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HIGHLIGHT

Hospitalizations for pulmonary embolism in Brazil

Post-COVID-19 sleep disorders

Transbronchial biopsy findings in patients with long COVID-19

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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Office: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 08000 616218. Website: www.sbpt.org.br. E-mail: sbpt@sbpt.org.br

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Celebrating World Asthma Day in Brazil: lessons learned from the pandemic. Can we do better?

Marcia Margaret Menezes Pizzichini[1], Regina Maria de Carvalho-Pinto[2], Emilio Pizzichini[1]

To celebrate World Asthma Day this year (May 3rd), the Global Initiative for Asthma (GINA)[1] has chosen "closing gaps in asthma care" as the theme for the Day. Of the 10 gaps listed, we have chosen to highlight "equal access to diagnosis and treatment of asthma."[1] In Brazil, a country with continental dimensions, the main challenge is to develop initiatives that allow easy and equitable access to asthma treatment, given the immense socioeconomic differences and disparities in local health care systems.

Three years have passed since the last JBP publication on the World Asthma Day (2019). In that editorial,[2] the authors described the asthma scenario in Brazil, questioning whether the advances in asthma management, achieved at that time, would allow us to state that the asthma "glass" was half full or half empty. The conclusion was that there were reasons to believe in both points of view, but effort and work were necessary to fill the glass.

On May 11, 2020, the WHO declared that COVID-19, a global, highly communicable, and potentially lethal disease, was pandemic, and that triggered extraordinary changes in lifestyle, economy, and beliefs about health and health care worldwide. In the present editorial we discuss the influence of COVID-19 on asthma care, the improvement in the asthma scenario in Brazil, even in times of COVID-19, and the prospects for refining asthma management.

Initial studies described that respiratory comorbidities, including asthma, were predictors of more severe outcomes and mortality for COVID-19 patients. The broadcasting of this information increased the awareness of the population and the medical community about the relevance of asthma and its appropriate treatment. In this regard, national societies, such as the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT) and the *Associação Brasileira de Alergia e Imunologia*, international societies, and the GINA quickly changed their priorities and issued educational notes emphasizing three major points: (1) adherence to control treatment in combination with a self-management action plan in cases of worsening of symptoms; (2) avoidance of nebulizer use because of the potential to spread COVID-19; and (3) adoption of preventive measures against the disease, such as the use of masks, hand hygiene, and social distancing.

Subsequent studies were unable to prove that asthma was a risk factor for COVID-19,[3,4] a paradox when compared with other respiratory viruses to which asthma patients are known to be susceptible. Asthma exacerbations caused by viral infections are common events and result in a seasonal increase in ER visits and hospitalizations.[5] However, the relationship between COVID-19 and asthma is still debatable.

What have the latest publications on COVID-19 and asthma shown? Adults and children with controlled asthma are not at an increased risk of hospitalization or death from COVID-19.[6] It remains unclear whether asthma is a protective factor for COVID-19 or it is an independent protective factor against mortality for patients with COVID-19.[4,6] Possible explanations for these findings include lockdowns and/or better asthma management.

In this regard, we highlight two recent population-based studies carried out in the United Kingdom. In a cohort of 100,165 asthma patients with at least one exacerbation within the last five years, Shah et al.[7] showed a substantial reduction in the rates of severe exacerbations reported in primary health care. Nevertheless, there was no significant reduction in the number of exacerbations requiring hospital care and/or hospitalization or in the number of asthma-related deaths. Additionally, Davies et al.[8] reported a 36% decrease in asthma-related ER admissions after lockdown. More importantly, in the week before the lockdown, there was a 127% increase in the number of inhaled and oral corticosteroid prescriptions for asthma patients when that was compared with the mean number of those prescriptions in the previous five years. After the lockdown, there was the biggest reduction in the number of severe asthma exacerbations ever recorded in the United Kingdom, which might partially have been the result of improved asthma management. Similar reductions in the rate of asthma-related hospitalizations were observed in Brazil during the first peak of COVID-19.[9]

Even in times of a pandemic, it is undeniable that there have been great advances in the asthma scenario in Brazil, thanks to the work of pulmonologists and pediatric pulmonologists from the SBPT and its Asthma Committee. In this sense, the 2020 SBPT Asthma Management Recommendations[10] were published, with updates on asthma treatment, adapting international guidelines to the Brazilian reality. The document emphasizes the need for a personalized approach, including pharmacological treatment, patient education, a written action plan, training in inhalation device use, and inhalation technique review at each visit. In the following year, the 2021 Brazilian Thoracic Association Recommendations for the Management of Severe Asthma[11] were published,

1. Programa de Pós-Graduação em Ciências Médicas, Universidade Federal de Santa Catarina – UFSC – Florianópolis (SC) Brasil.
2. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

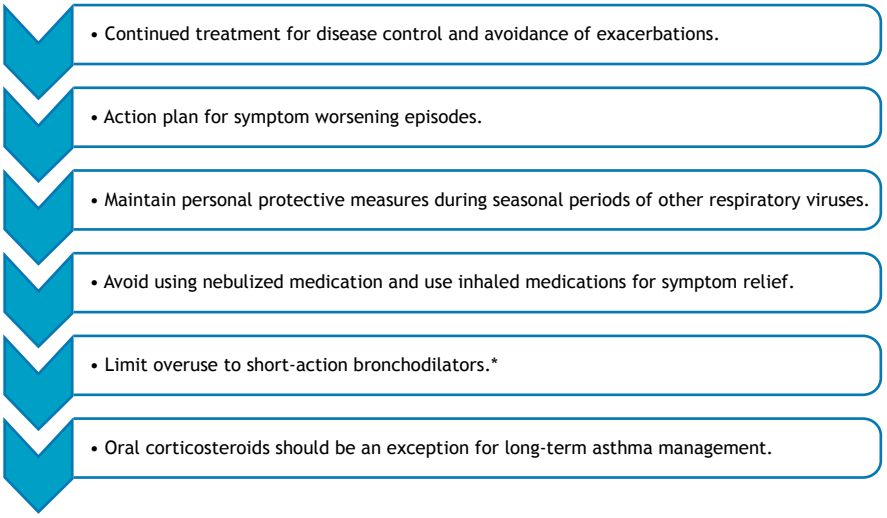

Figure1. Lessons from the COVID-19 pandemic that can guide the way forward.

highlighting that severe asthma is uncommon and requires correct diagnosis, phenotyping based on easily accessible biomarkers, personalized pharmacological and nonpharmacological treatment, and the criteria for evaluation response to monoclonal biologics.

Another important advance in the field of asthma was the update of the Brazilian Ministry of Health *Protocolo Clínico e Diretrizes Terapêuticas* (Clinical Protocol and Therapeutic Guidelines), published in 2021, which updates the strategies of asthma treatment and incorporates two monoclonal biologics (omalizumab and mepolizumab) for the treatment of severe asthma in the *Sistema Único de Saúde* (SUS, Brazilian Unified Health System). In the wake of these advances, omalizumab, mepolizumab, benralizumab, and dupilumab were also approved for use by the *Agência Nacional da Saúde Suplementar* (ANS, Brazilian National Health Insurance Agency). The incorporation of monoclonal biologics by the SUS and ANS enabled the access of these drugs to severe asthma patients, but this did not guarantee equity of treatment.

We recognize that some gaps were not filled in during the public consultations of the *Comissão Nacional de Incorporação de Tecnologias do SUS* (Brazilian National Commission for the Incorporation of Technologies in SUS), since the provision of other control medications. For example, an inhaled corticoid associated with a long-acting β_2 agonist bronchodilator via a metered-dose inhaler is a treatment option for some pediatric and adult patients with mild-to-moderate asthma. This association together with a long-acting antimuscarinic bronchodilator (tiotropium bromide) is a treatment option for preceding the use of monoclonal biologics, at least for some severe asthma patients, increasing access to treatment and/or reducing costs.

In summary, we acknowledge that asthma remains a public health problem in our country, but we have undoubtedly made significant progress. Although any death from asthma is unacceptable, its frequency has gradually been decreasing in Brazil.[12] In contrast, asthma morbidity is still troublesome and points to the need for directing our efforts toward other outcomes, such as asthma control, patients' quality of life, and accessibility to pharmacological and nonpharmacological treatments. In our viewpoint, it is necessary to improve patient-tailored therapeutic options in order to fill in the gaps, so that the patient's quality of life is similar to that of a patient without asthma. In this regard, lessons from the pandemic can guide the way forward (Figure 1). If we go on this path, we can assume that the medium-term results may result in satisfaction for patients and health care providers.

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Severe asthma phenotyping: does the definition of different phenotypes matter?

Marcia Margaret Menezes Pizzichini[1], José Eduardo Delfini Cançado[2]

Phenotyping severe asthma is a key component of asthma management, not only because of its pathobiological complexity and clinical heterogeneity, but also because of high costs of biologic treatment. Although severe asthma is uncommon, with an estimated prevalence between < 1%[1] and 3.7%[2] among all asthma patients, it is responsible for a major part of the disease burden. In Brazil, it has been shown that severe asthma is accountable for very high costs to families and to the Brazilian Unified Health Care System. [3]

The recently published Brazilian Thoracic Association "Recommendations for the Management of Severe Asthma"[4] adopted the 2014 International European Respiratory Society/American Thoracic Society definition of severe asthma.[5] Accordingly, severe asthma is defined as that confirmed by an objective method, with good patient adherence to treatment, and which, despite the elimination or minimization of factors associated with lack of disease control, requires high doses of inhaled corticosteroids (fluticasone propionate ≥ 1,000 µg or equivalent) associated with a second controller drug (a long-acting β_2 agonist and/or a long-acting muscarinic antagonists and/or an antileukotriene) or oral corticosteroids ≥ 50% of the days in the previous year in order to try to maintain disease control. The Global Initiative for Asthma (GINA)[6] defines severe asthma in a similar way, except for the dose of inhaled corticosteroids (fluticasone propionate > 500 µg or equivalent). The adoption of one of the definitions is relevant because the GINA's definition includes patients regarded by others as having moderate asthma.

In this issue of the *Jornal Brasileiro de Pneumologia*, Athanazio et al.[7] report the results of large (n = 385) cross-sectional multicenter study (designated the BRAEOS study) on phenotyping severe asthma. The authors used both prospective (blood sample and questionnaires of asthma control and quality of life) and retrospective data. The primary outcome was the prevalence of eosinophilic and allergic phenotypes. Inclusion criteria were having severe asthma as defined by the GINA for at least one year. Patients were excluded if they were current/former smokers (≥ 10 pack-years), had had a moderate/severe asthma exacerbation or any changes in their treatment within the past four weeks. Other exclusion criteria were treatment with biologics within the last three months (except omalizumab) and the presence of other lung diseases. Eosinophilic phenotype was defined by the presence of blood eosinophils ≥ 300 cells/mm^3. Allergic phenotype was defined as a combination of serum IgE > 100 UI/mL and history of allergy (clinically documented by history of respiratory allergy or atopy (positive specific IgE or skin prick test for aeroallergens). Late-onset asthma was defined as the onset of asthma symptoms by the age of ≥12 years. Point prevalence of eosinophilic asthma (primary outcome) was 40.0%. Additionally, 73.2% of the subjects had atopy (history of allergy confirmed by specific IgE or skin prick test).

We congratulate the authors of the BRAEOS study [7] for producing relevant data and providing insights on severe asthma across Brazil. But, has this large study provided us with definitive answers on the prevalence of severe eosinophilic asthma? One question that arises at first is the definition of severe asthma used in the study. It could be argued that a cutoff point > 500 µg/day of fluticasone propionate might have allowed the inclusion of less severe asthma patients in the study population and, therefore, had an influence on the data. However, the results of the study by Athanazio et al.[7] showed that most subjects were on higher doses of inhaled corticosteroids, and this is reassuring.

How about the definition of eosinophilic phenotype? It is undisputable that induced sputum cell count is the gold standard method to phenotype eosinophilic asthma. Yet, because it is perceived as a difficult method to perform, induced sputum is available only in a few asthma research centers. Currently, severe asthma phenotypes are based on the ease of accessible biomarkers aiming at introducing biologic treatment. In this regard, peripheral blood eosinophil count is an asset. The cutoff point for the eosinophilic phenotype, nonetheless, varies according to the biologic drug under study. In the BRAEOS study,[7] the authors chose the cutoff point of > 300 eosinophils/mm^3 to define eosinophilic asthma, which occurred in 40% of subjects. However, the eosinophilic phenotype raised to 70% when the cutoff point > 150 eosinophils/mm^3 was tested. These results illustrate the lack of agreement on what the eosinophilic phenotype is when measured by peripheral blood cell counts.

Having said that, could the BRAEOS study [7] underestimate the prevalence of eosinophilic asthma in our country for other reasons? Possibly. It is well known that peripheral blood eosinophil count suffers the influence of various factors, including the dose of inhaled and oral corticosteroids, diurnal variation, recent respiratory or systemic infections, etc. Therefore, a single blood cell count does not exclude blood eosinophilia. Hence, the Brazilian Thoracic Society[4] and the GINA[6] recommendations suggest that the exclusion of eosinophilic phenotype requires up to three blood eosinophil counts on different occasions. If necessary, corticosteroid treatment should be carefully tapered down to allow blood eosinophils to

1 Programa de Pós-Graduação em Ciências Médicas, Universidade Federal de Santa Catarina – UFSC – Florianópolis (SC) Brasil.
2 Faculdade de Ciências Médicas, Santa Casa de Misericórdia de São Paulo, São Paulo (SP) Brasil.

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resurface. Although the BRAEOS study [7] excluded patients with a recent history of respiratory infection, the study used a single measurement of blood eosinophils. This might also explain the low prevalence of the eosinophilic phenotype reported.

Another key finding from the BRAEOS study,[7] in keeping with current knowledge was that most of the subjects had atopy. Surprisingly, only 31.9% of those with a history of allergy had blood eosinophilia. This paradox is rather unsettling and it is not supported by the current knowledge of allergic asthma pathophysiology, a T2-high disease driven by IgE, IL-4, IL-5, eosinophils, basophils and mast cells.[8] Thus, biological plausibility suggests that allergic asthma is an eosinophilic disease, which makes us question again the low prevalence of the eosinophilic phenotype reported in the BRAEOS study.[7]

Finally, in the BRAEOS study,[7] nearly half of the subjects had late-onset asthma, defined as the onset of asthma symptoms in subjects ≥ 12 years of age. Although the cutoff point to define late-onset asthma is far from settled, varying from 12 to 65 years of age in different studies,[9] we argue that individuals who are 12 years old are children. Perhaps a better way to tackle this issue is to adopt a more rational classification of late-onset asthma by the cutoff points proposed in a recent multi-database cohort study.[10] In that study, Baan et al.[10] based the characterization of asthma on the age of the first diagnosis of the disease as documented by the treating physician on a database, classifying the participants as having either childhood-onset asthma (asthma diagnosis before 18 years of age), adult-onset asthma (asthma diagnosis between 18 and 40 years of age) or late-onset asthma (asthma diagnosis ≥ 40 years of age).

In conclusion, regardless of the points raised herein, the BRAEOS study[7] is the first to evaluate the phenotype of a large group of subjects with severe asthma in Brazil. The study shows the challenges of phenotyping severe asthma with the current definitions of a complex, uncommon, and heterogeneous subgroup of the asthma. Similar large-scale studies, with detailed longitudinal information on asthma phenotypes and repeated blood eosinophil measurements, would be ideal to build further evidence in Brazil. As the authors have pointed out, understanding the inflammatory profile of our patients with severe asthma is essential for specific target treatment and development of local public health policy strategies.

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What remains in the pulmonary tissue after acute COVID-19?

Amaro Nunes Duarte-Neto[1], Marisa Dolhnikoff[1]

What remains after the devastation of the critical phase of the COVID-19 pandemic, experienced in 2020-2021? After two years of the pandemic, health systems worldwide are facing problems that go beyond those faced at the beginning of the pandemic, such as diagnosis, case definition, appropriate treatment, and control of the spread of SARS-CoV-2. Some of the major questions at this point are which patients will not fully recover from the acute phase of the disease and what mechanisms are involved in the different outcomes. We now know that patients with COVID-19 of various clinical profiles can progress with Long COVID, a clinical condition with persistent systemic symptoms that can last for months or even years after the acute disease.[1] Given the large number of COVID-19 cases worldwide, long-term sequelae can lead to a large contingent of individuals with disabilities, who will require follow-up by specialists of different areas.

