated and over 70% were found to have had at least one comorbidity, cancer having been the most common. During the one-year follow-up period after the diagnosis of COVID-19, approximately 59% of the children revisited the pediatric emergency room and 50% required readmission. In addition, approximately 15% of the children died during that period, and all of those children had at least one comorbidity prior to being diagnosed with COVID-19. We demonstrated that the younger children and those with longer hospital stays were at a higher risk for readmission during the first year after a COVID-19 diagnosis, as well as that children with cancer and children with impaired functionality were at a higher risk of death within one year after the diagnosis.

A multicenter study conducted in the United States showed lower rates of hospital readmission than those found in the present study. Maddux et al. observed that 11% of patients were readmitted within a period of 2-4 months after the initial discharge, and only one patient was healthy before prior to COVID-19 diagnosis. In their study, readmissions were associated with exacerbations of underlying diseases.[10] In our study, most patients requiring readmission had at least one preexisting comorbidity. Therefore, we can assume that the readmissions of our patients were also associated with exacerbations of the underlying diseases. These data corroborate previous findings in the literature.

In the present study, the risk of readmission within one year after the diagnosis of COVID-19 was found to be higher among the younger patients. We believe that to be a novel finding. However, it is known that

Table 2. Univariate and multivariate Poisson regression analyses with robust variance with readmission within one year as the dependent variable.

Characteristic	Univariate analysis			Multivariate analysis		
	PR	95% CI	p	PR	95% CI	p
Age (years)	0.664	0.498-0.885	0.30	0.589	0.892-0.996	0.036
Length of hospital stay	1.005	1.002-1.008	0.001	1.004	1.001-1.007	0.007
Prematurity	1.687	1.084-2.626	0.020	-	-	-

PR: prevalence ratio.

Table 3. Univariate and multivariate Cox regression analyses with death within one year as the dependent variable.

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
FSS score	1.133	1.022-1.257	0.017	1.235	1.095-1.391	0.001
Cancer	16.749	3.536-79.332	0.000	33.516	5.747-195.456	< 0.001
Age (years	1.183	1.042-1.343	0.009	-	-	-
C-reactive protein	1.007	1.002-1.013	0.005	-	-	-
PICU admission	4.847	1.252-18.770	0.022	-	-	-

HR: hazard ratio; FSS: Functional Status Scale; and PICU: pediatric ICU.

the disease is more severe in infants, and being under one month of age is considered an important risk factor for admission to the PICU.[5,16] Being under 2 years of age has also been identified as a risk factor for death from COVID-19.[7,17,18]

The results of our analyses also indicate that a longer hospital stay after admission for COVID-19 increases the risk of a second hospitalization within one year after the first. The median length of hospital stay observed in our study was 10 days, considerably longer than the 3-6 days reported in previous studies.[10,17,19,20] That difference may be related to the heterogeneity of the studies and the different levels of complexity of the children included in the study samples.

To date, there have been few follow-up and mortality studies in the pediatric population with COVID-19.[6] In our study sample, the one-year mortality rate was 15.2%, which is considerably higher than the rates reported elsewhere. In a multicenter study that evaluated a sample of children hospitalized with COVID-19, Bhalala et al. demonstrated a 0.3% mortality rate at 28 days after discharge.[6] However, the median age was higher in their sample than in ours and the rates of preexisting comorbidities were lower in their sample, both of which could have influenced the differences between the results of the two studies. Notably, none of our patients had been immunized against COVID-19 and only two died from acute respiratory distress syndrome caused by COVID-19; all of the other deaths were associated with exacerbation of the underlying disease, which may have been related to COVID-19 sequelae.

Approximately 7.5% of the children in our sample died during hospitalization, which is similar to the outcome reported by Oliveira et al.[7] However, studies conducted in high-income countries have reported lower mortality rates.[5,6,11,19] In a systematic review involving a collective sample of approximately 3,800 children who died from COVID-19, Kitano et al. demonstrated that the mortality rates were higher in low- and middle-income countries than in high-income countries, the former group accounting for over 90% of the deaths from COVID-19 in the pediatric population.[18] Notably, the hospital where the present study was carried out is a referral center for the treatment of highly complex chronic diseases in southern Brazil and regularly receives critically ill patients, a fact that could explain the higher mortality rate in our sample.

In our study sample, the risk of death within one year after the diagnosis of COVID-19 was found to be higher among the children with cancer. Previous studies have shown that the rates of COVID-19-related mortality are higher for children with cancer than for healthy children or even for children with other comorbidities.[21-24] However, to our knowledge, there have been no studies evaluating the association between cancer and death within one year after the diagnosis of COVID-19 in pediatric patients. Despite the fact that patients with cancer are at a greater risk of developing the more severe forms of COVID-19,[22] Węcławek-Tompol et al. observed that children with cancer have a 97.3% probability of survival to 100 days after a diagnosis of COVID-19.[25]

In the present study, impaired functionality at hospital admission was also identified as a risk factor for death within one year after the diagnosis of COVID-19. Casassola et al. demonstrated that over half of children hospitalized with COVID-19 have impaired functionality, which they found to be associated with a longer hospital stay and a greater likelihood of requiring ventilatory support.[26] Their findings suggest that pediatric patients with reduced functionality tend to develop the more severe forms of COVID-19 and that one-year mortality rates would therefore be higher among such patients, thus corroborating our findings.

The study conducted by Maddux et al.[10] also underscored the importance of assessing the functionality of pediatric patients with COVID-19 during hospitalization. The authors found that 9% of their patients presented a deterioration in functionality

by the end of the hospital stay and that 3% had an even worse FSS score at the end of the follow-up, demonstrating that the functionality of pediatric patients may change even up to four months after discharge.[10] On the basis of these findings, we can assume that pediatric patients will continue to develop post-COVID-19 sequelae in the long term, resulting in a loss of functionality, which may be associated with death within one year after diagnosis.

Finally, over 70% of the patients in our study sample had at least one preexisting comorbidity and all of the patients who died during the one-year follow-up period were in that group. Similar data can be found in the literature.[17,26] Most of the children hospitalized with COVID-19 have preexisting comorbidities.[7,10,11] The presence of comorbidities is considered a risk factor for the development of more severe COVID-19 and for unfavorable outcomes such as death.[2,5,7,10,17]

Our study has some limitations. The data were obtained from local electronic medical records, which made it impossible to monitor readmissions at other health facilities. In addition, our study sample was heterogeneous, including patients with a variety of preexisting comorbidities, which could have influenced the mortality rates. Furthermore, only severe cases (those requiring hospitalization) were included, so our findings cannot be extrapolated to the pediatric population at large. Moreover, this was a single-center study and the sample size was small. Despite these limitations, our study has the longest follow-up of pediatric patients with COVID-19 to date.

We reiterate that most of the children diagnosed with COVID-19 had comorbidities, and that this characteristic was present in all of the cases with a fatal outcome. Younger age and longer hospital stays appear to be related to a higher risk of readmission. The presence of cancer and impaired functionality were associated with a greater risk of death within the first year after the diagnosis of COVID-19. Currently, little is known about the long-term consequences of COVID-19 in the pediatric population, which underscores the importance of our results. Our study adds to the literature some important risk factors to be monitored and emphasizes the importance of long-term follow-up, especially in pediatric patients who require hospitalization for COVID-19.

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AUTHOR CONTRIBUTIONS

CJS, GMC, GHA, DSM, LKBA, CM, and BZ: literature search.

CJS, GMC, GHA, and BZ: data collection.

CJS, GMC, DSM, LKBA, CM, and BZ: study design.

CJS, GMC, and BZ: analysis of data.

CJS, GMC, GHA, DSM, LKBA, CM, and BZ: manuscript preparation.

DSM, LKBA, CM, and BZ: manuscript revision.

All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Sleep parameters in patients with chronic hypersensitivity pneumonitis: a case-control study

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Study carried out in the Disciplina de Pneumologia, Departamento de Medicina, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.

ABSTRACT

Objective: To compare patients with chronic hypersensitivity pneumonitis (cHP) and controls with normal spirometry in terms of their sleep characteristics, as well as to establish the prevalence of obstructive sleep apnea (OSA) and nocturnal hypoxemia. Secondary objectives were to identify factors associated with OSA and nocturnal hypoxemia; to correlate nocturnal hypoxemia with the apnea-hypopnea index (AHI) and lung function, as well as with resting SpO_2, awake SpO_2, and SpO_2 during exercise; and to evaluate the discriminatory power of sleep questionnaires to predict OSA. **Methods:** A total of 40 patients with cHP (cases) were matched for sex, age, and BMI with 80 controls, the ratio of controls to cases therefore being = 2:1. The STOP-Bang questionnaire, the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index, the Berlin questionnaire and the **N**eck circumference, **o**besity, **S**noring, **A**ge, and **S**ex (NoSAS) score were applied to all cases, and both groups underwent full-night polysomnography. **Results:** The patients with cHP had longer sleep latency, lower sleep efficiency, a lower AHI, a lower respiratory disturbance index, fewer central apneas, fewer mixed apneas, and fewer hypopneas than did the controls. The patients with cHP had significantly lower nocturnal SpO_2 values, the percentage of total sleep time spent below an SpO_2 of 90% being higher than in controls (median = 4.2; IQR, 0.4-32.1 vs. median = 1.0; IQR, 0.1-5.8; p = 0.01). There were no significant differences between cases with and without OSA regarding the STOP-Bang questionnaire, NoSAS, and ESS scores. **Conclusions:** The prevalence of OSA in cHP patients (cases) was high, although not higher than that in controls with normal spirometry. In addition, cases had more hypoxemia during sleep than did controls. Our results suggest that sleep questionnaires do not have sufficient discriminatory power to identify OSA in cHP patients.

Keywords: Alveolitis, Extrinsic Allergic; Lung diseases, interstitial; Sleep apnea, obstructive; Hypoxia.

INTRODUCTION

Chronic hypersensitivity pneumonitis (cHP) is an interstitial lung disease (ILD) caused by an exaggerated immune reaction to inhaled antigens found in the environment.[1,2] cHP occurs in susceptible individuals, and its prevalence varies worldwide. Hypersensitivity pneumonitis (HP) is a very common ILD in Brazil.[3] Obstructive sleep apnea (OSA) and ILD have some comorbidities and symptoms in common, such as daytime sleepiness, fatigue, reduced quality of life, and pulmonary hypertension.[4-10] Only a few studies of chronic ILD have examined sleep, despite the fact that sleep disorders appear to be common in ILD patients.[4-8,11-13] In a study including 21 patients with fibrotic HP, the prevalence of OSA was found to be similar between patients with idiopathic pulmonary fibrosis (IPF) and those with cHP (83.3% vs. 76.2%).[11]

The objective of the present study was to compare patients with cHP and controls with normal spirometry in terms of their sleep characteristics, as well as to establish the prevalence of OSA and nocturnal hypoxemia. Secondary objectives were to identify factors associated with OSA and nocturnal hypoxemia; to correlate nocturnal hypoxemia with the apnea-hypopnea index (AHI) and lung function, as well as with resting SpO_2, awake SpO_2, and SpO_2 during exercise; and to evaluate the discriminatory power of sleep questionnaires to predict OSA.

METHODS

Study participants

This was a retrospective case-control study conducted between March of 2016 and December of 2019 at the Federal University of São Paulo, located in the city of

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São Paulo, Brazil. Patients diagnosed with cHP and meeting the inclusion criteria were consecutively included in the study. A total of 154 cHP patients were eligible during the period. Of those, 40 (cases) were selected for inclusion in the study. They were matched for sex, age (± 5 years), and BMI (± 5 kg/m^2) with 80 controls with normal spirometry.[14] The ratio of controls to cases was 2:1. When more than two controls were available for a case, the selection was made by random number generation.

The diagnosis of cHP was based on the criteria suggested by Salisbury et al.[15] Cases were not specifically selected because they had sleep problems or complaints, and controls had no history of lung disease. The exclusion criteria were as follows: age > 80 years; inability to perform spirometry; use of long-term home oxygen therapy or a resting SpO_2 ≤ 89%; a reduced FEV_1/FVC ratio (of < 0.7); ILD exacerbation or progressive ILD; a left ventricular ejection fraction of ≤ 50% on echocardiography; alcoholism; uncontrolled hypothyroidism; systemic diseases that could independently result in pulmonary hypertension; use of hypnotics; and unstable psychiatric disorder. The study was approved by the Research Ethics Committee of the Federal University of São Paulo (Protocol no. 1.162.941), and all participating patients gave written informed consent.

Study protocol

Patients with cHP (cases) underwent biochemical and hematological evaluation; arterial blood gas analysis; HRCT; and echocardiography. The modified Mallampati score and neck circumference were assessed in all cases. The STOP-Bang questionnaire, the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), the Berlin questionnaire, and the Neck circumference, obesity, Snoring, Age, and Sex (NoSAS) score were applied to all cases.[16-20] A high risk of OSA was defined as follows: five or more positive responses to the STOP-Bang questionnaire; two positive responses to the STOP-Bang questionnaire + being male; two positive responses to the STOP-Bang questionnaire + a BMI > 35 kg/m^2; or two positive responses to the STOP-Bang questionnaire + neck circumference ≥ 43 cm (for men) or ≥ 41 cm (for women).

Full-night polysomnography was performed in accordance with current standards.[21] Obstructive apnea was defined as a reduction in airflow ≥ 90% lasting at least 10 s with evidence of persistent respiratory effort. Obstructive hypopnea was defined as a reduction in airflow ≥ 30% for more than 10 s accompanied by ≥ 4% oxygen desaturation and evidence of respiratory effort. Respiratory effort-related arousals were also recorded, being defined as sequences of breaths lasting ≥ 10 s, with increased respiratory effort or flattening of the inspiratory curve, leading to awakening but not meeting the defined criteria for apnea or hypopnea. Nocturnal hypoxemia was defined as the percentage of total sleep time spent below an SpO_2 of 90% (T90). Significant nocturnal hypoxemia was defined as spending 10% or more of the total sleep time below an SpO_2 of 90%.[8] Spirometry and DL_{CO} measurement were performed in accordance with current standards. Oxygen saturation was assessed by oximetry at rest and at the end of a four-minute step test. Desaturation was characterized by a decrease ≥ 4% at the end of the test.

Statistical analysis

The data were expressed as mean ± standard deviation or median (interquartile range). The prevalence of OSA was compared between cases and controls by means of the chi-square test. The normal distribution of the data was assessed with the Shapiro-Wilk test. Between-group comparisons were made with the Mann-Whitney test, given that most of the variables had a nonparametric distribution. Correlations of the AHI with other variables were determined by Spearman's test. In the group of patients with cHP (cases), T90 and the degree of nocturnal hypoxemia were calculated and correlated by means of univariate analysis of pulmonary function test results, PaO_2, $PaCO_2$, sleep questionnaire data, oxygen desaturation at the end of exercise, and polysomnographic parameters. A value of $p < 0.05$ was considered significant.

RESULTS

The general characteristics of the study sample are shown in Table 1. The mean age was 59 years, with a predominance of females (75%). There was no difference between cases and controls in terms of age, sex, or BMI, as expected by the matching criteria. The modified Mallampati score showed that 30 (75%) of the cHP patients were at a high risk of OSA (Mallampati classes III and IV). The results of the pulmonary function tests and arterial blood gas analysis in the patients with cHP are shown in Table 2. There was a mild decrease in FVC and a moderate decrease in DL_{CO}. Mean $PaCO_2$ was in the lower reference range. Twenty-eight (70%) of the patients with cHP experienced oxygen desaturation at the end of exercise. Seventeen (42.5%) of the patients with cHP using corticosteroids at a dose ≥ 20 mg/day were included. When compared with those who were using a lower dose of corticosteroids or who were not receiving corticosteroid therapy, there was no difference in the AHI, BMI, neck circumference, or sleep quality as assessed by the PSQI (data not shown).

The results of polysomnography for both groups are shown in Table 3. The patients with cHP had longer sleep latency and lower sleep efficiency than did those in the control group. The arousal index was higher in the control group. Unexpectedly, the patients with cHP had a lower AHI, a lower respiratory disturbance index, fewer central apneas, fewer mixed apneas, and fewer hypopneas. An AHI ≥ 5 events/hour was common in cases and controls (67.5% vs. 82.5%; $X^2 = 3.44$; $p = 0.06$). Moderate to severe OSA was found in 47.5% of the controls and in 25% of the cases ($X^2 = 5.65$; $p = 0.02$). However, the patients with cHP had significantly

Table 1. General characteristics of cases and controls in the present study.[a]

Variable	Group	
	Control (n = 80)	cHP (n = 40)
Age, years	59.1 ± 11.5	59.3 ± 12.7
Female sex	60 (75)	30 (75)
BMI, kg/m^2	29.6 [25.5-33.6]	29.9 [25.9-35.1]
BMI < 25 kg/m^2	16 (20)	8 (20)
BMI ≥ 25-29.9 kg/m^2	26 (32.5)	13 (32.5)
BMI ≥ 30 kg/m^2	38 (47.5)	19 (47.5)

cHP: chronic hypersensitivity pneumonitis. [a]Data presented as mean ± SD, median [IQR], or n (%).

Table 2. Pulmonary function test results and arterial blood gas analysis results in patients with chronic hypersensitivity pneumonitis (n = 40).[a]

Pulmonary function testing	
FVC, % predicted	70.4 ± 17.9
FEV_1, % predicted	75.0 ± 20.4
FEV_1/FVC	0.84 ± 0.07
DL_{CO}, % predicted (n = 28)	56.9 ± 17.4
Arterial blood gas analysis (n = 37)	
$PaCO_2$, mmHg	36.1 ± 3.7
PaO_2, mmHg	80.1 ± 11.0
SaO_2, %	95.7 ± 1.6

[a]Data are presented as mean ± SD.

lower nocturnal SpO_2 values, the percentage of total sleep time spent below an SpO_2 of 90% being higher than in controls.

The STOP-Bang questionnaire, the NoSAS score, and the Berlin questionnaire showed that 12 (30%), 23 (57.5%), and 24 (60%) of the patients with cHP, respectively, were at a high risk of OSA. There were no significant differences between cases with and without OSA regarding the STOP-Bang questionnaire, NoSAS, and ESS scores. The sensitivity of the NoSAS score for cHP was 55%, with a specificity of 46%. The PSQI was higher in cases than in controls (9; IQR, 7-13 vs. 6; IQR, 4-9.8; $p < 0.01$).

In the cHP group, the AHI was directly correlated with the BMI ($r_s = 0.38$, $p = 0.02$) and T90 ($r_s = 0.67$, $p < 0.01$), as well as being inversely correlated with baseline, mean, and minimum SpO_2 during polysomnography, the correlation being highest with the last of the three ($r_s = -0.70$, $p < 0.001$). In addition, the AHI did not correlate with age, neck circumference, FVC, DL_{CO}, resting SpO_2, or SpO_2 at the end of exercise. Furthermore, T90 correlated inversely with percent predicted DL_{CO} ($p = 0.06$) and, more strongly, with awake SpO_2 at baseline on polysomnography ($r_s = -0.87$, $p < 0.001$; Figure 1). Of the 20 cHP patients with baseline $SpO_2 \geq 93\%$ on polysomnography, only 1 (5%) spent more than 10% of the total sleep time below an SpO_2 of 90%.

DISCUSSION

In the present study, the prevalence of OSA in patients with cHP was high; however, contrary to expectations, it was lower than that in a group of matched controls with normal spirometry, randomly selected from the general population. The reasons for this are obscure. Many problems can occur during the selection of cases and controls in this type of study.[22] In the group of patients with cHP in the present study, the AHI was directly correlated with the BMI, although not with FVC, DL_{CO}, resting SpO_2, or SpO_2 at the end of exercise. As expected, patients with cHP had more hypoxemia during sleep. The present study did not include individuals with markedly compromised lung function or low resting SaO_2. It has been shown that patients with more severe ILD have a higher oxygen desaturation index and a higher AHI.[4]

OSA is an important public health problem, with an increasing prevalence and a high rate of underdiagnosis in patients with ILD. We used sleep questionnaires in an attempt to identify cHP patients who were at an increased risk of OSA and who might benefit from polysomnography. However, we found no correlation between OSA risk as assessed by the questionnaires and a polysomnographic diagnosis of OSA. Therefore, the questionnaires had limited value in predicting OSA in cHP patients. In the present study, we subjectively assessed sleepiness using the ESS. A median ESS score of 5.5 shows that, in general, cHP patients are less sleepy, regardless of the presence of OSA. Although the ESS score has been found to be higher in patients with IPF than in normal controls,[9,23] it was within the normal range in the present study, showing that excessive daytime sleepiness was not significant. Mermigkis et al.[6] showed that only 20% of patients with IPF reported excessive daytime sleepiness. Thus, it is clear that the ESS score is poor at predicting OSA in patients with ILD. Our results confirm that the sleep questionnaires used in the present study have low accuracy in identifying individuals at risk of OSA, regardless of the cutoff point used for the AHI.[24] Polysomnography remains the only tool with sufficient sensitivity and specificity to confirm or exclude a diagnosis of OSA in patients with ILD.

In the present study, the cHP patients reported worse sleep quality than did the controls. Poor sleep quality and its impact on daytime functioning and quality of life can be underestimated in patients with ILD, in whom symptoms such as fatigue, tiredness, and drowsiness can be ascribed to lung disease. Our

Table 3. Polysomnography data and nocturnal oximetry results in cases and controls in the present study.[a]

Polysomnography	Group		p
	Control (n = 80)	cHP (n = 40)	
Sleep efficiency, %	80.6 [73.4-85.3]	76.5 [63.8-82.3]	0.01
Sleep latency, min	8.2 [3.7-16.4]	35 [10.3-57.8]	< 0.01
REM sleep latency, min	89.5 [62.8-140.1]	101.8 [71-162.8]	0.39
Stage 1 sleep, %	11.8 [7.7-20.8]	9.8 [6.3-14.4]	0.04
Stage 2 sleep, %	39.1 [32.8-46.1]	43.5 [34.8-48.2]	0.10
Stage 3 sleep, %	25.4 [19.9-30.7]	28 [21.1-33.7]	0.55
REM sleep (%)	19.5 [14.1-23.4]	18.7 [13.7-24.7]	0.90
Arousal index, events/h	21.9 [15.2-31.0]	14 [8.3-19.3]	< 0.01
Obstructive apnea, n	10 [1.0-30.8]	5.5 [0.3-15.8]	0.26
Central apnea, n	1.0 [0.0-3.0]	0.0 [0.0-1.0]	< 0.01
Mixed apnea, n	0.0 [0.0-3.0]	0.0 [0.0-1.0]	0.01
Hypopnea, n	61.0 [32.0-108.0]	34.5 [23.3-67.5]	0.02
RERA, n	4.0 [1.0-8.8]	2.5 [0.0-8.8]	0.23
Respiratory disturbance index	16.2 [8.3-33.1]	9.1 [6.0-6.0]	0.01
AHI, events/h	14.0 [7.0-31.6]	8.2 [4.0-14.9]	< 0.01
Baseline SpO_2, %	94.7 [93.3-94.9]	93.2 [90.9-94.3]	< 0.01
Mean SpO_2, %	93.9 [92.0-94.9]	92.0 [90.0-93.6]	<0.01
Minimum SpO_2, %	85.0 [80.0-88.0]	83 [78.3-87.0]	0.16
T90	1.0 [0.1-5.8]	4.2 [0.4-32.1]	< 0.01

cHP: chronic hypersensitivity pneumonitis; REM: rapid eye movement; RERA: respiratory effort-related arousal; AHI: apnea-hypopnea index; and T90: percentage of total sleep time spent below an SpO_2 of 90%. [a]Data are presented as median [IQR].

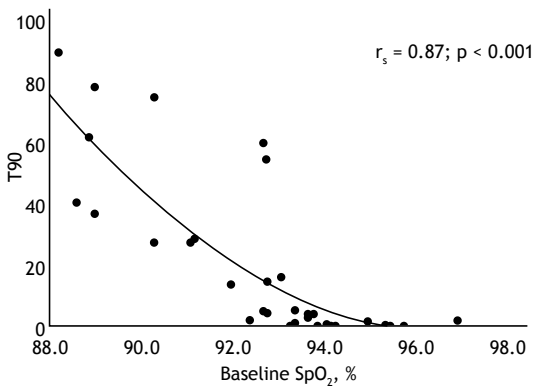

Figure 1. Correlation between baseline SpO_2 and the percentage of total sleep time spent below an SpO_2 of 90% (T90) on polysomnography.

results for cHP patients are similar to those reported by Mermigkis[9] and Krishnan et al.,[23] who found that the quality of sleep as measured by the PSQI was worse in IPF patients than in normal controls, and reduced sleep quality correlated with reduced health-related quality of life. The sleep pattern in patients with cHP is impaired, and we observed changes in sleep architecture, including increased sleep latency, reduced sleep efficiency, and a lower percentage of rapid eye movement (REM) sleep, the last finding having no statistical significance. Previous studies of patients with fibrotic ILD have shown increased non-REM (stage N1 and N2) sleep, reduced slow-wave sleep, and reduced REM sleep.[4,9,25] Several mechanisms can contribute to sleep fragmentation in patients with ILD, including hypoxemia. However, we found that the severity of ILD (as assessed by lung function parameters such as FVC, DL_{CO}, and SpO_2 during exercise or by arterial blood gas analysis) did not correlate with the AHI.

Studies examining sleep in patients with cHP have been few in number and have included patients with ILD of varying etiologies and samples consisting predominantly of patients with IPF, showing a high prevalence of OSA in this population; however, the prevalence of OSA was not compared between cases and healthy controls in those studies.[4-6,8,12,13] The study with the largest number of HP patients showed an OSA prevalence of 69.4% in patients with ILD, of 83.3% in patients with IPF, and of 76.2% in patients with cHP.[11]

In our study, nocturnal hypoxemia correlated significantly and as expected with PaO_2, awake SpO_2 during polysomnography, and DL_{CO}. Awake SpO_2 and SpO_2 during exercise have been shown to correlate significantly but weakly with nocturnal hypoxemia in some studies,[8,10,26,27] but not in others.[28-30] We found no correlation between nocturnal hypoxemia and SpO_2 during exercise. Troy et al.[8] found a significant correlation between T90 and ILD severity markers such as daytime SpO_2, SpO_2 during exercise, and DL_{CO}. Corte et al.[28] found that 78% of patients with nocturnal hypoxemia had no decrease in oxygen saturation after exercise. Therefore, nocturnal hypoxemia cannot be excluded when PaO_2 is normal at rest or during exercise.

The present study has limitations that should be noted. First, the sample size was relatively small, with a predominance of women. In Brazil, however, cHP is more common in women than in men, because indoor exposures are more common in the former than in the latter. Thus, the demographic characteristics of our study population are similar to those reported in the literature.[1] Furthermore, although OSA is more common in men, it becomes more common in postmenopausal women.[31,32] Cases and controls were matched for sex in the present study, meaning that the results cannot be attributed to differences between the sexes. Second, although cHP is common in Brazil, it is often diagnosed at an advanced or progressive stage, and this limits the inclusion of cHP patients. The fact that patients with cHP and hypoxemia during wakefulness or receiving oxygen therapy were not included in the present study is, therefore, another limitation, because the prevalence of OSA could be higher in this population. Third, the fact that the same investigator collected the anthropometric data and administered the questionnaires could have resulted in measurement bias. Finally, the first night effect (when patients are in unfamiliar surroundings) of polysomnography may have also influenced the results. However, given that this effect was common to cases and controls, this limitation becomes less critical.

In summary, the prevalence of OSA in cHP patients (cases) was high, although not higher than in controls with normal spirometry. In addition, cases had more hypoxemia during sleep than did controls. Nocturnal hypoxemia was common and related to baseline oxygen saturation during wakefulness. Our results suggest that sleep questionnaires do not have sufficient discriminatory power to identify OSA in cHP patients.

AUTHOR CONTRIBUTIONS

RBM and CACP: conceptualization; data curation; formal analysis; investigation; project administration; and drafting, reviewing, and editing of the manuscript. LRAB: conceptualization; formal analysis; and reviewing of the manuscript. MRS: reviewing and editing of the manuscript. ABB, ACLR, PSG, and SLKM: data collection. ST: funding acquisition. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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Performance of risk scores in patients with acute exacerbations of COPD

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ABSTRACT

Objective: Acute exacerbations of COPD (AECOPD) are common causes of hospitalization. Various scoring systems have been proposed to classify the risk of clinical deterioration or mortality in hospitalized patients with AECOPD. We sought to investigate whether clinical deterioration and mortality scores at admission can predict adverse events occurring during hospitalization and after discharge of patients with AECOPD. **Methods:** We performed a retrospective study of patients admitted with AECOPD. The National Early Warning Score 2 (NEWS2), the $NEWS2_{88-92\%}$, the **D**yspnea, **E**osinopenia, **C**onsolidation, **A**cidemia, and atrial **F**ibrillation (DECAF) score, and the modified DECAF (mDECAF) score were calculated at admission. We assessed the sensitivity, specificity, and overall performance of the scores for the following outcomes: in-hospital mortality; need for invasive mechanical ventilation or noninvasive ventilation (NIV); long hospital stays; hospital readmissions; and future AECOPD. **Results:** We included 119 patients admitted with AECOPD. The median age was 75 years, and 87.9% were male. The $NEWS2_{88-92\%}$ was associated with an 8.9% reduction in the number of individuals classified as requiring close, continuous observation, without an increased risk of death in the group of individuals classified as being low-risk patients. The $NEWS2_{88-92\%}$ and NEWS2 scores were found to be adequate in predicting the need for acute NIV and longer hospital stays. The DECAF and mDECAF scores were found to be better at predicting in-hospital mortality than the NEWS2 and $NEWS2_{88-92\%}$. **Conclusions:** The $NEWS2_{88-92\%}$ safely reduces the need for clinical monitoring in patients with AECOPD when compared with the NEWS2. The NEWS2 and $NEWS2_{88-92\%}$ appear to be good predictors of the length of hospital stay and need for NIV, but they do not replace the DECAF and mDECAF scores as predictors of mortality.