Although Long COVID still lacks standardization in its definition and nomenclature,[2,3] it is clear that it can affect different organs and systems; due to the high prevalence and severity of pulmonary involvement in the acute phase of COVID-19, chronic pulmonary involvement in Long COVID is one of the main concerns. Clinical and radiological studies show that the persistence of pulmonary symptoms, alterations in pulmonary function, and tomographic signs of pulmonary alterations months after the disease can affect between 24% and 50% (or even more) of hospitalized patients with COVID-19.[4,5] Clinical and epidemiological studies have determined the risk of developing lung fibrosis after disease onset.[5,6] Elderly patients with comorbidities (especially systemic arterial hypertension, obesity, and diabetes mellitus), previous lung disease, fever during the acute phase of the disease, prolonged viral clearance, prolonged hospitalization, prolonged mechanical ventilation, and extensive pulmonary involvement on HRCT scans in the acute phase are at a greater risk of developing pulmonary fibrosis and functional impairment after COVID-19.[5,6]

Histopathological changes in COVID-19 patients with persistent lung disease have been reported in few studies, most of them describing lung pathology in samples obtained from autopsy or lung explants from patients with severe acute illness and prolonged hospitalization. The main pulmonary alterations described in individuals with disease duration greater than 30 days include diffuse interstitial fibrosis, microscopic honeycomb change, bronchiolectasis, lymphocytic and macrophagic interstitial and intra-alveolar inflammation, interstitial capillary neoangiogenesis, recanalized thrombi involving small pulmonary arteries, and pulmonary infarction.[7-12] The fibrotic pattern of diffuse alveolar damage that characterizes severe disease is more prominent three weeks after disease onset.[8,12,13] The pathogenesis of those alterations is probably multifactorial, involving viral lesions in the acute phase, secondary pulmonary infections, and mechanical ventilation-associated injury.[7] Single-cell RNA sequencing of lung tissue from patients with late-stage COVID-19 shows similarity with lung tissue from patients with pulmonary fibrosis due to other conditions, with increased expression of extracellular matrix production genes.[14]

However, autopsy and explant studies cannot predict how much of the pulmonary changes are likely to resolve over time in patients who survive acute COVID-19 with varying degrees of severity. To date, studies on lung pathology involving COVID-19 survivors are lacking. In this sense, in this issue of the *Jornal Brasileiro de Pneumologia*, the welcome study by Baldi et al.[15] analyzed 6 post-COVID-19 patients and described the post-acute phase follow-up for at least a four-month period. Only one patient was mechanically ventilated during the acute phase. Although all six patients recovered at the end of follow-up, they presented with persistent respiratory symptoms and interstitial lung abnormalities on HRCT scans within at least four months after discharge. Transbronchial biopsies showed mild alterations present in all of the patients, mainly characterized by peribronchial remodeling with extracellular matrix deposition and focal alveolar septal thickening. Vascular changes such as thrombosis, vasculitis, and infarctions were not observed. The study[15] gains importance as one of the first studies to evaluate transbronchial biopsies of patients with COVID-19 with a follow-up period of several months. The limitations of the study have already been pointed out by the authors: small number of patients and limited amount of tissue for analysis, as transbronchial biopsy does not assess the peripheral lung tissue where most of the tomographic changes are located.[15] Ravaglia et al.[16] have recently described the morphological and immunomolecular features of transbronchial lung cryobiopsies performed in 10 patients with persistent lung disease after recovery for at least 30 days from COVID-19-related pneumonia. None of the patients had been mechanically ventilated, and all had persistent lung involvement on HRCT scans and persistent respiratory and/or systemic symptoms. Histological evaluation revealed three different "case clusters" characterized by specific clinical and radiological features. Cluster one ("chronic fibrosing") was characterized by post-infection progression of pre-existing interstitial pneumonias; cluster two ("acute/subacute injury") was characterized

1. Departamento de Patologia, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

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by different types and grades of lung injury ranging from organizing pneumonia and fibrosing nonspecific interstitial pneumonia to diffuse alveolar damage; and cluster three ("vascular changes") showed diffuse vascular increase, vascular dilatation, and distortion of capillaries and venules within otherwise normal parenchyma. The study was also limited by its small sample size and short time frame.[16] Konopka et al.[11] reviewed surgical lung biopsies from 18 patients with evidence of persistent interstitial lung disease between 2 and 12 months after the acute phase of COVID-19. Usual interstitial pneumonia was the most common histological pattern in those patients, possibly corresponding to diffuse fibrotic lung disease that preceded SARS-CoV-2 infection.

It is expected that new morphological studies characterizing Long COVID will soon emerge. Further studies are needed for a better understanding of the pathology and pathogenesis of post-COVID disease. Cryobiopsies can reduce sample size limitations, with the possibility of a better analysis of the main pulmonary compartments (airways and alveolar tissue) without increasing the risk of the transbronchial biopsy procedure. The evaluation of a larger number of cases with different profiles of the broad spectrum of the disease in the acute (mild, moderate, and severe disease) or late phase (persistence of clinical, functional, and tomographic impairment), matched to baseline characteristics (age, sex, BMI, and comorbidities), duration of illness, need of mechanical ventilation, and use of corticosteroids, will help us understand the different patterns of chronic lung involvement, the inflammatory elements and pathways involved, and the prevalence and distribution of irreversible lung changes in patients with pulmonary Long COVID. Hopefully, these morphological studies will give us insights into pathogenic mechanisms and provide knowledge that can impact treatment and prevention of chronic pulmonary changes in COVID-19.

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The impact of COVID-19 on sleep and circadian rhythm

Ozeas Lins-Filho[1], Rodrigo P Pedrosa[1]

The circadian rest-activity pattern is the biological rhythm of approximately 24 h, which corresponds to cyclical variations in behavior, physiology, and sleep-wake cycle, resulting from an intrinsic temporal control system. The stability of this biological rhythm reflects the optimal organic functionality and health; however, the desynchronization between the circadian system and the necessary hours of sleep can cause disturbances in this system and, consequently, sleep disorders. There are ways to assess the sleep-wake cycle, including the use of subjective and objective measures, such as sleep diaries and actigraphy. Moreover, nocturnal polysomnography is also used for objective assessment of sleep and various physiological parameters, being the best option for a complete evaluation of sleep parameters; despite this, polysomnography is used in the suspicion of sleep disorders.[1] Thus, the use of polysomnography has limitations for the assessment of those who have an impaired sleep-wake cycle.

Given the scenario that the entire world has found itself in since 2020, the relationship between SARS-CoV-2 infection and its negative impacts on sleep and circadian rhythm has been investigated. In the present issue of the *Jornal Brasileiro de Pneumologia*, Henríquez-Beltrán et al.[2] used as a measurement strategy actigraphy and nocturnal home polysomnography, respectively, as a measurement strategy to assess the circadian cycle and sleep disorders in patients who had COVID-19 between April and July of 2020. Evaluations occurred four months after the acute phase of COVID-19.

It has been reported that, during the acute phase of the infection, regardless of the symptoms or the need for hospitalization, COVID-19 promotes detrimental changes in sleep,[3] and that this scenario persists even six months after the acute phase, resulting in sequelae. In general, 63% of the patients experienced fatigue or muscle weakness, and 23% had sleep difficulties.[4]

Investigations on the influence of COVID-19 and the circadian rest-activity pattern are scarce, although the pandemic scenario has been related to the impairment of this pattern and elevated levels of symptoms of depression, anxiety, and stress during the lockdown period. Henríquez-Beltrán et al.[2] reported that patients with moderately severe COVID-19 had a higher prevalence of difficulty of falling asleep, staying asleep, and waking up early, whereas patients with more severe disease experienced difficulty staying asleep and waking up early.

Such outcomes are important to elucidate the association between the severity of COVID-19 and the sleep-wake cycle since the aforementioned variables reflect the behavior of the circadian cycle. In addition, a previous study observed that, three months after hospital discharge, 60.5% of the patients presented poor sleep quality (as determined by a subjective index and actigraphy), and sleep duration was < 7 h.[5] In addition, the presence of sleep disorders, such as obstructive sleep apnea (OSA), results in negative outcomes in this population.[6] Henríquez-Beltrán et al.[2] reported that the risk for OSA was higher in the moderate and severe COVID-19 groups. When evaluated by home polysomnography, the prevalences of OSA in the mild, moderate, and severe COVID-19 groups were, respectively, 27.8%, 64.7%, and 80.0%. The relationship between OSA and hospitalized COVID-19 patients has also been studied,[7] showing that the prevalence of OSA in those patients was 15.3%. This divergence is mainly due to the difference in the time of OSA assessment and the number of patients evaluated: 60[2] and 3,185.[7]

Henríquez-Beltrán et al.[2] reported that sleep quality was impaired in the patients regardless of disease severity. Similarly, there was a higher prevalence of insomnia in the three severity groups studied. In addition, actigraphy showed that the groups had a sleep duration < 7 h but good sleep efficiency.

Another circadian rest-activity pattern parameter—fragmentation of the rest-activity rhythm, determined by intraday variability—was shown to be impaired in all groups studied, but it was significantly higher in the moderate COVID-19 group.[2] Circadian disruption has been linked to an increased risk for diseases such as cardiovascular disease, diabetes, hypertension, obesity, insomnia, and cancer.[1] The outcome found in the study by Benítez et al.[5] is in line with the aforementioned findings,[2] and indicates that mental health should be taken into account as a marker linked to sleep deprivation after COVID-19.

Although Henríquez-Beltrán et al.[2] investigated few patients, there are COVID-19 sequelae that affect sleep parameters and circadian rest-activity patterns that persist even after an extended period after the acute phase of the disease, promoting fragmentation of the circadian rhythm at rest and impairing parameters associated with sleep and mental health.

In conclusion, the central message of the study[2] is clear: changes in sleep, circadian cycle pattern, and mental health appear to be common for at least four months after the acute phase of COVID-19, especially in patients who have developed more severe disease. However, these results should be viewed with caution.

1. Laboratório do Sono e Coração, Pronto Socorro Cardiológico de Pernambuco – PROCAPE – Universidade de Pernambuco, Recife (PE) Brasil.

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Challenges in the management of patients with pulmonary embolism in Brazil

Veronica Moreira Amado[1], Alfredo Nicodemos Cruz Santana[2,3]

Pulmonary thromboembolism (PTE) is a disease that has a high annual incidence (29-78 new cases per 100,000 person-years),[1] having ranked third among the leading causes of cardiovascular death in the last three decades.[2] Therefore, it is important to understand the economic impact of PTE and the factors involved in its prognosis. In the current issue of the *Jornal Brasileiro de Pneumologia* (JBP), an epidemiological study shows relevant data on the number of hospitalizations for PTE, costs of PTE treatment, and mortality of PTE in the five regions of Brazil.[3]

The risk of PTE increases with age, as does the risk of common aging-related comorbidities such as cardiovascular disease, chronic lung disease, and cancer.[4,5] Aging and age-related comorbidities contribute to increased length of hospital stay, costs, and risk of morbidity and mortality from thromboembolic events.[4] Given the increase in life expectancy in recent decades, with the aging rate in Brazil having increased by 268% from 1970 to 2010, particularly in the southern and southeastern regions of the country,[6] the number of hospital admissions for PTE has increased: the mean number of hospitalizations was 2.57/100,000 population in 2008 and 4.44/100,000 population in 2019.[3]

In countries in which there are major differences across regions, including high social inequality, widespread poverty, and limited access to health care, it can be assumed that delayed care results in poorer clinical status. These factors, together with inappropriate or inadequate home care after discharge, can lead to increased hospital stays, increased costs, and worse prognosis.[7] In recent years, new technologies have been developed for the diagnosis and treatment of PTE, contributing to an increase in hospital costs in Brazil and worldwide.[3,4] Although these new technologies can have a positive impact on patient management, they entail an increase in health care costs.[3,4]

For decades, initial anticoagulation therapy was performed in hospitals, even in cases in which the risk of morbidity and mortality was low, because of the need to transition from anticoagulation with unfractionated heparin or low-molecular-weight heparin to coumarins. In recent years, with the emergence of oral medications that dispense with this transition and the need for periodic control of the effect, shorter hospital stays and even initial home treatment have begun to be studied as alternatives to prolonged hospitalizations, although the safety of these strategies has yet to be confirmed.[8-10] In addition, these therapeutic alternatives have yet to be incorporated into the Brazilian Unified Health Care System at the national level. Furthermore, logistical difficulties in gaining access to health care facilities constitute a barrier to early hospital discharge in socioeconomically disadvantaged populations.[2,3]

In Brazil, hospital stays for PTE are still long, having remained practically unchanged in recent years. In 2008, the mean length of stay was 9.1 days; in 2019, it was 8.7 days. However, there was a trend toward a reduction in in-hospital mortality (which was 21.21% in 2008 and 17.1% in 2019). Nevertheless, this reduction was more pronounced in the southern and southeastern regions of the country; in-hospital mortality remained highest in northeastern Brazil (25.1%), evidencing the impact that socioeconomic inequalities have on the delivery of health care in Brazil.[3]

Epidemiological studies, such as the one published in this issue of the JBP,[3] provide a better understanding of the problems related to the delivery of health care, as well as informing public policies to improve the quality and cost-effectiveness of health care.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the conceptualization and critical analysis of the manuscript, having written, reviewed, revised, and approved it for submission.

CONFLICTS OF INTEREST

None declared.

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1. Universidade de Brasília, Faculdade de Medicina, Campus Darcy Ribeiro, Brasília (DF) Brasil.
2. Curso de Medicina e Enfermagem, Escola Superior de Ciências da Saúde, Hospital Regional da Asa Norte – HRAN – Brasília (DF) Brasil.
3. Núcleo Avançado de Tórax, Hospital Sírio-Libanês, Brasília (DF) Brasil.

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Widening of the mediastinum

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

A 68-year-old man presented with a 1-year history of progressive dysphagia, retrosternal discomfort, and 6-month history of weight loss (10 kg). A chest X-ray showed widening of the mediastinum on the right (Figure 1A).

A chest X-ray and a chest CT scan (Figure 1) showed that the widening of the mediastinum corresponded to a markedly dilated esophagus containing fluid, consistent with megaesophagus. Conceptually, megaesophagus represents dilatation of the esophagus due to several causes, such as achalasia, tumors, and connective tissue diseases.

On imaging (chest X-ray, esophagography, and chest CT), the classic megaesophagus appears as widening of the mediastinum, being characterized by a vertical soft-tissue density, usually with thin walls and heterogeneous contents consisting of food debris. It often contains an air-fluid level and is distally tapered (bird's beak appearance).

Achalasia is a primary esophageal motility disorder characterized by a lack of esophageal peristalsis and partial or absent relaxation of the lower esophageal sphincter, making it difficult for the bolus to pass. Achalasia can be divided into primary (idiopathic), which is the most common form worldwide, or secondary. The major secondary cause of achalasia in Brazil is Chagas disease (CD).[1-3]

CD, also known as American trypanosomiasis, is caused by the protozoan *Trypanosoma cruzi*, which is highly prevalent and causes significant morbidity in Latin America. Currently, an extremely high number of patients still suffer from this disease, most of whom are elderly. In CD-endemic areas, it is essential that the possibility of esophageal disease caused by CD be considered in patients with megaesophagus.[1-3] Our patient has had a confirmed diagnosis of CD for approximately 16 years.

CD can present in two forms: acute or chronic. The chronic form of CD develops a few decades after the initial infection, causing irreversible damage to the heart, esophagus (megaesophagus), and colon (megacolon). The symptoms of and morphological changes in the digestive tract are due to impairment of neurons and nerve ganglia. The most common symptom is dysphagia, followed by regurgitation, a feeling of fullness when eating or drinking, heartburn, and chest pain. Dysphagia runs a chronic course, lasting for several years, and is progressive. Patients with CD-associated megacolon experience severe prolonged constipation for years or decades. A final diagnosis of chronic CD is based on serological tests. Surgery is currently the best form of treatment.[1-3]

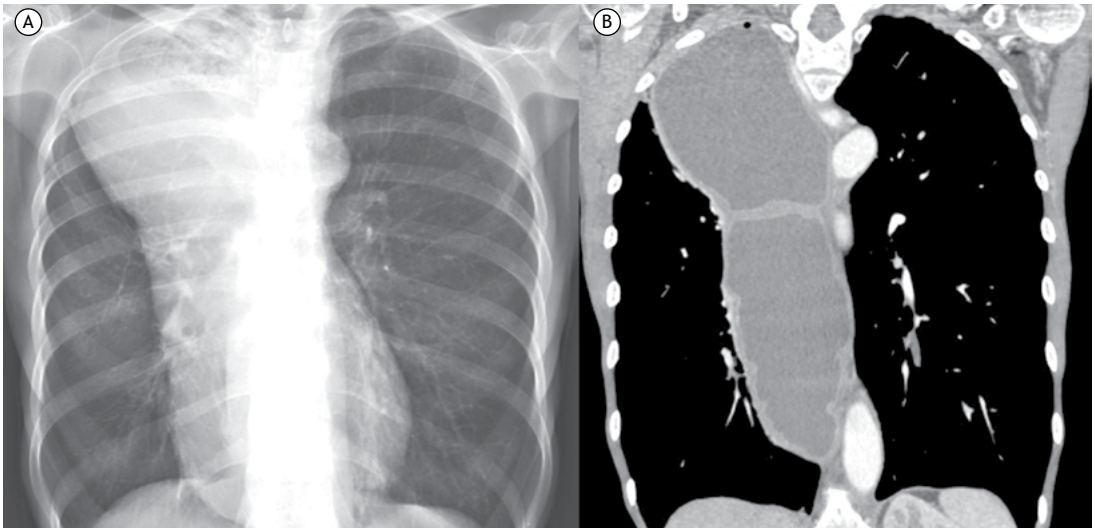

Figure 1. In A, posteroanterior chest X-ray showing widening of the mediastinum on the right. In B, coronally reconstructed CT scan of the chest revealing a markedly dilated esophagus with hypodense intraluminal contents consistent with food debris. Also note tapering of the distal esophagus.

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1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.

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Calculating the statistical limits of normal and Z-scores for pulmonary function tests

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

BACKGROUND

Interpretation of pulmonary function tests (PFTs) requires comparison with the range of expected values in order to discriminate the effects of disease from the normal variability observed in healthy individuals.[1] Modern PFT systems provide several different reference equations with automated computation of predicted values and limits of normal. The pulmonologist in charge of the PFT lab should understand how these variables are calculated in order to minimize the risk of overdiagnosis or underdiagnosis.

OVERVIEW

Given the extreme variability of lung function according to sex, age, and body dimensions (particularly height), some basic statistical concepts are applied to differentiate "normality" versus "abnormality". A pragmatic strategy assumes that a) pulmonary function variables measured in a population of interest are equally distributed around the mean; and b) there are more values closer to the mean than further away. Thus, a bell-shaped (Gaussian) curve emerges when we plot the distribution of the values (Figure 1). In a Gaussian distribution, a given percentile represents the value below which a certain percentage of scores fall.

In this context, if a variable has clinical meaning only when abnormally low (e.g., FEV_1), the lower limit of normal (LLN) is set at the value which corresponds to the lowest 5% of the reference population. The LLN can also be roughly estimated as the predicted value minus 1.645 standard deviations from the mean (Z-score; Figure 1A). In simpler words, it means that at the 5th percentile (corresponding to a Z-score of −1.645), there is a 5% chance that the results of a healthy individual will be at or below this level. Accepting a 5% false-positive rate is usually considered acceptable for most clinical applications of PFTs.[2] A different scenario emerges when values in both directions (i.e., too low or too high) are clinically relevant, as is the case for some "static" lung volumes which can be reduced in restrictive ventilatory defects or increased in obstructive ventilatory disorders. An acceptable strategy is to divide the 5% error on each end of the distribution using a Z-score of ± 1.96 (Figure 1B),[3] establishing the LLN and the upper limit of normal. In Figure 1, a 63-year-old man presents with a measured FEV_1 of 2.07 L (65% of the predicted value). This corresponds to a Z-score of −2.38, that is, below the calculated LLN of 2.41

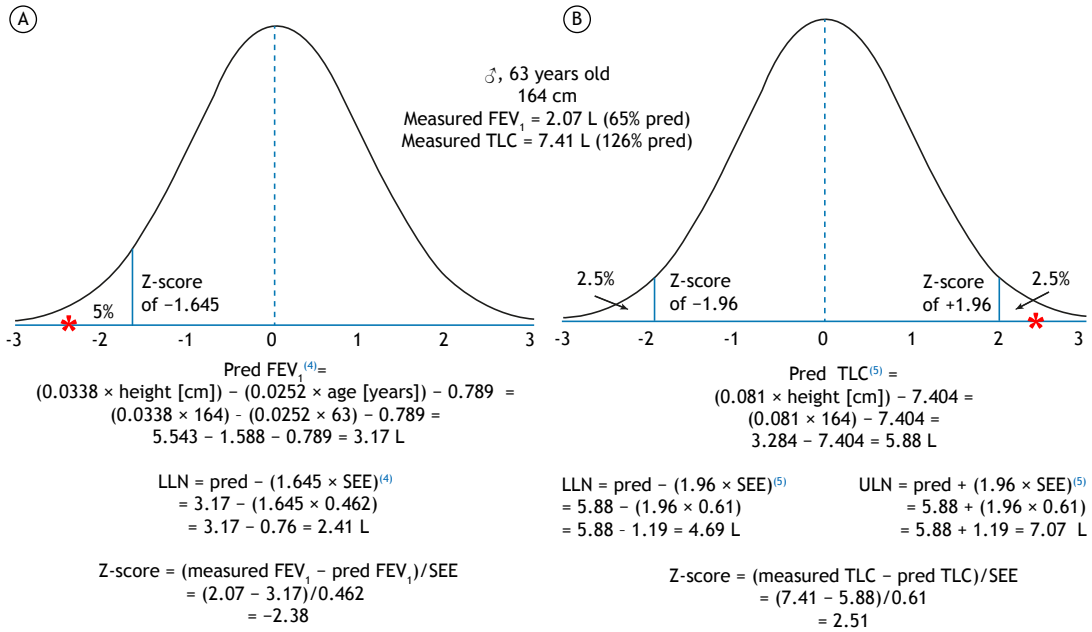

Figure 1. Calculation of key parameters (predicted value, limits of normal, Z-score) necessary for pulmonary function test interpretation: in A, a variable (e.g., FEV_1)[4] for which only abnormally low values have clinical meaning; in B, a variable (e.g., TLC)[5] for which both abnormally low or high values can be of clinical relevance. pred: predicted; LLN: lower limit of normal; ULN: upper limit of normal; SEE: standard error of the estimate (derived from the respective regression equations).

1. Pulmonary Function Laboratory and Respiratory Investigation Unit, Division of Respirology, Kingston Health Science Center & Queen's University, Kingston, ON, Canada.
2. Unidade de Fisiologia Pulmonar, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

L, indicating an abnormally low value (Figure 1A). His measured TLC of 7.41 L, in turn, corresponds to 126% of the predicted value or a Z-score of +2.51, signaling thoracic hyperinflation (Figure 1B).

CLINICAL MESSAGE

The statistical limits of normal do not necessarily separate disease from health. It should also be recognized that there will always be some uncertainty in values close to (i.e., slightly below or above) the LLN or the upper limit of normal: clinical judgment is paramount. The 5th percentile used to define an abnormal test result can be changed depending on the pretest probability of disease, that is, it can either be increased (e.g., in heavy smokers with exertional dyspnea) or decreased (e.g., in asymptomatic non-smokers).

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Building clinical and translational research teams

Cecilia María Patino[1,2], Juliana Carvalho Ferreira[1,3]

PRACTICAL SCENARIO

A group of pulmonary and critical care investigators in Latin America are interested in developing a master's research program as a means of reducing pulmonary and critical care-related morbidity and mortality in urban settings. They conducted a scoping review of existing training models that they could use and came to agreement on evaluating the competency-based model in clinical and translational research[1] The overall goal of the Latin American program was to gather a cadre of investigators that conduct research proposed by the National Institutes of Health (NIH) in order to accelerate the development or adoption, as well as the dissemination, uptake, and implementation of new medical and health-related interventions to improve respiratory health in Latin America.

WHAT IS CLINICAL AND TRANSLATIONAL RESEARCH?

Translational science is the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public.[1] These interventions can include diagnostics, therapeutics, medical procedures, behavioral changes, access to health care, and health-related laws, in addition to how interventions are effectively disseminated, implemented, and evaluated in the community. This field focuses on understanding the scientific and operational principles underlying each step of the translational process, from developing new treatments to demonstrating their usefulness, as well as to disseminating and implementing the findings. The National Institutes of Health has divided this process into a spectrum of five different types of research areas: preclinical, clinical, dissemination, implementation, and public health,[1] but the spectrum is not necessarily linear, with each stage building upon and informing the other (Figure 1). Clinical and translational research prioritizes unmet needs that include preventing disease, overcoming disease, and decreasing the burden of disease in local communities. Translational teams produce crosscutting solutions for common and persistent challenges and emphasize creativity and innovation. They also leverage cross-disciplinary science teams, enhance efficiency and speed of research, use boundary-crossing partnerships, and use rigorous and reproducible research approaches.[2]

THE COMPETENCIES OF CLINICAL AND TRANSLATIONAL RESEARCH

Translational research teams should include professionals with diverse skills, and their core competencies go beyond each individual's specialization. The NIH training competency framework proposes both well-known as well as innovative competencies that the research students would need to develop and master to practice clinical and translational research successfully (Table 1).[1] In our practical scenario, once the group reaches a consensus on the competencies, the next step is to identify faculty with expertise and experience in clinical and translational research, as well as providing the necessary didactic and experiential training opportunities. It is important for the group that the students both "learn" and "conduct" clinical and translational research while in training. The group will evaluate the program during the following two years to report successes and adaptations of this program.

Table 1. Key competencies of a clinical and translational researcher.

Researcher	Competency
Rigorous researcher	Shows strong and state-of-the-art methodological and statistical skills that are rigorous and reproducible
Team player	Leverages and respects research expertise across team members
Boundary crosser	Broadly collaborates across disciplines to advance interventions
Process innovator	Innovates to overcome barriers to advancing intervention development and implementation
Domain expert	Has deep understanding and knowledge within one or more disciplines
Skilled communicator	Communicates well across a broad spectrum of audiences
Systems thinker	Evaluates external forces, interactions, and relationships across all stakeholders involved in developing and implementing successful interventions, including patients, family dynamics, medical professionals, and health care systems

Adapted from the National Institutes of Health.[1]

1. Methods in Epidemiologic, Clinical, and Operations Research–MECOR–program, American Thoracic Society/Asociación Latinoamericana del Tórax, Montevideo, Uruguay.
2. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles (CA) USA.
3. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

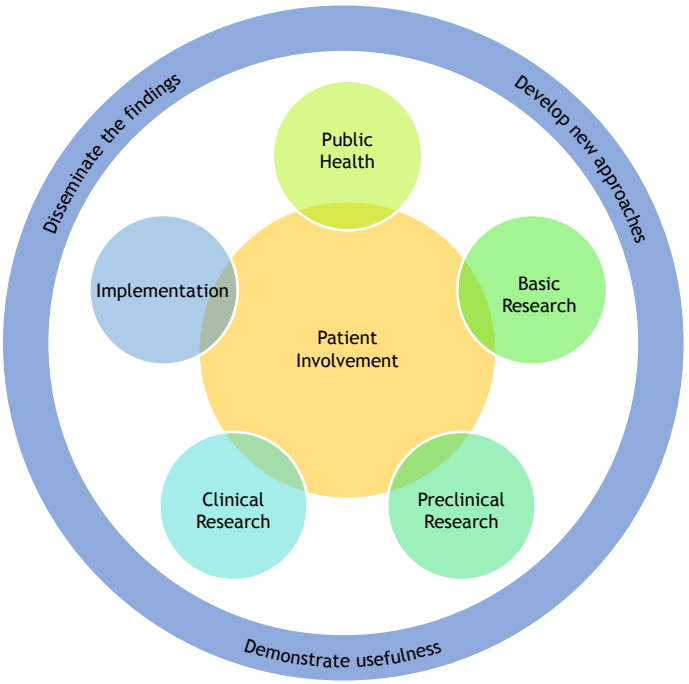

Figure 1. The translational science spectrum. Adapted from the National Institutes of Health.[3]

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Prevalence of the eosinophilic phenotype among severe asthma patients in Brazil: the BRAEOS study

Rodrigo Athanazio[1], Rafael Stelmach[1], Martti Antila[2], Adelmir Souza-Machado[3], L. Karla Arruda[4], Alcindo Cerci Neto[5], Faradiba Sarquis Serpa[6], Daniela Cavalet Blanco[7], Marina Lima[8], Pedro Bianchi Júnior[9], Márcio Penha[10], Marcelo Fouad Rabahi[11]

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Consultoria Médica e Pesquisa Clínica – CMPC – Sorocaba (SP) Brasil.
3. Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador (BA) Brasil.
4. Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto (SP) Brasil.
5. Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.
6. Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória, Vitória (ES) Brasil.
7. Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
8. Hospital Dia do Pulmão, Blumenau (SC) Brasil.
9. Divisão de Imunologia Clínica e Alergia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
10. AstraZeneca Brasil, Cotia (SP) Brasil.
11. Departamento de Clínica Médica–Pneumologia, Faculdade de Medicina, Universidade Federal de Goiás, Goiânia (GO) Brasil.

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Study carried out at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo (SP), Consultoria Médica e Pesquisa Clínica, Sorocaba (SP), Instituto de Ciências Médicas da Universidade Federal da Bahia, Salvador (BA), Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto (SP), Universidade Estadual de Londrina, Londrina (PR), Escola de Medicina da Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS), Hospital Dia do Pulmão, Blumenau (SC), Faculdade de Medicina da Universidade Federal de Goiás, Goiânia (GO), and Faculdade de Medicina da Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To assess the prevalence of the eosinophilic and allergic phenotypes of severe asthma in Brazil, as well as to investigate the clinical characteristics of severe asthma patients in the country. **Methods:** This was a cross-sectional study of adult patients diagnosed with severe asthma and managed at specialized centers in Brazil. The study was conducted in 2019. **Results:** A total of 385 patients were included in the study. Of those, 154 had a blood eosinophil count > 300 cells/mm^3 and 231 had a blood eosinophil count of ≤ 300 cells/mm^3. The median age was 54.0 years, and most of the patients were female, with a BMI of 29.0 kg/m^2 and a history of allergy (81.6%). The prevalence of patients with a blood eosinophil count > 300 cells/mm^3 was 40.0% (95% **CI:** 35.1-44.9), and that of those with a blood eosinophil count > 300 cells/mm^3 and a history of allergy was 31.9% (95% **CI:** 27.3-36.6). Age and BMI showed positive associations with a blood eosinophil count > 300 cells/mm^3 (OR = 0.97, p < 0.0001; and OR = 0.96, p = 0.0233, respectively), whereas the time elapsed since the onset of asthma symptoms showed an increased association with a blood eosinophil count > 300 cells/mm^3 (OR = 1.02, p = 0.0011). **Conclusions:** This study allowed us to characterize the population of severe asthma patients in Brazil, showing the prevalence of the eosinophilic phenotype (in 40% of the sample). Our results reveal the relevance of the eosinophilic phenotype of severe asthma at a national level, contributing to increased effectiveness in managing the disease and implementing public health strategies.

Keywords: Asthma; Epidemiology; Eosinophils; Phenotype; Allergy and immunology.

INTRODUCTION

Asthma is a complex heterogeneous condition, affecting over 300 million people worldwide.[1] In Brazil, the prevalence of asthma among adults has been estimated at 4.4%, with severe asthma accounting for 3.7% of all asthma cases.[2-4]

Severe asthma places a great burden on the health care system, with several unmet needs. According to the GINA, severe asthma is "asthma that is uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors, or that worsens when high dose treatment is decreased."[5]

Given the variety of inflammatory, clinical, and functional characteristics of severe asthma, the disease can have several phenotypes.[6] A high level of eosinophils (in serum or induced sputum) characterizes a specific inflammatory phenotype associated with poor symptom control and an increased number of exacerbations.[7] Although several biologic agents targeting the T2 inflammatory pathway use different blood eosinophil cutoff points, there is still no consensus regarding the cutoffs for severe asthma (i.e., 150 cells/mm^3, 300 cells/mm^3, or 400 cells/mm^3).[8,9] Peripheral blood eosinophil counts as high as 400 cells/mm^3 have been linked to increased asthma exacerbations.[8] Nevertheless, adult-onset asthma patients with a blood eosinophil count ≥ 300 cells/mm^3 present with a distinct phenotype of severe asthma, with frequent exacerbations and a poor prognosis. Studies of anti-eosinophilic therapies suggest that patients with blood eosinophil counts ≥ 300 cells/mm^3 benefit from targeted treatment.[9,10] It is known that an eosinophil count > 150 cells/mm^3 can be characterized as a specific phenotype of disease that is more severe.[8] However,

Correspondence to:
Rodrigo Athanazio. Instituto do Coração, Avenida Dr. Enéas Carvalho de Aguiar, 44, 5º andar (Pneumologia), Cerqueira César, CEP 05403-900, São Paulo, SP, Brasil.
Tel.: 55 11 3661-5695. E-mail: rathanazio@yahoo.com.br
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the higher the cutoff, the greater the clinical differences across phenotypes and the greater the clinical benefits of therapies targeting the T2 inflammatory pathway.[8,9]

Although eosinophilic inflammation of the airways has been classically associated with allergic asthma, there is evidence that eosinophilia is present in severe asthma patients without a history of "atopy."[11-14] Patients with severe asthma and high eosinophil levels typically present with increased levels of anxiety and depression, as well as decreased quality of life (QoL),[15] consuming more health care resources.