Keywords: Pulmonary disease, chronic obstructive/mortality; Symptom flare up; Early warning score; Length of stay; Patient readmission.

INTRODUCTION

COPD is one of the three leading causes of death worldwide. The prevalence and burden of COPD are expected to rise, prompting an increased number of hospital admissions for acute exacerbations of COPD (AECOPD).[1] AECOPD lead to disease progression and hospitalization, being associated with poor prognosis and increased mortality.[2] Therefore, various scoring systems have been proposed to classify the risk of clinical deterioration or mortality in patients with AECOPD.[3,4]

The National Early Warning Score (NEWS) is widely used in the United Kingdom to identify clinical deterioration in hospitalized patients with acute disease and is based on repeated assessment of RR, SpO_2, systolic blood pressure, pulse rate, level of consciousness, and temperature. It classifies patients as having a low, moderate, or high risk of deterioration.[5] The National Early Warning Score 2 (NEWS2) added the parameter *confusion* to the assessment of consciousness, as well as a new classification system for SpO_2. The original NEWS had a single scale for SpO_2, with worse scores being assigned to patients with an SpO_2 of < 96%, leading to titration of oxygen therapy to a target SpO_2 ≥ 96%.[5] However, providing excess oxygen to patients with AECOPD increases the need for ventilation as well as mortality.[6,7] Another problem is that COPD patients commonly have chronic hypoxemia, leading to false alerts. Therefore, the NEWS2 includes two SpO_2 scales: the original scale for patients with hypoxemic respiratory failure and a new scale for patients with hypercapnic respiratory failure (Table S1).[5] However, as expert societies recommend a target SpO_2 of 88-92% for all COPD patients,[1,8,9] a single-scale NEWS2 ($NEWS2_{88-92\%}$) was devised to simplify the application of the score and reduce the risk of providing excess oxygen.

Regarding mortality scores, the **D**yspnea, **E**osinopenia, **C**onsolidation, **A**cidemia, and atrial **F**ibrillation (DECAF) score is a validated tool to predict in-hospital mortality in patients with AECOPD, classifying patients as being low-, moderate-, or high-risk patients at admission.[10,11] Given that the occurrence of an AECOPD in the previous year is the best predictor of new AECOPD and is associated with increased mortality, a modified DECAF score (mDECAF) has been developed, assessing exacerbations in the previous year rather than atrial fibrillation.[1,12]

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Although the NEWS and mortality scores have been used in the context of AECOPD, their role in predicting different types of events (e.g., ventilation, long stays, readmissions, and future AECOPD) during hospitalization and after discharge of patients with AECOPD has yet to be fully studied. Therefore, the objectives of the present study were to investigate whether the NEWS2 and DECAF scores calculated at admission can be predictors of events occurring during hospitalization and after discharge of patients with AECOPD and to understand the extent to which the modified versions of the NEWS2 and the DECAF score (the $NEWS2_{88-92\%}$ and the mDECAF score, respectively) are comparable to the original versions.

METHODS

In this retrospective study, we analyzed data obtained from the medical records of a consecutive sample of patients with AECOPD admitted to the Pulmonology Department of the *Centro Hospitalar e Universitário de Coimbra*, in the city of Coimbra, Portugal, between January of 2017 and November of 2018. We included hospitalized patients diagnosed with COPD in accordance with the GOLD criteria,[1] excluding patients with other respiratory conditions (e.g., asthma and interstitial lung disease). The present study was approved by the Research Ethics Committee of the *Centro Hospitalar e Universitário de Coimbra* (Protocol no. OBS.SF.180-2022).

The NEWS2 and DECAF scores were calculated on the basis of patient data at hospital admission. The NEWS2 scores were calculated by assessing RR, SpO_2, systolic blood pressure, pulse rate, level of consciousness, and temperature. Patients with a NEWS2 score of 0-4 were classified as being low-risk patients, those with a NEWS2 score of 5 or 6 were classified as being moderate-risk patients, and those with a NEWS2 score of 7 or higher were classified as being high-risk patients. A NEWS2 score of 5 or higher should prompt hourly observations, whereas a NEWS2 score of 7 or higher should prompt close, continuous observation.[6] Of note, because NEWS2 scores were calculated retrospectively for this study, the classification had no impact on how patients were managed during hospitalization. The NEWS2 score was calculated with the use of scale 1 for hypoxemic patients and scale 2 for hypercapnic patients. The $NEWS2_{88-92\%}$ score was calculated with the use of scale 2 for all patients.

The DECAF score was retrospectively calculated on the basis of the extended Medical Research Council dyspnea scale score (5a or 5b), eosinopenia (< 0.05 × 10^9/L), consolidation, acidemia (pH < 7.3), and atrial fibrillation; the mDECAF score was calculated by assessing the same parameters, the exception being atrial fibrillation, which was replaced by the occurrence of an AECOPD in the previous year. Patients with a DECAF score of 0 or 1 were classified as being low-risk patients, those with a DECAF score of 2 were classified as being moderate-risk patients, and those with a DECAF score of 3-6 were classified as being high-risk patients.[10,11]

We assessed and compared the aforementioned scores for the following outcomes: in-hospital mortality, use of invasive mechanical ventilation (IMV), use of noninvasive ventilation (NIV), a length of stay (LOS) > 14 days (i.e., a LOS above the 75th percentile), hospital readmissions, and future AECOPD. In addition, we assessed the sensitivity and specificity of the scores, as well as their overall performance.

Statistical analysis

Quantitative variables with normal distribution were expressed as means and standard deviations, and variables with non-normal distribution were expressed as medians and interquartile ranges. Categorical variables were expressed as absolute and relative frequencies. Continuous variables with normal distribution were compared by means of t-tests, and those with non-normal distribution were compared by means of the Mann-Whitney test. Categorical variables were compared be means of the chi-square test.

The performance of the NEWS2, $NEWS2_{88-92\%}$, DECAF, and mDECAF scores for the aforementioned outcomes was assessed and compared by means of ROC curves. We calculated the performance of the NEWS2 and $NEWS2_{88-92\%}$ using low-risk and high-risk thresholds (5 and 7, respectively).

We did not perform sample size calculation. We included all of the patients that met the eligibility criteria during the study period.

A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed with the IBM SPSS Statistics software package, version 26.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 119 patients admitted with AECOPD were included in the present study (Figure S1). Their characteristics are described in Table 1. The median age of participants was 75 years (IQR, 10), and 87.9% were male. Of the 119 study participants, 5% had GOLD stage I COPD, 35% had GOLD stage II COPD, 42% had GOLD stage III COPD, and 18% had GOLD stage IV COPD. The median percent predicted FEV_1 was 44.8% (IQR, 25.8%), corresponding to severe obstruction. The overall in-hospital mortality rate was 6.7%. A total of 42 patients (35.3%) required NIV, and 3 (2.5%) required IMV. The median LOS was 8 days (IQR, 6), and 26.1% of the patients had a long LOS. Readmission rates ranged from 13.8% at 30 days after discharge to 34.9% at 180 days after discharge. Sixty-three percent of the patients had a new AECOPD, and 42.9% had a severe AECOPD in the following year.

Patient risk classification based on the NEWS2 and $NEWS2_{88-92\%}$ scores is shown in Figure 1. Of the total of patients, 63.0% and 54.1%, respectively,

Table 1. Characteristics of the study participants.[a]

Variable	Total sample (N = 119)
Age, years	75 [10]
Sex	
Male	101 (84.9%)
Female	18 (15.1%)
Smoking history, pack-years	48 [67]
Smoking status	
Never smoker	26 (21.8%)
Former smoker	69 (58.0%)
Current smoker	24 (20.2%)
COPD, GOLD stage	
I	6 (5.0%)
II	42 (35.3%)
III	50 (42.0%)
IV	21 (17.6%)
FEV_1, % predicted	44.8 [25.8]
AECOPD in the previous year	34 (28.6%)
Consolidation	55 (46.2%)
Acidemia, pH < 7.3	20 (16.8%)
Hypercapnia	49 (53.8%)
NIV	42 (35.3%)
IMV	3 (2.5%)
Antibiotic therapy	106 (89.1%)
Patient risk classification NEWS2 score	
Low risk, 0-4	41 (36.9%)
Moderate risk, 5 or 6	24 (21.6%)
High risk, ≥ 7	46 (38.7%)
$NEWS2_{88-92\%}$ score	
Low risk, 0-4	51 (45.9%)
Moderate risk, 5 or 6	24 (21.6%)
High risk, ≥ 7	36 (32.4%)
DECAF score	
Low risk	3 (2.5%)
Moderate risk	31 (26.1%)
High risk	85 (71.4%)
mDECAF score	
Low risk	1 (0.8%)
Moderate risk	24 (20.2%)
High risk	94 (79.0%)
LOS, days	8 [6]
Long LOS	31 (26.1%)
Death	8 (6.7%)
Readmission at 30 days	15 (13.8%)
Readmission at 60 days	19 (17.4%)
Readmission at 90 days	25 (22.9%)
Readmission at 180 days	38 (34.9%)
AECOPD in the following year	
Total	75 (63.0%)
Severe	51 (42.9%)

AECOPD: acute exacerbation(s) of COPD; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; NEWS2: National Early Warning Score 2; DECAF: **D**yspnea, **E**osinopenia, **C**onsolidation, **A**cidemia, and atrial **F**ibrillation; mDECAF: modified DECAF; and LOS: length of stay. [a]Data presented as n (%) or median [IQR].

were classified as having a moderate or high risk (i.e., requiring close, continuous observation) on the basis of their NEWS2 and $NEWS2_{88-92\%}$ scores. This corresponds to an 8.9% reduction in the number of patients requiring close, continuous observation on the basis of the $NEWS2_{88-92\%}$ score. The $NEWS2_{88-92\%}$ tended to be associated with reduced scores, tending to classify patients as having a lower risk in comparison with the NEWS2 (Figure S2).

The distribution of the outcome variables by risk group as assessed by the different scores is shown in Table 2. Although the $NEWS2_{88-92\%}$ classified a greater number of patients as being low-risk patients, there was no significant difference in mortality between patients classified as being low-risk patients by the NEWS2 and those classified as being low-risk patients by the $NEWS2_{88-92\%}$ (2.4% vs. 4.0%; p = 0.331). In fact, none of the patients classified as being low-risk patients died on the day of admission.

Regarding the LOS, the patients who were not classified as being low-risk patients by the NEWS2 and who were reclassified as being low-risk patients by the $NEWS2_{88-92\%}$ showed no difference in the median LOS when compared with patients already belonging to the low-risk group for both scores. Patients classified as being high-risk patients by the NEWS2 or $NEWS2_{88-92\%}$ had a significantly longer LOS than did those in the low- or moderate-risk group. The same was true for NIV during hospitalization, which was significantly more used in moderate- and high-risk patients than in low-risk patients for both scores (Table 2). There were no significant differences regarding the other outcomes.

Patient risk classification on the basis of the DECAF and mDECAF scores is shown in Figure 1. There were no significant differences in any of the outcomes studied between the DECAF and mDECAF scores (Table 2).

The $NEWS2_{88-92\%}$ and the NEWS2 had, respectively, good and adequate discriminatory power to predict NIV use (AUC = 0.70; 95% CI, 0.60-0.80 vs. AUC = 0.66; 95% CI, 0.56-0.77) and IMV use (AUC = 0.81; 95% CI, 0.62-0.99 vs. AUC = 0.77; 95% CI, 0.54-0.99). Both scores had good discriminatory power to predict a longer LOS (AUC = 0.74; 95% CI, 0.63-0.85 vs. AUC = 0.72; 95% CI, 0.61-0.83). In contrast, neither score had discriminatory power to predict future AECOPD or hospital readmissions, and their accuracy in predicting mortality was low (Table S2).

The mDECAF score showed good discriminatory power to predict mortality (AUC = 0.77; 95% CI, 0.62-0.92), whereas no significant results were observed for the DECAF score. The DECAF and mDECAF scores had high discriminatory power to predict IMV use (AUC = 0.89; 95% CI, 0.72-1.00 vs. AUC = 0.88; 95% CI, 0.69-1.00), but not NIV use, future AECOPD, or hospital readmissions (Table S2).

Table 3A shows the performance of the NEWS2 and $NEWS2_{88-92\%}$ at low- and high-risk thresholds (5 and 7, respectively). The performance of the mDECAF score at a high-risk threshold (= 3) is shown in Table 3B. The sensitivity and specificity of the DECAF scores for low-risk groups (a threshold of 2) were not calculated,

Table 2. Outcomes by risk group, as assessed by the National Early Warning Score 2 and Dyspnea, Eosinopenia, Consolidation, Acidemia, and atrial Fibrillation scores.[a]

Variable	Low risk	Moderate risk	High risk	p
Death				
NEWS2	1/41 (2.4%)	2/24 (8.3%)	4/46 (8.7%)	0.438
$NEWS2_{88-92\%}$	2/50 (4.0%)	1/25 (0.0%)	4/35 (11.4%)	0.331
DECAF score	*	1/31 (3.2%)	7/85 (8.2%)	0.560
mDECAF score	**	1/24 (4.2%)	7/94 (7.4%)	0.818
LOS, days				
NEWS2	7 [6]	7 [10]	10 [7]	0.001
$NEWS2_{88-92\%}$	7 [6]	8 [7]	13 [9]	0.002
DECAF score	17 [17]	7 [9]	10 [8]	0.160
mDECAF score	**	7 [9]	9 [8]	0.392
NIV				
NEWS2	10/41 (24.4%)	7/24 (29.2%)	25/46 (54.3%)	0.01
$NEWS2_{88-92\%}$	12/50 (24.0%)	8/25 (32.0%)	22/35 (62.9%)	0.001
DECAF score	*	10/31 (32.3%)	32/85 (37.6%)	0.374
mDECAF score	**	12/24 (50.0%)	29/94 (30.9%)	0.875
IMV				
NEWS2	0/41 (0.0%)	0/24 (0.0%)	2/46 (4.3%)	0.237
$NEWS2_{88-92\%}$	0/50 (0.0%)	0/25 (0.0%)	2/35 (5.7%)	0.113
DECAF score	*	1/31 (3.2%)	2/85 (2.4%)	0.928
mDECAF score	**	0/24 (0.0%)	3/94 (3.2%)	0.664
AECOPD in the following year				
NEWS2	25/40 (62.5%)	16/22 (72.7%)	30/41 (73.2%)	0.531
$NEWS2_{88-92\%}$	30/48 (62.5%)	17/23 (73.9%)	23/31 (74.2%)	0.453
DECAF score	*	23/30 (76.7%)	51/77 (66.2%)	0.245
mDECAF score	**	17/22 (77.3%)	57/87 (65.5%)	0.452
Severe AECOPD in the following year				
NEWS2	18/40 (38.8%)	10/22 (45.5%)	22/41 (53.7%)	0.700
$NEWS2_{88-92\%}$	21/48 (43.8%)	12/23 (52.2%)	16/31 (51.6%)	0.715
DECAF score	*	17/30 (56.7%)	34/77 (44.2%)	0.134
mDECAF score	**	11/22 (50.0%)	39/87 (44.8%)	0.508
Readmission at 30 days				
NEWS2	4/40 (10.0%)	4/22 (18.2%)	7/40 (17.5%)	0.568
$NEWS2_{88-92\%}$	4/48 (8.3%)	4/23 (17.4%)	6/30 (20.0%)	0.290
DECAF score	*	5/30 (16.7%)	10/76 (13.2%)	0.699
mDECAF score	**	4/22 (18.2%)	10/86 (11.6%)	0.031
Readmission at 60 days				
NEWS2	6/40 (15.0%)	4/22 (18.2%)	9/40 (22.5%)	0.689
$NEWS2_{88-92\%}$	6/48 (12.5%)	4/23 (17.4%)	8/30 (26.7%)	0.280
DECAF score	*	6/30 (20.0%)	13/76 (17.1%)	0.678
mDECAF score	**	5/22 (22.7%)	13/86 (15.1%)	0.064
Readmission at 90 days				
NEWS2	8/40 (20.0%)	6/22 (27.3%)	11/40 (27.5%)	0.696
$NEWS2_{88-92\%}$	8/48 (16.7%)	6/23 (26.1%)	10/30 (33.3%)	0.232
DECAF score	*	8/30 (26.7%)	17/76 (22.4%)	0.565
mDECAF	**	5/22 (22.7%)	19/86 (22.1%)	0.183
Readmission at 180 days				
NEWS2	14/40 (35.0%)	7/22 (31.8%)	17/40 (42.5%)	0.658
$NEWS2_{88-92\%}$	14/48 (29.2%)	8/23 (34.8%)	15/30 (50.0%)	0.174
DECAF score	*	11/30 (36.7%)	27/76 (35.5%)	0.435
mDECAF score	**	7/22 (31.8%)	30/86 (34.9%)	0.376

AECOPD, acute exacerbation(s) of COPD; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; NEWS2: National Early Warning Score 2; DECAF: **D**yspnea, **E**osinopenia, **C**onsolidation, **A**cidemia, and atrial **F**ibrillation; mDECAF: modified DECAF; and LOS: length of stay. [a]Data presented as n/total (%) or median [IQR]. *Analysis was not performed, because only 3 patients were classified as being low-risk patients by the DECAF score. **Analysis was not performed, because only 1 patient was classified as being a low-risk patient by the mDECAF score.

because only 1 and 3 patients were classified as being low-risk patients by the DECAF and mDECAF scores, respectively.

The NEWS2 had a high sensitivity for mortality, whereas the NEWS2 and $NEWS2_{88-92\%}$ had a high sensitivity for a longer LOS and the need for NIV. The

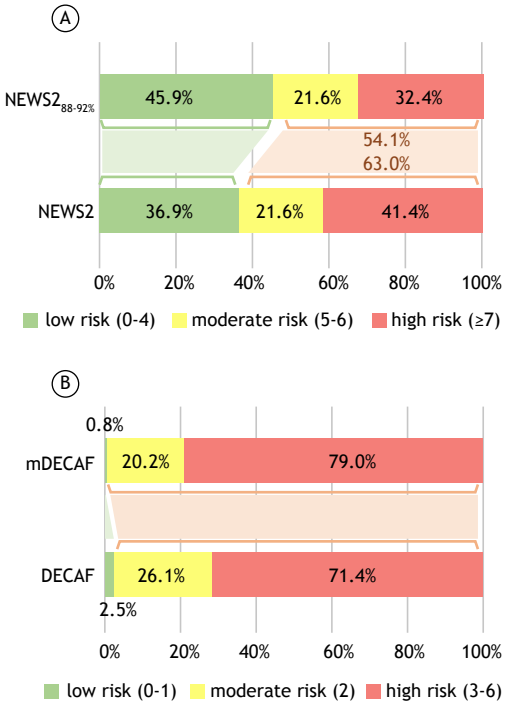

Figure 1. Patients classified as being low-, moderate-, or high-risk patients on the basis of the National Early Warning Score 2 (NEWS2) and NEWS2$_{88-92\%}$ scores (in A), and on the basis of the **D**yspnea, **E**osinopenia, **C**onsolidation, **A**cidemia, and atrial **F**ibrillation (DECAF) and modified DECAF (mDECAF) scores (in B). Note: Risk categories were compared between scores (e.g., low risk on the basis of the NEWS2 score vs. low risk on the basis of the NEWS2$_{88-92\%}$ score). Values of p were calculated by means of Fisher's exact test ($p < 0.001$).

NEWS2 and NEWS2$_{88-92\%}$ had a high specificity for mortality, a longer LOS, and NIV use, the NEWS2$_{88-92\%}$ showing better results than the NEWS2.

DISCUSSION

In the present study, the NEWS2 and NEWS2$_{88-92\%}$ scores were moderately accurate in predicting a longer LOS and the need for NIV or IMV, but not mortality. In contrast, the mDECAF score was able to predict mortality, albeit not necessarily accurately, and the need for IMV. However, none of the scores were good at predicting outcomes after discharge.

Patients hospitalized for AECOPD have an in-hospital mortality rate that is not negligible. In our sample, there was an in-hospital mortality rate of 7%, which is consistent with the literature (4-8%).[10,11]

In our study, the DECAF and mDECAF scores performed better than the NEWS2 and NEWS2$_{88-92\%}$ in predicting in-hospital mortality in patients admitted with AECOPD. Although the NEWS2 score at admission has been used as a mortality predictor in the United Kingdom, our results suggest that such scores should not be used for this purpose, being consistent with those of other studies.[13] Unlike the NEWS scores, the DECAF score has been validated as a predictor of in-hospital mortality at admission for AECOPD.[10,11] Furthermore, our results show that the mDECAF score performed better than the original DECAF score. This is consistent with recent studies showing the prognostic impact of an AECOPD in the previous year.[12,14]

Although the NEWS2 is calculated on the basis of common clinical parameters, it presupposes a blood gas analysis at evaluation or knowledge of the type of respiratory failure that the patient experienced. The use of the NEWS2$_{88-92\%}$ in all of the patients in the present study, regardless of the type of respiratory failure, was associated with a reduction of 8.9% in the number of individuals requiring close, continuous observation in comparison with the NEWS2, without a significant increase in mortality in individuals reclassified as being low-risk patients. In fact, none of the patients classified as being low-risk patients died on the same day the score was applied. Echevarria et al. compared the NEWS2 and NEWS2$_{88-92\%}$ and found no differences in mortality.[13] In fact, several guidelines advise titration of oxygen saturation to a target of 88-82% in patients with AECOPD, a value that is associated with reduced mortality, hypercapnia, and respiratory acidosis.[1,8,9,15]

In addition to supporting previous results regarding in-hospital mortality, our study is, to the best of our knowledge, the first to compare the performance of the NEWS2, NEWS2$_{88-92\%}$, and DECAF scores in predicting the need for NIV, the use of IMV, and the LOS. The NEWS2 and NEWS2$_{88-92\%}$ were found to perform better than the DECAF scores in predicting the need for NIV, the need for IMV, and a longer LOS. This finding should be explored in future studies involving a larger sample size. If confirmed, it can have implications for patient management, including prediction of the resources required and admission of patients on the basis of the required level of care. The NEWS2/NEWS2$_{88-92\%}$ and DECAF scores were not good at predicting long-term outcomes such as future AECOPD and hospital readmissions, reflecting the fact that they have been developed for different purposes.

Our study has some limitations. Because this was a retrospective study, there are some missing data. In addition, the NEWS2 and NEWS2$_{88-92\%}$ scores were calculated on the basis of patient data collected at the time of admission, because data from other time points were unavailable. Finally, the fact that this was a single-center study and that the sample size was small might have led to reduced accuracy of the estimates and type II errors. Despite the aforementioned limitations, key strengths of our study include the fact that all of the patients presenting with AECOPD were consecutively included and the fact that this was the first study to compare the performance of the NEWS and DECAF scores in predicting the need for acute NIV, the need for IMV, and the LOS.

Future larger, multicenter prospective studies are warranted, as are studies evaluating the use of the NEWS2 and NEWS2$_{88-92\%}$ during the entire LOS, in order to investigate whether titrating oxygen saturation to 88-92% in all patients has implications for clinical course,

Table 3. Sensitivity and specificity of the categories defined by low-risk and high-risk thresholds on the basis of the National Early Warning Score 2 scores (part A) and the Dyspnea, Eosinopenia, Consolidation, Acidemia, and atrial Fibrillation scores (part B).

Part A								
	Score ≥ 5 (moderate risk)				Score ≥ 7 (high risk)			
	NEWS2		$NEWS2_{88-92\%}$		NEWS2		$NEWS2_{88-92\%}$	
	Sn (95% CI)	Sp (95% CI)	Sn (95% CI)	Sp (95% CI)	Sn (95% CI)	Sp (95% CI)	Sn (95% CI)	Sp (95% CI)
Death	0.86 (0.79-0.92)	0.39 (0.29-0.48)	0.71 (0.63-0.80)	0.47 (0.38-0.56)	0.57 (0.48-0.67)	0.60 (0.51-0.69)	0.57 (0.48-0.66)	0.69 (0.61-0.78)
LOS >14 days	0.86 (0.79-0.92)	0.45 (0.35-0.54)	0.82 (0.75-0.90)	0.55 (0.46-0.65)	0.64 (0.55-0.73)	0.66 (0.58-0.75)	0.61 (0.52-0.70)	0.77 (0.69-0.85)
NIV	0.76 (0.68-0.84)	0.45 (0.36-0.54)	0.71 (0.63-0.80)	0.57 (0.47-0.66)	0.60 (0.50-0.69)	0.70 (0.61-0.78)	0.53 (0.43-0.62)	0.80 (0.72-0.87)
IMV	1.00 (1.00-1.00)	0.38 (0.29-0.47)	1.00 (1.00-1.00)	0.47 (0.38-0.56)	0.04 (0.01-0.08)	1.00 (1.00-1.00)	0.06 (0.01-0.10)	1.00 (1.00-1.00)
AECOPD in the following year	0.65 (0.56-0.74)	0.47 (0.37-0.57)	0.56 (0.47-0.66)	0.56 (0.47-0.66)	0.42 (0.33-0.52)	0.66 (0.57-0.75)	0.34 (0.25-0.43)	0.75 (0.67-0.83)
Severe AECOPD in the following year	0.64 (0.55-0.73)	0.42 (0.32-0.51)	0.58 (0.49-0.68)	0.53 (0.43-0.63)	0.44 (0.34-0.54)	0.64 (0.55-0.73)	0.34 (0.25-0.43)	0.72 (0.63-0.80)
Readmission at 30 days	0.73 (0.65-0.82)	0.41 (0.32-0.51)	0.73 (0.65-0.82)	0.52 (0.42-0.61)	0.47 (0.37-0.56)	0.62 (0.53-0.72)	0.47 (0.37-0.56)	0.72 (0.64-0.81)
Readmission at 60 days	0.68 (0.59-0.77)	0.41 (0.31-0.51)	0.68 (0.59-0.77)	0.52 (0.42-0.62)	0.47 (0.38-0.57)	0.63 (0.53-0.72)	0.47 (0.38-0.57)	0.74 (0.65-0.82)
Readmission at 90 days	0.68 (0.59-0.77)	0.42 (0.32-0.51)	0.68 (0.59-0.77)	0.53 (0.44-0.63)	0.44 (0.34-0.54)	0.62 (0.53-0.72)	0.44 (0.34-0.54)	0.74 (0.66-0.83)
Readmission at 180 days	0.63 (0.54-0.73)	0.41 (0.31-0.50)	0.63 (0.54-0.73)	0.55 (0.45-0.64)	0.45 (0.35-0.54)	0.64 (0.55-0.73)	0.42 (0.33-0.52)	0.77 (0.68-0.85)
Part B								
	Score ≥ 2 (moderate risk)				Score ≥ 3 (high risk)			
	DECAF		mDECAF		DECAF		mDECAF	
	Sn (95% CI)	Sp (95% CI)	Sn (95% CI)	Sp (95% CI)	Sn (95% CI)	Sp (95% CI)	Sn (95% CI)	Sp (95% CI)
Mortality	-	-	-	-	0.86 (0.65-1.10)	0.29 (0.20-0.37)	0.88 (0.65-1.10)	0.22 (0.14-0.29)
LOS > 14 days	-	-	-	-	0.71 (0.55-0.87)	0.27 (0.18-0.37)	0.81 (0.67-0.95)	0.22 (0.13-0.30)
NIV	-	-	-	-	0.24 (0.11-0.37)	0.30 (0.20-0.40)	0.69 (0.55-0.83)	0.16 (0.07-0.24)
IMV	-	-	-	-	0.67 (0.13-1.20)	0.28 (0.19-0.36)	1.00 (1.00-1.00)	0.22 (0.14-0.29)
AECOPD in the following year	-	-	-	-	0.69 (0.59-0.80)	0.26 (0.11-0.40)	0.76 (0.66-0.86)	0.14 (0.03-0.26)
Severe AECOPD in the following year	-	-	-	-	0.69 (0.56-0.81)	0.27 (0.16-0.38)	0.76 (0.65-0.88)	0.19 (0.09-0.29)
Readmission at 30 days	-	-	-	-	0.67 (0.43-0.91)	0.29 (0.20-0.38)	0.67 (0.43-0.91)	0.19 (0.11-0.27)
Readmission at 60 days	-	-	-	-	0.68 (0.48-0.89)	0.29 (0.20-0.38)	0.68 (0.48-0.89)	0.19 (0.11-0.27)
Readmission at 90 days	-	-	-	-	0.72 (0.54-0.90)	0.30 (0.20-0.40)	0.76 (0.59-0.93)	0.20 (0.11-0.29)
Readmission at 180 days	-	-	-	-	0.74 (0.60-0.88)	0.31 (0.20-0.42)	0.79 (0.66-0.92)	0.21 (0.12-0.31)

NEWS2: National Early Warning Score 2; Sn: sensitivity; Sp: specificity; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; AECOPD: acute exacerbation(s) of COPD; DECAF: **D**yspnea, **E**osinopenia, **C**onsolidation, **A**cidemia, and atrial **F**ibrillation; and mDECAF: modified DECAF.

reducing or increasing the frequency of observations on the basis of patient risk classification and, ultimately, the associated financial costs.