It is of utmost importance to gain a deeper understanding of the epidemiological distribution of eosinophilic phenotypes among patients with severe asthma in order to optimize the management of this condition. This study sought to investigate the prevalence of different eosinophilic phenotypes among severe asthma patients managed at specialized centers in Brazil, as well as to characterize and compare clinical features between two phenotypes based on the blood eosinophil count. The study objectives were to assess the prevalence of the eosinophilic phenotype (a blood eosinophil count > 300 cells/mm^3) among severe asthma patients, identify an overlap between the eosinophilic phenotype and the allergic phenotype, and compare the eosinophilic phenotype with the noneosinophilic phenotype in terms of clinical features and patient-reported outcomes. The prevalence of eosinophils was evaluated by using a cutoff point > 150 cells/mm^3,[5] and the impact of chronic oral corticosteroid (C-OCS) use was also evaluated.

METHODS

Study design and population

The BRAEOS study was a cross-sectional study conducted in Brazil and involving ten centers specializing in the management of patients with asthma. Patients were enrolled during 2019 over a period of 10 months.

The target population consisted of adult patients who had been diagnosed with severe asthma at least one year prior to inclusion in the study. Severe asthma was defined as asthma requiring treatment with high-dose inhaled corticosteroids (as determined by GINA)[5] and long-acting β_2 agonists or leukotriene receptor antagonists/theophylline during the previous year; asthma requiring treatment with oral corticosteroids for ≥ 50% of the days in the previous year to prevent it from becoming "uncontrolled"; or asthma that remained "uncontrolled" despite this therapy.[5] Patients were excluded if they were current/former smokers (with a smoking history ≥ 10 pack-years), experienced a moderate/severe asthma exacerbation in the 4 weeks prior to enrollment, or received a burst of systemic corticosteroids in the 4 weeks prior to enrollment. Other exclusion criteria included previous use of biologic agents for asthma treatment (the exception being omalizumab), any changes in the pharmacological treatment of asthma in the past 3 months, and concomitant lung diseases.

Data collection and variables

Data were collected during an appointment in which patients were assessed for asthma control and QoL; blood samples were collected for determination of eosinophil and total serum IgE levels; and patient medical charts were reviewed for data on demographic characteristics, smoking status, asthma-related clinical data, a history of allergy (clinically documented preexisting history and/or a positive aeroallergen-specific IgE screen, a positive skin prick test for aeroallergens, or both), comorbidities, the Charlson Comorbidity Index,[16] pharmacological treatment, and lung function. Lung function data included pre- and post-bronchodilator FEV_1 (in % of predicted) and post-bronchodilator FEV_1/FVC.

An eosinophilic phenotype was defined as a blood eosinophil count > 300 cells/mm^3. A blood eosinophil count > 150 cells/mm^3 was used as a secondary outcome. An allergic phenotype was defined as a combination of high total serum IgE level (> 100 IU/mL) and a history of allergy.

Late-onset asthma was defined as the onset of asthma symptoms at the age of 12 years or older.[17] Moderate asthma exacerbation was defined as the use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dosage) for at least 3 days, the use of a single injectable dose of corticosteroids, or an emergency department/urgent care center visit (of < 24 h) for asthma requiring systemic corticosteroids.[18] Severe asthma exacerbation was defined as an inpatient hospital stay (≥ 24 h) because of asthma.[5,19]

Patient-reported outcomes

Patients completed the Saint George's Respiratory Questionnaire (SGRQ)[20] and the 5-item Asthma Control Questionnaire (ACQ-5)[21] to assess their perception of QoL and asthma control, respectively. SGRQ scores were expressed as percentage of overall impairment (a score of 100 indicating the worst possible health status and a score of 0 indicating the best possible health status). The total ACQ-5 score ranges from 0 (totally controlled asthma) to 6 (severely uncontrolled asthma). An ACQ-5 score > 1.5 indicated uncontrolled asthma.

Statistical analysis

The sample size was calculated for a prevalence study based on the primary endpoint defined as the proportion of patients with a blood eosinophil count > 300 cells/mm^3, assuming a conservative estimate of a prevalence of 50%. With a margin of error of 5%, a sample of 385 patients with severe asthma was calculated to be required.

Descriptive statistics were used in order to summarize data (means, standard deviations, medians, and minimum/maximum values for numerical variables; and absolute numbers and percentages for categorical variables). Missing data were not replaced.

The primary analysis dataset included all of the patients with blood eosinophil counts available for

eosinophilic phenotype characterization. Data were summarized for the sample as a whole and broken down by eosinophilic phenotype, as well as being summarized and compared by C-OCS use (n = 387).

Comparisons between eosinophilic groups and C-OCS users/nonusers were computed with the chi-square test or Fisher's exact test for categorical variables and with the Student's t-test or the Mann-Whitney test for numerical variables. Multivariate logistic regressions were performed to explore the association between clinical characteristics and the eosinophilic phenotype, with 95% CIs and adjusted ORs. All statistical tests were two-tailed, and the level of significance was set at 5%. All statistical analyses were performed with the Statistical Analysis System, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical considerations

All patients provided written informed consent prior to study entry. The study was approved by the research ethics committees/institutional review boards of the participating centers and was performed in accordance with the applicable regulatory and legal requirements.

RESULTS

Of the 387 patients included in the study, 385 had available blood eosinophil counts and were therefore included in the analysis. Of those 385 patients, 154 had an eosinophil count > 300 cells/mm^3 and 231 had an eosinophil count ≤ 300 cells/mm^3 (Table 1). The main results are presented by eosinophilic phenotype. All 387 patients were included in the analysis of C-OCS use.

Of the sample as a whole, most (78.4%) were women, the median age being 54.0 years. The median BMI was 29.0 kg/m^2, and approximately 16% were former smokers. Nearly 50% (188/370) of our patients had late-onset asthma. Most patients (81.6%) had a history of allergy, with confirmed atopy (a positive aeroallergen-specific IgE screen or a positive skin prick test for aeroallergens) in 73.2%. The mean post-bronchodilator FEV_1 was 67.7 ± 17.9%, and the mean post-bronchodilator FEV_1/FVC ratio was 66.5 ± 11.8.

Moderate asthma exacerbations were absent in 26.6% of patients, and 36.7% had had ≥ 3 moderate exacerbations in the previous year. At least one severe asthma exacerbation was found in 4.4% of the patients in that same period. The overall mean exacerbation rate in the previous year was 2.77 (2.71 for moderate exacerbations and 0.07 for severe exacerbations).

Regarding pharmacological treatment for asthma, all patients were on inhaled corticosteroids, and 99.0% were treated with long-acting β_2 agonists. A total of 13.5% of patients were receiving treatment with long-acting muscarinic antagonists, and 11.9% were receiving treatment with omalizumab. In the previous 12 months, 75.5% of patients had received a median of 3.0 corticosteroid bursts. The median OCS dose was 5.0 ± 10.2 mg of prednisone.

The proportion of patients with eosinophils > 300 cells/mm^3 was 40.0% (95% CI: 35.1-44.9), whereas 73.0% (95% CI: 68.6-77.4) had eosinophils > 150 cells/mm^3.

Approximately 80% of the patients had a history of allergy, and 31.9% (95% CI: 27.3-36.6) had both a blood eosinophil count > 300 cells/mm^3 and a history of allergy. A total of 286 patients (74.3%) had total serum IgE levels > 100 IU/mL (95% CI: 69.9-78.7), and 62.6% (95% CI: 57.8-67.4) had total serum IgE levels > 100 IU/mL and a history of atopy (Table 2).

The median age of eosinophilic patients was lower than that of noneosinophilic patients (p = 0.0422). The median BMI was significantly lower in eosinophilic patients than in noneosinophilic patients (p = 0.0395). Eosinophilic patients showed an overall exacerbation rate of 3.20 exacerbation/patient-years, a moderate exacerbation rate of 3.13 exacerbation/patient-years, and a severe exacerbation rate of 0.06 exacerbation/patient-years. Noneosinophilic patients showed an overall exacerbation rate of 2.49 exacerbation/patient-years, a moderate exacerbation rate of 2.42 exacerbation/patient-years, and a severe exacerbation rate of 0.08 exacerbation/patient-years, with no statistically significant differences between groups (Table 1).

In the sample as a whole, the mean blood eosinophil count was 309.8 ± 263.5 cells/mm^3. The mean blood eosinophil count was 540.9 ± 274.2 cells/mm^3 for eosinophilic patients and 155.7 ± 79.5 cells/mm^3 for noneosinophilic patients. The median total serum IgE level was 259.0 IU/mL for eosinophilic patients, IgE levels being higher in eosinophilic patients than in noneosinophilic patients (p = 0.0150; Table 3).

With regard to rhinitis, gastroesophageal reflux, type 2 diabetes, and nasal polyps, there were statistically significant differences between the two groups. The median Charlson Comorbidity Index was lower in eosinophilic patients (p = 0.0125; Figure S1).

In the sample as a whole, the median SGRQ symptom score was 55.6 (median activity score, 60.8; median impact score, 39.9; Table 4) and the median total SGRQ score was 49.8. There were no statistically significant differences between eosinophilic and noneosinophilic phenotypes regarding total and individual domain scores.

The median ACQ-5 score was 2.0, and 63.4% of patients had uncontrolled asthma. No statistically significant differences were found between eosinophilic and noneosinophilic phenotypes.

A logistic regression model was built with clinical variables of interest (Table 5). Lower age (OR = 0.97; p < 0.0001) and lower BMI (OR = 0.96; p = 0.0233) showed a positive association with the eosinophilic phenotype. On the other hand, the time elapsed since the onset of asthma symptoms (OR = 1.02; p = 0.0011) showed an increased association with an eosinophil count > 300 cells/mm^3.

Results by C-OCS use included 387 patients (14 patients with C-OCS use and 373 patients without C-OCS

Table 1. Characteristics of the study participants and pharmacological treatment of asthma for the sample as a whole and for the eosinophilic phenotype.

Characteristic	Total (N = 385)	Blood eosinophil count > 300 cells/mm³ (n = 154)	Blood eosinophil count of ≤ 300 cells/mm³ (n = 231)	p
Age, years				
Median (IQR)	54.0 (43.0-62.0)	52.5 (42.0-61.0)	54.0 (44.0-63.0)	0.0422*
Sex, n (%)				
Female	302 (78.4)	117 (76.0)	185 (80.1)	0.3364†
BMI (kg/m²)				
Median (IQR)	29.0 (24.8-33.7)	28.4 (24.6-32.4)	29.4 (25.0-34.6)	0.0395*
Smoking status, n (%)				
Never smoker	323 (83.9)	124 (80.5)	199 (86.1)	0.1411†
Former smoker	62 (16.1)	30 (19.5)	32 (13.9)	
Onset of asthma symptoms, n (%)				
Early-onset asthma[a]	182 (49.2)	64 (43.2)	118 (53.2)	0.0618†
Late-onset asthma[b]	188 (50.8)	84 (56.8)	104 (46.8)	
...Missing data	15			
Moderate asthma exacerbations (in the previous 12 months), n (%)				
0 exacerbations	102 (26.6)	39 (25.3)	63 (27.4)	0.0812†
1 exacerbation	70 (18.2)	23 (14.9)	47 (20.4)	
2 exacerbations	71 (18.5)	24 (15.6)	47 (20.4)	
≥ 3 exacerbations	141 (36.7)	68 (44.2)	73 (31.7)	
Severe asthma exacerbations (in the previous 12 months), n (%)				
0 exacerbations	368 (95.6)	148 (96.1)	220 (95.2)	0.9018††
1 exacerbation	13 (3.4)	4 (2.6)	9 (3.9)	
2 exacerbations	2 (0.5)	1 (0.6)	1 (0.4)	
≥ 3 exacerbations	2 (0.5)	1 (0.6)	1 (0.4)	
Overall exacerbation rate (in the previous 12 months)	2.77	3.20	2.49	--
Moderate exacerbation rate (in the previous 12 months)	2.71	3.13	2.42	--
Severe exacerbation rate (in the previous 12 months)	0.07	0.06	0.08	--
History of atopy	311 (81.6)	123 (80.9)	188 (82.1)	0.7718†
FEV_1, % predicted, n (%)				
Pre-bronchodilator				
N	277	107	170	0.6078¶
Mean ± SD	60.4 ± 17.8	61.1 ± 17.3	59.9 ± 18.1	
Post-bronchodilator				
N	251	96	155	0.6801*
Mean ± SD	67.7 ± 17.9	68.9 ± 18.7	66.9 ± 17.5	
Post-bronchodilator FEV1/FVC ratio				
Mean ± SD	66.5 ± 11.8	67.3 ± 12.4	66.0 ± 11.3	0.3824¶
Pharmacological treatment, n (%)				
Inhaled corticosteroid	385 (100.0)	154 (100.0)	231 (100.0)	
.....Median dose, µg[c] (IQR)	1,600.00 (1,200.00-2,400.00)	1,600.00 (1,200.00-2,400.00)	1,600.00 (1,200.00-2,400.00)	0.3316*
LABA	381 (99.0)	153 (99.4)	228 (98.7)	
LAMA	52 (13.5)	20 (13.0)	32 (13.9)	
SABA	333 (86.5)	136 (88.3)	197 (85.3)	
SAMA	8 (2.1)	2 (1.3)	6 (2.6)	
Chronic oral corticosteroid	14 (3.6)	5 (3.2)	9 (3.9)	
Leukotriene receptor antagonist	58 (15.1)	26 (16.9)	32 (13.9)	
Xanthine	13 (3.4)	7 (4.5)	6 (2.6)	
Omalizumab	46 (11.9)	18 (11.7)	28 (12.1)	
Macrolides	5 (1.3)	3 (1.9)	2 (0.9)	
LABA + LAMA + inhaled corticosteroid for the treatment of asthma, n (%)				
Yes	51 (13.2)	19 (12.3)	32 (13.9)	

LABA: long-acting β_2 agonist; SABA: short-acting β_2 agonist; LAMA: long-acting muscarinic antagonist; and SAMA: short-acting muscarinic antagonist. [a]Early-onset asthma: onset of symptoms < 12 years of age. [b]Late-onset asthma: onset of symptoms ≥ 12 years of age. [c]Cumulative inhaled corticosteroid dose is presented on the basis of the equivalent budesonide dose. *Mann-Whitney test. †Chi-square test. ††Fisher's exact test. ¶Student's t-test.

use). The proportion of patients without severe asthma exacerbations in the previous 12 months was significantly lower in C-OCS users than in C-OCS nonusers (78.6% vs. 96.2%). The proportion of patients with a history of stroke and heart failure was significantly higher in C-OCS users than in C-OCS nonusers (14.3% vs. 1.9% for both; Table S1).

DISCUSSION

In the BRAEOS study we found a high prevalence of eosinophilic patients (40% for a blood eosinophil cutoff > 300 cells/mm^3 and 73% for a blood eosinophil cutoff > 150 cells/mm^3), with a great overlap between the eosinophilic and allergic phenotypes. Our results are in accordance with those of several other studies of patients with severe asthma. One cohort study performed at a tertiary referral center and using a blood eosinophil cutoff > 300 cells/mm^3 revealed an eosinophilic phenotype prevalence of 41%.[22] Two observational studies using a blood eosinophil cutoff > 400 cells/mm^3 reported an eosinophilic asthma prevalence of 16-38%.[23,24] On the other hand, the Belgian Severe Asthma Registry used a blood eosinophil cutoff > 200 cells/mm^3 and showed a prevalence of 53%.[25] Although these studies were conducted in different settings and used distinct study populations in terms of asthma severity, they provide a broad picture of the distribution of the eosinophilic profile and a framework for interpreting our results.