In conclusion, the NEWS2 and $NEWS2_{88-92\%}$ scores calculated at admission in patients presenting with AECOPD appear to be adequate in predicting the need for acute NIV and a longer LOS. In addition, it is unlikely that the use of the $NEWS2_{88-92\%}$ would have resulted in an increased risk of death in the low-risk group. In fact, the use of the $NEWS_{88-92\%}$ can reduce the number of patients requiring closer clinical surveillance, reducing human resource costs and hospital expenses without compromising patient safety. The DECAF and mDECAF scores calculated at admission in patients presenting with AECOPD appear to be better predictors of in-hospital mortality than the NEWS2 and $NEWS2_{88-92\%}$ scores.

AUTHOR CONTRIBUTIONS

LG, BS-P, and CR: design of the study. LG and BS-P: analysis of the data and writing of the manuscript. LG, SP, BS-P, and CR: 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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Effects of air temperature on the risk of death from COPD in major microregions in Brazil: a time series study

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ABSTRACT

Objective: To evaluate the association between the risk of death from COPD and air temperature events in ten major Brazilian microregions. **Methods:** This was a time series analysis of daily COPD deaths and daily mean air temperatures between 1996 and 2017. Using distributed nonlinear lag models, we estimated the cumulative relative risks of COPD mortality for four temperature percentiles (representing moderate and extreme cold and heat events) in relation to a minimum mortality temperature, with a lag of 21 days, in each microregion. **Results:** Significant associations were found between extreme air temperature events and the risk of death from COPD in the southern and southeastern microregions in Brazil. There was an association of extreme cold and an increased mortality risk in the following microregions: 36% (95% CI, 1.12-1.65), in Porto Alegre; 27% (95% CI, 1.03-1.58), in Curitiba; and 34% (95% CI, 1.19-1.52), in São Paulo; whereas moderate cold was associated with an increased risk of 20% (95% CI, 1.01-1.41), 33% (95% CI, 1.09-1.62), and 24% (95% CI, 1.12-1.38) in the same microregions, respectively. There was an increased COPD mortality risk in the São Paulo and Rio de Janeiro microregions: 17% (95% CI, 1.05-1.31) and 12% (95% CI, 1,02-1,23), respectively, due to moderate heat, and 23% (95% CI, 1,09-1,38) and 32% (95% CI, 1,15-1,50) due to extreme heat. **Conclusions:** Non-optimal air temperature events were associated with an increased risk of death from COPD in tropical and subtropical areas of Brazil.

Keywords: Pulmonary disease, chronic obstructive/mortality; Temperature; Climate.

INTRODUCTION

In 2019, COPD was the fourth leading cause of death in Brazil according to the Global Burden of Disease.[1] In addition, COPD prevalence in the Americas is the highest among WHO regions.[2] At the same time, climate change has already been a reality, including in Brazil,[3] and the new challenge is to study the relationship between chronic diseases and environmental variables. Furthermore, extreme air temperatures are a risk factor for the occurrence and exacerbation of lung diseases, as well as mortality, and, according to the Intergovernmental Panel on Climate Change, this exposure will become more frequent and intense with the progression of the climate transition.[4,5]

It is still unclear whether the effect of air temperature on COPD has a higher association with cold or warm temperatures. A national level Chinese study using a similar methodology to that in this study found that colder air temperatures were more often associated with the occurrence of death from COPD,[6] whereas a study involving 12 cities in the USA, using a different methodology, estimated that the effect of heat during summer was responsible for an increase of up to 25% in COPD deaths.[7] In addition to these studies,[6,7] the relationship between temperature and different COPD outcomes has been studied all over the world.[8]

Considering the relative lack of research on this topic in Brazil, the objective of this study was to investigate the relationship between air temperature and COPD mortality in several geographic microregions that are representative of all macroregions in Brazil.

METHODS

In this time series study, the relationship between daily mean air temperature and the number of daily deaths from COPD in ten Brazilian microregions was evaluated. The two largest microregions of each of the five Brazilian macroregions (North, Northeast, Central-West, Southeast, and South) were selected, except in the Central-West macroregion, where the first and third largest microregions were selected due to the geographical proximity of the second largest (Goiânia) to the first one (Brasília). Thus, the selected microregions were the following: Belém and Manaus

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(North), Salvador and Fortaleza (Northeast), Campo Grande and Brasília (Central-West), São Paulo and Rio de Janeiro (Southeast), and Porto Alegre and Curitiba (South). The study comprised a total of 105 Brazilian municipalities, representing different climate regions in the country, within a period of 22 years (from January 1, 1996, to December 31, 2017).

Data on mortality from COPD were collected via the Brazilian Ministry of Health Information Department, specifically retrieved from the Mortality Information System[9] based on the primary cause of death (COPD) which was defined in accordance with the Tenth Edition of the International Classification of Diseases (codes J41-J44).[6]

Daily mean temperature data were estimated from the ERA-Interim reanalysis, developed by the European Center for Medium-Term Weather Forecasting, which provides four daily air temperature values at points on a uniform horizontal grid with approximately 13 km of space between them.[10,11] This reanalysis model is conceived from a forecasting system combined with the assimilation of meteorological information from ships, satellites, planes, radars, radiosondes, and surface meteorological stations.[12] By calculating the mean of the four values of air temperature, we obtained the mean daily temperatures for those points. Then, to obtain the daily mean temperature for the microregions, we calculated the mean value of all points identified within the territory of each microregion.

Although data from meteorological stations are more reliable, their irregular distribution, incomplete time series, and large territorial gaps from such stations make a time series analysis unfeasible. Thus, the data from ERA-Interim solve these difficulties due to a correlation equal to or greater than 96% when compared with data from existing surface meteorological stations.[13] In addition, air temperature means are the most used data as parameters for analysis in climate and health studies. Although there is variation in air temperature within each microregion, the mean daily air temperature is representative of the temperature behavior in each microregion.[13]

To study the association between daily COPD deaths and mean daily air temperature, generalized additive models were fitted with a negative binomial distribution together with a natural cubic spline of time with eight degrees of freedom per year to adjust for long-term trend and seasonality, as well as days of the week to adjust for short-term seasonality.

For inferential analysis and modeling, which characterizes the focus of the present study, distributed lag nonlinear models were used.[14] After selecting a natural spline with five degrees of freedom for the exposure-response function, a polynomial function with one intercept and four degrees of freedom for the lag-response function, and 21 days of lag, we estimated, for each microregion, the cumulative relative risks of death from COPD in percentiles of air temperature distribution with the minimum mortality temperature (MMT)—that is, the reference temperature at which there is minimum risk of mortality in the accumulated lag[15]—corresponding to the total accumulated risk. The 2.5th and 10th percentiles were chosen to represent, respectively, extreme cold and moderate cold, as were the 90th and 97.5th percentiles to represent moderate heat and extreme heat.

We estimated the fractions and numbers of events attributable to non-optimal temperatures, accumulated up to the 21st day, with the forward method[16] of current exposure to future risks. We calculated the following components:

a. Attributable risk (AR) to extreme cold (between the lowest temperature and the 2.5th percentile)
b. AR to moderate cold (between the 2.5th and 10th percentiles)
c. AR to mild cold (between the 10th percentile and the MMT)
d. AR to mild heat (between MMT and the 90th percentile)
e. AR to moderate heat (between the 90th and 97.5th percentiles)
f. AR to extreme heat (between the 97.5th percentile and the highest temperature)

We analyzed the residuals of the models to detect possible serial autocorrelations and performed a sensitivity analysis to assess the robustness of the main model against the ones produced with many different parameter alterations (supplementary Table S1 and Figure S1). The R software, version 3.4.0 (The R Project for Statistical Computing, Vienna, Austria) was used, especially the *dlnm* package.[17] The related scripts are available on Github (https://github.com/joao-med/COPD-Temperature).

Due to the public nature of the data, the research was exempted from approval by a research ethics committee in accordance with Resolution No.510 of the Brazilian National Health Council.

RESULTS

We analyzed a total of 208,169 COPD deaths in ten Brazilian microregions, ranging from 3,812 deaths in the Campo Grande microregion, with 0 to 5 daily cases, and 67,806 deaths in the São Paulo microregion, with 0 to 26 daily cases (Table 1 and Figure 1).

In all microregions analyzed, the lowest mean air temperatures were identified in the middle of the year (months of June and July) except in Manaus, Belém, and Fortaleza microregions. Meanwhile, the highest mean air temperatures occurred at the end and the beginning of the year (between October and March). These variations correspond to winters (lower temperatures) and late summers (higher temperatures) in the southern hemisphere. During the studied period, the lowest mean air temperature was in the Curitiba microregion (18.7°C), whereas the highest one was in the Fortaleza microregion (27.3°C). In addition, the highest and the lowest air temperatures were found

Table 1. Distribution of daily mortality from COPD in the Brazilian microregions studied, 1996-2017.

Variable	Microregion									
	Brasília	Campo Grande	Porto Alegre	Curitiba	São Paulo	Rio de Janeiro	Salvador	Fortaleza	Belém	Manaus
Population[a]	2,411,628	820,088	3,598,717	2,977,488	13,468,309	11,210,768	336,7109	318,1579	2,047,843	1,874,407
COPD deaths										
Total number	6,906	3,812	30,232	17,616	67,806	54,916	7,070	7,224	8,130	4,457
Mean annual number	314	173	1374	801	3,082	2,496	321	328	370	203
Mean annual rate[b]	13.02	21.13	38.19	26.89	22.88	22.27	9.54	10.32	18.05	10.81
Daily distribution										
Minimum value	0	0	0	0	0	0	0	0	0	0
25th percentile	0	0	2	1	6	5	0	0	0	0
Median	1	0	3	2	8	7	1	1	1	0
Mean	1	0	4	2	8	7	1	1	1	1
75th percentile	1	1	5	3	10	8	1	1	2	1
Maximum value	6	5	17	12	26	20	6	7	8	6
Mean daily rate[b]	0.04	0.06	0.10	0.07	0.06	0.06	0.03	0.03	0.05	0.03

[a]Average population for the period. [b]Rates per 100,000 population.

in the Campo Grande (32.7°C) and Curitiba (4.5°C) microregions, respectively. Simultaneously, the MMT varied from 17.9°C to 28.5°C in the Curitiba and Belém microregions, respectively (Table 2 and Figure 1).

There was an association between COPD deaths and air temperature, especially in the most populous microregions such as São Paulo, Rio de Janeiro, and Porto Alegre _(the first two in the Southeast macroregion and the last one in the South one). These three microregions had the highest mean daily death rates (Table 1), which contributed to a more reliable estimate of the relative risks (Table 3 and Figure 2).

The percentile attributable to extreme cold showed an increased risk of death from COPD of 36%, 27%, and 34%, respectively, in the Porto Alegre, Curitiba, and São Paulo microregions, while moderate cold showed a significant increase of 20%, 33%, and 24% in the same microregions. Furthermore, an increased risk of moderate heat was estimated to be 17% and 12%, respectively, in the São Paulo and Rio de Janeiro microregions. Regarding extreme heat, the microregions that showed significant results were Campo Grande, São Paulo, and Rio de Janeiro, with increases in the mortality risk of 55%, 23%, and 32%, respectively (Table 3).

The fraction of COPD deaths attributable to cold air temperature over the entire study period (from 1996 to 2017) was 8.83% in the São Paulo microregion, whereas, in the Porto Alegre microregion, with the combination of extreme and moderate cold temperatures, that value was 3.35%. Regarding heat, the attributable fraction was 3.21% in the São Paulo microregion. Considering extreme heat only, the attributable fraction was 1.40% in the Campo Grande microregion, whereas that was 1.86% in the Rio de Janeiro microregion, considering both extreme and moderate heat (Table 4).

Regarding the attributable deaths for different mean air temperatures during the studied period, the São Paulo microregion had the most significant results: the range corresponding to moderate cold and mild cold might have been responsible for, respectively, 1,267 (95% CI, 770-1,727) and 4,108 deaths (95% CI, 1,631-6,525). Meanwhile, the number of deaths attributable to mild and moderate heat were, in this order, 1,097 (95% CI, 50-2,032) and 771 (95% CI, 361-1,169). On the other hand, extreme heat might have been responsible for 412 deaths (95% CI, 226-562) in the Rio de Janeiro microregion, which showed the most significant result between 1996 and 2017.

In the Fortaleza and Salvador microregions, no associations were present in any lag. However, associations with extreme cold or extreme heat were present in almost all lags in all of the other microregions (Figures S2 and S3).

DISCUSSION

The present study carried out a comprehensive analysis of the Brazilian territory and population,

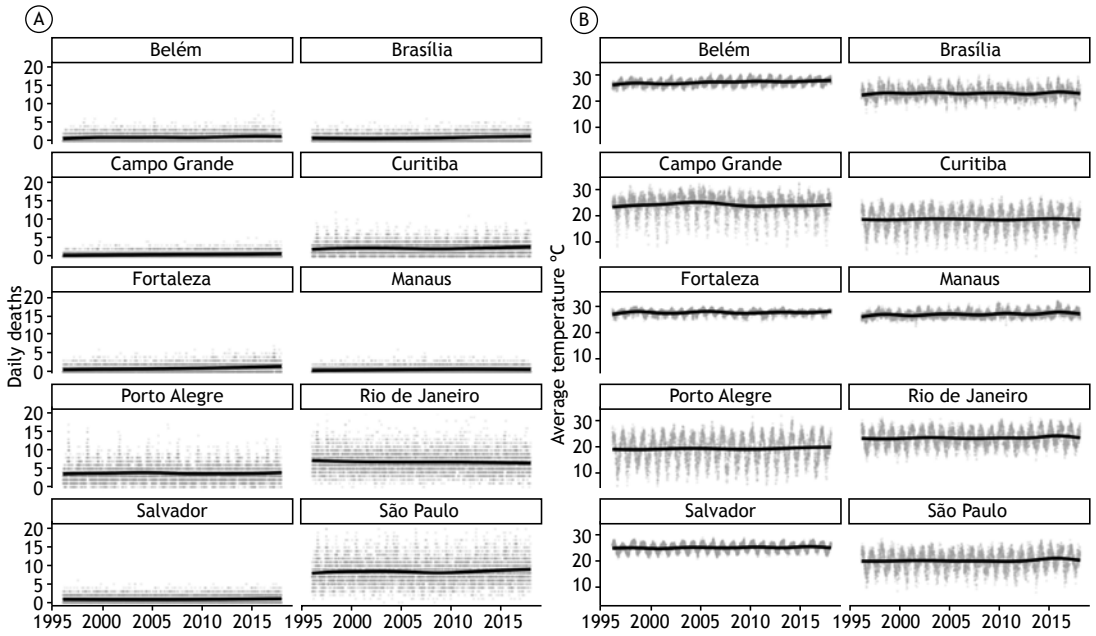

Figure 1. Daily distribution of deaths from COPD (J41-44) and mean temperatures (°C) between 1996 and 2017 in the microregions studied. Each day is represented as a gray dot, and the line on each graph represents the time trend.

evaluating the impact of air temperature on COPD mortality in tropical and subtropical areas. Moreover, due to the scarcity of material available with similar analyses, we expanded the knowledge on health and climate, bringing important information for better decision making and consequent improvement of public health. We investigated ten Brazilian microregions, located in all macroregions and representing the major climate types of the country, with an estimated number of 27,090,704 people and 208,169 deaths from COPD during the period between 1996 and 2017. Furthermore, we identified a significant association between extreme air temperature events and the risk of death from COPD in the southern and southeastern microregions of the country, with an emphasis on the microregion of São Paulo, where there was the highest number of recorded deaths. In this microregion, 1,836 deaths were attributable to exposure to non-optimal air temperature conditions in the period analyzed, and the risk of death from COPD increased significantly in both cold and warm moderate and extreme temperature events, regardless whether below or above the MMT.

Another important feature that strengthens our analysis is the use of distributed lag nonlinear models that capture complex relationships between the relationship of air temperature and COPD deaths,[14,18] by calculating nonlinear relationships and exposure implications from a lagged perspective. This methodology also provides relative and attributable risk estimation for different temperatures and lags.[14,19]

To compare our research with the various results presented around the world, it is worth noting that a similar study in China published in 2018 found a fraction of 12.6% (95% CI, 10.31-12.57) of COPD deaths attributable to air temperature, presenting a curve where most of the deaths were due to colder temperatures.[6] Likewise, for the same air temperature conditions, we found an attributable fraction of 12.04% (95% CI, 4.8-18.98) in the São Paulo microregion and an analogous modeled curve.

Regarding the risk of death from COPD, an American study found by means of logistic regression models a 19% increased chance among elderly individuals with COPD of dying on the same day when the maximum temperature was lower than or equal to the 1st percentile, as compared with patients without COPD.[20] This finding is consistent with our results of COPD mortality risk at the extremely cold temperature (in percentile) in the Porto Alegre, Curitiba, and São Paulo microregions. In turn, a study with data between 1980 and 2000 in New Zealand reported that the mortality rate was 18% higher in winter than that expected when compared with other months, 31% of excess deaths being attributable to respiratory disease.[21] Finally, a large study in Taiwan found that a 5°C decrease in mean daily temperature correlated significantly with increased hospital admissions due to COPD on the same day and on the 28 consecutive days.[22]

Considering that the likely mechanisms influencing COPD mortality would first have to lead to an exacerbation of the disease, exposure to low air temperatures might facilitate this event by several means. Since an increase in morbidity and mortality is already expected in winter,[18,23] some explanations are usually pointed out, such as those indicating the relationship between cold temperature and decreased

Table 2. Distribution of daily mean temperature (in ºC) and temperatures related to minimum risks accumulated up to lag 21 (days) in the Brazilian microregions studied, 1996-2017.

Distribution	Microregion									
	Brasília	Campo Grande	Porto Alegre	Curitiba	São Paulo	Rio de Janeiro	Salvador	Fortaleza	Belém	Manaus
Minimum value	15.3	8.3	4.9	4.5	8.4	13.8	21.3	23.7	23.5	22.0
1st percentile	18.5	13.4	8.0	9.3	12.7	16.9	22.5	24.8	24.5	24.2
2.5th percentile	19.2	15.6	9.6	10.8	13.9	17.9	22.9	25.2	24.8	24.5
10th percentile	20.4	19.9	12.7	13.6	16.3	19.6	23.6	26.0	25.4	25.1
25th percentile	21.5	22.8	16.0	16.1	18.4	21.2	24.4	26.7	26.1	25.7
Median	22.7	24.8	19.8	19.0	20.8	23.4	25.7	27.4	26.9	26.5
Mean	22.8	24.3	19.3	18.7	20.6	23.4	25.6	27.3	27.0	26.6
75th percentile	24.1	26.5	23.0	21.7	23.1	25.7	26.8	27.9	27.9	27.3
90th percentile	25.5	27.9	24.9	23.4	24.6	27.4	27.4	28.3	28.7	28.2
97.5th percentile	27.1	29.4	26.6	24.8	26.1	28.7	28.0	28.7	29.3	29.4
99th percentile	27.9	30.2	27.5	25.5	26.8	29.4	28.3	29.0	29.6	30.0
Maximum value	29.7	32.7	31.9	27.6	29.0	31.3	29.5	29.7	30.7	31.8
Minimum mortality temperature	20.9	27.2	21.7	17.9	21.8	25.1	27.1	24.8	28.5	26.5

Table 3. Relative risks and respective 95% CIs (accumulated up to 21 days) of death from COPD due to exposure to mean temperatures in the microregions studied, taking as a reference a minimum risk temperature, 1996-2017.

Mean temperature	Microregion									
	Brasília	Campo Grande	Porto Alegre	Curitiba	São Paulo	Rio de Janeiro	Salvador	Fortaleza	Belém	Manaus
Extreme cold	1.18 (0.94; 1.48)	1.03 (0.62; 1.71)	1.36 (1.12; 1.65)	1.27 (1.03; 1.58)	1.34 (1.19; 1.52)	1.09 (0.95; 1.25)	1.59 (0.89; 2.85)	1.15 (0.82; 1.59)	1.61 (0.97; 2.68)	1.36 (0.78; 2.37)
Moderate cold	1.02 (0.94; 1.10)	1.04 (0.67; 1.60)	1.20 (1.01; 1.41)	1.33 (1.09; 1.62)	1.24 (1.12; 1.38)	1.06 (0.94; 1.19)	1.41 (0.85; 2.34)	1.35 (0.68; 2.70)	1.24 (0.82; 1.87)	1.15 (0.70; 1.88)
Moderate heat	1.31 (0.96; 1.78)	1.05 (0.94; 1.18)	1.10 (0.92; 1.30)	1.15 (0.92; 1.43)	1.17 (1.05; 1.31)	1.12 (1.02; 1.23)	1.03 (0.95; 1.10)	1.30 (0.69; 2.43)	1.00 (0.94; 1.07)	1.07 (0.71; 1.60)
Extreme heat	1.36 (0.97; 1.91)	1.55 (1.07; 2.25)	1.17 (0.96; 1.43)	1.22 (0.93; 1.59)	1.23 (1.09; 1.38)	1.32 (1.15; 1.50)	1.25 (0.92; 1.71)	1.33 (0.69; 2.56)	1.05 (0.73; 1.53)	1.09 (0.66; 1.82)

Extreme cold: 2.5th percentile of average temperature. Moderate cold: 10th percentile of average temperature. Moderate heat: 90th percentile of average temperature. Extreme heat: 97.5th percentile of average temperature.

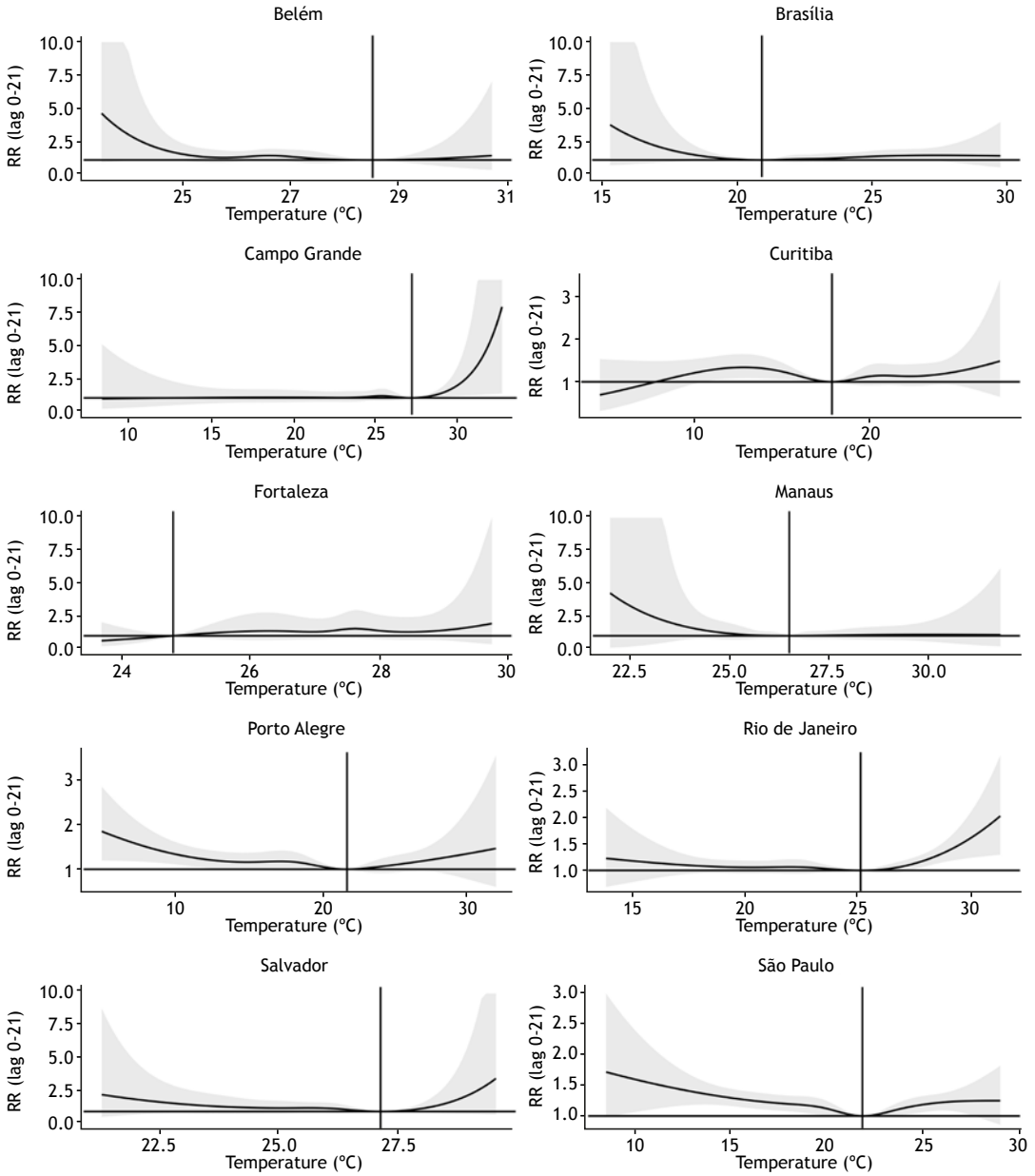

Figure 2. Accumulated relative risk (RR) curves by temperature. The gray margins indicate the confidence interval of the measurement, the vertical line indicates the minimum mortality temperature, and the lines below the x-axis indicate single measurements of temperature.

lung function,[18] infection by viral agents,[21] direct effect of cold on bronchoconstriction, and decreased mucociliary clearance that may result in exacerbation of COPD progressively.[20]

Regarding warmer air temperatures, the moderate heat percentile in the São Paulo microregion was found to be a risk factor for COPD mortality, as was in the Rio de Janeiro one. By the possible effect of heat, the aforementioned American study estimated that the effect of increasing air temperatures during summer was responsible for an increase of up to 25% in the causes of death from COPD.[7] Accordingly, another research carried out specifically in New York City found, through a generalized additive model, that each 1°C above the temperature of 29°C (75th percentile) meant a 7.6% increase in the risk of hospital admission for COPD with a 3-day lag.[24] Finally, another American study estimated a 4.7% increase in the risk of same-day COPD hospitalization among the elderly for every 5.6°C increase in mean ambient temperature during summer.[25]

Concerning this issue, heat exposure is related to events that may lead to bronchoconstriction mediated by cholinergic factors,[8] hyperventilation in extreme

Table 4. Fractions and numbers (95% CIs) of COPD deaths attributable to exposure to mean temperatures in the microregions studied, 1996-2017.

Variable	Average temperature	Microregion									
		Brasília	Campo Grande	Porto Alegre	Curitiba	São Paulo	Rio de Janeiro	Salvador	Fortaleza	Belém	Manaus
Attributable fraction, %	Extreme cold	–	–	1.22 (0.55; 1.74)	–	0.90 (0.44; 1.24)	–	–	–	1.13 (0.02; 1.69)	–
	Moderate cold	–	–	2.13 (0.58; 3.36)	2.43 (0.78; 3.93)	1.87 (1.16; 2.52)	–	–	–	–	–
	Mild cold	–	–	–	4.12 (1.32; 6.80)	6.06 (2.34; 9.75)	–	–	–	–	–
	Mild heat	–	–	–	–	1.62 (0.20; 3.03)	–	–	–	–	–
	Moderate heat	–	–	–	–	1.14 (0.50; 1.73)	1.11 (0.44; 1.69)	–	–	–	–
	Extreme heat	–	1.40 (0.30; 1.94)	–	–	0.45 (0.16; 0.71)	0.75 (0.39; 1.02)	–	–	–	–
	Total	–	1.4 (0.30; 1.94)	3.35 (1.13; 5.10)	6.55 (2.10; 10.73)	12.04 (4.80; 18.98)	1.86 (0.83; 2.71)	–	–	1.13 (0.02; 1.69)	–
Attributable deaths, n	Extreme cold	–	–	368 (144; 524)	–	607 (312; 848)	–	–	–	92 (6; 137)	–
	Moderate cold	–	–	644 (144; 1015)	428 (125; 663)	1,267 (770; 1,727)	–	–	–	–	–
	Mild cold	–	–	–	726 (199; 1,155)	4,108 (1,631; 6,525)	–	–	–	–	–
	Mild heat	–	–	–	–	1,097 (50; 2,032)	–	–	–	–	–
	Moderate heat	–	–	–	–	771 (361; 1,169)	612 (254; 940)	–	–	–	–
	Extreme heat	–	53 (13; 73)	–	–	305 (86; 478)	412 (226; 562)	–	–	–	–
	Total	–	53 (13; 73)	1,012 (288; 1,539)	1,154 (324; 1,818)	8,155 (3,210; 12,779)	1,024 (480; 1,502)	–	–	92 (6; 137)	–

Extreme cold: temperature between the 0th percentile and the 2.5th percentile. Moderate cold: temperature between the 2.5th percentile and the 10th percentile. Mild cold: temperature between the 10th percentile and MMT. Light heat: temperature between the MMT and the 90th percentile. Moderate heat: temperature between the 90th percentile and the 97.5th percentile. Extreme heat: temperature between the 97.5th percentile and the 100th percentile. Attributable fraction: proportion of deaths attributable to cold and heat from 1996 to 2017. Attributable deaths: number of deaths attributable to cold and heat.

temperature events,[26] and release of cytokines such as IL-1 and IL-6.[3] In addition to direct relationships, high air temperatures may increase the risk of exacerbations by interacting with variables such as air pollution, ozone level in the atmosphere, and clinical history of cardiovascular disease.[23,26]

Epidemiological studies since the 1940s have shown an association between cold temperatures and adverse cardiovascular effects.[27] A study in China published in 2023 demonstrated that temperature extremes, either cold or hot, increased the risk of mortality from ischemic heart disease in different regions of the country.[28] As for Brazil, a study investigated the relationship between air temperature and mortality from cerebrovascular diseases, in which non-optimal temperatures (either cold or hot) were associated with an increased risk of death in all Brazilian regions.[29] However, it should be noted that a clear effect of exposure is not always found in all localities.[8] This can be mainly explained by factors such as acclimatization of the local population, intrinsic variations in climate, such as mean air temperature, temperature range, and relative humidity, as well as access to health care services, quality infrastructure, air conditioning, and other socioeconomic factors.[3,30] In this context, access to a quality health care services, establishment of bronchodilator therapy, changes in habits, such as smoking cessation and initiation of physical activity, might change the quality of life and life expectancy and could be associated with the response of the disease to different temperatures.[22] Furthermore, although our study did not detail the population groups in the microregions, there is evidence in the literature that the elderly, women, and people with a low educational level are more vulnerable to health events, such as deaths from stroke, in non-optimal temperatures.[29] Other variables such as COPD stages and number of exacerbations were important limitations of the study, since they represent significant disease prognostic data. However, these clinical variables are not present in mortality databases. Other studies, using different data sources and analysis methods, could add information about the importance of these clinical variables as modifiers of the effect of air temperature on COPD mortality.

Likewise, a recent study on COPD hospitalizations suggested that the lack of association between heat and hospitalizations could be related to higher socioeconomic development and consequent better access to the health care system in the southern region of Brazil.[3] In turn, the present study found no significant relationship between heat and COPD mortality in the two southern microregions analyzed (Porto Alegre and Curitiba); in the meantime, cold was associated as a risk factor for mortality. The aforementioned finding does not exclude the possibility that the socioeconomic development of a region is related to the outcome, but it points out that new studies should introduce these variables together with air temperature.

When considering the limitations of the study, although many confounders and trends were controlled by the time scale and models used, the addition of data regarding air pollution, including particulate materials and gases such as nitrogen dioxide, ozone, and sulfur dioxide, could have increased the predictive power of the models.[8,18,23,24,30] However, these data are extremely limited in all regions and periods studied. The low daily frequency of deaths in some of the regions studied also made it impossible to estimate the effects of temperature on specific demographic groups by sex and age; considering the importance of this knowledge for public health, a more detailed analysis should be carried out in future studies, using data only from the most populous microregions, such as São Paulo.

In conclusion, this study expands the knowledge about the relationship between air temperature and mortality from COPD and contributes to studies that show significant effects of global warming on both health risk and burden on health care systems after extreme events. Thus, it is necessary to institute preventive measures from the recognition of this phenomenon to create local confrontation guidelines. Thus, it is important to guide the most vulnerable population about measures to mitigate possible deleterious effects on health, in addition to preparing and adapting public services and professionals to the increased demand for health care during such periods.

AUTHOR CONTRIBUTIONS

All authors contributed to study conception and design. JPMG, MCN, and WCMF: material preparation; and data collection and analysis. IMR: material preparation; data collection and analysis; and drafting of the manuscript.. All authors reviewed the manuscript and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Changes in lung function in adolescents with substance use disorders: an exploratory study

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ABSTRACT

Objective: To compare lung function between adolescents with and without substance use disorder (SUD). **Methods:** This was an observational, cross-sectional exploratory study. The sample consisted of 16 adolescents with SUD and 24 age-matched healthy controls. The adolescents in the clinical group were recruited from a psychiatric inpatient unit for detoxification and rehabilitation; their primary diagnosis was SUD related to marijuana, cocaine, or polysubstance use. Questionnaires and pulmonary function tests were applied for clinical evaluation. **Results:** We found that FVC, FEV_1, and their percentages of the predicted values were significantly lower in the adolescents with SUD than in those without. Those differences remained significant after adjustment for BMI and the effects of high levels of physical activity. The largest effect size (Cohen's d = 1.82) was found for FVC as a percentage of the predicted value (FVC%), which was, on average, 17.95% lower in the SUD group. In addition, the years of regular use of smoked substances (tobacco, marijuana, and crack cocaine) correlated negatively with the FVC%. **Conclusions:** This exploratory study is innovative in that it demonstrates the early consequences of smoked substance use for the lung health of adolescents with SUD.

Keywords: Adolescent; Substance-related disorders; Lung/physiopathology; Respiratory tract diseases/etiology; Cocaine; Cannabis.

INTRODUCTION

Experimentation with psychoactive substances, licit or illicit, frequently occurs during adolescence. Global epidemiological data indicate that approximately 20% of individuals between 16 and 24 years of age report using at least one illegal drug in the last year.[1] It has also been estimated that 19.33% of adolescents between 13 and 15 years are already cigarette smokers, which is alarming.[2] In addition, data from the U.S. Centers for Disease Control and Prevention indicate a similarly high prevalence (17.6%) of tobacco use during the transition from adolescence to adulthood (from 18 to 24 years of age).[3] In recent years, there has also been an increase in the estimated rates of marijuana use among adolescents.[4,5]

Early patterns of substance use are linked to an increased likelihood of developing a substance use disorder (SUD).[6] Individuals with an SUD present a persistent, compulsive pattern of substance use, which leads to significant impairment in various aspects of their life, including physical and mental health, as well as relationships and daily functioning. Although SUD is a significant public health concern worldwide, particularly regarding the consequences for mental health, little is known about its effects on respiratory and pulmonary function in the adolescent population.[7]

It has been reported that the long-term use of inhaled psychoactive substances has adverse pulmonary effects such as bronchial inflammation,[8] acute lung injury, and COPD.[7,9] Studies suggest that smoking crack cocaine results in multiple pulmonary alterations,[10] including lung lesions that may be worsened because of the toxicity caused by a pattern of polysubstance use which often occurs among people with problems related to cocaine use.[11] There is also evidence suggesting that most heroin users have some degree of airway obstruction and that frequent inhalation of the substance is one of the risk factors for developing COPD.[12,13] Pulmonary emphysema and asthma have been linked to the chronic

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use of heroin[14,15] and crack cocaine.[16] However, compromised lung function, as assessed by tests such as spirometry, is also evident after a prolonged period of marijuana use, as indicated by significantly lower FEV_1.[9,17] Pulmonary function tests have also shown that the measures associated with restrictive lung disease are 50% lower among heroin smokers than among tobacco smokers and nonsmokers, as well as that there is a high prevalence of COPD among heroin smokers.[14]

The impact that smoking tobacco, marijuana, crack cocaine, and heroin has on lung function has primarily been studied in adults, particularly in chronic users with an extensive consumption history. However, there remains a significant gap in our understanding of how SUD affects adolescents and their lung health. In addition, investigating this age group is relevant for identifying which spirometric parameters might be more affected by early substance misuse. Therefore, the aim of this study was to compare lung function measures between adolescents with and without SUD. Our exploratory findings may better characterize pulmonary alterations resulting from substance use, even during adolescence.

METHODS

Ethics

The study was performed in accordance with the principles stated in the Declaration of Helsinki. Before the research protocol, including the study procedures and questionnaires, was submitted for ethical committee review and project appreciation, approval was sought from both the school and the hospital. Ethical consent was then obtained for all protocols from the local institutional review board and appropriate ethics committees to confirm that the study met national and international guidelines for research on humans (Ethical approval numbers and dates: 4.128.393 / July 1, 2020; 5.223.468 / February 3, 2022). Written informed consent was obtained from parents or legal guardians, as well as from the participants themselves.

Study design and sampling procedures

This was an observational, cross-sectional exploratory study. The sample, recruited between September of 2021 and December of 2022, comprised 16 adolescents with SUD and 24 age-matched healthy controls. The inclusion criteria were being male and being between 15 and 18 years of age. Individuals with chronic psychotic disorders were excluded, as were those who were categorized as illiterate, mainly because illiteracy and psychosis could introduce biases in the completion of questionnaires and the collection of clinical data.

The participants in the SUD group were recruited from a psychiatric inpatient unit for alcohol and drug detoxification at a hospital in the city of Porto Alegre, Brazil. Over 21 days of hospitalization, they were treated by a multidisciplinary team of clinical physicians, psychiatrists, psychologists, nurses, nursing technicians, occupational therapists, and physical educators. The patients also followed a diet plan, together with a medication protocol for detoxification and management of withdrawal symptoms. The protocol comprised mostly chlorpromazine, at doses ranging from 50 mg/day to 125 mg/day. All participants in the clinical group had an SUD (related to marijuana, powder cocaine, crack cocaine, or polysubstance use) as their primary diagnosis. The diagnosis was confirmed by psychiatric evaluation according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition criteria. It is noteworthy that our data were collected during the COVID-19 pandemic and that all patients admitted to the unit therefore underwent mandatory SARS-CoV-2 testing. None of the patients included in our study had a current diagnosis of COVID-19. The participants in the control group were recruited from private schools in the same city. A questionnaire about drug use behavior was applied in order to determine their eligibility. None of the control group participants had a history of regular use of substances such as alcohol, tobacco, marijuana, and cocaine.

Two questionnaires were utilized in the study: a basic sociodemographic questionnaire; and the sixth version of the Addiction Severity Index (ASI-6). The sociodemographic questionnaire covered level of education, age, socioeconomic status, and frequency of physical activity, high levels of physical activity being defined as engaging in moderate- to high-intensity exercise more than three times a week, each session lasting for at least one hour. The ASI-6 consists of a semi-structured interview assessing the history of alcohol and other drug use, including information such as the age at initiation, duration, frequency, and quantity of consumption.[18] A year of regular use is defined as that during which a substance was used at least three times a week. We analyzed data from years of regular use of alcohol, tobacco, marijuana, powder cocaine, and crack cocaine. We generated an additional variable—years of regular use of smoked substances—estimated for the inhaled substance most regularly used by the participant (tobacco, marijuana, or crack cocaine). For example, if the participant reported five years of regular marijuana use and three years of regular tobacco use, their score on this variable was five years. In addition, all variables related to years of regular consumption were adjusted for the age of participants by calculating the ratio between years of regular consumption and current age. Medical records were reviewed to collect data on medication use and previous illnesses. We checked vital signs, weight, and height, as well as calculating BMIs, for which the data were standardized to Z-scores.

Spirometry was carried out according to the acceptability and reproducibility criteria of the American Thoracic Society/European Respiratory Society.[19] All measurements were corrected for the local barometric pressure and temperature on the day of the tests. Initial weight and height were measured

using a scale and a tape measure. The tests were performed individually, with the subjects standing, without the use of a nose clip, and with a KOKO spirometer (Longmont, CO, USA). The parameters assessed were FVC, FEV_1, the FEV_1/FVC ratio, and $FEF_{25-75\%}$. For better visualization of the results, the spirometric parameters are expressed as absolute values and as percentages of the predicted values according to international reference equations.[20] In the SUD group, spirometry was performed in the second week of detoxification, to avoid the effects of acute withdrawal.

Statistical analysis

Quantitative variables were tested concerning data distribution, and no evidence of non-normality was found. Therefore, quantitative variables are expressed as means and standard deviations. The Shapiro-Wilk test was chosen for normality analysis of data distribution because it is better suited for use with small sample sizes. Qualitative variables are expressed as absolute values and percentages. The groups were compared by using the t-test for independent samples. The effect size for t-tests was estimated by calculating Cohen's d statistic, which categorizes the effect size as small (0.2-0.4), medium (0.5-07), or large (≥ 0.8), particularly for spirometric measures. Qualitative variables were compared between groups by using the chi-square test. For spirometric variables with significant intergroup differences, we performed analysis of covariance (ANCOVA), adjusting for possible confounding factors. To assess potential associations between spirometric data and clinical data, we performed a Spearman correlation analysis restricted to the SUD group. All analyses were performed with the SPSS Statistics software package, version 17.0 (SPSS Inc., Chicago, IL, USA). Values of $p < 0.05$ were considered statistically significant.

RESULTS

Table 1 shows the demographic and clinical characteristics of the sample. We observed that the groups did not differ in age, BMI, height, or weight, although the proportion of individuals with a high level of physical activity was greater in the control group, as was that of those with a high monthly family income (> 5,000 Brazilian reals). The proportion of individuals with a low monthly family income (< 1,000 Brazilian reals) was greater in the SUD group. In addition, we observed differences in the level of education, the mean number of years of schooling being higher in the control group than in the SUD group.

Regarding years of substance use in the SUD group, tobacco and marijuana were used for the longest times (approximately three years of regular use). Regarding the estimated variable of years of regular use of smoked substances, the mean was approximately four years. For each participant in the SUD group, we also calculated the ratio between the years of regular consumption of each substance and the current age. The mean ratios were as follows: 2.75 ± 7.5 for lifetime regular alcohol use; 22.8 ± 18.8 for lifetime regular tobacco use; 23.1 ± 15.4 for lifetime regular marijuana use; 16.1 ± 15.4 for lifetime regular powder cocaine use; 3.75 ± 7.6 for lifetime regular crack cocaine use; and 27.1 ± 17.4 for lifetime regular use of any smoked substance.

Spirometry

When comparing lung function data (Table 2), we found that the absolute FVC, FVC as a percentage of the predicted value (FVC%) and FEV_1 as a percentage of the predicted value (FEV_1%) were significantly lower in the SUD group than in the control group. The absolute FEV_1/FVC ratio was significantly higher in the SUD group than in the control group. Effect sizes

Table 1. Anthropometric, demographic, and clinical characteristics of the sample.

Variable	Group		Statistic	p
	SUD (n = 16)	Control (n = 24)		
Age (years), mean ± SD	15.37 ± 1.02	15.33 ± 0.96	t = 0.13	0.632
BMI (Z-score), mean ± SD	23.3 ± 3.63	20.7 ± 2.36	t = 1.59	0.119
Height (cm), mean ± SD	170.3 ± 4.86	171.8 ± 7.42	t = 0.71	0.480
Weight (kg), mean ± SD	67.6 ± 11.44	62.2 ± 8.10	t = 1.66	0.105
High physical activity level, n (%)	0 (0.0)	13 (54.2)	x^2 = 12.84	< 0.001
Family income (< R$1,000/month), n (%)	13 (81.2)	0 (0.0)	x^2 = 28.88	< 0.001
Family income (R$1,000-5,000/month), n (%)	3 (18.8)	1 (4.2)	x^2 = 2.26	0.132
Family income (> R$5,000/month), n (%)	0 (0.0)	23 (95.8)	x^2 = 36.07	< 0.001
Years of schooling, mean ± SD	7.68 ± 1.57	10.33 ± 1.57	t = 6.59	< 0.001
Years of alcohol use, mean ± SD	0.37 ± 1.08	-	-	-
Years of tobacco use, mean ± SD	3.37 ± 2.62	-	-	-
Years of marijuana use, mean ± SD	3.37 ± 2.30	-	-	-
Years of powder cocaine use, mean ± SD	2.12 ± 2.27	-	-	-
Years of crack cocaine use, mean ± SD	0.50 ± 1.09	-	-	-
Years of smoked substance use, mean ± SD	4.00 ± 2.52	-	-	-

SUD: substance use disorder; χ^2: chi-square test; and R$: Brazilian reals (1 real currently equals 0.20 US dollars).

Table 2. Comparison of spirometry variables.[a]

Variable	Group		Statistic	p	Cohen's d
	SUD (n = 16)	Control (n = 24)			
FVC (absolute)	4.31 (0.56)	4.92 (0.84)	t = 2.54	0.015	0.85 (large)
FVC (pred%)	92.00 (11.16)	109.95 (16.26)	t = 3.84	< 0.001	1.28 (large)
FEV_1 (absolute)	3.88 (0.46)	4.25 (0.65)	t = 1.94	0.059	0.65 (medium)
FEV_1 (pred%)	96.25 (9.86)	110.33 (15.36)	t = 3.24	0.002	1.09 (large)
FEV_1/FVC ratio (absolute)	0.92 (0.12)	0.86 (0.44)	t = 2.18	0.036	0.18 (small)
FEV_1/FVC ratio (pred%)	104.37 (8.11)	100.20 (5.04)	t = 2.00	0.052	0.61 (medium)
$FEF_{25-75\%}$ (absolute)	4.56 (0.69)	4.72 (0.85)	t = 0.61	0.544	0.20 (small)
$FEF_{25-75\%}$ (pred%)	100.43 (14.63)	114.70 (34.07)	t = 1.57	0.123	0.54 (medium)

SUD: substance use disorder; pred%: and percentage of the predicted value [a]Values expressed as mean ± SD.

ranged from small to large. The largest effect size was for FVC%, corresponding to the most significant difference between the two groups: 17.95% lower in the SUD group. We found no significant differences between the two groups in terms of the absolute FEV_1, the FEV_1/FVC ratio as a percentage of the predicted value, absolute $FEF_{25-75\%}$, or $FEF_{25-75\%}$ as a percentage of the predicted value.

We utilized ANCOVA to determine whether the group effect on specific lung function parameters persisted even after adjustment for the influences of BMI and a high physical activity level. The significant group effects persisted for all variables: absolute FVC ($F = 6.67$, $p = 0.014$); FVC% ($F = 10.80$, $p = 0.002$); FEV_1% ($F = 5.60$, $p = 0.023$); and the absolute FEV_1/FVC ratio ($F = 5.74$, $p = 0.022$). The BMI also had a significant effect ($p < 0.05$) in the ANCOVAs referring to the two FVC variables (FVC and FVC%). No significant effects were found for the high level of physical activity variable.

Finally, we performed correlation analyses restricted to data from the SUD group, in order to determine whether age, BMI, height, weight, chlorpromazine dose, and years of substance use correlated with the measures of lung function (Table 3). We found that BMI correlated positively with the absolute FVC, FVC%, and the absolute FEV_1/FVC ratio. The years of regular use of smoked substances/age ratio correlated negatively with FVC%. None of the spirometric parameters were found to correlate significantly with age, height, weight, chlorpromazine dose, or the years of regular consumption/age ratio for tobacco, marijuana, powder cocaine, crack cocaine, or alcohol.

Considering the positive correlation between BMI and the spirometric variables, we repeated this analysis across our entire sample, including the control group. This second analysis showed no significant association between BMI and spirometric variables ($p > 0.05$ for all).

DISCUSSION

This study compared lung function between adolescents with and without SUD. We found differences in specific measures of FVC and FEV_1, the percentages of their predicted values, and the FEV_1/FVC ratio. These changes remained significant after adjustment for the effects of covariates such as BMI and physical activity level. The largest effect size was found for the FVC%, suggesting that adolescents with SUD have less air that can be exhaled forcefully. In addition, the years of regular use of smoked substances correlated negatively with the FVC%. This exploratory study is innovative in that it demonstrates the early pulmonary consequences of SUD in an adolescent population, whose trajectory of chronic substance use is still unfolding. Although we found lung function to be lower in the SUD group, it is noteworthy that the percentages of the predicted values for the spirometric parameters FVC and FEV_1 were within the normal range (above 80%) in both groups, suggesting that there is no lung function impairment associated with SUD during adolescence. Nevertheless, our study partially corroborates the growing body of evidence showing a clinically relevant loss of lung function related to the chronic smoking of tobacco, marijuana, crack cocaine, and heroin.

There is growing evidence that marijuana use can promote pulmonary changes associated with COPD, most commonly characterized by decreases in FEV_1 and FVC.[21,22] The recurrent use of marijuana in combination with tobacco increases the alterations and pulmonary impairment, as assessed by pulmonary function tests. That is because cigarettes are smoked more frequently than is marijuana, especially by adults.[22] In the case of the association between marijuana and COPD, data indicate that individuals who smoke marijuana and tobacco are twice as likely to develop severe respiratory symptoms of the disease.[23,24] These findings are relevant given the profile of our clinical sample, in which tobacco and marijuana were the substances that were consumed most commonly and for the longest periods.[24] In addition, because of the mechanisms of injury potentiated by the toxicity of the substances, their regular use can worsen the clinical presentation of lung diseases such as asthma and COPD.[25,26] For example, evidence suggests that cocaine use exacerbates asthma, as well as increasing symptom severity and the length of the hospital stays due to lung disease.[27]

Table 3. Correlation analyses in the substance use disorder group (n = 16).

Variable	FVC (absolute)		FVC (pred%)		FEV_1 (pred%)		FEV_1/FVC ratio (absolute)	
	r	p	r	p	r	p	r	p
Age	0.286	0.283	0.200	0.458	0.271	0.310	−0.091	0.736
BMI Z-score	0.580	0.018	0.733	0.001	0.322	0.223	−0.668	0.005
Height	0.422	0.104	−0.073	0.788	−0.089	0.742	−0.302	0.256
Weight	0.016	0.953	0.120	0.659	0.025	0.926	−0.053	0.846
Chlorpromazine use	−0.317	0.231	−0.401	0.124	−0.157	0.560	0.408	0.116
Tobacco use*	−0.138	0.610	−0.331	0.210	−0.143	0.598	0.335	0.205
Marijuana use*	0.211	0.433	−0.153	0.572	−0.156	0.564	−0.163	0.547
Crack cocaine use*	−0.358	0.174	−0.494	0.052	−0.231	0.389	0.458	0.075
Smoked substance use*	−0.519	0.039	−0.370	0.158	−0.261	0.328	0.450	0.080
Powder cocaine use*	−0.134	0.621	−0.119	0.661	−0.043	0.874	0.177	0.513
Alcohol use*	0.031	0.910	−0.161	0.551	−0.173	0.522	−0.225	0.403

pred%: percentage of the predicted value. *Years of regular use/age ratio.

We found no associations between spirometric parameters and the years of regular smoking of tobacco, marijuana, or crack cocaine, as well as no associations between spirometric parameters and the regular use of substances that are not smoked, such as alcohol and powder cocaine. This should be interpreted cautiously, considering our small sample size. However, when estimating a variable that considered the prolonged use of marijuana, crack cocaine, or tobacco, we found an inverse correlation between years of regular use and FVC%. That finding partially corroborates the results of a cohort study conducted by Sherrill et al., who showed progressive reductions in FEV_1 and the FEV_1/FVC ratio in marijuana smokers over a six-year follow-up period, suggesting that the substance is associated with a continuous decline in lung function over the years, which can be accelerated in the case of concurrent cigarette smoking.[28]

Our study has significant limitations. First, the sample size was small and the study was exploratory in nature. However, considering that few studies have investigated lung function in an adolescent population with SUD, we have contributed to expanding a little-explored field. Second, participants in the SUD group had been admitted to a detoxification treatment program, including the prescription of psychotropic drugs, especially chlorpromazine. Nevertheless, our correlation analyses between the dose of chlorpromazine and the spirometry variables revealed no significant associations. Third, we found significant differences in socioeconomic indicators such as level of education and family income, suggesting that there are major differences between adolescents with and without SUD in terms of life trajectory, family background, and psychosocial factors. However, many studies indicate that poverty, a low level of education, and other markers of social vulnerability are risk factors for SUD,[29,30] making it more challenging to match the SUD group with a healthy reference group of socioeconomic peers. Fourth, because SUD was the primary health problem of the patients, no clinical lung assessment was performed during the treatment program. Lastly, the adolescents with SUD who were enrolled in the study were recruited from among a group of inpatients and were therefore representative of adolescents with relatively severe disease.

Despite its limitations, our study suggests that lung function is impaired in adolescents with SUD. Therefore, clinicians need to be aware of the history of substance use in patients with airway alterations, and our data suggest that lung function changes can start in adolescence. Future studies with fewer limitations may generate more robust evidence on pulmonary alterations in this population and suggest paths for the clinical applicability of these findings.

AUTHOR CONTRIBUTIONS

DBK: drafting of the manuscript. DBK, MM, MG, and LEWS: data collection. JHC: data curation. JHC, MM, MG, LEWS, MVFD, FF, MHJ, and TWV: revision of the manuscript. MVFD, MHJ, and TWV: study design. FF: data analysis. TWV: supervision. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Serum lymphocytes and cytokines: diagnostic value and influence on the immune status in patients with pulmonary tuberculosis

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ABSTRACT

Objective: To determine the absolute number of serum T lymphocytes and cytokine levels and the characteristics of patients with active pulmonary tuberculosis and to assess their effect on the immune status of these patients and their diagnostic and predictive value for tuberculosis. **Methods:** We included 1,069 patients with active tuberculosis, 51 patients with latent tuberculosis infection, and 600 health individuals. Absolute serum T-lymphocyte counts and cytokine levels were quantified. **Results:** T lymphocytes were significantly reduced in patients with active tuberculosis when compared with healthy individuals. The immune function of patients gradually decreased with age and was stronger in female patients than in males. Th1 cells expressed higher levels of cytokines than did Th2 cells. Logistic regression analysis showed that reduced $CD3^+$ T, $CD8^+$ T, and NK cell counts, as well as reduced IL-4 and IFN-γ expression, were independent influencing factors for active tuberculosis. ROC analysis showed that the sensitivity and specificity of absolute $CD3^+$ T and $CD8^+$ T lymphocyte counts and combined factors were significantly higher than were those of IL-4 and IFN-γ for diagnosing active tuberculosis. **Conclusions:** Serum T-lymphocyte counts and cytokine levels can assess the immune status of tuberculosis patients; they are also useful biomarkers for predicting and diagnosing tuberculosis.

Keywords: Lymphocytes; Cytokines; Tuberculosis; Immunity.

INTRODUCTION

Tuberculosis is an inflammatory disease caused by *Mycobacterium tuberculosis* (Mtb) infection, and pulmonary tuberculosis is the most common form of clinical presentation.[1] The WHO Global Tuberculosis Report 2022[2] reported 10.6 million new cases of tuberculosis globally in 2021, with an incidence rate of 134 per 100,000 population. Although antituberculosis drugs are available and the number of related deaths has decreased globally in recent years, tuberculosis is still the leading cause of death from a single infectious disease.[3]

Efficacious $CD4^+$ T lymphocytes can be divided into at least three distinct subpopulations: Th1, Th2, and Th17 cells. These subpopulations are functionally controlled by regulatory $CD4^+$ T cells and have a high degree of specialization. Moreover, IFN-γ produced by Th1 cells plays an essential role in host resistance to primary infection with Mtb. In addition, IFN-γ enhances the antibacterial activity of macrophages and promotes the production of reactive nitrogen intermediates, which can eliminate bacteria intracellularly.[4,5] Both animal models and human trials have shown that IFN-γ expression levels do not provide relevant and reliable protection against Mtb infection.[3]

Analysis of the number of T lymphocytes and levels of cytokines, such as IL-2, IL-4, TNF-α, IFN-α, and IFN-γ, can provide a precious research base for disease through noninvasive methods to study the state of the immune system in patients.[6,7] In this study, we analyzed the absolute number of T lymphocytes and cytokine levels in the serum of patients with active tuberculosis (ATB) and patients with latent tuberculosis infection (LTBI), as well as those of healthy individuals (HI), to provide a reference for diagnosing tuberculosis and assessing the immune status of the participants.

METHODS

In this study, we included 1,069 patients with ATB, 600 HI, and 51 patients with LTBI. According to the WHO report,[2] the diagnosis of ATB is based on clinical evaluation, microbiology, molecular testing (such as GeneXpert Ultra), and imaging findings. LTBI is defined as a positive IFN- γ release assay result with no other clinical manifestations or with negative microbiological, molecular, and imaging results (Table 1).

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Exclusion criteria were as follows: autoimmune diseases or concomitant immune disorders; AIDS; glucocorticoid therapy; concomitant heart, liver, kidney, or other important organ diseases; severe hypertension; poor mental condition; concomitant diabetes mellitus; pregnancy or lactation; and drug-resistant tuberculosis. The study was approved by the Research Ethics Committee of the Third People's Hospital of Kunming (protocol no. KSLL20230320007).