In the present study, a blood eosinophil cutoff > 300 cells/mm^3 was used for the primary objective. Although several biologic agents targeting the T2 inflammatory (eosinophilic) pathway use different cutoff points, there is still debate about the cutoff point that should be used (i.e., 150 cells/mm^3, 300 cells/mm^3, or 400 cells/mm^3).[26-28] It is known that eosinophilic patients with a blood eosinophil count > 150 cells/mm^3 show more severe disease that can be characterized as a distinct phenotype.[5,9] By using a higher cutoff, such as 300 cells/mm^3, the clinical differences between phenotypic groups and the potential benefit of therapies to treat type 2 inflammation become more evident. This allows the identification of specific groups with better chances of benefiting from targeted therapy.[28]

With regard to the overall characteristics of the study participants, the median age was 54.0 years, most were female, and the proportion of obesity was high. A severe clinical presentation was observed in the study population, as evidenced by a history of exacerbation, as well as elevated eosinophil and IgE levels. These findings are consistent with those of other studies.[29-31] The ACQ-5 scores showed that approximately two thirds of the sample had uncontrolled asthma symptoms. Lung function findings revealed a high prevalence of fixed airway obstruction despite optimized treatment with high doses of inhaled corticosteroids and other long-term control medications.[32] High SGRQ scores revealed poor QoL, which reflects the disease severity

Table 2. Prevalence of the eosinophilic and allergic phenotypes in the sample as a whole (N = 385).

Variable	n (%) – [95% CI]
Overall sample	
Blood eosinophil count > 300 cells/mm^3	154 (40.0) - [35.1-44.9]
Blood eosinophil count > 150 cells/mm^3	281 (73.0) - [68.6-77.4]
History of allergy	311 (81.6) - [77.7-85.5]
Blood eosinophil count > 300/mm^3 and a history of allergy	123 (31.9) - [27.3-36.6]
Total serum IgE > 100 IU/mL	286 (74.3) - [69.9-78.7]
Total serum IgE > 100 IU/mL and a history of allergy	241 (62.6) - [57.8-67.4]
History of allergy[a] in patients with a blood eosinophil count > 300 cells/mm^3 (n = 154)	123 (79.9) - [73.5-86.2]

[a]History of allergy: clinically documented preexisting history of respiratory allergy or atopy (a positive aeroallergen-specific IgE screen or a positive skin prick test for aeroallergens).

Table 3. Laboratory test results for the sample as a whole and for the eosinophilic phenotype.

Test	Total (N = 385)	Blood eosinophil count > 300 cells/mm^3 (n = 154)	Blood eosinophil count of ≤ 300 cells/mm^3 (n = 231)	p
Eosinophils, cells/mm^3				
Mean ± SD	309.8 ± 263.5	540.9 ± 274.2	155.7 ± 79.5	
Eosinophils, n (%)				
0 to ≤ 100 cells/μL	64 (16.6)	0 (0.0)	64 (27.7)	
101 to ≤ 200 cells/μL	92 (23.9)	0 (0.0)	92 (39.8)	
201 to ≤ 300 cells/μL	75 (19.5)	0 (0.0)	75 (32.5)	
301 to ≤ 400 cells/μL	60 (15.6)	60 (39.0)	0 (0.0)	
401 to ≤ 500 cells/μL	34 (8.8)	34 (22.1)	0 (0.0)	
> 501 cells/μL	60 (15.6)	60 (39.0)	0 (0.0)	
Total serum IgE (IU/mL)				
Median (IQR)	259.0 (93.2-605.0)	336.3 (113.0-817.0)	235.2 (75.4-503.1)	0.0150*

*Mann-Whitney test.

Table 4. Patient-reported outcomes for the sample as a whole and for the eosinophilic phenotype.

Variable	Total (N = 385)	Blood eosinophil count > 300 cells/mm³ (n = 154)	Blood eosinophil count of ≤ 300 cells/mm³ (n = 231)	p
SGRQ				
Symptoms score (%)				
Median (IQR)	55.6 (39.3-71.9)	54.3 (40.2-75.2)	57.6 (38.2-70.1)	0.4658*
Activity score (%)				
Median (IQR)	60.8 (49.2-74.6)	60.4 (47.7-73.6)	61.1 (53.2-79.2)	0.2691*
Impact score (%)				
Median (IQR)	39.9 (23.3-55.6)	38.8 (21.6-54.0)	42.2 (24.2-58.3)	0.1320*
Total score (%)				
Median (IQR)	49.8 (35.3-63.1)	48.8 (34.6-61.0)	50.4 (35.8-65.4)	0.2405†
ACQ-5				
Total score				
Median (IQR)	2.0 (1.0-2.8)	1.8 (1.0-2.8)	2.2 (1.0-3.0)	0.3290*
ACQ-5 categories, n (%)				
Well-controlled	141 (36.6)	59 (38.3)	82 (35.5)	0.5745††
Uncontrolled	244 (63.4)	95 (61.7)	149 (64.5)	

SGRQ: Saint George's Respiratory Questionnaire; and ACQ-5: 5-item Asthma Control Questionnaire. *Mann-Whitney test. †Student's t-test. ††Chi-square test.

Table 5. Logistic regression model for variables of interest.

	OR[a]	95% CI for OR	p
Age, years	0.97	[0.95-0.98]	< 0.0001
Body mass index	0.96	[0.93-0.99]	0.0233
Time elapsed since the onset of asthma symptoms, years	1.02	[1.01-1.04]	0.0011
Likelihood ratio			< 0.0001

[a]Reference for the dependent variable: a blood eosinophil count of ≤ 300 cells/mm³.

in the study population and highlights the burden of disease.

With regard to the two inflammatory phenotypes of interest, eosinophilic patients had lower BMI, had fewer comorbidities, and tended to be younger than did noneosinophilic patients. They also presented with a longer time elapsed since the onset of asthma symptoms, higher IgE values, a higher number of corticosteroid bursts, and a tendency to experience a higher annual exacerbation rate in comparison with noneosinophilic patients. Although the findings regarding the eosinophilic phenotype point to an apparently clinically healthier group of patients (younger, with lower BMI and fewer comorbidities), these patients required more bursts of oral corticosteroids in the previous year than did noneosinophilic patients. This may provide a pathophysiological explanation for the cause of the exacerbations.[33] Whereas in eosinophilic patients the inflammatory process could play a predominant role, in noneosinophilic patients, factors such as obesity and other comorbidities might be associated with the occurrence of the exacerbations.[34]

Inhaled corticosteroid doses and asthma control were similar between the two eosinophilic groups. This reflects the severity of this condition in both groups. Nonetheless, these findings might be valuable for adjustment of routine clinical practice with distinct management approaches. Possible approaches include adding biologic agents for specific phenotypes and increasing inhaled corticosteroid doses in eosinophilic patients or decreasing inhaled corticosteroid doses in noneosinophilic patients to minimize long-term side effects. Another strategy is to improve the control of comorbidities in noneosinophilic patients instead of introducing new anti-inflammatory drugs.

In our study, asthma severity was more evident in the C-OCS users, with more endotracheal intubations, more exacerbations, and worse QoL. C-OCS users required additional care, which ultimately led to increased costs related to the management of the disease. In this setting, biologic agents seem to be an appropriate therapeutic option with proven results, reducing the exacerbation rates and oral corticosteroid doses. In one trial,[35] benralizumab showed a 75% C-OCS dose reduction vs. a 25% dose reduction in the placebo group, as well as a 100% C-OCS dose reduction in 52% of patients. Studies examining mepolizumab and dupilumab have shown similar results.[36] We found a very low proportion of C-OCS users in comparison with real-life settings in Europe.[33] This might be explained by the fact that many pulmonologists/allergists avoid prescribing C-OCSs in routine clinical practice, even for patients with uncontrolled asthma. However, the number of oral corticosteroid bursts was high, and this

may be related to a high risk of C-OCS side effects.[34] This suggests that targeted therapies to improve the control of severe asthma may be highly beneficial by reducing the use of C-OCSs.

Given the considerable overlap of eosinophilic asthma and atopy found in the present study, a high number of these patients would be potential candidates for therapies that target both conditions: anti-IgE therapy for patients with atopy and anti-IL-5 for those with eosinophilic asthma.[37] The body of evidence, however, is not sufficiently consistent to allow us to conclude which of these therapies should be first introduced in this patient population, given that previous studies have reported similar efficacy.[38] It is known that the T2 inflammatory response, which centers around the eosinophil as the final effector cell, can be initiated by an allergic (Th2) or nonallergic (non-Th2) pathway, triggered by external factors such as smoking, viruses, pollutants, and bacteria.[39]

One of the major limitations of the present study is its cross-sectional design, limiting causal inference. However, the regression models allowed us to explore associations between patient characteristics and the eosinophilic profile. Induced sputum eosinophil count, a recognized biomarker of airway inflammation and disease severity, was not performed, because it is not widely available in clinical practice.[26,27] However, some studies have suggested that there is a strong correlation between blood and sputum eosinophil counts.[40] Another limitation of the present study is that not every patient with a history of atopy and high IgE levels had skin prick test or allergen-specific IgE results available. Our prevalence result might be slightly underestimated because of the inclusion of patients using oral corticosteroids and omalizumab. However, given that these patients account for less than 15% of the study sample and that the objective of the study was to estimate the prevalence of the eosinophilic phenotype in severe asthma patients in Brazil, we consider this impact to be minimal. Nevertheless, for this subgroup of C-OCS users, the results of the statistical analysis should be interpreted with caution because of the small number of cases in our study.

The BRAEOS study was a multicenter study involving a population representative of several regions of Brazil, which is a country of continental dimensions. Data were collected in a systematic way and following internationally validated definitions, allowing adequate comparability of the results. Therefore, the BRAEOS study was able to characterize the population of patients with severe asthma in Brazil, emphasizing the eosinophilic phenotype (40% of the sample) and showing associations with a lower BMI, fewer comorbidities, and a higher number of corticosteroid bursts. Not surprisingly, C-OCS users had more severe disease, with more exacerbations, more cardiovascular comorbidities, and poorer health-related QoL. Our results reveal the relevance of the eosinophilic phenotype of severe asthma at a national level, contributing to increased effectiveness in managing the disease and implementing public health strategies.

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DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article and/or its supplementary materials.

AUTHOR CONTRIBUTIONS

RA and MP: conceptualization, project administration, methodology, data analysis, and drafting of the manuscript. RA, RS, MA, AS-M, LKA, ACN, FSS, DCB, ML, MR, and PBJ: data collection, data analysis, and drafting of the manuscript. All authors reviewed and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

Rodrigo Athanazio has participated in clinical studies funded by or has received conference/consultancy fees from the following pharmaceutical companies: AstraZeneca, Chiesi, GlaxoSmithKline, Novartis, Sanofi, Pfizer, Roche, and Vertex. Rafael Stelmach has participated in clinical studies funded by or has received conference/consultancy fees from the following pharmaceutical companies: AstraZeneca, Boehringer Ingelheim, Eurofarma, GlaxoSmithKline, Novartis, and Sanofi. Martti Antila has participated in clinical studies funded by AbbVie, AstraZeneca, EMS, Eurofarma, GlaxoSmithKline, Humanigen, Janssen, Novartis, Sanofi, Angion Biomedica, BeiGene, and Rigel Pharmaceuticals, Inc., as well as having received consultancy fees from Abbott Laboratories, Aché, AstraZeneca, Chiesi, Eurofarma, IPI ASAC Brasil, and Sanofi. Adelmir Souza-Machado has no conflicts of interest to declare. L. Karla Arruda has received research support or lecture fees from AstraZeneca, Novartis, Sanofi, GlaxoSmithKline, and Takeda. Alcindo Cerci Neto has no conflicts of interest to declare. Faradiba Sarquis Serpa has been a member in advisory boards and a speaker for Novartis, Sanofi, and Takeda-Shire, as well as having participated in clinical trials funded by Novartis and AstraZeneca. Daniela Cavalet Blanco has no conflicts of interest to declare. Marina Lima has received conference and lecture fees from AstraZeneca. Marcelo Rabahi has participated in clinical research funded by AstraZeneca and Boehringer Ingelheim. Pedro Bianchi Júnior has received sponsorship from

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ORIGINAL ARTICLE

Routine spirometry in cystic fibrosis patients: impact on pulmonary exacerbation diagnosis and FEV_1 decline

Carolina Silva Barboza de Aquino[1], Joaquim Carlos Rodrigues[1], Luiz Vicente Ribeiro Ferreira da Silva-Filho[1,2]

1. Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Centro de Pesquisa Experimental, Instituto de Ensino e Pesquisa, Hospital Israelita Albert Einstein, São Paulo (SP) Brasil.

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Study carried out at the Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: Pulmonary disease in cystic fibrosis (CF) is characterised by recurrent episodes of pulmonary exacerbations (PExs), with acute and long-term declines in lung function (FEV_1). The study sought to determine whether routine spirometry increases the frequency of PEx diagnosis, resulting in benefits to long-term pulmonary function. **Methods:** CF patients in the 5- to 18-year age bracket were followed for 1 year, during which they underwent spirometry before every medical visit. The main variables were the frequency of PEx diagnosis and use of antibiotics; the use of spirometry as a criterion for PEx diagnosis (a decline ≥ 10% in baseline FEV_1); and median percent predicted FEV_1 over time. The data were compared with those for the previous 24-month period, when spirometry was performed electively every 6 months. **Results:** The study included 80 CF patients. PExs were diagnosed in 27.5% of the visits, with a mean frequency of 1.44 PExs per patient/year in 2014 vs. 0.88 PExs per patient/year in 2012 ($p = 0.0001$) and 1.15 PExs per patient/year in 2013 ($p = 0.05$). FEV_1 was used as a diagnostic feature in 83.5% of PExs. In 21.9% of PExs, the decision to initiate antibiotics was solely based on an acute decline in FEV_1. The median percent predicted FEV_1 during the follow-up year was 85.7%, being 78.5% in 2013 and 76.8% in 2012 ($p > 0.05$). The median percent predicted FEV_1 remained above 80% during the two years after the study. **Conclusions:** Routine spirometry is associated with higher rates of diagnosis and treatment of PExs, possibly impacting long-term pulmonary function.

Keywords: Cystic fibrosis; Respiratory function tests; Respiratory tract infections; Spirometry.

INTRODUCTION

Pulmonary disease is the main cause of morbidity and mortality for patients with cystic fibrosis (CF), which is characterised by recurrent episodes of acute worsening of pulmonary symptoms, known as pulmonary exacerbations (PExs).[1-3] The severity of lung disease is assessed by FEV_1, which is a well-documented predictor of mortality[4,5] and which is used as an outcome in clinical trials[6,7] and as a parameter to indicate and monitor therapeutic responses,[8] as well as to refer patients for lung transplantation.[9] The annual rate of decline in FEV_1 has been used as a predictor of survival and is a robust outcome measure in clinical trials, although it is still underused because of the individual variability of FEV_1 over time.[10-12]

FEV_1 is also routinely used as one of the parameters for diagnosing PExs, which are established by a combination of clinical features and spirometry results.[6] PExs have a major impact on long-term survival, quality of life, and deterioration of lung function.[13] Roughly a quarter of patients do not recover their baseline lung function after intravenous or oral antibiotic treatment.[14,15] Despite their significant role in the progression of lung disease, PExs are still not fully understood, and a clear definition and well-established criteria for their diagnosis are lacking. This results in discrepancies in the treatment approach to PExs between many CF centres, increasing the risk of significant pulmonary function decline for the patients.[16] In recent years, some authors have recommended antibiotic therapy for an acute decline in FEV_1 (a decline ≥ 10% in percent predicted FEV_1 at baseline), even in the absence of clinical signs and symptoms.[17,18] They argue that this approach is associated with a greater likelihood of recovering lung function and has long-term benefits.[17,18]

Several international CF guidelines recommend routine FEV_1 measurements at all medical encounters,[19-21] but this practice is not universally adopted for several reasons. In developing countries such as Brazil, there are centres with limited technical and financial resources, which limit the availability of pulmonary function tests. In our CF centre, patients usually undergo medical consultations every 2 months, and spirometry used to be performed every 6 months. The objective of the present study was

Correspondence to:
Carolina Silva Barboza de Aquino. Serviço de Pneumologia Pediátrica, Instituto da Criança, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, Avenida Dr. Enéas de Carvalho Aguiar, 647, CEP 05403-000, São Paulo, SP, Brasil.
Tel.: 55 11 2661-8500 or 55 71 99978-2681. E-mail: aquinocarolina04@yahoo.com.br
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to evaluate the impact that performing spirometry at every encounter has on the frequency of diagnosis of PExs, as well as on long-term pulmonary function.

METHODS

This was a prospective study including CF patients in the 5- to 18-year age bracket followed at the outpatient clinic of our institution. The diagnosis of CF was based on newborn screening or clinical manifestations, in combination with two positive sweat chloride tests (> 60 mmol/L) and/or identification of two pathogenic variants in the *CFTR* gene. The study was approved by the local research ethics committee (CAAE: 28176614.7.0000.0068), and parents or caregivers gave written informed consent. A modified written informed consent was obtained from all of the patients over 7 years of age.