Peripheral blood specimens from HI, patients with ATB, and those with LTBI were collected in 3 mL blood collection tubes. For cytokine assays, the blood samples were centrifuged at 1,000 × g for 10 min, and the serum was tested using cytokine assay kits (Risskell Bio, Qingdao, China) in order to determine the levels of cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17, TNF-α, IFN-α, and IFN-γ) in accordance with the manufacturer instructions, We used the MR Flow Analysis software (AZE Ltd., Tokyo, Japan) for the analysis of results. For flow cytometry assays, the blood specimens were mixed and a flow cytometry kit (DIALAB GmbH, Wiener Neudorf, Austria) was used for determining $CD3^+$ T, $CD4^+$ T, $CD8^+$ T, $CD4^+$/$CD8^+$, $CD19^+$B, NK, and NKT lymphocyte counts in accordance with the manufacturer instructions. We used the LEGENDplex software (BioLegend, San Diego, CA, USA) for result analysis. Both cytokine and flow cytometer assays were performed using a BriCyte E6 flow cytometer (Mindray, Shenzhen, China).

Statistical analyses were performed and plotted using the IBM SPSS Statistics software package, version 24.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism, version 8.0 (GraphPad Software Inc., San Diego, CA, USA), respectively. Quantitative data were described as mean ± SD when they conformed to a normal distribution using a t-test, whereas those with non-normal distribution were described as median [IQR] using the nonparametric Mann-Whitney test. Comparisons between multiple groups were made using the Kruskal-Wallis test, and differences between multivariate models were determined using the nested t-test. The analysis of the relevant influencers was performed by logistic regression analysis. The diagnostic value of these variables was analyzed using ROC curves. Statistical significance was set at $p < 0.05$.

RESULTS

The number of $CD3^+$ T, $CD4^+$ T, $CD8^+$ T, and NK cells was lower in patients with ATB when compared with HI, and this difference reached statistical significance. In addition, the absolute number of $CD3^+$ T cells in the LTBI group was lower and significantly different than in the HI group, whereas the absolute numbers of $CD4^+$ T, $CD8^+$ T, and NK cells were higher, but not statistically significant. In the ATB group, the levels of IL-1β, IL-2, IL-8, and IL-17 were higher, and those of IL-4, IL-6, TNF-α, and IFN-γ were lower than those in the HI group. As for the LTBI group, the levels of IL-1β, IL-5, and IFN-γ were lower, and those of IL-6, IL-8, IL-10, IL-12p70, IL-17, and TNF-α were higher than those in the HI group. All of these differences reached statistical significance, which suggested that inflammatory factors are differentially expressed in ATB and LTBI (Figure 1).

We analyzed the expression of indicators associated with statistically significant differences between the ATB and HI groups by sex and age. In the ATB group, the number of $CD3^+$ T, $CD4^+$ T, and $CD8^+$ T cells was lower in men than in women; the difference was statistically significant, indicating that female patients with ATB are more immunocompetent than are males (Figure 2A). The expression of $CD3^+$ T, $CD4^+$ T, and $CD8^+$ T cell numbers gradually decreased with age, this difference reaching statistical significance. This suggests that older ATB patients have poorer immune function than do adolescent patients. Cytokine IFN-γ expression was significantly lower in men than in women, while the remaining expression levels did not differ significantly across age and sex (Figure 2B).

To determine the effect of ATB on the frequency of Th1/Th2 cells, we analyzed the expression levels of IL-1β, IL-2, TNF-α, IFN-γ, IL-4, IL-5, IL-6, and IL-10 in that group. As shown in Figure 3, those with ATB exhibited significant Th1 (IFN-γ and IL-1β) expression, while only IL-6 levels were increased (Th2 cells). In contrast, Th1 cells expressed higher levels of cytokines than did Th2 cells, and the difference was statistically significant, suggesting that the levels of cytokines expressed by Th1 cells in ATB may be specific for Mtb.

To investigate the factors associated with the influence of T lymphocytes and cytokines on ATB and LTBI, we screened for statistically different factors between the ATB, LTBI, and HI groups to be included in the impact factor analysis (Figure 1). Logistic regression results showed that reduced absolute numbers of $CD3^+$ T, $CD8^+$ T, and NK cells, as well as reduced expression levels of IL-4 and IFN-γ, were independent influencing factors for ATB (Figure 4A). Reduced expression levels of IL-1, IL-5, and IFN-γ

Table 1. Characteristics of the study participants.[a]

Characteristic	ATB	LTBI	HI
Number of participants	1,069	51	600
Male	587 (54.9)	27 (52.9)	331 (55.2)
Age, years	45.4 ± 17.4	36.3 ± 17.6	41.7 ± 17.2
Positive IGRA	1,069 (100)	51 (100)	0 (0)
Positive imaging	1,032 (96.5)	0 (0)	0 (0)

ATB: active tuberculosis; LTBI: latent tuberculosis infection; HI: healthy subjects; and IGRA: IFN-γ release assay. [a]Values expressed as n, n (%), or mean ± SD.

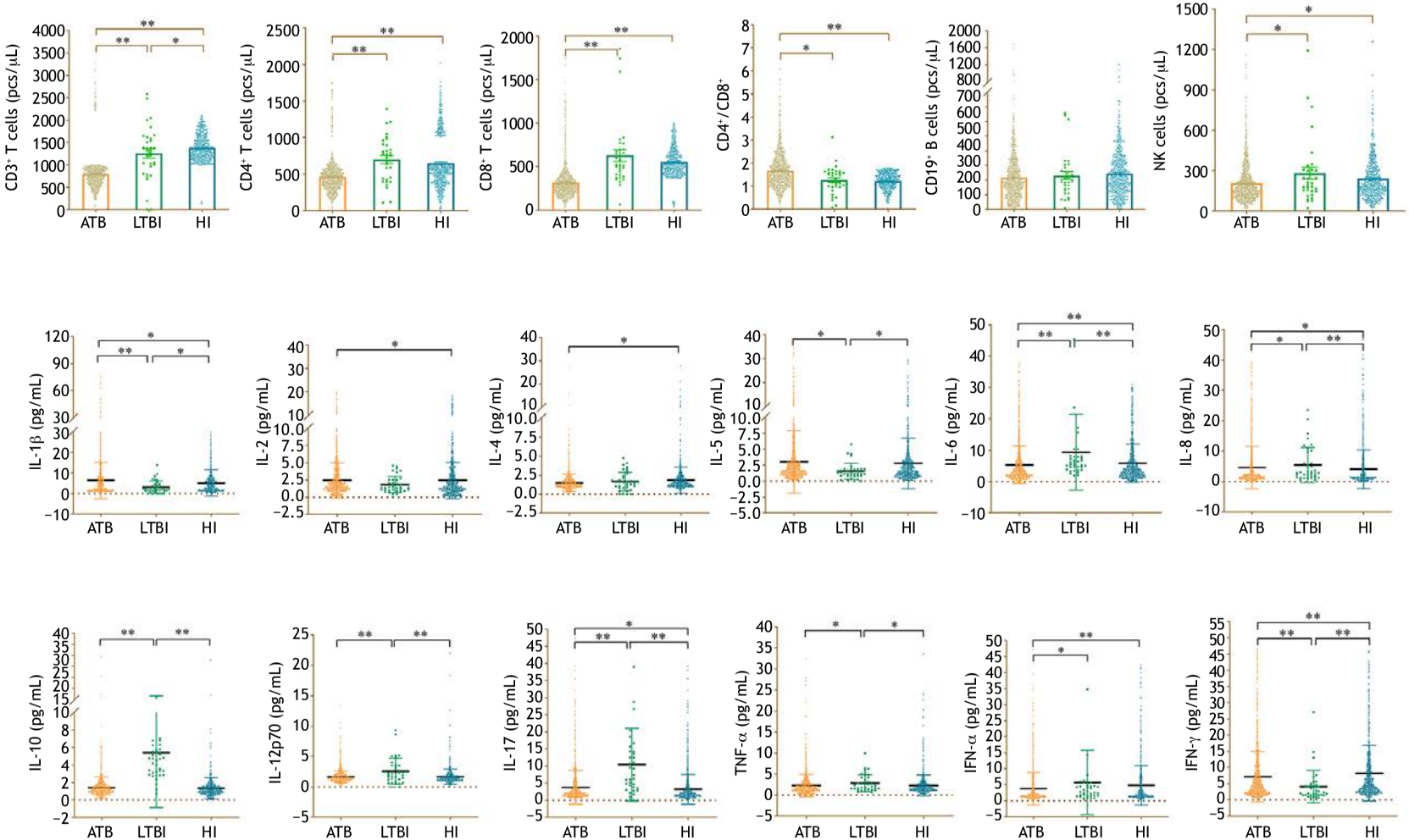

Figure 1. Expression of lymphocytes and cytokines by study group showing that the absolute numbers of $CD3^+$ T, $CD4^+$ T, $CD8^+$ T, and NK cells in the active tuberculosis (ATB) group were all lower than normal. The latent tuberculosis infection (LTBI) group had a higher-than-normal number of lymphocytes, except for the absolute number of $CD3^+$ T cells. The ATB group had higher levels of IL-1β, IL-2, IL-8 and IL-17, but lower levels of IL-4, IL-6, TNF-α, and IFN-γ, than did the healthy individual (HI) group. pcs: pieces. *$p < 0.05$. **$p < 0.01$.

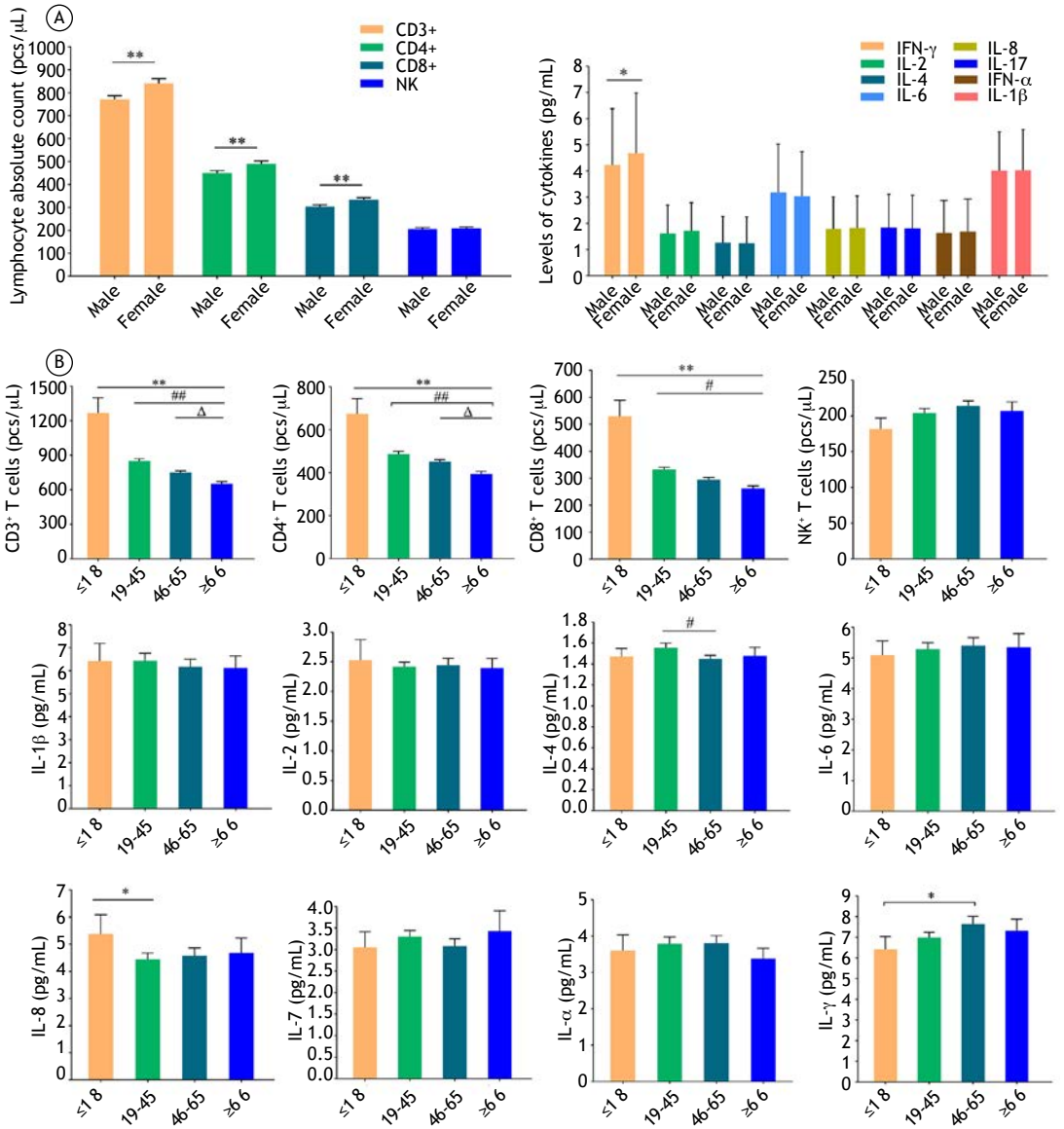

Figure 2. In A, absolute numbers of $CD3^+$ T, $CD4^+$ T, and $CD8^+$ T lymphocytes in active tuberculosis patients showing significant differences between men and women, except for NK cells. There were no significant differences in cytokines levels between male and female patients, except for IFN-γ levels. In B, the absolute numbers of $CD3^+$ T, $CD4^+$ T, and $CD8^+$ T lymphocytes showing significant differences among the age groups (in years) of patients with active tuberculosis. The overall cytokine levels did not significantly differ among the age groups. pcs: pieces. *$p < 0.05$. **$p < 0.01$.

and increased expression levels of IL-12p70 were independent influencing factors for LTBI (Figure 4B). These influencing factors are a guide to the diagnosis and differentiation of ATB and LTBI.

To assess the diagnostic and predictive value of the associated factors that have an impact on ATB and LTBI, we performed ROC analyses of the associated factors. The results showed that the absolute $CD3^+$ T and $CD8^+$ T lymphocyte counts and combined factors (sensitivity and specificity were, respectively, 0.955 and 0.993; 0.774 and 0.955; and 0.951 and 0.977) were significantly more valuable for the diagnosis of ATB than were the absolute number of NK cells and the levels of IL-4 and IFN-γ (Figure 5A). As for the ROC analysis for LTBI, IL-12p70 and IFN-γ expression levels, as well as combined factors, showed diagnostic value (sensitivity and specificity were, respectively, 0.568 and 0.862; 0.493 and 0.908; and 0.649 and 0.725), and combined factors had the highest diagnostic value (Figure 5B).

DISCUSSION

Tuberculosis is an inflammatory disease whose progression or cure is largely determined by the relative strength of Mtb against the host immune system and is therefore considered to be caused by an unbalanced

immune response to Mtb infection.[8] Immunity in tuberculosis patients is dominated by cellular immunity, in which T cells are believed to play a vital role in the containment of Mtb infection for controlling the infection directly or indirectly. The cytokines of the organism are a vital part of the immune system as messengers, and their role in the fight against the invasion of Mtb is complex and multifaceted and is influenced by different host states.[9] Therefore, a comprehensive and systematic exploration of the relationship of lymphocytes and cytokines with Mtb infection is needed to provide a theoretical basis for a better understanding of the immune status of tuberculosis patients by immunology-based detection and diagnosis.

The present study showed that the absolute number of T lymphocytes was lower in patients with ATB than in HI. The difference was statistically significant, ATB patients having a poorer immune status than the healthy population. The absolute numbers of $CD4^+$ T, $CD8^+$ T, and NK cells were higher in LTBI patients when compared with HI, although this difference was not significant; however, the number of T cells available from peripheral blood can help assess the progression of the infection.[10] This study also showed that female patients with ATB are more immunocompetent than males. This is also consistent with findings of a previous study on sex differences and immune function.[11] In addition, the immune function of the patient gradually decreases with age. In contrast, as for cytokine-mediated inflammatory responses, the differences in expression in regard to age and sex were not significant. Our results showed that the levels of some cytokines, such as IL-1β, IL-5, IL-6, IL-10, and TNF-α, differed in ATB and LTBI. The reason for this phenomenon is that the cytokines produced in response to Mtb infection may reduce their immune response to limit tissue damage, and overproduction of cytokines may lead to failure to control the infection.[12] This can provide us with ideas for identifying ATB and LTBI.

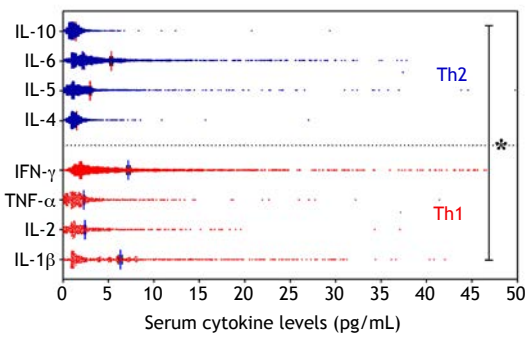

Figure 3. In the active tuberculosis group, Th1-type cytokine levels were higher than were Th2-type cytokine levels. The dot plot shows the mean and standard error of each cytokine level. Differences between overall Th1/Th2 cytokine levels were analyzed by nested t-test. *$p < 0.05$.

An essential factor in the control of tuberculosis is the characteristics of $CD4^+$ T cells that react after infection.[13] Usually, $CD4^+$ T cells produce more than one cytokine, especially Th1-type cytokines (IFN-γ and TNF-α), which are thought to be associated with protective immune responses and play an essential role in antituberculosis immunity.[14] Our data showed that ATB has significantly elevated Th1-type cytokine (IFN-γ) levels. These are cytokines specific for Mtb antigens.[15] Thus, our study confirms the vital role of Th1 cells in the pathogenesis of tuberculosis and suggests that Th1 cell occurrence may be specific for Mtb. However, higher amounts of Th1 cytokines may lead to a more severe disease that could reflect an increased bacterial load.[16] In conclusion, our study suggests that cytokines expressed by Th1 play a vital role in the pathogenesis of ATB.

We can speculate on the correlates of risk of ATB by the absolute number of T lymphocyte subpopulations and the levels of some cytokines. Logistic regression analysis showed that significantly lower absolute $CD3^+$ T, $CD8^+$ T, and NK cell counts, as well as significant lower IL-4 and IFN-γ expression levels, had an independent influence on ATB and they could be used as evidence of potential biomarkers

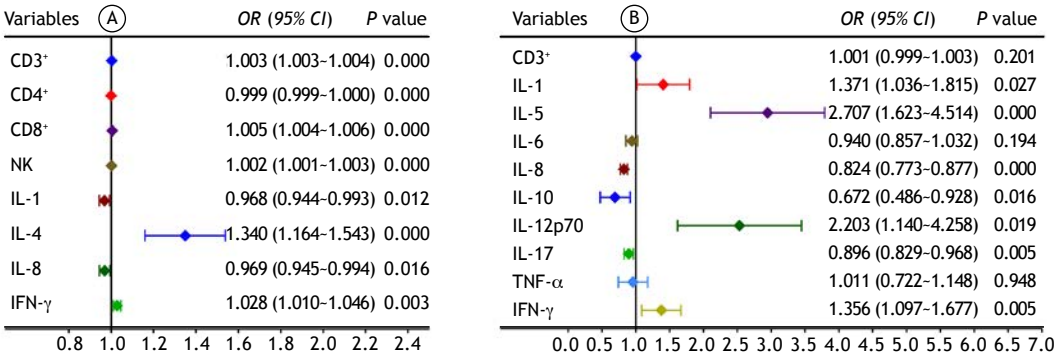

Figure 4. In A, logistic regression analysis shows that reduced absolute numbers of $CD3^+$ T, $CD8^+$ T, and NK cells, and reduced expression levels of IL-4 and IFN-γ were independent influencing factors for active tuberculosis ($p < 0.05$). In B, the analysis shows that reduced expression levels of IL-1, IL-5, and IFN-γ and increased expression levels of IL-12p70 were independent influencing factors for latent tuberculosis infection ($p < 0.05$).

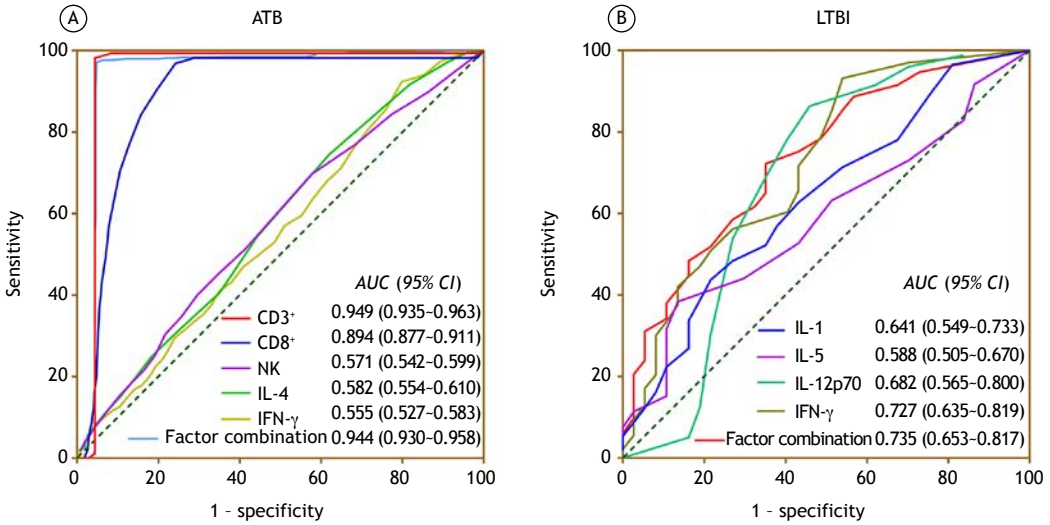

Figure 5. In A, ROC curves for active tuberculosis (ATB). Absolute CD3+ T and CD8+ T lymphocyte counts, as well as those of combined factors, showed a high diagnostic value for ATB ($p < 0.01$). In B, ROC curves for latent tuberculosis infection (LTBI). Expression levels of IL-12p70, IFN-γ, and combined factors showed diagnostic value for LTBI assessment. Combined factors had the highest diagnostic value ($p < 0.01$).

for tuberculosis surveillance. To identify LTBI, we also analyzed its influencing factors, and the results suggest that influencing factors of related diseases are mostly different; this may be a reference for the differential diagnosis of ATB and LTBI. To assess the diagnostic and predictive value of these influencers, we performed a ROC analysis. The results showed that the absolute $CD3^+$ T and $CD8^+$ T lymphocyte counts and combined factors were significantly more valuable, sensitive, and specific for the diagnosis of ATB than were IL-4, IL-12p70, and IFN-γ expression levels, and that combined factors are valuable in the diagnostic evaluation of LTBI. The diagnostic value of these biomarkers can also be assessed from the sensitivity and specificity of the ROC curves. When these factors are considered together, they have a better value in the diagnosis of Mtb infection or ATB.

In conclusion, the results of this study suggest that serum T lymphocytes and cytokines are essential reference indicators for assessing the immune status of patients with ATB. The absolute numbers of $CD3^+$ T, $CD8^+$ T, and NK cells, as well as the expression levels of IL-4 and IFN-γ, can be useful biomarkers for predicting and diagnosing tuberculosis. These markers, especially the combined factors, play a reference role in diagnosing and treating tuberculosis.

AUTHOR CONTRIBUTIONS

ZM: study concept; drafting, editing, and reviewing of the manuscript; and software analysis. SL: data analysis; draft preparation; methodology; and statistical analysis. YL, CL, and XW: data collection and experimental observation. XT, RD, and SZ: test operation. LW: funding acquisition; and editing and reviewing of the manuscript. All of the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Progressive fibrotic interstitial lung disease

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ABSTRACT

Many interstitial lung diseases (ILDs) share mechanisms that result in a progressive fibrosing phenotype. In Brazil, the most common progressive fibrosing interstitial lung diseases (PF-ILDs) are chronic hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, unclassified ILD, and connective tissue diseases. PF-ILD is seen in approximately 30% of patients with ILD. Because PF-ILD is characterized by disease progression after initiation of appropriate treatment, a diagnosis of the disease resulting in fibrosis is critical. Different criteria have been proposed to define progressive disease, including worsening respiratory symptoms, lung function decline, and radiological evidence of disease progression. Although the time elapsed between diagnosis and progression varies, progression can occur at any time after diagnosis. Several factors indicate an increased risk of progression and death. In the last few years, antifibrotic drugs used in patients with idiopathic pulmonary fibrosis have been tested in patients with PF-ILD. The effects of nintedanib and placebo have been compared in patients with PF-ILD, a mean difference of 107.0 mL/year being observed, favoring nintedanib. The U.S. Food and Drug Administration and the Brazilian Health Regulatory Agency have approved the use of nintedanib in such patients on the basis of this finding. Pirfenidone has been evaluated in patients with unclassified ILD and in patients with other ILDs, the results being similar to those for nintedanib. More studies are needed in order to identify markers of increased risk of progression in patients with ILD and determine the likelihood of response to treatment with standard or new drugs.

Keywords: Alveolitis, extrinsic allergic; Idiopathic pulmonary fibrosis; Lung diseases, interstitial; Connective tissue diseases.

INTRODUCTION

Interstitial lung diseases (ILDs) are a diverse collection of illnesses defined by lung parenchymal inflammation and fibrosis. Only approximately 30% of ILD cases have a known cause. Although idiopathic pulmonary fibrosis (IPF) is the most common of the idiopathic ILDs, it only accounts for a modest proportion of patients—approximately 20% in referral centers.[1] A large multicenter cohort study in Brazil found that connective tissue disease (CTD)-associated ILD is the most common cause, in 27% of patients, closely followed by hypersensitivity pneumonitis (HP), in 23%, IPF, in 14%, and unclassified ILD, in 10%.[2] These results differ from those reported in other countries.[2]

CTD, chronic hypersensitivity pneumonitis (CHP), unclassified ILD, IPF, nonspecific interstitial pneumonia (NSIP), sarcoidosis, organizing pneumonia, and ILDs associated with occupational exposures are examples of ILDs that can progress. In a seminal study,[3] these disorders were initially grouped together under the label progressive fibrosing interstitial lung diseases (PF-ILDs). It has recently been proposed that these disorders be collectively referred to as progressive pulmonary fibrosis.[4]

Because PF-ILD is characterized by disease progression after initiation of appropriate treatment, a diagnosis of the disease resulting in pulmonary fibrosis is crucial.[5] In the case of CTD-associated ILD, this includes the use of one or more courses of immunosuppressants and, in the case of HP, removal of the offending antigen. Differentiating IPF from non-IPF is particularly important because the prognosis of IPF is worse than that of other ILDs and because of the different types of pharmacotherapy. Although IPF is the most common idiopathic fibrotic ILD, fibrosis in non-IPF ILDs is frequently preceded by or linked with inflammation. A seminal study found that treating IPF with corticosteroids and immunosuppressants leads to worse outcomes.[6] Despite major heterogeneity, ILD subtypes share morphological traits and pathogenic processes, giving birth to the concept of a progressive fibrosing phenotype, which may be applied to a wide range of fibrotic ILDs.[7]

PREVALENCE

The prevalence of PF-ILD is difficult to establish; however, 30% of ILD patients are anticipated to progress to more advanced disease despite treatment.[8] The difficulty in determining the exact prevalence of PF-ILD is most likely related to the rarity of the disease, the lack

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of a widely accepted definition, the broad spectrum of diseases, and the difficulty in establishing a diagnosis.[9,10] Clinical parameters associated with a higher likelihood of disease progression should be better defined.

PROGRESSION CRITERIA

The currently recommended criteria for evaluating PF-ILD are shown in Charts 1 and 2.[3,4] It should be noted that the progression criteria proposed in one of the aforementioned studies[3] are applied after 24 months of observation, and those proposed in the other study[4] are applied after 12 months of observation.[3,4] However, ILD progression should be checked on a regular basis because it can occur later in the monitoring period, resulting in certain markers of late progression being ignored.[11,12]

Dyspnea is the most significant factor influencing the quality of life of ILD patients. In IPF trials, dyspnea plays a significant and independent role in predicting survival. It is crucial to remember, however, that exertional dyspnea and lower exercise tolerance are multifactorial in patients with ILD, and their associations with functional variables are not straightforward.[13] When PF-ILD is associated with systemic disorders, a decrease in exercise capacity could indicate muscle or joint issues, anemia, pulmonary vascular disease, or left ventricular failure.

Several different outcomes have been used in order to estimate disease progression, although hospitalizations for exacerbations and the initiation of oxygen therapy have the most impact.[13] There is currently no single commonly accepted definition of acute exacerbation for all ILDs with a progressive fibrotic pattern. For IPF, specific exacerbation criteria have been proposed.[14] An acute exacerbation is defined by a sudden, severe worsening of respiratory function, with increased dyspnea and hypoxemia and new ground-glass opacities on HRCT.[14] Acute exacerbations of IPF can be idiopathic or due to infection or aspiration, but they are associated with substantial morbidity and death.[15]

Some individuals with rheumatic disease-associated ILD develop acute exacerbations, which are characterized by rapid ILD progression, substantial mortality during or soon after the exacerbation, and a very low 1-year survival rate.[16] In one study, 18 of 101 patients with biopsy-proven HP experienced acute exacerbations.[17] A reduced DL_{CO} and a radiological usual interstitial pneumonia (UIP) pattern were found to be risk factors for acute exacerbation.[17] The in-hospital mortality rate was 44.4%.[17] Patients with acute exacerbations had significantly lower median survival from diagnosis than did those without (26.0 months vs. 55.0 months; $p = 0.008$).[17] Severe dyspnea, a histological or radiological pattern of UIP, low oxygenation, low FVC, and a low baseline DL_{CO} were all risk factors for acute exacerbations in ILD patients.[17]

Acute exacerbations, on the other hand, have their own definition and do not provide a way to characterize fibrosis progression.[4] In practice, however, clinicians should reassess patients after exacerbations and use these assessments in order to determine whether progression has occurred.

Desaturation during exertion and/or at rest is a significant characteristic of fibrotic ILD, indicating poor outcomes such as pulmonary hypertension and decreased daily physical activity. When ILD patients require long-term oxygen therapy to ease dyspnea and hypoxemia, their lung function impairment has progressed to a severe degree, with a dismal

Chart 1. Criteria for evaluating progressive fibrosing interstitial lung diseases.[a]

Decline ≥ 10% predicted in FVC in the last 24 months
Decline ≥ 5% to < 10% predicted in FVC in the last 24 months with one or two of the following: Progressive worsening of symptoms Increased extent of fibrosis on HRCT
Progressive worsening of symptoms and increased extent of fibrosis on HRCT

[a]Based on Flaherty et al.[3]

Chart 2. Criteria for evaluating progressive fibrosing interstitial lung diseases.[a]

PPF is defined as at least two of the following three criteria occurring within the past year with no alternative explanation:
1. Worsening respiratory symptoms
2. Physiological evidence of disease progression (either of the following): • Decline in FVC ≥ 5% predicted within 1 year of follow-up • Decline in DL_{CO} (corrected for hemoglobin) ≥ 10% predicted within 1 year of follow-up
3. Radiological evidence of disease progression (one or more of the following): • Increased extent or severity of traction bronchiectasis and bronchiolectasis • New ground-glass opacity with traction bronchiectasis • New fine reticulation • Increased extent or increased coarseness of reticular abnormality • New or increased honeycombing • Increased lobar volume loss

PPF: progressive pulmonary fibrosis. [a]Based on Raghu et al.[4]

prognosis.[13,18] In a worldwide survey,[18] 139 (17%) of 826 individuals with diverse ILDs who were either normoxic or had isolated exertional hypoxemia at baseline developed resting hypoxemia. The median transplant-free survival after the onset of resting hypoxemia was 8.2 months (IQR, 3.2-17.8 months).[18]

Because the correlation between functional trajectories and HRCT findings in patients with PF-ILD is not always direct, imaging techniques are generally noninvasive and can provide information on diagnosis and prognosis, with serial images being used for follow-up assessment, as well as to assess complications and disease progression, in conjunction with clinical and functional data. A gradual fibrosing phenotype with worsening clinical parameters but apparently stable HRCT findings (or vice versa) is therefore possible.

Because the entire chest must be examined subjectively, imaging approaches rely significantly on visual analysis and are limited by the use of qualitative assessment, with minor changes being difficult to identify on serial images.[19] Although computer-based quantitative HRCT evaluation is a more objective and reproducible method of measuring progression than is visual assessment, it is not extensively used and must be verified and standardized before it can be widely employed in the real world.[20]

The best interval for repeat HRCT to assess disease progression is uncertain. Limited evidence suggests that chest HRCT should be repeated within 12-24 months in patients with systemic sclerosis and stable lung function, when it may be valuable for early diagnosis of progression and might influence the outcome. This interval should be shorter (3-4 months) in conditions with a high risk of quicker progression (e.g., familial fibrosis caused by telomere mutations) or with changes in symptoms and lung function tests.

Although it may be easy to identify disease progression on HRCT in some situations, it is not always evident whether there has been fibrosis progression. This is especially true in the context of HP, in which follow-up HRCT scans can show progression of ground-glass opacity without traction bronchiolectasis but cannot determine whether this ground-glass opacity represents progressive "fine fibrosis" or an inflammatory nonfibrotic interstitial infiltrate.[21]

Deterioration in lung function is a critical requirement for PF-ILD and is most typically assessed by means of FVC and DL_{CO}. Because of their well-established connection with prognosis, changes in FVC are the most routinely used physiological parameter to monitor patients with IPF. Because this shift varies according to the criterion of interest and is heavily influenced by ILD diagnosis, it is unclear which proposed PF-ILD criteria identify those who are most likely to undergo a subsequent reduction in FVC.[22]

Decline in FVC can be calculated in three ways: an absolute change (e.g., a decline of < 100 mL in a drug vs. placebo trial); a relative decline of 10% (e.g., from 60% predicted to 54% predicted; 60% − 54% × 100/60% = 10%); and an absolute decline of 10% (e.g., from 60% predicted to 50% predicted). In the proposed decline criterion, "relative decline" refers to a percentage value in respect to the original value, whereas "absolute decline variation" refers to the predicted value.[3,4]

Absolutes (relative to predicted values) of 10% and 5% have been suggested as indicators of decline.[3,4] These metrics are simpler to calculate; however, a relative reduction of 10% in FVC may be preferable to an absolute decline of 10% in measuring disease progression because the sensitivity for detecting progression is higher.[23,24] When symptoms or imaging abnormalities deteriorate, modest changes in FVC, such as a drop of 5-10% in the predicted value, should be considered.[4,5]

A decrease in DL_{CO} (adjusted for hemoglobin) is a substantial predictor of mortality in patients with fibrotic lung disorders.[25] Previous research has shown that a 15% decrease in DL_{CO} from its initial value is clinically meaningful.[25] However, an absolute reduction of more than 10% was contemplated in a recent consensus statement.[4] Studies comparing these two techniques for predicting disease progression are required.

Before attributing any decrease in DL_{CO} to progressive fibrosis, we must rule out other reasons for a decreasing DL_{CO}. When the only other indicator that is changing is the severity of symptoms, pulmonary vascular disease should be evaluated because it can lead to an isolated reduction in DL_{CO} without any change in the degree of pulmonary fibrosis.[26] Other findings, such as increased fibrosis on HRCT and decreased FVC, are usually required in order to rule out the possibility that a decrease in DL_{CO} is due to disease progression.[4] In any case, a decrease in DL_{CO} indicates a poor prognosis.

RISK ELEMENTS

Several data points in the first evaluation of patients with fibrotic ILD lead to a higher chance of progression (Chart 3).[8,26,27,42] In scleroderma, some specific abnormalities are linked to increased ILD progression and a poor prognosis, including smoking, being Black, diffuse cutaneous involvement, and concurrent myopathy, as well as autoantibodies such as anti-topoisomerase I/anti-Th/To and anti-U11/U12 ribonucleoprotein antibodies.[35,38,40,43]

PF-ILD MANAGEMENT

Pharmacological and nonpharmacological treatments are used in the management of PF-ILD. Nonpharmacological management techniques such as oxygen therapy, rehabilitation, lung transplantation, and palliative care are critical but will not be covered here.[44] In patients with IPF, treatment with an

Chart 3. Major risk factors for interstitial lung disease progression.[a]

- Advanced age
- Male sex
- Family history (short telomeres)
- Clubbing of the fingers
- Need for oxygen therapy
- > 20% extent of fibrosis on HRCT
- Extensive traction bronchiectasis on HRCT
- FVC of < 50-65% predicted
- DL_{CO} of < 50% predicted
- An SpO_2 of < 85% during exercise
- No identification or avoidance of antigens in CHP
- Pulmonary hypertension

CHP: chronic hypersensitivity pneumonitis. [a]Based on Valenzuela & Cottin,[8] as well as on other references.[15-42]

antifibrotic drug should begin as soon as the diagnosis is made.

Antifibrotic drugs used in patients with IPF have recently been studied in patients with PF-ILD. In a study published in 2019,[3] the efficacy of nintedanib vs. placebo was investigated in 663 patients with fibrosing lung diseases that had progressed after two years of surveillance. Of the 663 patients, 173 (26%) had CHP, 170 (26%) had CTD, 125 (19%) had NSIP, 114 (17%) had unclassified ILD, and 81 (12%) had other ILDs.[3] The adjusted rate of FVC reduction with nintedanib was 80.8 mL/year vs. 187.8 mL/year with placebo, with a mean difference of 107.0 mL/year (95% CI, 65.4-148.5; p = 0.001).[3] The adjusted rate of FVC deterioration in patients with an IPF-like fibrotic pattern was 82.9 mL/year with nintedanib and 211.1 mL/year with placebo, a difference of 128.2 mL/year (95% CI, 70.8-185.6; p = 0.001).[3] In the absence of unusual findings, an IPF-like pattern was defined as the presence of a UIP pattern on HRCT but no diagnosis of IPF or probable IPF on CT.[3]

The effect of nintedanib vs. placebo in reducing the rate of FVC decline (mL/year) was consistent across the five ILD subgroups included in the study: CHP (73.1 mL/year; 95% CI, −8.6 to 154.8), autoimmune diseases (104.0 mL/year; 95% CI, 21.1-186.9), NSIP (141.5 mL/year; 95% CI, 46.0-237.2), unclassified ILD (68.3 mL/year; 95% CI, −31.4 to 168.1), and other ILDs (197.1 mL/year; 95% CI, 77.6-316.7).[45] The study was not designed to have enough power to determine whether certain subgroups benefited. Nonetheless, the findings show that nintedanib reduces the progression of ILD in individuals with chronic fibrosing disease and a progressive phenotype. This is true regardless of the cause of the disease. In a separate data analysis, 134 patients (40.4%) in the nintedanib group and 181 (54.7%) in the placebo group experienced disease progression or died (hazard ratio, 0.66; 95% CI, 0.53-0.83; p = 0.001). Exacerbations were less common in the nintedanib group (hazard ratio, 0.67; 95% CI, 0.46-0.98; p = 0.04).[46] As expected, the most prevalent side effect of nintedanib was diarrhea. The U.S. Food and Drug Administration and the Brazilian Health Regulatory Agency have approved the use of nintedanib in such cases on the basis of the findings of the aforementioned study.[3]

Antigen identification is associated with improved survival in patients with CHP.[47] Even in patients with fibrosis, complete antigen clearance, especially when paired with clinical improvement, is associated with extended survival in a considerable proportion of patients.[27,48] Complete elimination of exposure is required for disease control. In Brazil, however, exposure to mold in the home is prevalent, complicating disease management. Immunosuppressants can be used in these patients in order to minimize the inflammatory response and fibrosis development.[49] The use of antifibrotics in this situation is debatable.

There have been no prospective trials of CHP patients using immunosuppressants. Azathioprine and mycophenolate are the most commonly used drugs.[49] Treatment with corticosteroids alone should be considered in acute cases or during episodes of aggravation in chronic situations. In some circumstances, immunosuppressants allow the use of lower corticosteroid doses or even corticosteroid discontinuation.

Antifibrotic therapy should be considered for patients who continue to deteriorate despite antigen avoidance or when there is a high likelihood that they will not respond (no evidence of inflammation on HRCT; bronchoalveolar lavage fluid without lymphocytosis; FVC of < 50% of predicted; UIP findings on HRCT or in lung biopsy material; and extensive traction bronchiectasis).[50-53] In a study evaluating patients with CHP, the mean difference in functional decline between the placebo and treated groups was 73.1 mL, but the range was considerable (95% CI, −8.6 to 154.8).[3] No information was provided regarding the diagnostic criteria used or the eventual removal of antigen exposure. Patients with CHP and UIP (particularly fibroblastic foci) in lung biopsies have poorer results.[54] Antifibrotic drugs may be more effective in these cases. The results of CHP treatment with pirfenidone have recently been published.[55] The COVID-19 pandemic halted enrollment after 40 patients had been randomly assigned. At week 52, there was no significant difference in percent predicted FVC across groups (mean difference, −0.76%; 95% CI, −6.34 to 4.82). The experiment was insufficiently powered to detect a change in the major endpoint, rendering it inconclusive.

Two studies examined the use of pirfenidone in individuals with unclassified ILD as well as other types of ILD.[56,57] Following a multidisciplinary debate, one phase 2 study explored the efficacy and safety of pirfenidone in patients with ILD of uncertain etiology.[56] Up to 6 months prior to participation, patients had a > 5% decline in FVC or worsening of symptoms, linked to deteriorating ILD. The primary goal was a change in FVC evaluated by home spirometry; however, because of outliers, FVC measured at trial visits, a secondary endpoint, was analyzed, indicating less decline in the treated group than in the placebo group

(−17.8 mL vs. −113 mL). The other study examined patients with an FVC decline of 5% or more in the previous 24 months despite standard treatment.[57] The primary outcome was the change in percent predicted FVC at week 48. A total of 127 patients were randomly assigned to receive treatment with pirfenidone or placebo. CHP was the most common ILD (in 45% of the study participants). The study was terminated prematurely after 127 individuals had been randomized, because of low recruitment. Pirfenidone had a slight advantage; however, some data points were missing.

A meta-analysis[56-58] included the two aforementioned studies. The median difference in FVC was 100 mL (95% CI, 98.1-101.9), and the six-minute walk distance (25.2 m; 95% CI, 8.3-42.1) favored pirfenidone over placebo. Changes in DL_{CO} also favored pirfenidone (median difference, 3.0 mL/min/mmHg; 95% CI, 0.75-5.25), and the risk of DL_{CO} decreasing by more than 15% favored pirfenidone (relative risk, 0.27; 95% CI, 0.08-0.95).

In summary, a diagnosis of fibrotic ILD is required for appropriate initial management. Antifibrotics constitute a treatment option for patients with increasing deterioration. More research is needed in order to identify markers of increased risk of progression in patients with ILD and determine the likelihood of response to therapy with standard or novel medications.

AUTHOR CONTRIBUTIONS

CACP: conceptualization; and drafting, reviewing, and editing of the manuscript. SC and ACR: drafting of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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Mobile health applications designed for self-management of chronic pulmonary diseases in children and adolescents: a systematic mapping review

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ABSTRACT

Objective: Mobile health (mHealth) applications are scarce for children and adolescents with chronic pulmonary diseases (CPDs). This study aimed to map and describe the contents of the mHealth apps available for use in children and adolescents with CPDs. **Methods:** We performed a systematic mapping review of published scientific literature in PubMed, Scopus, and Cochrane Library by February of 2023, using relevant keywords. Inclusion criteria were as follows: children aged < 18 years with CPDs; and studies published in English on mHealth apps. **Results:** A total number of 353 studies were found, 9 of which met the inclusion criteria. These studies described seven mHealth apps for Android and iOS, designed either for asthma (n = 5) or for cystic fibrosis (n = 2). Five content areas were identified: education/information; pharmacological treatment; emergency; support; and non-pharmacological treatment. The studies (4, 2, and 3, respectively) showed consistent findings using qualitative, quantitative, and mixed methodologies. **Conclusions:** This mapping review provided a guided selection of the most appropriate mHealth apps for use in children and adolescents with CPDs based on the needs of each target population. However, these mHealth apps have limited capabilities to reinforce disease self-management and provide information related to treatment compliance.

Keywords: Lung diseases; Child, Adolescent; Treatment adherence and compliance; Telemedicine; Self-management.

INTRODUCTION

In pediatrics, effective disease management includes taking medications as prescribed, attending medical appointments, self-monitoring symptoms, identifying and minimizing exposures to environmental triggers, adhering to a personalized action plan, and communicating with health-care providers about symptoms and treatments.[1] Traditionally, clinic visits serve as the primary setting for pediatric patients to receive disease education and self-management support. However, children and caregivers are increasingly looking for self-manageable information and assistance and are directed to alternate ways of support such as using relevant websites and mobile health (mHealth) applications (apps).[2]

Mobile phone usage is rapidly increasing around the world.[3] In 2019, almost 46% of children between 5 and 17 years of age in Europe had a smartphone, and 41% of these used it daily.[4] This new reality has been conducive to the adoption of this technology to support medical and public health practice services.[5] Therefore, mHealth apps have become a promising tool to provide support to kids and caregivers so that they could manage therapy regimens and symptoms, aiming to enhance the self-management of chronic diseases and, consequently, improve the quality of life of these patients. Apps created for managing chronic pulmonary diseases (CPDs) usually include functions such as written reminders, information about medication intake, symptom records, and pulmonary function monitoring, as well as education about disease pathology.[2,6-9]

Further to this attempt, the exchanged information between patients and clinicians (such as patients' pre-visit reports as an Adobe Acrobat PDF file prior to the clinical visit) can be broadened by mHealth technology. In other words, this technology can facilitate the estimation of the symptoms and the modification of pharmacological and non-pharmacological treatment regimens when necessary, as well as the process of detecting a disease exacerbation.[2,8] Although mHealth apps are optimally designed to provide support in disease self-management and to empower individuals to comply with treatment, very few apps have been investigated regarding their impact on clinical outcomes.

This review article aims to map and classify the existing studies about mHealth apps designed to be used for the pharmacological and non-pharmacological management of CPDs in children and adolescents. Acknowledging some boundaries in the classification of the existing

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apps, clinicians can make evidence-based decisions regarding which app is the most suitable for use or can suggest new fields of interest when realizing any research gaps.

METHODS

Study design

A systematic mapping review methodology was used in order to find published studies regarding mHealth apps designed for self-management of CPDs in children and adolescents.[10] Our approach was based on the principles defined by the Social Care Institute for Excellence.[11] A systematic map is increasingly being used in health care service research aiming to map out and categorize a topic in the literature to undertake new and more detailed work.[10] This method is useful for summarizing and organizing a broad, heterogeneous evidence base to identify more specific investigations.[11] A protocol was registered on the Open Science Framework platform (https://doi.org/10.17605/OSF.IO/ADKGF) since the International Prospective Register of Systematic Reviews is not currently accepting registrations for mapping reviews.

Eligibility criteria

Inclusion criteria were articles published in the English language by February of 2023. Studies on children with CPDs (such as asthma, cystic fibrosis, and non-cystic fibrosis bronchiectasis) who were younger than 18 years of age, and who used mHealth apps that had a user-friendly behavioral approach were included in this review. Abstracts, book reviews, book chapters, narrative reviews, preclinical studies, scoping reviews, systematic reviews, meta-analyses, case series/reports, commentaries, letters to the editor, editorials, clinical practice guidelines, protocols, and studies whose full texts were unavailable were excluded. Furthermore, studies were excluded if they were related to adults or to other chronic or acute pediatric diseases (such as musculoskeletal and neurological diseases), or if the research process for mHealth app design and interventions were not described. In this mapping review, unpublished reports and gray literature were chosen not to be searched.

Search strategy

A systematic electronic literature search was performed across three electronic databases (PubMed, Scopus, and Cochrane Library) by February of 2023 by one of the researchers (VS). Search strategy was designed using keywords and MeSH terms related to mHealth apps, pharmacological/non-pharmacological treatment, children/adolescents, and CPDs (Supplementary material).

Screening and article selection

Studies were screened for inclusion by reviewing the title and abstract. Search results were exported to Endnote X9 (Clarivate, Philadelphia, PA, USA). After exclusion of duplicates, two investigators (VS and PK) independently screened the titles, abstracts, and full texts of the studies to make a final decision. Studies that did not meet the eligibility criteria were excluded. Afterward, a secondary search was performed from citations in the included articles and in previous reviews about the use of mHealth apps. The full texts of all relevant studies were sought, downloaded, and further evaluated for compliance with the eligibility criteria. In case of disagreements, a third reviewer (EK) was consulted to make the final decision, thus ensuring the minimization of bias when deciding whether to include a study or not. Finally, all of the members of the research team decided on the inclusion of the selected studies by consensus.

Data extraction

Given the relatively few relevant studies in the literature, we decided to include studies using different methodologies. A template including the study methodology, study setting, year of publication, and main perspectives was developed to guide data extraction. VS and EP independently extracted the data from the included articles, and EK undertook final verification. Any disagreement was discussed and resolved by consensus.

Based on Fernández-Sotos et al.,[12] a key methodological aspect for a successful systematic mapping review is the definition of research questions (RQs) to be answered. Therefore, the selected RQs in this mapping review were as follows:

- RQ1: What are the mHealth apps available for use in children and adolescents with CPDs?
- RQ2: What is the content of each mHealth app?

Risk of bias/quality of the studies

The main aim of a systematic mapping review is to describe the state of the art of the topic.[11] Risk of bias is determined in a generic way by classifying the study type. This systematic mapping review was conducted to provide an overview of the existing mHealth apps regardless of methodological quality or risk of bias derived from each study. Therefore, sources of evidence are not critically appraised, and they were reviewed in terms of research coherence and utility of findings on the main research focus.[12]

RESULTS

Flow of studies

The electronic search strategy identified 353 relevant papers. After removing duplicates, 164 studies were reviewed by title and abstract. A total of 129 studies were excluded. Of the 35 full-text studies assessed for eligibility, 9 were included for further study. Figure 1 shows the flow chart of the study selection process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.

Characteristics of the studies selected

Table 1 provides a summary of the characteristics of the studies included. Four studies were conducted based on qualitative methods,[2,8,13,14] two were quantitative descriptive studies,[15,16] and three studies adopted mixed research methods.[7,17,18] Four, two, and three studies, respectively, were conducted in Europe,[2,7,8,16] in the USA,[14,15] and in Australia[13,17,18] between 2017 and 2022. Four of the studies used a sample of pediatric patients with CPDs,[2,13,15,16] two other studies used a sample consisting of all of the stakeholders (patients, health care professionals [HCPs], and parents),[8,14] and one study used a sample of the Australian First Nations Health and Care with HCPs and carers of children with asthma.[18] In addition, one study used a sample consisting of mHealth apps,[7] and another study used a sample consisting of students.[17]

RQ1: What are the mHealth apps available for use in children and adolescents with CPDs?

Among the studies included in the present systematic mapping review, seven specific mHealth apps[7] were mentioned (Table 2). In detail, two of the reviewed studies assessed an app named Genia, which is addressed to patients with cystic fibrosis (CF).[2,14] Two studies examined the mHealth application named MyCyFAPP, which was developed as a self-management tool for patients with CF and their families.[8,16] In addition, five apps (for iOS and Android) were addressed to patients with asthma: Kiss my Asthma;, Ask Me, AsthMe!; ASTHMAXcel; Asthma First Aid; and Menzies Asthma APP.[7,13,15,17,18]

The Genia app was designed for iOS and aims to foster collaboration among CF patients (mean age = 17.8 years), their families, and health care teams, with

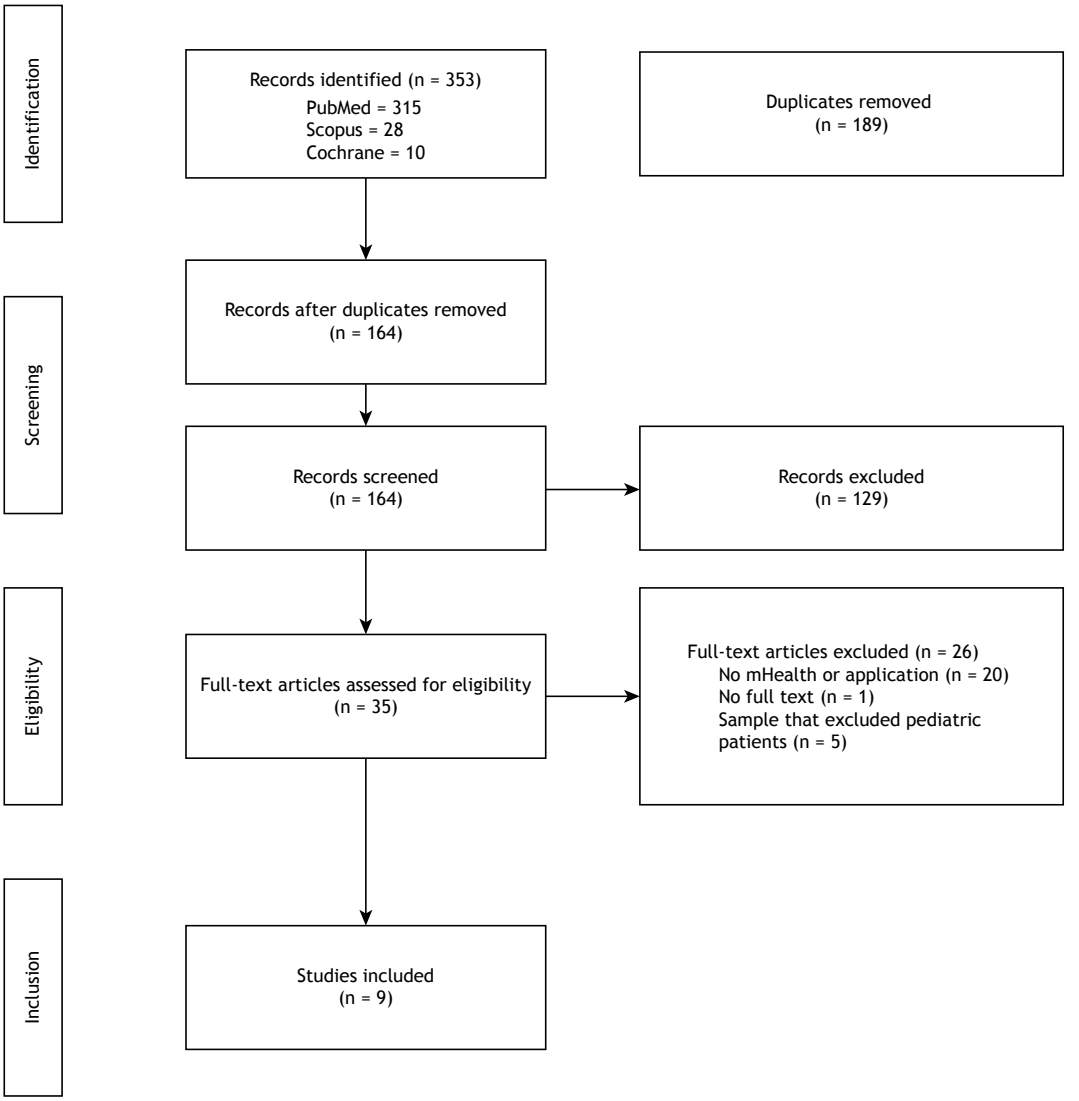

Figure 1. Flow chart of the selection process in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

a particular focus on giving children and adolescents a central role in the decision-making process. The app was created by Upstream Dream, a Swedish-based company, and it was funded as a collaborative project with Genentech. As a platform and an app-based patient support system, the Genia app emphasizes user participation, feedback provision, and collaborative content shaping. The core functionality of the system was commissioned as part of a collaborative learning initiative related to a special clinical microsystem, named Lund Pediatric Cystic Fibrosis. This involved clinicians, researchers, family members, and CF patients in order to determine the contents of the app, and core functions were optimized and inspired by patients.[2,14]

The MyCyFAPP app was designed for Android to be used by children and adolescents with CF (< 18 years of age), their families, and HCPs, who can jointly and seamlessly manage the treatment of the disease. A multidisciplinary project (designated Horizon 2020 and spanning four years—from January 1st, 2015 to December 31st, 2018) was created and funded by the European Commission Framework Program for Research and Innovation. Patients and families can rely on the app to self-manage nutrition and other aspects of non-pharmacological and pharmacological treatment. HCPs use this tool to monitor and track patient progress, ensuring feedback between the two parties when deemed necessary.[8,16]

The Kiss my Asthma app was developed by a research team from the University of Sydney, the Woolcock Institute of Medical Research, and the University of Melbourne, with funding from the Asthma Australia's National Research Fund. The app is available on both iOS and Android platforms, and it provides users (< 18 years of age) with convenient access to their asthma action plan, medication reminders, tips on avoiding triggers, and strategies for managing asthma. Additionally, the app offers educational resources about asthma and allows users to set personal goals. By making small changes, users can reduce the frequency of asthma flare-ups and improve their overall asthma control. The ultimate aim of the app is to help users lead normal lives and not let asthma symptoms affect their daily activities.[13]

The Ask Me, AsthMe! app was designed for iOS to help children (12-18 years of age) and their families increase their knowledge about pediatric asthma and manage asthma symptoms effectively. The app was created by the New York City Health and Hospitals Corporation without any funding. It is an app with a number of functions aiming to help users understand childhood asthma and asthma parameters. In fact, the app has been positively evaluated and considered to be able to contribute to the management of childhood asthma.[7]

Table 2. mHealth apps and target patient population.

App	Target population
Genia[2,14]	Cystic fibrosis
MyCyFAPP[8,16]	Cystic fibrosis
Kiss my Asthma[13]	Asthma
Ask Me, AsthMe![7]	Asthma
ASTHMAXcel[15]	Asthma
Asthma First Aid[17]	Asthma
Menzies Asthma[18]	Asthma

Table 1. Summary characteristics of the studies included in the mapping review.

Characteristic	Number of studies (reference)
Methodology	
Qualitative	4[2,8,13,14]
Quantitative	2[15,16]
Mixed methods	3[7,17,18]
Study setting	
Europe	4[2,7,8,16]
USA	2[14,15]
Australia	3[13,17,18]
Year of publication	
2017	3[8,13,16]
2018	1[2]
2019	-
2020	1[15]
2021	3[7,14,17]
2022	1[18]
Main perspective	
Pediatric patients (CF/Asthma)	4[2,13,15,16]
Stakeholders (CF patients, parents, and HCPs)	2[8,14]
AFNHC's HCPs Health professionals and carers of children with asthma	1[18]
Sample of apps	1[7]
Sample of students	1[17]

CF: cystic fibrosis; HCPs: health care professionals; and AFNHC: Australian First Nations Health and Care.