Beginning in January of 2014, all of the CF patients visiting our outpatient clinic underwent spirometry, with the results being immediately available to the attending physician during the consultation. Spirometry was performed with a previously calibrated Koko® spirometer (nSpire Health, Inc., Longmont, CO, USA), in accordance with the recommendations of the American Thoracic Society and the European Respiratory Society. Percent predicted FEV_1 values were calculated with the Global Lung Initiative equation.[22] All included patients were followed for 12 consecutive months from the date of entry, and encounters were usually scheduled 2-3 months apart, with unscheduled, urgent visits when necessary. At the end of each encounter, the attending physician completed a questionnaire about whether or not a PEx was diagnosed at the time, whether or not antibiotic therapy was prescribed, and whether or not the pre-consultation spirometry had contributed to the treatment decision. Only the PExs diagnosed during patient encounters were considered for the analyses of frequency, but many patients were seen at unscheduled encounters. The choice of antibiotics was guided by culture, in accordance with the Brazilian guidelines for the diagnosis and treatment of CF.[21]

Data collected during the 12-month follow-up period were compared with data for the 24 months prior to the study, during which spirometry was performed at 6-month intervals. To facilitate the description of the outcomes, the 24 months prior to the study were referred to as the years 2012 and 2013, and the follow-up year was referred to as 2014. The data for the 24 months prior to the study were collected from patient medical records. Additionally, FEV_1 values for the years 2015 and 2016 were obtained from the Brazilian CF Patient Registry. The registry contains the best FEV_1 (in L) in a given year and the anthropometric data collected on the same day, allowing the calculation of percent predicted FEV_1 values.

The primary outcome analysed was a diagnosis of PEx, defined as a new prescription of antibiotic therapy for a clinical worsening of respiratory symptoms. A secondary outcome was the utility of the spirometry results for the diagnosis of PEx, established by the attending physician using as a criterion an FEV_1 decline ≥ 10% with or without worsening pulmonary symptoms indicative of PEx. A tertiary outcome was percent predicted FEV_1 at baseline, defined as the best percent predicted FEV_1 in a given year. Qualitative data are described as absolute and relative frequencies (proportions), whereas quantitative data are summarised as means and standard deviations or medians and interquartile ranges, depending on the pattern of distribution of each variable. A paired t-test and the Wilcoxon signed-rank test were performed to evaluate the contribution of spirometry to the clinical decisions, as well as to compare mean FEV_1 values before and after the intervention. For the comparative analysis of data in the three periods, only patients with historical data were included. Analysis of the three periods was performed in pairs, 95% CIs being included. The probability of making a type I error was set at $p < 0.05$. All analyses were performed with the IBM SPSS statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The study included a total of 80 patients. The mean age was 12.1 years (Figure 1). The characteristics of the patients are displayed in Table 1. During the follow-up, there were 418 encounters and an average of 5.2 consultations per patient/year. PExs were diagnosed in 27.5% of the encounters (115 occasions), at an average frequency of 1.44 PExs per patient/year (Figure 2). This was a significantly higher frequency than that observed in the year 2012 (0.88 PExs/patient/year), but there was a marginal difference in the year 2013 (1.15 PExs/patient/year).

The vast majority of PExs were treated on an outpatient basis with oral antibiotics in 85% of the occasions and inhaled antibiotics in 5% of the cases (with or without oral antibiotics). Hospitalisation for intravenous antibiotics was indicated in 10.4% of the cases. Pulmonary function (FEV_1) was cited by the attending physician as a criterion for the diagnosis of PEx in 83.5% of the cases. In 21.9% of the cases diagnosed with a PEx, the decision to initiate antibiotic therapy was exclusively defined by the acute decline in FEV_1 (Figure 3). Furthermore, in approximately 9% of the occasions, physicians reported that spirometry contributed to excluding an episode of PEx.

The median percent predicted FEV_1 was 85.7% (IQR: 54.7-102.7) during the follow-up period. The value was considerably higher than that for the 24 months prior to the study (76.9% [IQR: 57.6-95.2] for 2012 and 78.5% [IQR: 54.0-101.2] for 2013), but the difference was not statistically significant (Figure 4). When the data from the years 2015 and 2016 were included in the analysis, we observed a steady linear decline of approximately 2% per year in median percent predicted FEV_1 values during the

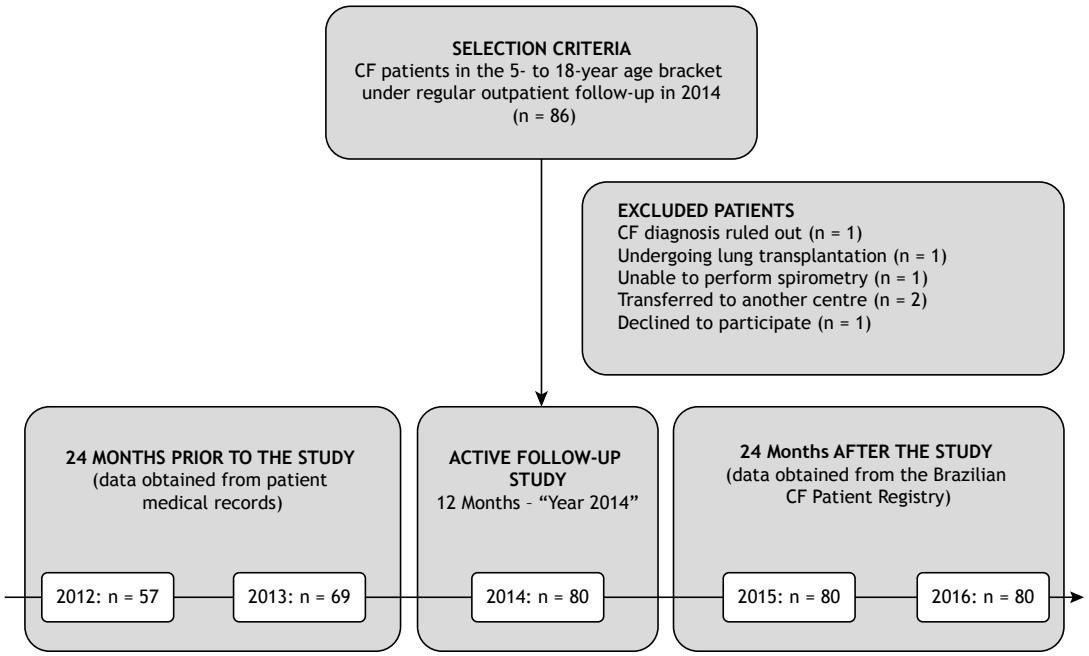

Figure 1. Study design. The study was completed in October of 2015, at which time the last patient to be included in the analysis completed 12 months of follow-up. CF: cystic fibrosis.

Table 1. Baseline characteristics of the study population (N = 80).[a]

Characteristic	Result
Sex	
Female	31 (38.7)
Male	49 (61.3)
Age, years	12.13 ± 3.43
Age at diagnosis, years	2.60 ± 3.71
Genotype	
F508del heterozygote	30 (40.5)
F508del homozygote	32 (43.3)
Other	12 (16.2)
Pancreatic insufficiency	80 (100)
BMI, kg/m^2	17.38 ± 3.64
Shwachman-Kulczycki score	73.4 ± 14.7
Microbiology	
Staphylococcus aureus	67 (84.8)
MRSA	16 (20.2)
Pseudomonas aeruginosa	37 (46.8)
Chronic medication use	
Dornase alfa	71 (89.9)
Inhaled tobramycin	33 (41.8)
Hypertonic saline	29 (36.7)
Azithromycin	30 (39.2)
CFTR modulators	0
FEV_1, % predicted	
≥ 90 (normal)	32 (40)
70-89 (normal/mild)	21 (26.3)
40-69 (moderate)	18 (22.5)
< 40 (severe)	9 (11.2)

MRSA: methicillin-resistant *Staphylococcus aureus*; and CFTR: cystic fibrosis transmembrane conductance regulator. [a]Values expressed as n (%) or mean ± SD.

follow-up period. However, they remained above 80% in the years following the study (Figure 4).

DISCUSSION

This study shows that performing spirometry at each encounter has a significant impact on the diagnosis of PExs during the outpatient management of CF patients. Spirometry was also associated with a meaningful increase in lung function. These findings reinforce the recommendations of several guidelines that spirometry be performed at each patient encounter and also indicate that recognising and treating PExs more often results in better lung function for CF patients.

An FEV_1 decline ≥ 10% was identified in 83.5% of PExs, and this finding was frequently used for the clinical decision to start antibiotics. Hence, a tendency was observed to diagnose more PExs and thus to prescribe more courses of antibiotics in comparison with the years prior to the study. Although there is still no clear definition of a PEx, the most used criterion[6] requires that a decline ≥ 10% in baseline FEV_1 be associated with another 3 out of 11 clinical features to establish a PEx diagnosis.[6] Currently, there is still much controversy regarding the definition of PEx.[16] Most definitions usually involve a medical decision to start a new course of antibiotics guided by worsening of the respiratory disease, as evidenced by intensification or new pulmonary signs and symptoms. Nevertheless, it is clear that FEV_1 measurements are very important.[16,23]

Frequent measurement of FEV_1 is vital to monitor its variations and to assess the severity of pulmonary disease in CF. Morgan et al.[24] showed that baseline FEV_1 variability is a predictor of subsequent declines in lung function at all stages of the disease. They concluded that quantification of FEV_1 changes is

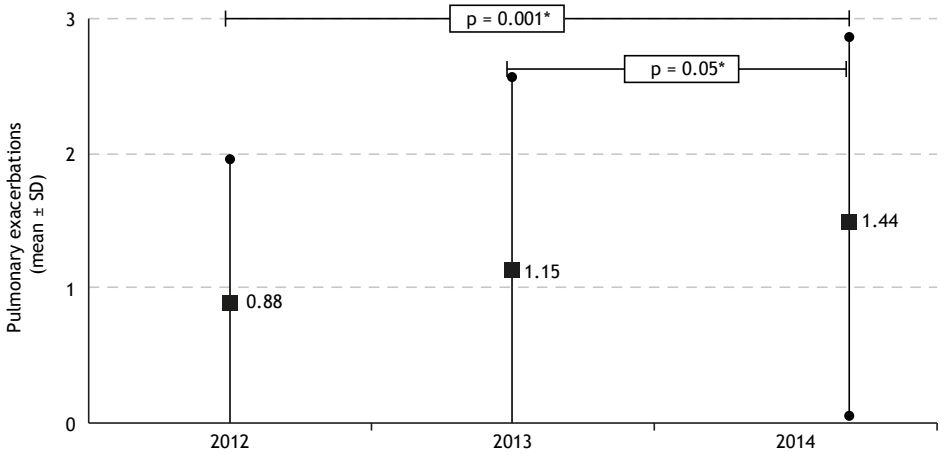

Figure 2. Frequency of pulmonary exacerbations in the study population (N = 80), expressed as the mean ± SD of pulmonary exacerbations per patient/year during the follow-up period and the two previous years. *Wilcoxon signed-rank test.

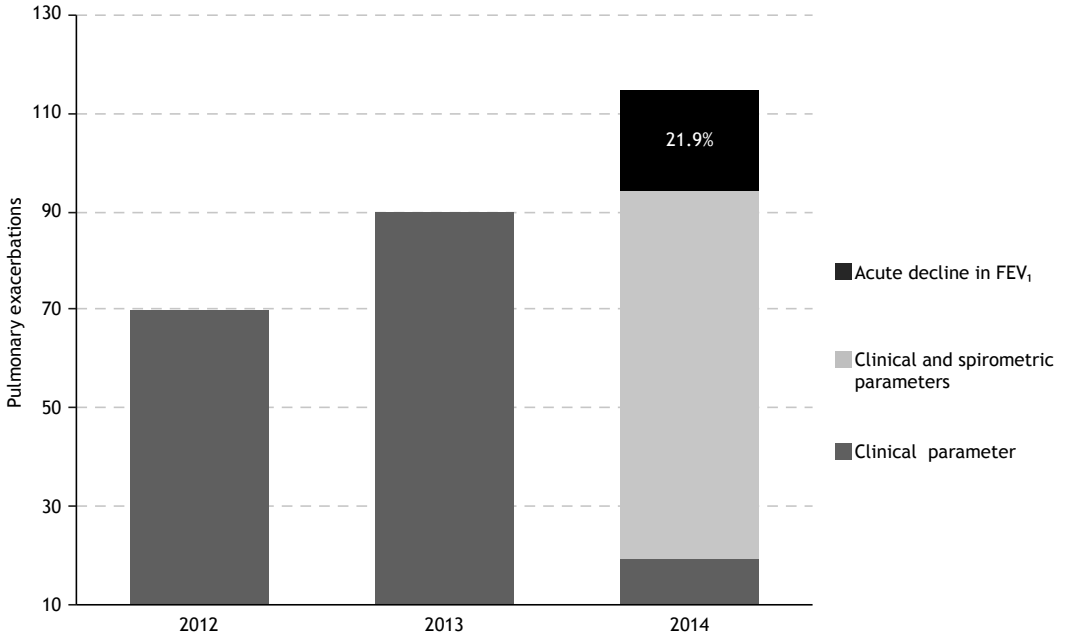

Figure 3. Absolute frequency of pulmonary exacerbation diagnosis in the study population (N = 80) in the years 2012, 2013, and 2014. The year 2014 displays the criteria used in order to diagnose pulmonary exacerbations.

important for identifying patients with a greater risk of decline in lung function.[24] Additionally, there are data suggesting that patients with higher baseline FEV_1 have a higher risk of FEV_1 decline over time,[17] which may be due to the fact that they receive fewer therapeutic interventions when facing a decline in their FEV_1 (such as antibiotics and hospitalisations).[25] The current study showed that 21.9% of PEx diagnoses were recognised exclusively by the acute decline in FEV_1 in the absence of other signs and symptoms of worsening pulmonary disease.

A significant increase in the diagnosis of PEx was observed in the current study as a result of frequent FEV_1 measurements. However, other studies have shown that doctors do not treat all episodes of FEV_1 decline, even when they occur at a rate ≥ 10%.[23] In a retrospective analysis of data from an epidemiologic study of CF,[26] Wagener et al.[23] showed that 29.3% of patients with an acute decline in FEV_1 ≥ 10% were not treated with antibiotics, particularly if they had not been admitted for intravenous treatment for PEx in the previous year. This may result in a significant decline in lung function over time because half of the functional declines seen in CF patients are associated with the occurrence of PExs.[16] A higher frequency of PExs and a shorter interval between them are associated with a greater decline in FEV_1, especially if the interval between PExs is less than 6 months.[13]

Most of the PExs identified in the present study had a mild to moderate presentation characterised by a

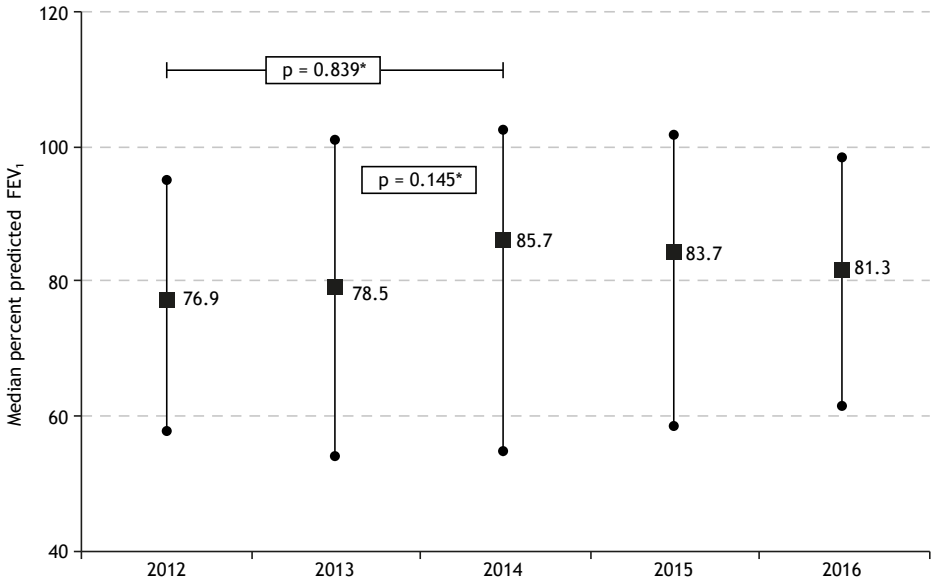

Figure 4. Median percent predicted FEV_1 values (IQR) during the study period. Data for the years 2015 and 2016 were obtained from the Brazilian Cystic Fibrosis Patient Registry. *Wilcoxon signed-rank test.

higher proportion of oral antibiotic use (85%), with only 10% of patients requiring hospitalisation for intravenous antibiotics. Although these events appeared to have a minor impact, most of the orally treated patients with PExs exhibited a decline in FEV_1. This could indicate a slow or long-term decline and a lack of perception. Recent data indicate that even orally treated PExs may have a significant impact on lung function decline, even in patients without a significant decline in FEV_1 at the time of the PEx diagnosis.[15] There are still controversies in establishing a patient's baseline FEV_1 and defining how much recovery is expected following the treatment of a PEx. Nevertheless, it is reasonable to suggest that it is more detrimental to fail to diagnose and treat a PEx than to overtreat patients for an incorrect diagnosis.[16]

This study has several limitations. The study was not randomised, and we did not assess FEV_1 variations over time as an outcome measure or other aspects that could impact lung function decline, such as microbiological colonisation and adherence to treatment. Patients who had more advanced lung disease and who experienced frequent and prolonged hospitalisations were not included, because they had few outpatient consultations. The FEV_1 data for the years 2015 and 2016 were not obtained during regular consultations, being instead obtained from the Brazilian CF Patient Registry. In addition, a longer follow-up would be necessary to determine the annual rate of decline in FEV_1 and to identify additional risk factors. A possible bias is a change in behaviour of attending physicians facing more frequent lung function data. On the other hand, this was a real-life study, and the results were so impressive for our practice that spirometry was definitely incorporated into the routine of CF outpatient consultations, providing data for future studies.