ASTHMAXcel is an evidence-based, personalized app for managing asthma symptoms, developed by a team of asthma physicians, software programmers, and behavioral scientists. The work was funded by the Allergic Respiratory Diseases Research Award sponsored by the American Lung Association and the American Academy of Allergy, Asthma and Immunology Foundation. The project was supported by the Stony Wold-Herbert Fund Community Service Grant and the Genentech Research Grant. As part of the ASTHMAXcel program, a gamified mobile app called ASTHMAXcel Adventures was developed for children and adolescents with asthma (7-17 years of age), available on iOS and Android platforms. The app features short educational videos and interactive games that combine animation with informative storytelling. It has an introductory screen with five levels for users to choose from. Each level comprises one to three tutorial videos and corresponding games that require users to answer questions related to the videos.[15]

The Asthma First Aid app is a useful tool for an asthma emergency, available on both iOS and Android platforms. It was created by Asthma Australia (National Health and Medical Research Council Centre for Research Excellence in Lung Health) as an educational tool for children with asthma (12-18 years of age), their families, and their carers, providing easy access to emergency response steps. It covers both first aid in event of an asthma emergency plus the ability to review each of the four first aid steps.[17]

The Menzies Asthma app is a First Nations-specific, multi-lingual app that is based on the current pediatric pictorial asthma flipchart, with "voice-over" in seven First Nations languages and English. This project was funded by Asthma Australia and it was produced by the Child Health Division of Menzies School of Health Research. It uses interactive images, audio, and quizzes to teach children (4-18 years of age) about asthma. It is an innovative and culturally acceptable method of delivering evidence-based respiratory health education to culturally and linguistically diverse populations among First Nations people in Australia.[18]

RQ2: What is the content of each mHealth app?

Table 3 shows the main aspects searched in relation to the content of each app. Five main content areas were identified: education/information, pharmacological treatment, emergency, support, and non-pharmacological treatment.

Six of the included apps offer information about the disease through educational videos, contributing to self-management of the disease and improving the cognitive background of both children and parents.[7,8,13,15-18] Four apps function as pharmacological diaries.[2,7,8,13,14,16] Furthermore, four apps indicate emergency procedures for pediatric patients with asthma attacks.[7,13,17,18] Information about symptoms and medication reminders is provided in four apps.[2,7,8,13,14,16] Finally, two of the apps can provide non-pharmacological elements focusing on nutritional aspects of children with CF and compliance with performing respiratory physical therapy exercises using an emotion expression scale score.[2,8,14,16]

Education/information

The MyCyFAPP has educational resources and tools for customized nutritional self-management of the disease and patient empowerment. These educational tools are a nutritional recommendation handbook, full of practical examples and applicable recommendations written in plain and easy-to-read language, including images, infographics, and layouts; a mobile game for tablets, named My Happy Pat, which was designed for children with CF between 4 and 11 years of age; a tool specifically designed to create recipes based on complete and reliable nutritional composition databases, named MyFoodCAL; a tool that enhances and reformulates existing nutritional composition databases by adding new foods and filling nutritional information gaps, named MyFoodFACTS; and an online tool to compile case reports, named MyFoodREC.[8,16]

For patients with asthma, there are also educational resources available to help learning about the disease, including symptoms, causes, and effective management techniques. The Ask Me, AsthMe! app provides educational resources to help users (patients and parents) to learn about asthma, its symptoms and causes, and manage their condition more effectively.[7] The ASTHMAXcel app contains educational videos on how asthma affects the airways, medications and how they work, flow meter monitoring, and instructions on how to use inhalers and spacers properly.[15] Additionally, the Kiss my Asthma, the Asthma First Aid, and the Menzies Asthma apps provide educational

Table 3. Main content areas in each mHealth app.

App	Education/ information	Pharmacological treatment	Emergency	Support	Non-pharmacological treatment
Genia[2,14]		☺		☺	☺
MyCyFAPP[8,16]	☺	☺		☺	☺
Kiss my Asthma[13]	☺	☺	☺	☺	
Ask Me, AsthMe![7]	☺	☺	☺	☺	
ASTHMAXcel[15]	☺				
Asthma First Aid[17]	☺		☺		
Menzies Asthma APP[18]	☺		☺		

instructions on how to manage asthma attacks and when to seek medical attention.[13,17,18]

Pharmacological treatment

The Genia app allows patients to track their medication intake and share comments, helping users keep a record of when they took their medicine and note which medicine was, thereby facilitating medication management.[2,14] The MyCyFAPP includes a personalized medication plan for each individual user.[8,16] This plan includes a customized dosage per intake, recurrence, and medication termination, and provides reminders for medical doses. Users can also track their medication adherence over time using this resource.[8,16] For children with asthma, the Kiss my Asthma and the Ask Me, AsthMe! apps contain a field for recording a medication diary.[7,13] This can help children keep track of their medication schedule and ensure that they are adhering to their prescribed treatment plan.

Emergency

The Kiss my Asthma app offers access to an action plan, first aid instructions, and emergency contacts, as well as information about asthma, asthma medication and devices, and provides instructions for anxiety management.[13] The Ask Me, AsthMe! app provides step-by-step instructions on what to do in an emergency situation. The instructions are organized in color-coded zones, making it easy to understand and follow them.[7] The Asthma First Aid app allows users to follow first aid steps in real time in an attack mode and review the first aid steps using a sample of scenarios in a training scenario mode.[17] The Menzies Asthma app helps children learn the four steps to take during an asthma emergency and what to do when symptoms do not improve.[18]

Support

By using the Genia app, patients or parents can record health observations and symptoms between visits daily (e.g., physical activity or gastrointestinal problems), track medication intake, and complete pre-visit reports, including treatment preferences and goals, prior to a clinical appointment. This patient-reported information allows patients to document their disease activity and preferences in real time between clinical visits.[2,14] The MyCyFAPP provides medication reminders that help users remember to take their medications on time, reminders of HCP appointments, and progress tracking. The app also includes a symptom tracker, which allows users to monitor their symptoms over time and share this information with HCPs, offering flexibility to accommodate appointments with daily recurrences, termination dates, or different medicine dosages.[8,16] For patients with asthma, the Kiss my Asthma app provides the option through which the user can receive self-defined notifications about the use of an asthma control device as well as information about the supporting environment and direct contact information. This tool can help children stay on track with their treatment plans and monitor their asthma control.[13]

Non-pharmacological treatment

The Genia app functions as a self-report diary by allowing children with CF to record and save observations about various aspects of their condition.[2,14] It includes features related to lung function, airway clearance, physical activity, appetite, and other supportive therapies. They can share their thoughts, feelings, and any observations that they have regarding their therapy routine. It gives them a chance to express how they perceive the therapy, whether they find it helpful or challenging, and if they have any concerns or suggestions related to it. By collecting this information through the Genia app, HCPs and caregivers can gain valuable insights into the child's perspective and make informed decisions regarding their treatment plan. It also empowers children to participate in their care actively and be involved in the management of their condition.[2,14] The MyCyFAPP offers a personalized nutrition plan, which is tailored to the individual's needs based on their age, weight, height, and other factors. The nutrition plan provides information on recommended calorie intake, meal planning, and portion sizes, and allows users to track their daily food intake.[8,16]

DISCUSSION

This review aimed to map and classify the existing studies about mHealth apps designed to be used for the pharmacological and non-pharmacological self-management of CPDs in children and adolescents.

The implementation of a co-design approach that engages multiple stakeholders holds great promise in facilitating CPD self-management.[2,8] This collaborative process serves two key purposes: firstly, it helps identify and address divergences among stakeholders, thus leading to effective solutions. Secondly, it enables to design concepts that align with functional requirements (e.g. reminders, notifications, educational resources, and support), as well as nonfunctional aspects such as privacy and time saving.[8] Research on the development of mHealth technology promotes the incorporation of the end user in the design process; however, their input is often incorporated late or sporadically during the design phase.[19] Some apps in this domain have successfully embraced co-design to enrich their content and support disease self-management.[2,8] The design of the apps is very important so that users can increase their interaction and gain more benefits from the therapeutic treatment. However, only one app was tested in clinical studies with regard to its effectiveness in supporting disease self-management.[20]

The selected mHealth apps in this mapping review cover a range of essential areas, providing valuable content in five key domains: education/information,

pharmacological treatment, emergency assistance, support, and non-pharmacological treatment. Each of these components offers distinct benefits and outcomes to the users.

The education/information aspect provides valuable knowledge and resources to enhance disease understanding and management.[7,8,13,15-18] Pharmacological treatment modules focus on supporting medication adherence and optimizing treatment outcomes.[2,7,13,14,16] Emergency assistance features ensure prompt access to assistance and resources during critical situations, such as an asthma attack.[7,13,17,18] Non-pharmacological treatment tools provide alternative approaches and strategies for disease self-management.[2,8,14,16] These comprehensive components collectively contribute to a holistic and well-rounded user experience with the selected mHealth apps. Lastly, support functionalities offer a sense of community and emotional support to individuals with the condition.[2,7,13,14,16]

The reassessment of the apps by users (children, adolescents, parents, and HCPs) has been proven to be invaluable for improving the functionality of each app. Users express a strong desire to communicate with their HCPs, share comprehensive information about their symptoms, and receive reminders for medication adherence. Users' requests during app reassessment play a pivotal role in significantly modifying the content within the apps. As a result, features such as symptom monitoring, suggested therapies, prescribed medications, and other activities related to daily therapy have been incorporated to enhance usability and user-friendliness. It is worth noting that, initially, the apps did not fully encompass these functionalities; however, they have undergone substantial improvements with user evaluation and feedback.[2,8,14] Interestingly, it should be noted that there were limitations in the capabilities of some mHealth apps to reinforce disease self-management fully and provide comprehensive information related to compliance with treatment.

Overall, this review highlights the potential of mHealth technology in empowering children and adolescents with CPDs through self-management. The findings underscore the significance of a co-design approach that engages all relevant stakeholders. By leveraging the strengths of mHealth apps across education, pharmacological treatment, emergency assistance, support, and non-pharmacological treatment domains, self-management support and patient-physician communication can be provided to children with CPDs and their families, and this powerful tool can enhance their ability to manage disease symptoms and improve health outcomes and quality of life. Further research with randomized control trials and long-term follow-up of the use of these apps in pediatric populations with CF, asthma, and non-CF bronchiectasis are necessary to address the potential benefits of these apps in supporting pediatric patients to manage their conditions effectively.

This systematic mapping review has some limitations. Even though our research included three different scientific databases, the research strategy was jeopardized by the exclusion of other databases that could have brought more studies into light. Furthermore, our search was limited to studies published only in English, which might have excluded valuable sources of information published in other languages. However, we believe that there is relatively little research evidence addressing the specific questions selected, which is reflected by the small number of studies fitting the quite specific inclusion criteria in this review. Moreover, the heterogeneity of methodologies and contexts in the included studies presents a challenge in drawing together related and contrasting findings. In addition to the aforementioned limitations, it is worth noting that there was a lack of direct communication between our team of researchers and the authors of the studies, which limited the opportunity for further considerations and potential insights. The absence of such collaboration might have resulted in a potential decrease in the depth and breadth of information gathered in this review.

FINAL CONSIDERATIONS

mHealth apps are increasingly becoming an integral part of the new era of eHealth. These tools incorporate various features and functions, aiming to support users and improve compliance with treatment, and, as a consequence, improving disease self-management. Specifically focusing on apps for children/adolescents, mHealth apps are designed with a user-centric approach, taking into consideration feedback from patients, parents/caregivers, and HCPs. This collaborative effort aims to enhance the functionality of the apps, ensuring that they meet the specific needs and preferences of their intended users. This mapping review identified five content areas in mHealth apps for children with CPDs: education/information, pharmacological treatment, emergency, support, and non-pharmacological treatment. The challenge for HCPs lies in selecting a final and improved product. To guarantee usability and effectiveness in achieving clinical outcomes such as promoting adherence to pharmacological and non-pharmacological treatments and improving the quality of life, further clinical studies involving these patients are necessary. These studies will provide valuable insights into the impact and efficacy of the apps, ultimately contributing to their continued development and refinement.

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AUTHOR CONTRIBUTIONS

VS and EK: study concept and design; drafting of the manuscript; critical review of intellectual content; and

writing of the final version of the manuscript. VS, PK, EP, TM, and PD: data analysis and interpretation. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Initial insights on vaping-associated illnesses in Colombia: evidence for action

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TO THE EDITOR:

Electronic cigarettes or electronic nicotine delivery systems (ENDS) and similar systems without nicotine (SSWN) have been some of the most trending products in recent decades. Worldwide, their successful marketing has especially been effective among the population under 30 years of age.[1] Much is still unknown about how e-cigarettes can affect human health.[2] Although several authors have been outspoken against the potential risks associated with chemical products contained in ENDS or SSWN devices, some of which are considered toxic and carcinogenic,[3] it was not until 2020 that the code U07.0 of the International Classification of Diseases, 10th revision (ICD-10) was utilized to refer to diseases associated with vaping.[4]

In this context, we analyzed the first data on vaping-related diseases in the Colombian population. We compiled microdata from the 2019 *Encuesta Nacional sobre Consumo de Sustancias Psicoactivas* (ENCSP, National Survey of Psychoactive Substances) and the *Sistema de Información de Prestaciones de Salud* (RIPS, Health Benefits Information System), including sex, age, location, and final condition (alive or deceased) between January of 2020 and July of 2022.[5] Data from each database was analyzed separately. Associations with e-cigarette or vaping use were estimated using crude prevalence ratios (PRs) and respective 95% CIs. Adjusted PRs were obtained using Poisson regressions with the software R, version 4.2.1 (The R Foundation for Statistical Computing, Vienna, Austria). Variable selection was based on two systematic literature reviews.[6]

By analyzing ENCSP data, we found that the prevalence of e-cigarette usage was 4.37% (95% CI, 4.20-4.56). Regular e-cigarette consumption in the country was mainly concentrated in Bogotá, Caldas, Antioquia, Valle del Cauca, and Boyacá, which accounted for 60.1% of users. When stratifying marijuana use with tobacco smoking, it was found that 26.4% (n = 2,635/9,954) of cigarette smokers younger than or equal to 45 years of age regularly consumed marijuana. In the group over 45 years of age, the proportion of cigarette and marijuana smokers was 10% (n = 680/6,603). In the relationship between the use of vaping and cigarette analysis, it was found that, in the group younger than or equal to 45 years of age, 76.8% (n = 1,535/1,998) of vapers were also cigarette smokers. In turn, it was found that 95.0% (n = 171/180) of people over 45 years of age were vapers and cigarette smokers. A total of 42.2% (n = 845/1,998) of vapers younger than or equal to 45 years of age regularly consumed marijuana. This proportion dropped to 27.33% (n = 49/180) in the group over 45 years of age. In the multiple analysis, it was found that age (PR = 0.932; 95% CI, 0.928-0.936; $p < 0.001$), male sex (PR = 1.27; 95% CI, 1.16-1.39; $p < 0.001$), cigarette smoking (PR = 6.42; 95% CI, 5.73-7.20; $p < 0.001$), and marijuana use (PR = 2.36; 95% CI, 2.15-2.59; $p < 0.001$) were independent variables associated with the risk of vaping (Table 1). A linear relationship was found between the socioeconomic status and the risk of vaping ($\chi^2 = 385.102$; p-trends < 0.01).

From the RIPS database we observed 245 cases of vaping-related disease. Most of the reported cases occurred in men older than 45 years (82.8%). A total of 59 deaths were reported in the period evaluated. Again, mortality mostly occurred among men ($p < 0.05$) older than 60 years. The departments reporting deaths due to vaping-related disease were Antioquia (69%) and Boyacá (27%), followed by Sucre (1.69%) and Tolima (1.69%). The severity rate was 24.38% (95% CI, 19.40-30.16). We found no association of the independent variables sex, age, and health insurance with mortality ($p > 0.05$).

Lung injury associated with the use of e-cigarettes or vaping is a reality that represents a health risk in Colombia. It was found that the prevalence of consumption of e-cigarettes was 4.37%. Recent reports from Brazil have shown that 7.3% (95% CI, 6.0-8.9) of people have used e-cigarettes or hookahs at some point in their lives, and young adults have the highest experimentation rates for e-cigarettes (19.7%; 95% CI, 15.1-17.0).[7]. In addition, the departments with the highest tobacco consumption coincided with those with the highest case rates of vaping-related disease. Furthermore, it was possible to determine a greater risk of e-cigarette consumption in men under 45 years of age who also regularly consumed cigarettes or marijuana. This finding is consistent with those reported in the literature, which documented higher consumption in the young adult population.[8]

The concomitant consumption of marijuana and e-cigarettes reported in the 2019 ENCSP data is striking. Our results are consistent with those reported in the literature. [9] A meta-analysis focusing on evaluating the concomitant usage of e-cigarette and marijuana in adolescents found that those who reported e-cigarette use had 6.04 times greater odds (OR = 6.04; 95% CI, 3.80-9.60) of reporting marijuana use than did those who did not vape.[9] Some authors have underscored that the current strategy of identifying lung injury associated with e-cigarettes has limitations. The announcement of the inclusion of vaping-related disease under the ICD-10-CM (Clinical Modification) U07.0 in late 2019 was

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Table 1. Factors associated with the use of e-cigarettes or vaping according to the 2019 *Encuesta Nacional sobre Consumo de Sustancias Psicoactivas* (National Survey of Psychoactive Substances).

Factor	Variable	Crude association		Multiple association	
		PR	95% CI	PR	95% CI
Sex	Male	2.304	2.113-2.514	1.278	1.169-1.397
	Female	1		1	
Age, years		0.946	0.943-0.950	0.932	0.928-0.936
Cigarette smoking	Yes	7.247	6.551-8.033	6.423	5.737-7.201
	No	1		1	
Marijuana use	Yes	8.003	7.347-8.715	2.364	2.150-2.599
	No	1		1	
Socioeconomic stratum	1 (lowest)	1		1	
	2	2.020	1.769-2.313	1.950	1.707-2.232
	3	2.766	2.423-3.166	2.650	2.320-3.035
	4	3.738	3.152-4.428	3.473	2.925-4.119
	5	3.892	3.066-4.892	3.756	2.955-4.728
	6 (highest)	4.255	3.168-5.609	4.063	3.020-5.365

PR: prevalence ratio;

overshadowed by the COVID-19 pandemic, reducing the potential for universal uptake.[10]

It is nothing new that smoking continues to be a significant risk factor for a considerable number of negative health outcomes. However, smoking is becoming less common and those users are migrating to ENDS or SSWN products. In this sense, it is imperative that Latin-American countries develop a regulatory core that allows the characterization of the supply of products that exist on the market to determine the contents of chemical substances that could have a negative effect on human health. The incorporation of flavors and odors, which might encourage the use of these products in underage populations, should also be prohibited.

An adequate interpretation of these findings should consider that the data analyzed from health service delivery records may have limitations. First, there are aspects related to the quality of the data, and the lack of dissemination of information about the clinical presentation of vaping-related disease reduces the possibility of its identification. On the other hand, the ICD-10 U07.0 that is reported in the RIPS could have biases and even have been used incorrectly.

AUTHOR CONTRIBUTIONS

JMR, AJI, and JN: study conception and design; and drafting of the manuscript. YT, JMR, and AJI: data analysis. All authors contributed to editing and reviewing of the draft and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Robot-assisted thoracoscopic surgery resection of a ground-glass nodule in the right middle lobe

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TO THE EDITOR:

Small peripheral lung tumors presenting with ground-glass opacity (GGO) components have recently become more common. Most of these lesions are early-stage adenocarcinomas and have a promising prognosis. Although minimally invasive surgery is commonly used in order to diagnose and treat these lesions, video-assisted thoracoscopic surgery and robot-assisted thoracoscopic surgery (RATS) resection of small or low-attenuation pulmonary nodules can be difficult because of the difficulty in locating or palpating them. Microcoils, hook wires, and liquid markers such as methylene blue and indocyanine green (ICG) are used in perioperative localization techniques.

Here, we discuss the case of a patient with stage I lung cancer presenting with an area of GGO in the middle lobe, corresponding to an adenocarcinoma. Using a robotic C-arm (Artis zeego; Siemens Healthineers, Erlangen, Germany) in a hybrid operating room and a robotic platform (da Vinci Si; Intuitive Surgical, Sunnyvale, CA, USA), we successfully performed single-stage, CT-guided localization and resection of the lung nodule.

A 77-year-old male patient with a history of two lung resections for lung cancer presented with a solitary pulmonary nodule. During the follow-up period, a pure GGO showing slow, progressive growth and measuring 24 mm was found in the middle lobe, raising a high suspicion of lung cancer. The patient was offered surgical treatment. The planned procedure was a middle lobe segmentectomy with perioperative localization of the nodule by CT-guided placement of a fiducial marker (a 3.7-mm VortX 18 coil; Boston Scientific, Marlborough, MA, USA) and ICG injection. The CT scans were acquired with the Artis zeego robotic C-arm (Siemens Healthineers). The Firefly® fluorescence imaging feature of the da Vinci Si robotic platform (Intuitive Surgical) was also used during the perioperative period, together with C-arm fluoroscopy.

An initial CT scan (6-s *syngo* DynaCT; Siemens Healthineers) was performed for surgical planning. The needle path was laid out with the *syngo* Needle Guidance software (Siemens Healthineers); a laser beam was used in order to project the estimated needle position. Subsequently, ventilation was stopped, and the lung was kept inflated. The fiducial marker was placed with a 19-gauge needle under fluoroscopy, which was followed by ICG injection with biological glue.

With the patient in the left lateral decubitus position, wedge resection was performed in the middle lobe. We used a 4-arm robotic platform and placed the robotic 8-mm ports in the usual position for lung resection. Because the patient had previously undergone surgery, there were many thick pleural adhesions, pulmonary decortication therefore being necessary. Because it was impossible to determine the needle entry point into the middle lobe, we used the Firefly® fluorescence imaging feature of the robotic platform in order to detect ICG in the nodule. Subsequently, the robotic C-arm was docked (Figure 1A), and fluoroscopy was used in order to localize the fiducial marker. An endoscopic stapler was positioned under radioscopic and near-infrared imaging to ensure adequate surgical margins (Figure 1B), and the nodule was resected. The specimen was removed, and the fiducial in the frozen section confirmed the presence of a neoplasm. The final pathological stage was lepidic pT1a adenocarcinoma.

A general correlation exists between GGOs seen on chest CT scans and microscopically lepidic growth patterns.[1,2] Surgical resection constitutes an excellent diagnostic and therapeutic option. However, pure GGOs can be difficult to localize intraoperatively because they are rarely visible in the visceral pleura and are mostly nonpalpable. Preoperative localization techniques are recommended in such cases, with dye injection, fluorescence imaging, and fiducial marker placement being the most commonly used techniques. They all have limitations, and the decision regarding the most appropriate method should be made in the context of a multidisciplinary discussion with the goal of achieving success.

ICG is a nontoxic dye that can be visualized under near-infrared fluorescence, even in deeper tissues. Although we were able to detect ICG fluorescence in the middle lobe, the presence of pleural adhesions and the need for decortication were complicating issues that were encountered in the case reported here and that have been reported elsewhere.[3] Because it is not always possible to determine the presence of pleural adhesions, alternative strategies must be available. Our goal was to perform complete hilar and mediastinal lymphadenectomy. On the basis of our previous experience with thick pleural adhesions and the difficulty in performing lymphadenectomy in this setting, we chose RATS over video-assisted thoracoscopic surgery.

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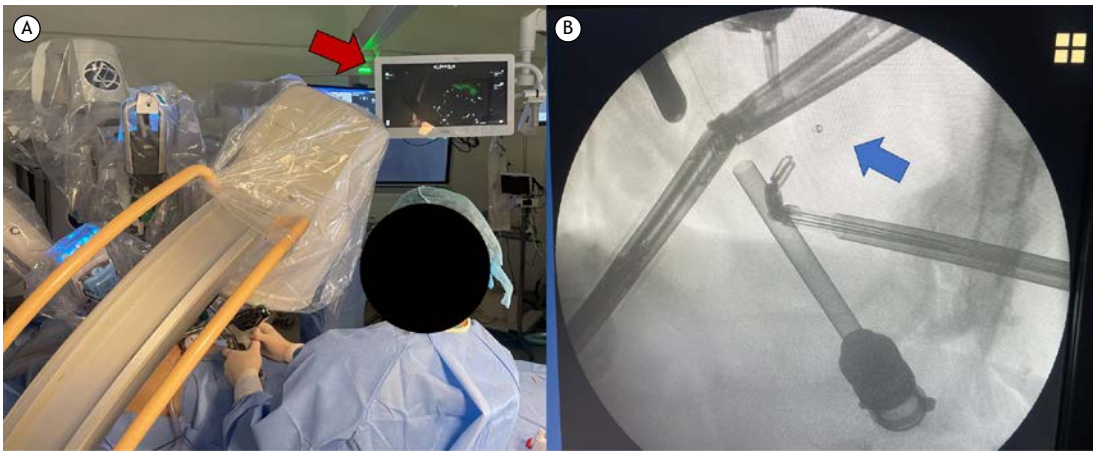

Figure 1. Intraoperative images showing the final position of the robotic arms, the robotic C-arm, and the bedside assistant. In A, photograph of the operating room layout, showing the robotic platform positioning the lung. Note indocyanine green fluorescence in the lung parenchyma (red arrow). Note also the bedside assistant placing an endoscopic stapler in the target area. In B, intraoperative radioscopy showing the position of the endoscopic stapler, with good surgical margins. Note the fiducial marker (blue arrow).

Because the robotic arms used for RATS occupy considerable space in the operative field, docking a C-arm to localize a fiducial can be troublesome, especially in the thoracic apex. However, in our case, because the nodule was in close proximity to the oblique fissure separating the lower lobe from the rest of the lung, the robotic C-arm was placed below the robotic ports without the need to undock the robotic system. This allowed us to manipulate the lung and position the lobe for endoscopic stapling. One difficulty that we encountered when performing the procedure was inserting the stapler through the assistant port. As can be seen in Figure 1, the robotic C-arm was in close proximity to the stapler, and we had to place it carefully to avoid collision. The use of a robotic stapler arm could be helpful in this setting.

This report shows that C-arm fluoroscopy and near-infrared fluorescence can be used for robotic lung surgery. However, a multidisciplinary approach is recommended to plan an appropriate strategy and evaluate feasibility.

AUTHOR CONTRIBUTIONS

All authors participated in the drafting and revision of the manuscript, as well as in the approval of the final version.

CONFLICTS OF INTEREST

None declared.

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Family perception of a telehealth program for people with cystic fibrosis during the COVID-19 pandemic in northeastern Brazil

Adriana V B Faiçal[1,2], Edna L Souza[2], Regina Terse-Ramos[2]

TO THE EDITOR:

Cystic fibrosis (CF) is a chronic disorder that requires follow-up in a specialized service involving a multidisciplinary team.[1] Despite advances in treatment, many challenges remain related to adherence and delivery of care in different localities.[2] In the face of the COVID-19 pandemic, normal care activities were suspended to comply with lockdown recommendations, and alternative ways were needed to adapt care plans.[3]

Telehealth has been particularly helpful where access to care is difficult because of the need to travel long distances to a referral center.[4] It has been associated with improvements in efficiency and equal or greater patient satisfaction than have face-to-face visits.[5] Although the results are positive, few studies have been conducted in low-income countries.[2]

Bahia is a state located in the northeast region of Brazil with large geographical dimensions, placing 4th in the Brazilian ranking of number of CF diagnoses.[6] The state has two referral centers, both located in the capital, Salvador. Most people travel for many hours to attend clinical appointments. Incorporating remote assessments allows data to be collected more frequently in a person's natural environment in addition to reducing the burden of the number of in-person visits.[4,5] Therefore, this study aimed to evaluate families' perceptions of a telehealth program for people with CF during the COVID-19 pandemic in northeastern Brazil.

Until then, telehealth had not been used routinely. As a strategy for coping with the health crisis, a remote care program was carried out for individuals with CF between September of 2020 and October of 2021 through a platform of the *Universidade Federal da Bahia*.

Participants were recruited from the CF referral center. If they agreed with the care provided by the model, appointments were scheduled. Exclusion criteria were as follows: individuals who had comorbidities that limited their participation in the study, as well as the existence of behavioral or intellectual difficulties that did not allow remote interaction. This project included telemonitoring, individual and group telerehabilitation, behavioral/emotional support, and health education. Videos, webinars, and booklets were freely available.

At the end of the 12 months of the study, participant satisfaction was assessed using an adapted questionnaire (Telehealth Satisfaction Scale),[7] using Google Forms. A similar questionnaire was validated for use in Brazil in 2022.[8] The institutional research ethics board approved the study (Protocol no. 4.237.807). All patients and/or guardians signed the free and informed consent form in addition to the assent form, when indicated.

This study enrolled 51 participants between two months and 21 years of age—median (IQR) = 76 (36-120) months—who were predominantly males (53%), and only 10 patients (20%) resided in the city of Salvador. In 70.6% of the sample, family income was up to three Brazilian national minimum wages, and 45% of guardians completed secondary education.

A total of 393 appointments were performed. There were two discontinuations, and pulmonary exacerbations occurred in 5 children (9.8%) during the study. Participants older than 14 years of age and parents/guardians of those under this age completed the questionnaire. The level of satisfaction with this model of care was high, and most participants rated as excellent the time and explanations provided by the CF team, as well as the privacy and convenience of telehealth; 51% of the participants rated the visual quality of the equipment, personal comfort, and ease of use of the telehealth system as excellent (Figure 1).

Considering the lack of in-person visits, 36.6% reported moderate concern about the lack of spirometry and throat/sputum cultures, while only 19.5% expressed a major concern about the lack of physical examinations. However, only 22% of participants had previous experience with remote care, and most stated that they would welcome the inclusion of telehealth in treatment routines.

This study reported on the experience of implementing remote care during COVID-19 in a referral center for people living with CF (PwCF) in Brazil. A high level of satisfaction with telehealth was observed. Given the critical timing of access to on-site services, most of the participants stated that they were not very concerned about absenteeism during routine. In addition, most indicated that they would like to receive some visits remotely.

Faced with the advent of novel therapies, particularly CFRT modulators, changes in the care model must address current challenges by adopting a proactive perspective. Previous studies reported that telehealth is feasible and acceptable to provide care for PwCF.[3,4,9]

Learned lessons in recent years have shown that the use of telehealth can continue in the post-pandemic period and reduce the burden on families. In addition, well-being and safety can be improved through a flexible telehealth model, and enhancing patient education and communication with the team of experts can be useful

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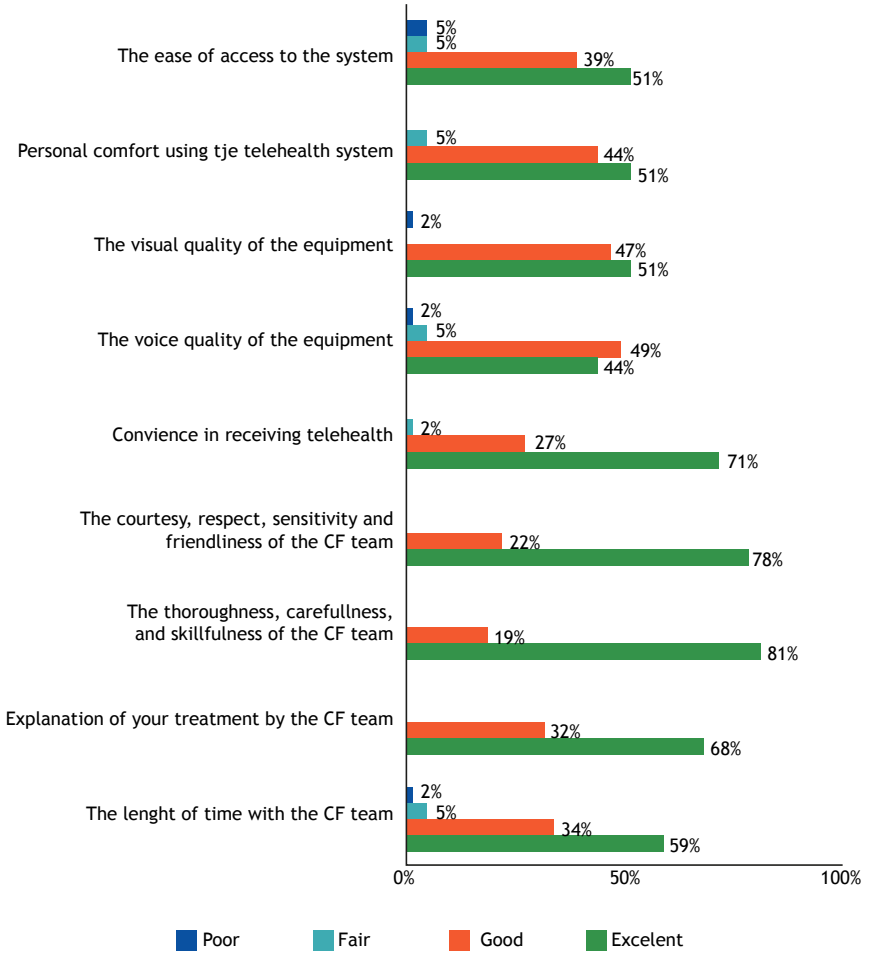

Figure 1. Responses to questions of the adapted questionnaire involving satisfaction with telehealth for people with cystic fibrosis followed at a referral center in Bahia, Brazil, 2020-2021.

to ensure the best clinical outcomes for PwCF and help address geographic disparities.[4,9]

Despite the huge benefits mentioned above, critical considerations must be made about telehealth for PwCF, as we cannot generalize the benefits to everyone. Individual needs as well as social and cultural contexts must be considered. Recognizing the potential of digital approaches and the opportunities to plan a hybrid care model can be crucial to ensure better outcomes.[9,10]

A limitation of this study was the small sample of individuals and the design used. However, considering the pandemic scenario, the authors developed a prompt response to overcome the imposed limitations. The strength of this study lies in the possibility of replicating it for other rare diseases.

In summary, a high level of satisfaction was found with telehealth, which played an important role in addressing the challenges associated with the COVID-19 pandemic. For the management of PwCF, digital approaches hold promise for the future. Their implementation can help improve quality of life, reduce costs, and expand support for people with chronic diseases.

This study highlights the possibilities of the use of affordable technological tools to provide care to the CF community, mainly in low-income countries where there is a scarcity of resources and limited access to referral centers. However, further research is needed to explore these outcomes and the standardization of technologies for clinical care.

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AUTHOR CONTRIBUTIONS

AVBF: study design; data collection and analysis; and drafting and reviewing the manuscript. ELS and RTR: study supervision and manuscript revision. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Pulmonary hypertension outcomes during the COVID-19 pandemic in Brazil

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TO THE EDITOR:

In March of 2020, COVID-19 was characterized by the WHO as a pandemic infection, and it has been considered an international public health emergency ever since. A few months after the start of the pandemic, Brazil was the country with the second highest number of confirmed COVID-19 cases worldwide. Risk factors for developing severe COVID-19, especially before vaccine availability, were advanced age and presence of comorbidities, such as cardiovascular and chronic pulmonary diseases.[1]

Pulmonary hypertension (PH) is a severe pathophysiological disorder, with pulmonary vascular involvement that can lead to right ventricular failure and death. Hospitalizations from any cause (i.e., PH-related or non-PH-related) are known to impact the outcomes of PH patients negatively.[2,3] However, conflicting data were made available on PH outcomes during the first year of the COVID-19 outbreak.[4,5] Subsequently, more robust studies showed a high COVID-19 mortality rate in PH patients.[6-9] Furthermore, in South America, there have been no reports on the impact of COVID-19 in PH patients so far. The purpose of the present study was to describe the estimated incidence rate and case-fatality rate of COVID-19 in PH patients followed at a PH referral center in Brazil.

All patients evaluated at the Pulmonary Hypertension Outpatient Clinic of the Federal University of São Paulo after the beginning of the pandemic (March of 2020), remotely or in person, were contacted between June and August of 2021 to identify those who had had COVID-19 confirmed by RT-PCR since the pandemic outbreak. Telephone contact was made at least three times on different days. All patients with a confirmed PH diagnosis were included in the present study and had their electronic medical records reviewed and their survival status assessed. The medical records of patients hospitalized at the *Hospital São Paulo* (the university hospital) were assessed, whereas self-reported information and hospital discharge summaries of patients hospitalized at affiliated hospitals were considered. Patients who had COVID-19 ($PH_{COVID\text{-}19(+)}$) were compared with patients who did not have COVID-19 ($PH_{COVID\text{-}19(-)}$). Comparisons between survivors and nonsurvivors were made using the chi-square test. Significance was set at $p < 0.05$. The research was approved by the university's ethics research committee (Protocol n. 38361220.3.0000.5505) and was conducted in accordance with the Declaration of Helsinki.

During the study period, 426 patients were evaluated, 272 of whom had a PH diagnosis (Panel 1A). PH patients had a mean age of 54 ± 17 years, and 71% were female. The most common PH etiologies were pulmonary arterial hypertension (PAH; 51.1%) and chronic thromboembolic PH (25.0%), 59.4% of whom were under double or triple combination therapy. Among the PH patients, 39 had had confirmed COVID-19; therefore, the estimated COVID-19 incidence rate was 14.3%. The overall COVID-19 incidence rate in the general Brazilian population during the same period was 9.7% (Panel 1B).[10]

The proportion of females in the $PH_{COVID\text{-}19(+)}$ group was higher when compared with the $PH_{COVID\text{-}19(-)}$ group (84.6% vs. 68.8%). No differences were found regarding age, PH etiology, and PH treatment between the groups (Panel 1C). Among $PH_{COVID\text{-}19(+)}$ patients, 41.0% had a New York Heart Association (NYHA) functional class III/IV and a cardiac index of 2.7 ± 0.7 L/min/m^2 in their most recent stratification assessment (Panel 1C).

In the $PH_{COVID\text{-}19(+)}$ group, hospitalization was required in 15 (38.5%) of the cases, and 44.4% were hospitalized at the university hospital. Approximately 50% (n = 8) of these hospital admissions were in the ICU, and 26% (n = 4) required mechanical ventilation. Complications during hospitalization were respiratory failure due viral pneumonia, in 6; right heart failure, in 4; and Guillain-Barré syndrome, thrombocytopenia with major bleeding, and anaphylaxis, in 1 each. Overall, there were 9 deaths: PAH, in 4; chronic thromboembolic PH, in 3; and multifactorial PH, in 2. No differences were found between survivors and nonsurvivors regarding age, sex, PH etiology, PH therapy, hemodynamics, comorbidities, and vaccination status. However, there was a high proportion of immunosuppressive therapy use and a tendency toward severe disease (NYHA III/IV), connective tissue disease, and obesity in nonsurvivors when compared with survivors (Panel 1C). All deaths were related either to acute COVID-19 or to PH decompensation after COVID-19. The case-fatality rate of COVID-19 in PH patients was 23.1% and that of PH alone (i.e., $PH_{COVID\text{-}19(-)}$) was 3.4% ($p < 0.0001$; Panel 1D). The overall case-fatality rate in the general Brazilian population during the same period was 2.7% (Panel 1D).[10]

To our knowledge, our study is the first describing the incidence rate and the case-fatality rate of COVID-19 among PH patients in South America. Our findings show that while the incidence rate of COVID-19 was similar between PH patients and the overall Brazilian population, the case-fatality rate was significantly higher among PH patients, indicating that PH patients infected with COVID-19 are significantly prone to worse outcomes in relation to patients without PH. With regard to account cardiovascular disease, the overall lethality rate was 2.3% in Wuhan, China, but there was an increase in mortality due to cardiovascular disease (10.5%), showing a high mortality risk in this population.[1] These findings are

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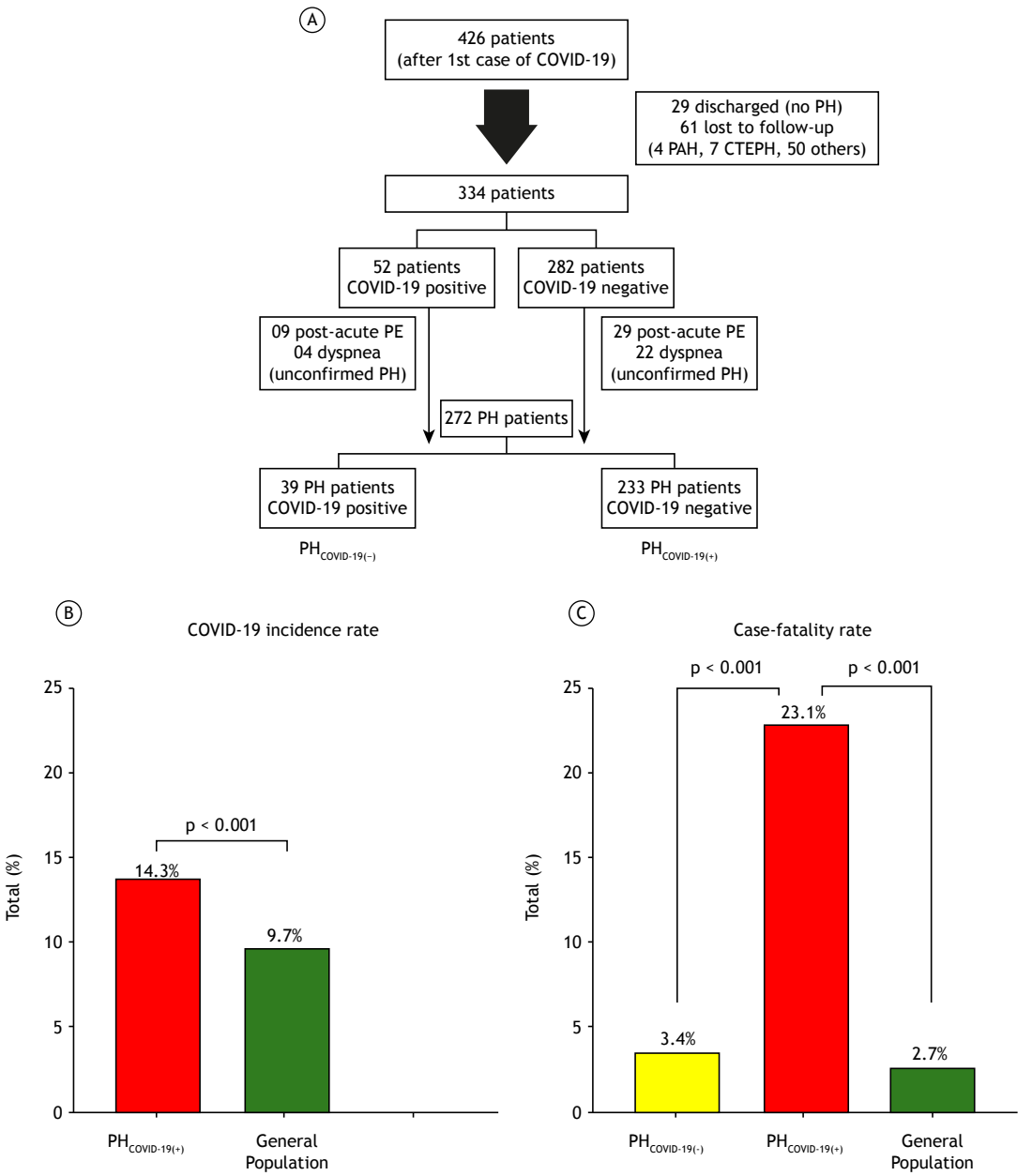
relevant especially for low- and middle-income countries and might help the care of PH patients, as new variants of COVID-19 still emerge in such geographical locations.

Our results indicate a high case-fatality rate of COVID-19 in PH patients, which is in line with previously published data from an international multicenter PH survey,[6] a U.S. single-center report,[7] the French PH registry,[8] and an Italian cohort.[9] In a recent cohort study in Italy, there were low incidence but high mortality rates due to COVID-19 in PAH patients.[9] In 2011, a study involving 205 patients with PAH showed that 16% of hospitalizations were due to infection and overall in-hospital mortality was 14%,[2] suggesting the increased mortality rate was due to COVID-19. It is of note that 67% of deaths among our patients with $PH_{COVID19(+)}$ were directly related to the acute phase of the infection. In the French cohort, the overall mortality was 24.6% and was associated with being male, being older, having comorbidities, and having more severe PH; nonetheless, no difference was found in relation to PH therapy.[8] Interestingly, this similar case-fatality rate was observed despite the fact that the availability of PH-specific drugs is lower in Brazil than in Europe and the USA. Besides that, $PH_{COVID-19(+)}$ patients presenting with connective tissue disease and receiving immunosuppressant therapy had lower survival rates, suggesting an additive effect in reducing cardiorespiratory function and in the number of COVID-19 complications, probably related to the lack of vaccination. At this writing, we have a decrease in the incidence of COVID-19 infection around the world; however, we still do not know the infection seasonality,



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Baseline characteristic	PH (n = 272)		p	PH + COVID-19 (n = 39)		p
	COVID-19 negative (n = 233)	COVID-19 positive (n = 39)		Survivors (n = 30)	Nonsurvivors (n = 9)	
Age, years	53 ± 16	53 ± 17	NS	51 ± 16	60 ± 20	NS
Female	159 (68.2)	33 (84.6)	0.039	25 (83.3)	8 (88.9)	NS
PH etiology						
PAH	119 (51.1)	20 (51.3)		16 (53.3)	4 (44.4)	
CTEPH	53 (22.7)	15 (38.5)	NS	12 (40.0)	3 (33.3)	NS
Inoperable/persistent	-	10 (66.7)		9 (75)	1 (33.3)	
Operable	-	5 (33.3		3 (25)	2 (66.7)	
Other PH	61 (26.2)	04 (10.3)		2 (6.7)	2 (22.2)	
PH therapy						
Monotherapy	51 (21.9)	07 (17.9)		05 (16.7)	2 (22.2)	
Double therapy	84 (36.1)	15 (38.5)	NS	11 (36.7)	4 (44.4)	NS
Triple therapy	20 (08.6)	04 (10.3)		03 (10.0)	1 (11.1)	
None	78 (33.5)	13 (33.3)		11 (36.7)	2 (22.2)	
Other treatment						
Immunosuppressant	-	10 (25.6)	-	4 (13.3)	6 (66.7)	0.001
Anticoagulant	-	18 (46.2)	-	13 (86.7)	5 (71.4)	NS
NYHA functional class	-					
I/II	-	23 (59.0)	-	20 (66.7)	3 (33.3)	0.075
III/IV	-	16 (41.0)	-	10 (33.3)	6 (66.7)	
Hemodynamic						
RAP, mmHg	-	10 ± 5	-	10 ± 5	9 ± 3	NS
mPAP, mmHg	-	49 ± 14	-	49 ± 15	45 ± 8	NS
PAOP, mmHg	-	11 ± 2	-	11 ± 2	10 ± 2	NS
IC, L/min/m^2	-	2.7 ± 0.7	-	2.7 ± 0.6	2.8 ± 0.8	NS
PVR, dyn.s.cm^{-5}	-	737 ± 417	-	722 ± 398	794 ± 525	NS
Comorbidities						
High blood pressure	-	13 (33.3)	-	11 (36.7)	2 (22.2)	NS
Connective tissue disease	-	12 (30.8)	-	7 (23.3)	5 (55.6)	0.066
Obesity	-	9 (23.1)	-	9 (31.0)	0 (0.0)	0.061
Liver disease	-	6 (15.4)	-	6 (20.0)	0 (0.0)	NS
Diabetes mellitus	-	6 (15.4)	-	5 (16.7)	1 (11.1)	NS
Coronary artery disease	-	4 (10.3)	-	4 (13.8)	0 (0.0)	NS
Chronic kidney disease	-	2 (5.1)	-	1 (3.3)	1 (11.1)	NS
≥ 2 comorbidities	-	12 (30.8)	-	10 (33.3)	2 (22.2)	NS
Vaccine before COVID-19 infection	-	9 (23.1)	-	8 (26.7)	1 (11.1)	NS

Values expressed as n (%) or mean ± SD.

Panel 1. In A, flow chart of patient selection process. COVID-19 incidence (In B) and case-fatality (in D) rates among the patients with pulmonary hypertension studied in comparison with the Brazilian general population. In C, table showing the characteristics of the patients with pulmonary hypertension studied with and without COVID-19. FUP: follow-up; PE: pulmonary embolism; PH: pulmonary hypertension; $PH_{COVID19(+)}$: patients with PH who had previous COVID-19; $PH_{COVID19(-)}$: patients with PH who did not have previous COVID-19; NS: not significant; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; NYHA: New York Heart Association; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PAOP: pulmonary artery occlusion pressure; CI: cardiac index; PVR: pulmonary vascular resistance;

the real long-term effectiveness of current vaccines, and the possibility of new more virulent emergent variants.

This study has some limitations. This was a single-center, observational retrospective study based on electronic medical records and patient-reported outcomes; therefore, our results may not apply to all PH patients. The study relied on the confirmation of COVID-19 by RT-PCR, which was available only for severe and hospitalized cases in Brazil during most of the study period; for that reason, the incidence rate of COVID-19 among PH patients might have been underestimated. For inpatients from affiliated hospitals, some details about hospitalization were missed because of self-reported information. Finally, this survey was conducted prior to the full vaccination of most of the patients studied. Hence, we were unable to evaluate the protective effect of full vaccination on the outcomes.

In summary, our report highlights the negative impact of COVID-19 on the outcomes of PH patients. Although the COVID-19 incidence rate was similar to that in the Brazilian general population, the case-fatality rate was higher in our patients. These findings are particularly relevant for low- and middle-income countries and could help with the care of PH patients,

as new COVID-19 variants continue to appear in these geographical locations.

AUTHOR CONTRIBUTIONS

All authors contributed to study conceptualization, as well as to the writing, reviewing, and editing of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Lady Windermere syndrome

David Silva Gomes[1], João Cravo[1]

During an outpatient consultation, a 66-year-old woman, 46 kg, and diagnosed with bronchiectasis 8 years prior reported having had cough with little expectoration and fatigue for several years, as well as night sweats in the past 2 years. In the previous year, she was treated for pneumonia with clinical improvement. Nevertheless, months later, she had night sweats again and worsening of fatigue. A chest CT revealed worsened nodular bronchiectasis with surrounding parenchymal densification in the middle lobe and lingula (Figure 1). A scheduled bronchoscopy was performed. Mycobacterial PCR assay was positive on bronchoalveolar lavage fluid for nontuberculous mycobacteria, and the culture revealed macrolide-susceptible *Mycobacterium intracellulare*. The patient received a daily regimen of azithromycin, rifampin, and ethambutol for 14 months with substantial improvement.

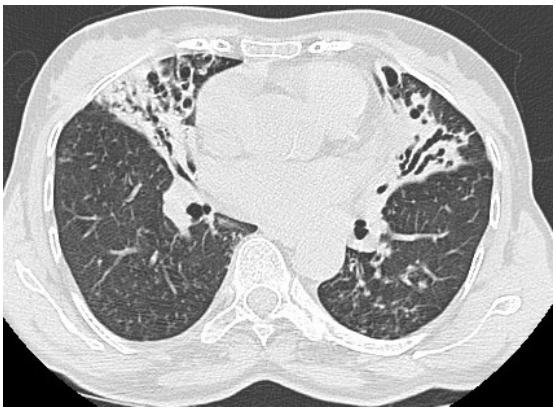

Figure 1. An axial chest CT scan showing nodular bronchiectasis with surrounding parenchymal densification in the middle lobe and lingula.

Lady Windermere syndrome is rare, corresponding to a pattern of pulmonary infection with *M. avium* complex, and is a cause of bronchiectasis.[1] Due to its insidious course, with nonspecific symptoms, it is probably underdiagnosed.[2] Although voluntary suppression of cough has been described as one possible pathogenesis of Lady Windermere syndrome,[1] this was not identified in our patient.

Bronchiectasis, especially in the middle lobe and lingula, in elderly White immunocompetent women should always prompt investigation for nontuberculous mycobacterial infection.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

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None declared.

CONFLICTS OF INTEREST

None declared.

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Unveiling the great mimicker: a rare case of sarcoidosis

Mariana Argel[1], Carla António[1], Jorge Vale[1]

Sarcoidosis is a multisystem granulomatous disease with a wide range of clinical and radiographic manifestations.[1] Cavitation is rare in sarcoidosis.[2]

A 27-year-old man from Ukraine presented to the emergency department with hemoptysis. A CT scan showed extensive thin-walled cavities and multiple enlarged mediastinal and hilar lymph nodes (Figure 1A-C). The patient had been evaluated two years earlier, and a chest CT scan performed at that time revealed a diffuse perilymphatic micronodular pattern (Figure 1D). However, he was lost to follow-up.

Laboratory test results showed elevated serum levels of angiotensin-converting enzyme and normal serum levels of *Aspergillus*-specific IgG. Analysis of BAL fluid revealed lymphocytic alveolitis (lymphocytes: 36%; CD4/CD8 ratio, 5.2), being negative for malignant cells and microbiology (including mycobacteria and fungi). No CD1a-positive cells were identified. A PET scan showed increased uptake in the mediastinal, hilar, and right supraclavicular lymph nodes, as well as in the spleen and lung cavity walls. An excisional biopsy of the right supraclavicular lymph node revealed noncaseating granulomas with giant cells and Schaumann bodies (Figure 1E).

After a multidisciplinary team discussion, a diagnosis of stage IV sarcoidosis was established. The patient was started on corticosteroids and methotrexate, with clinical and functional improvement.

AUTHOR CONTRIBUTIONS

MA: conceptualization; investigation; and drafting, reviewing, and editing of the manuscript. CA and JV: investigation; and reviewing and editing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

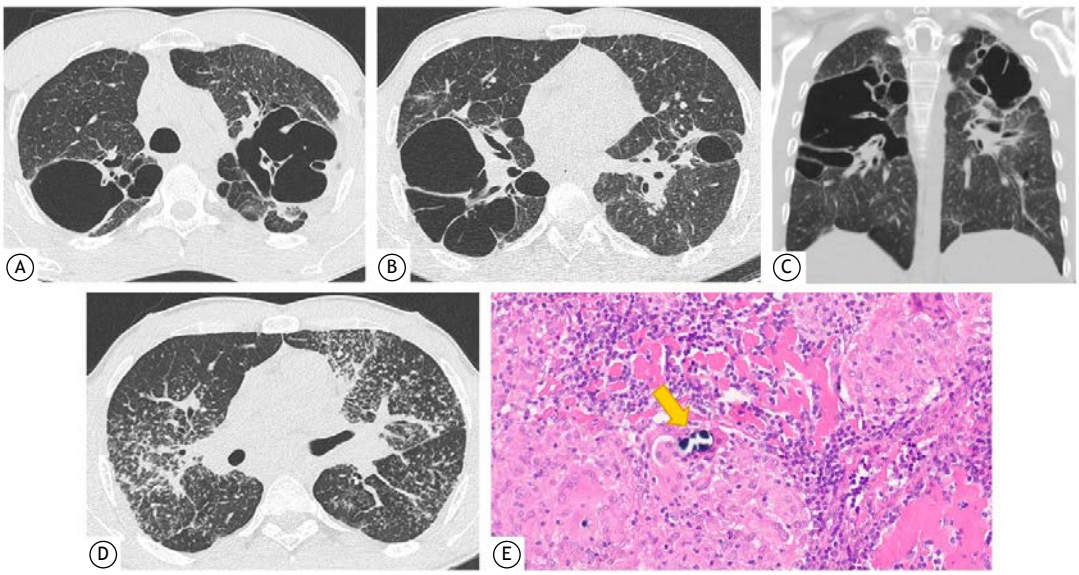

Figure 1. In A, B, and C, chest CT scans showing extensive, irregular, thin-walled cavities bilaterally, predominantly in the upper lobes and perihilar region, reaching 9 cm in diameter and associated with architectural distortion of the lung parenchyma. In D, chest CT scan performed two years earlier, showing extensive perilymphatic and subpleural micronodules associated with areas of densification of the lung parenchyma in the perihilar region, forming fibrotic masses/clusters. In E, photomicrograph (H&E; magnification, ×200) showing a giant cell with intracytoplasmic Schaumann body (yellow arrow).

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References: References should be listed in order of their appearance in the text and should be numbered consecutively with Arabic numerals. The presentation should follow the Vancouver style, updated in October of 2004, according to the examples below. The titles of the journals listed should be abbreviated according to the style presented by the List of Journals Indexed in the Index Medicus of the National Library of Medicine, available at: http://www.ncbi.nlm.nih.gov/entrez/journals/loftext.noprov.html. A total of six authors may be listed. For works with more than six authors, list the first six, followed by 'et al.'

Examples: Journal Articles

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

Abstracts

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

Chapter in a Book

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

Official Publications

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

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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/

Other situations:

In other situations not mentioned in these author instructions, authors should follow the recommendations given by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2004. Available at http://www.icmje.org/.

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CONHEÇA O NOVO APLICATIVO DA BAYER!

O aplicativo **Risco na HP** facilita a utilização das estratégias para estratificação de risco do seu paciente, de acordo com as diretrizes do **Registro Francês**[1, 2], **Registro COMPERA**[3,4], **REVEAL 2.0 e REVEAL Lite 2**

O aplicativo Risco na HP está disponível para download gratuito nas principais lojas de aplicativo.

Baixar na App Store

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O aplicativo Risco na HP foi desenvolvido com base em publicações científicas1-6 para realizar uma estimativa na estratificação de risco da Hipertensão Pulmonar.

A responsabilidade pela determinação da conduta terapêutica para cada paciente é do médico e sua equipe. O aplicativo apenas facilita a utilização das estratégias de avaliação de risco. As informações apresentadas pelo aplicativo não devem ser utilizadas isoladamente.

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.

PP-VEN-BR-0037-1 | Fevereiro 2022

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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