The hypothesis that earlier diagnosis and more frequent treatment of PExs are associated with improved lung function in CF patients seems to be very likely. The median percent predicted FEV_1 increased from 78.5% to 85.7% during the follow-up period. Although this difference was not statistically significant, the improvement was sustained in the following years in which the pre-consultation spirometry protocol was maintained, with a median percent predicted FEV_1 above 80%.

New data stemming from the use of technological resources such as electronic home monitoring suggest that serial measurements of FEV_1 can improve the ability to detect a PEx at home, with high sensitivity and specificity.[27] Furthermore, in a recent study, Schechter et al. reported the promising results of a standardised approach to recognising and treating PExs as early as possible.[28] The approach emphasised frequent measurements of FEV_1, being very sensitive and consistent with regard to intervention, which is triggered by changes as small as 5% in percent predicted FEV_1. They reported a significant and marked improvement in lung function, with mean percent predicted FEV_1 values increasing from 87% to 98% in 5 years.[28]

In conclusion, the present study demonstrated that performing spirometry in CF patients during routine visits resulted in a significant increase in the frequency of PEx diagnosis and treatment. The impact of such a simple initiative can be substantial and even more relevant in countries such as Brazil, with reduced treatment resources and financial constraints. Further

studies could be of value to identify other aspects that impact lung function in CF patients in Brazil.

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AUTHOR CONTRIBUTIONS

CSBA, JCR, and LVRFSF: conception and planning of the study. CSBA and LVRFSF: drafting and revision of the manuscript. LVRFSF: approval of the final version.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Hospitalizations for pulmonary embolism in Brazil (2008-2019): an ecological and time series study

Jéssica Alves Gomes[1], José Elias Bezerra Barros[1], André Luis Oliveira do Nascimento[1], Carlos Alberto de Oliveira Rocha[1], João Paulo Oliveira de Almeida[1], Gibson Barros de Almeida Santana[1], Divanise Suruagy Correia[2], Márcio Bezerra Santos[3], Rodrigo Feliciano do Carmo[4,5], Carlos Dornels Freire de Souza[1,6]

1. Núcleo de Estudos de Medicina Social e Preventiva, Departamento de Medicina, Universidade Federal de Alagoas, Arapiraca (AL), Brasil.
2. Faculdade de Medicina, Universidade Federal de Alagoas, Maceió (AL), Brasil.
3. Departamento de Morfologia, Universidade Federal de Sergipe, Aracaju (SE), Brasil.
4. Faculdade de Ciências Farmacêuticas, Universidade Federal do Vale do São Francisco, Petrolina (PE), Brasil.
5. Programas de Pós-Graduação em Biociências e Ciências da Saúde e Biológicas, Universidade Federal do Vale do São Francisco, Petrolina (PE), Brasil
6. Programa de Pós-Graduação em Saúde da Família, Universidade Federal de Alagoas, Arapiraca (AL), Brasil.

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ABSTRACT

Objective: To assess the temporal trends of hospitalizations for pulmonary embolism (PE) in Brazil, its regions, and states between 2008 and 2019. **Methods:** An ecological and time series study was conducted. Data were obtained from the Hospital Information System (SIH) of the Brazilian Ministry of Health. The inflection point regression model was applied for temporal trend analyses. Trends were classified as increasing, decreasing, or stationary according to the slope of the regression line. The Annual Percent Charge (APC) and the Average Annual Percent Change (AAPC) were calculated considering a confidence interval of 95% and *p*-value <0.05. Furthermore, spatial distribution maps of epidemiological indicators related to PE in Brazil were elaborated. **Results:** There was an increasing trend in the hospitalization rate for PE in Brazil, ranging from 2.57 in 2008 to 4.44/100,000 in 2019 (AAPC=5.6%; p<0.001). Total and average hospitalizations costs also showed increasing trend in the country (AAPC=9.2% and 3.0%, respectively). Still, there was a decrease in the in-hospital mortality rate (from 21.21% to 17.11%; AAPC=-1.9%; p<0.001). Similar trends were observed in most regions. The average hospitalization time in Brazil showed a stationary trend. The hospitalization rate has also increased in 18 states (66.67%). Seven states showed a decrease in the mortality rate (25.93%), except for Roraima, which showed an increasing trend. **Conclusion:** Hospitalizations for PE represent a serious public health problem in Brazil and the temporal patterns observed herein demonstrate an increasing trend in all regions and states of the country.

Keywords: Pulmonary embolism; Epidemiology; Ecological studies; Time series.

INTRODUCTION

Pulmonary Embolism (PE) is considered a severe clinical condition, characterized by obstruction, usually by a thrombus, in the pulmonary artery or in one of its branches,[1] causing hypoxemia, release of potent vasoconstrictors, increased pulmonary vascular resistance and ventricular afterload.[2,3]

Currently, PE is considered one of the leading causes of death in hospitalized patients.[4] After a first episode of embolism, there is a 39.9% greater chance of recurrence in the following ten years, with the risk of death being higher during the first two years.[5] Additionally, the mortality rate is around 15.3% in three months, and it ranges from 25% to 30% in five years if left untreated.[6]

Ageing is one of the main factors associated with increased risk of developing thromboembolism.[7] In Brazil, it is estimated that in 2050, the elderly population will reach 30.3 million, approximately 14.6% of the total number of Brazilians. Also, the increase in life expectancy has been accompanied by epidemiological changes and an increase in chronic diseases and risk factors, such as obesity and cardiovascular diseases (hypertension, myocardial infarction and heart failure), which increase the risk of pulmonary embolism.[7] In 2020, for example, data from Vigitel survey (*Surveillance of risk factors and protection for chronic diseases by telephone survey*) showed a prevalence of obesity in 21.5% of respondents, and hypertension in 25.5% of them in Brazilian capitals.[8]

In the period between 2003 and 2013, the annual number of inpatient episodes for patients diagnosed with pulmonary embolism showed an increase in incidence rate from 20.6 to 35.0.[1] On the other hand, the availability and use of risk stratification and diagnosis tools in the hospital environment has supported the early

Correspondence to:
Carlos Alberto de Oliveira Rocha. Universidade Federal de Alagoas, Campus Arapiraca, Rodovia AL-115, Bom Sucesso, CEP 57309-005, Arapiraca, AL, Brasil.
Tel.: +55 82 3482-1800. E-mail: carlos.alberto@arapiraca.ufal.br
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identification of patients at low risk of complications, who are discharged early, impacting the reduction of hospital costs.[9]

In Brazil, previous studies on PE epidemiology are scarce. In addition, those available in the scientific literature may not reflect the current reality, as the time periods of the analyzes are already outdated. In this sense, Brazil lacks new evaluations on the temporal trend of PE at national level, which are quite important for the design and implementation of public health strategies. Thus, this study aimed to assess the temporal trend of hospitalizations for PE in Brazil, its regions, and states between 2008 and 2019.

METHODS

An ecological and time-series study was conducted using data from PE hospital admissions from January 2008 to December 2019 in Brazil, its regions, and states. A 10-year time series was used as it allows identifying changes in the occurrence of the studied phenomenon. Furthermore, 2020 was not included due to the COVID-19 pandemic. During this period, the Brazilian population increased from 191 million inhabitants to about 210 million, being the Southeast (88 million) and Northeast (56 million) regions the most populous.[10]

In this study, the following variables were assessed: i) number of hospitalizations; ii) hospitalization rate per 100,000 inhabitants; iii) total and average cost (BLR) of the Hospital Admission Authorization (AIH); iv) hospitalization time (in days); v) average of hospitalization time (in days); and vi) number of deaths and in-hospital mortality rate (%). Data were extracted from the Hospital Information System (SIH), through the Department of Informatics of the Brazilian Unified Health System.[11]

Importantly, SIH gathers information from about 70% of public hospital admissions in the country.[11] Its data collection instrument is AIH, currently issued by the states and based on a single numerical series annually defined by decree of the Brazilian Ministry of Health.[11] Data related to the ICD-1/I26 were collected. Moreover, the population data used in the study were obtained from the Brazilian Institute of Geography and Statistics (IBGE),[10] considering 2010 census and inter-census projections for the other years.

Time trend analyzes were performed using the inflection point regression model (Joinpoint Regression Model). This method consists of a regression model that tests whether a line with multiple segments is statistically more adequate to describe the temporal evolution of a set when compared to a straight line or fewer segments.[12] In addition, the Annual Percent Change (APC) and the Average Annual Percent Change (AAPC) were calculated considering a confidence interval of 95% (95% CI) and significance of 5% (p-value<0.05). The trend can be classified either as increasing (APC/AAPC+ and p-value<0.05), decreasing (APC/AAPC- and p-value<0.05), or stationary (p-value>0.05). The model automatically identifies at which point in time an inflection occurred. In this sense, each analyzed location may present different trends at different points in time. Time trend analyzes were performed using the Joinpoint regression software program (version 4.5.0.1, National Center Institute, Bethesda, MD, USA).

To map the spatial distribution of the epidemiological indicators related to hospital admissions for PE, firstly was obtained the digital cartographic mesh (in shapefile format) of Brazil, segmented by regions and states, in the Geographic Projection System latitude/longitude. Mesh was also obtained from IBGE database.[10] Subsequently, maps were constructed, considering data on all epidemiological indicators assessed herein. Results were represented on choroplethic maps. We used QGis software, version 3.4.11 (QGIS Development Team; OpenSource Geospatial Foundation Project) to create the maps.

Considering the use of secondary data, in which it is not possible to identify any subject, this study did not require the approval by an ethics committee.

RESULTS

Spatial distribution of the epidemiological indicators on pulmonary embolism in Brazil (2008-2019)

In the analyzed period (2008-2019), a total of 81,152 cases of PE were recorded in Brazil, which corresponds to a hospitalization rate of 3.38 per 100,000 inhabitants. These hospitalizations have cost a total of BRL 138 million and an average of BRL 1,676.30 per hospitalization. The sum of the total hospitalization time was 774,427 days and the average was 9.5 days per hospitalization. Among them, 16,332 evolved to death (in-hospital mortality rate =20.1%; Figure 1 A-H).

The Southeast region ranked first in five indicators: number of hospitalizations (n=44,945), total cost of hospitalizations (BRL 79,291,311.70), total time of hospitalization (450,176 days), number of deaths (9,277), and average cost per hospitalization (BRL 1,744). Neverheless, the South region had the highest hospitalization rate (5.7/100,000) and the Northeast had the highest average of hospitalization time (10.3 days) and in-hospital mortality rate (25.1%).

Regarding Brazilian states, São Paulo had the highest number of hospitalizations (n=23,540), total cost of hospitalization (BRL 42,959,761.00), total time of hospitalization (n=273,280), and number of deaths (n=5,203). Nevertheless, the longest average time of hospitalization was observed in the Federal District (14 days); the state of Sergipe had the highest average cost per hospitalization (BRL 2,219.90); the highest rate of hospitalization was recorded in Minas Gerais (6.75/100,000); and the highest in-hospital mortality rate was registered in Paraiba state (45.3/100,000).

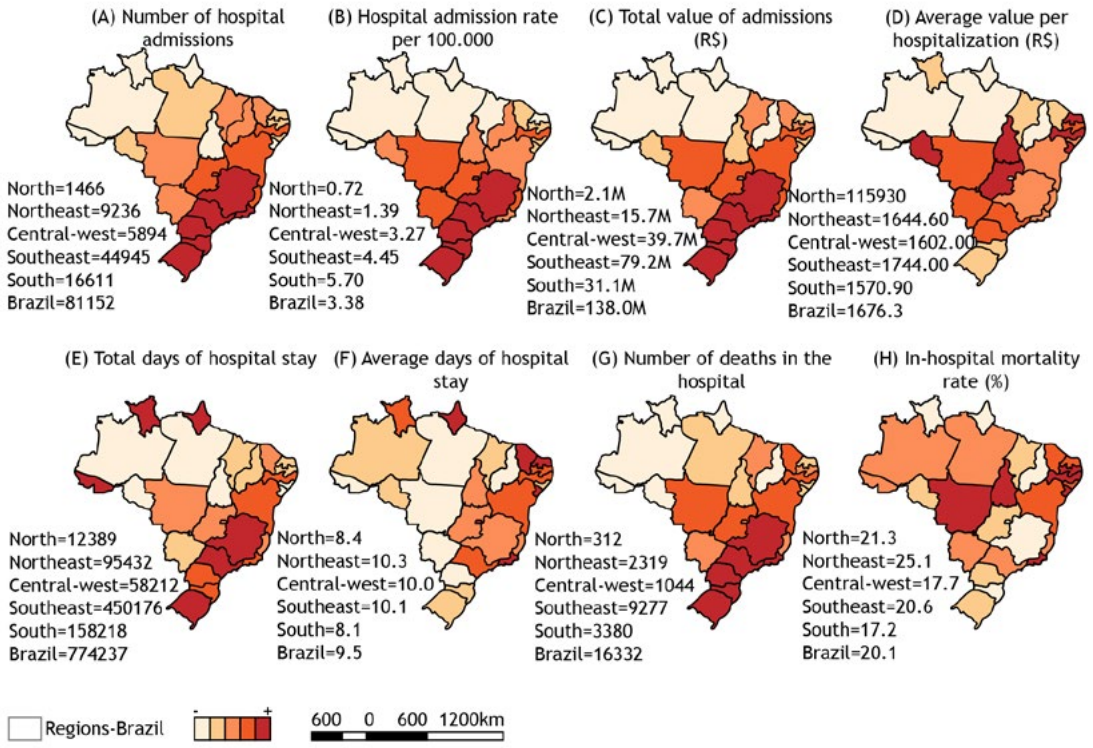

Figure 1. Spatial distribution maps of epidemiological indicators related to hospital admissions for Pulmonary Embolism (PE) in the states and regions of Brazil between 2008 and 2019.

Time trend analysis of national, regional, and state indicators

An increasing time trend in the hospitalization rate was observed in Brazil (from 2.57 in 2008 to 4.44/100,000 in 2019; AAPC=5.6%; p<0.001). Likewise, the Northeast, Central-West, Southeast, and South regions showed increasing trends in hospitalization rates. Importantly, the Northeast region showed the greatest increase in the period studied (AAPC=11,7%; p<0,001), while the North region had a stationary trend. Regarding the data by state, 66.67% (n=18) had an increasing trend, while in 33.33% the trend was stationary. The state of Roraima (in the North region) had the highest growth in hospitalization rate (AAPC=42.7%; p<0.001; Figure 2; Table S1).

Likewise, the total cost of hospitalizations also showed an increasing trend in Brazil (from BRL 6.3 million to 16.5 million; AAPC=9.2%; p<0.001). This temporal pattern was observed in all Brazilian regions, especially in the Northeast (AAPC=15.9%; p<0.001). Additionally, 20 states (74.07%) showed an increasing trend in the total costs, while 7 states (25.93%) presented a stationary trend. The state of Roraima showed the highest increasing rate during the period studied (AAPC=113%; p<0.001; Figure 3; Table S2).

Furthermore, the average cost per hospitalization also showed an increasing trend in Brazil (from BRL 1,298.24 to 1,775.4; AAPC=3%; p<0.001) and in all its regions. The North and Central-West regions showed the greatest increase in the period (AAPC=5.1%; p<0.001 in both), and the Northeast region showed the smallest increase (AAPC=2% p<0.001). Similarly, increasing temporal patterns were observed in 12 states (44.44%; Figure 4; Table S3).

On the other hand, the average time of hospitalization showed a stationary trend in Brazil (from 9.1 to 8.7 days; AAPC=-0.4%; p=0.4) and in all regions. Notwithstanding, the Southeast region showed a decreasing trend from 2010 to 2019 (APC=-1.6%; p<0.001). Similar patterns were observed in three other regions: Central-West (2012-2018; APC=-3.2%; p<0.001), South (2013-2018; APC=-2.5%; p<0.001) and Northeast (2013-2018; APC=-1.7%; p<0.001). As to the analyses per state, six (22.22%) showed an increasing trend, while three (11.11%) showed a decreasing trend (Figure 5; Table S4).

Finally, the in-hospital mortality rate due to PE showed a decreasing trend (from 21.21% to 17.11%; AAPC=-1.9%; p<0.001) in Brazil and in the Southeast region (AAPC=-2.7%; p<0.001). Conversely, other regions showed a stationary pattern. Interestingly, region South showed an inflection point, showing a decreasing trend from 2011 onwards (APC=-4.8%; p<0.001). In the analysis by states, only Roraima

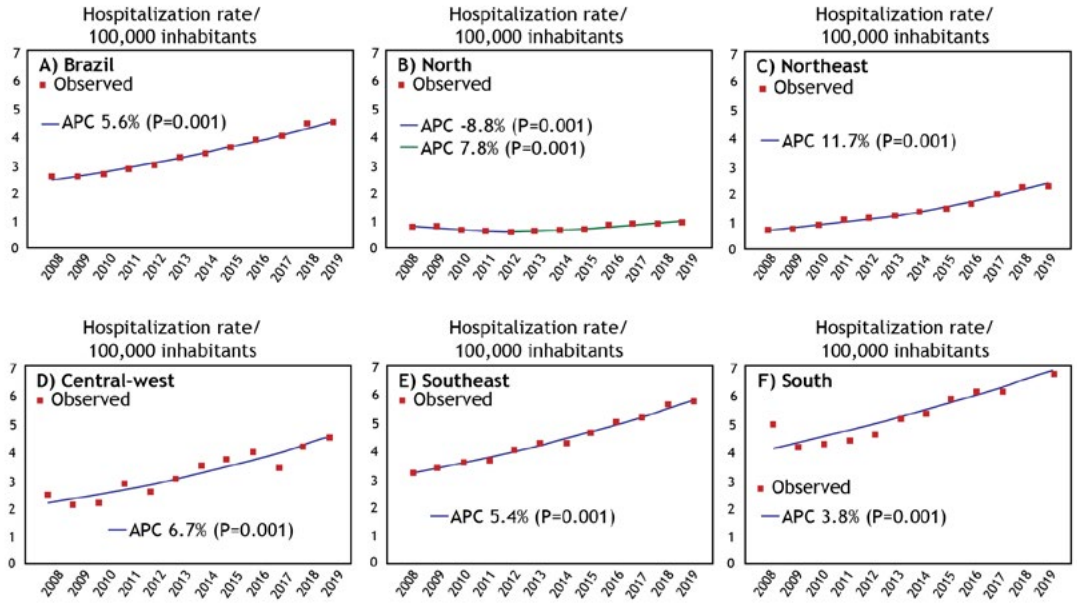

Figure 2. Temporal trend of the hospitalization rate due to pulmonary embolism (PE) in Brazil, its regions, between 2008 and 2019.

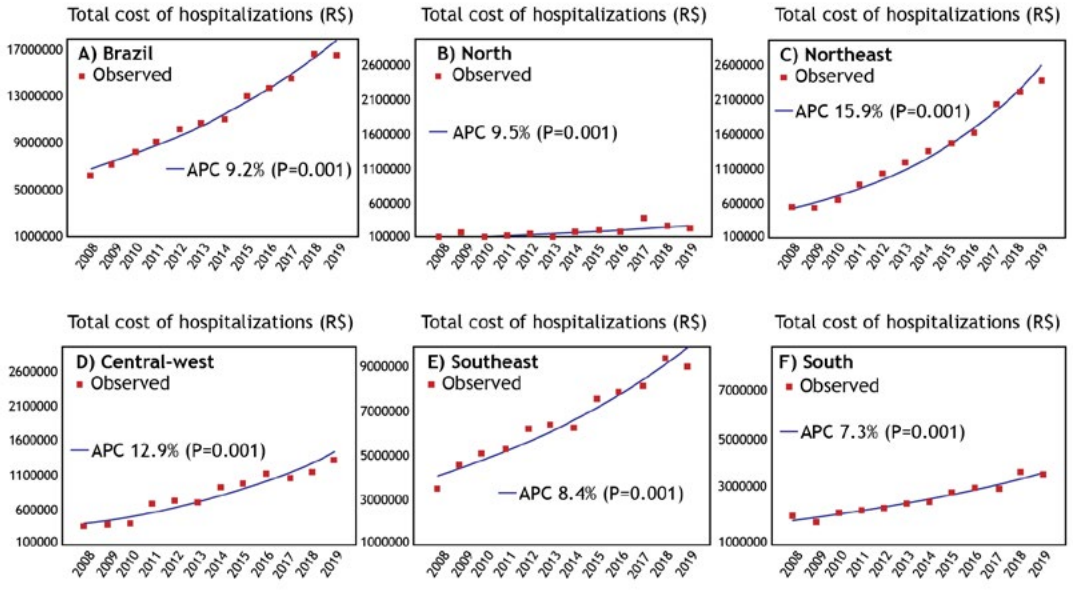

Figure 3. Temporal trend of the total cost of hospitalizations due to pulmonary embolism (PE) in Brazil, its regions, between 2008 and 2019.

showed an increasing trend of in-hospital mortality rate (APC=85.7%; p<0.001), while 7 states (25.93%) had a stationary trend (Figure 6; Table S5).

The specific analyzes of each of the regions of Brazil or its states are presented in the Supplementary Tables.

DISCUSSION

An ecological and population-based study was carried out to assess the temporal trends of hospital admissions caused by PE in Brazil between 2008 and 2019. Our data showed an increasing trend in the rate and in the

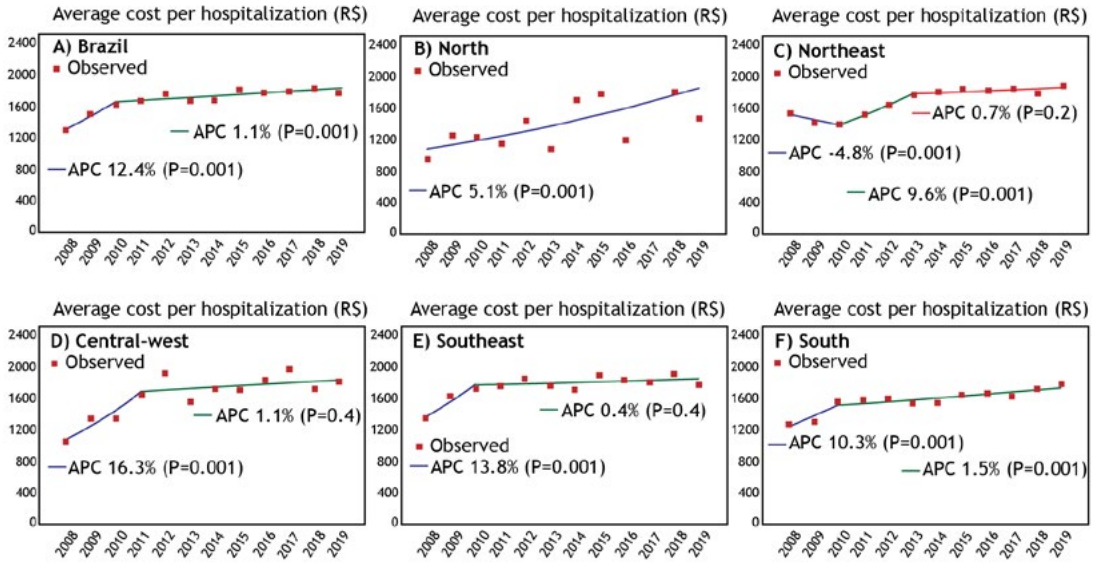

Figure 4. Temporal trend of the average cost per hospitalizations due to pulmonary embolism (PE) in Brazil, its regions, between 2008 and 2019.

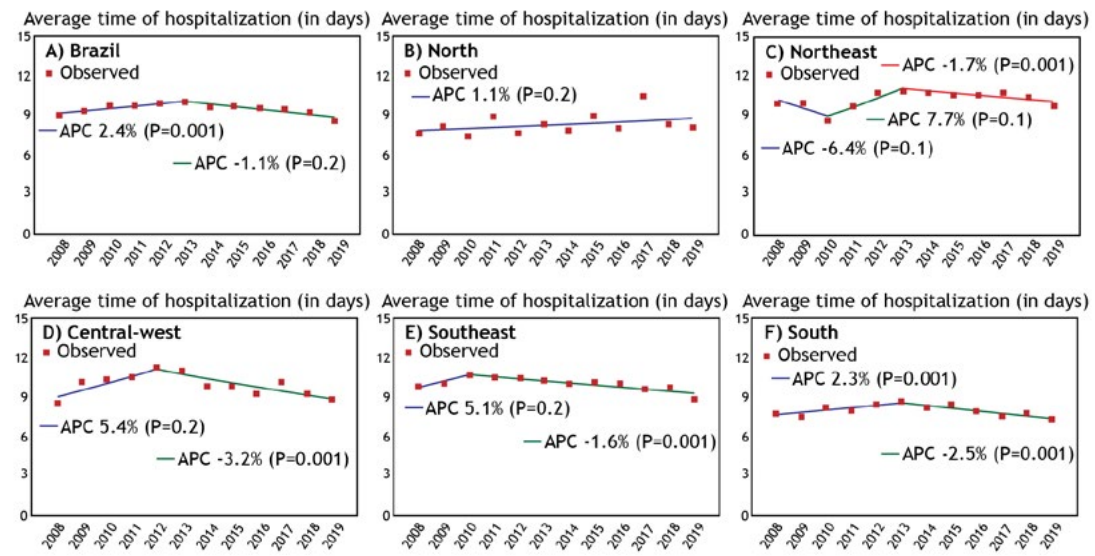

Figure 5. Temporal trend of average time of hospitalization (in days) due to pulmonary embolism (PE) in Brazil, its regions, between 2008 and 2019.

total cost of hospitalizations for PE in Brazil. However, a decreasing trend in the in-hospital mortality rate due to PE was observed. Besides, important spatial variations in the epidemiological indicators associated with PE, as well as in temporal trends among Brazilian regions and states were demonstrated.

Notably, the increase in the hospitalization rate due to PE observed in this study may be related to the context of demographic and epidemiological transition that Brazil has been going through in recent decades, with a decline in birth and mortality rates, and a significant increase in the population's life expectancy.[13,14] The aging of the population also leads to an increase in the occurrence of cardiovascular diseases such as PE, which corresponds to one of the most prevalent diseases in the elderly, especially in those over 65 years old.[7]

It is estimated that in 2050, the number of elderly in Brazil will exceed that of children under 15 years old.[10]

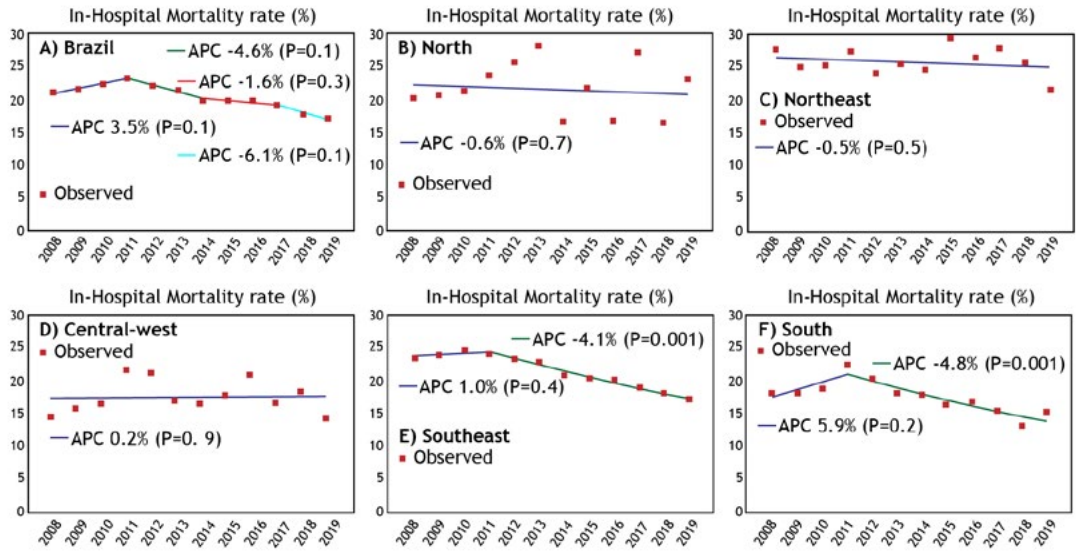

Figure 6. Temporal trend of in-hospital mortality rate (%) due to pulmonary embolism (PE) in Brazil, its regions, between 2008 and 2019.

In 2040, it is expected that there will be about 153 elderly people for every 100 young people under 15 years of age.[15] Furthermore, the proportion of those over 65 years old will increase from 9.6% in 2020 to 31.3% in 2075. In 2100, this proportion is expected to be 34.1%.[16] As a result, an increase in the prevalence of many non-communicable chronic diseases (NCDs) is also expected, such as cardiovascular diseases, cancer, and respiratory diseases, which represent risk or aggravating factors for the occurrence of PE.[17,18]

In Brazil, the South region has the highest rate of aging (54.94%).[19] This may explain the higher rate of hospitalization for PE observed (5.7/100,000) in this study, when compared to other regions. Also, the Southeast and South regions have better hospital infrastructure and availability of technological resources in the country.[14] Consequently, the population has a greater access to diagnostic tools, such as computed tomography angiography (CT-angiography), which allows for an early diagnosis and the identification of cases that would not be captured by other methods. In addition, scores, diagnostic flowcharts, and risk stratification can be used, which allows for more adequate management and better patient outcome.[9,20-22]

Additionally, the use of oral anticoagulant drugs, such as rivaroxaban, dabigatrana and apixabana, has been shown to be an effective measure for the clinical improvement of patients.[23,24] These drugs have reduced the monitoring and hospital stay time of the patient and has led to an increase in early discharge. However, access to these drugs is still not adequate, especially for patients in the public system, which may explain the stationary trend in the average length of stay for PE.

The stable trends observed in the average time of hospitalization, at national and regional levels, may be associated with the availability of technological and pharmaceutical resources. For example, despite the stationary trend observed in Brazil, hospital stay days in the Northeast region are longer than in the South (24.5% higher). Regardless of the social, economic, and health advances achieved in recent decades in Brazil, access to the health system is still unequal.[25,26] Patients from the South and Southeast regions are more likely to have access to better health services when compared to those in the North and Northeast regions.[25] These findings reinforce the importance and need to adopt strategies to mitigate existing socioeconomic and technological inequalities in Brazil and improve access to early diagnosis and adequate treatment for PE.

In the USA, the average PE hospitalization time was 4 days, with a progressive reduction between 2000 (4) and 2015 (2 days).[27] In another study carried out in Portugal, the average time of hospitalization was 12.3 days, with a slight reduction between 2003 (12.3) and 2013 (11.5 days).[1] In our study, this average was 9.5 days between 2008 and 2019. Despite the reduction from 9.1 to 8.7 days in the average time of hospitalization, our analyzes showed a stationary trend. These variations may be related to health network structure in each country.

Herein, the average and total cost of hospitalizations for PE showed increasing trends in the period studied. These studies show that the implementation of venous thromboembolism (VTE) algorithms in hospitals is important to reduce in-hospital VTE. This education program could decrease costs too.[28,29] A VTE prophylaxis

thrombus prevention program implemented in four hospitals in Salvador/BA showed a significant increase in the use of correct heparin doses (53% before implementation of the program and 75% after).[29]

The increase in the total cost is probably due to the growth in hospitalizations that occurred in the country and its regions. Alternatively, the increase in the average cost per hospitalization may be related to the use of more advanced methods of diagnosis and treatment in hospitals. Although these improvements lead to a reduction in hospital stay, they are more costly to health systems and increase the average and total cost of hospitalizations. Similarly, this growth was also observed in other countries, such as the USA, where all age groups showed an average increase in the cost of hospitalization, ranging from $13,000.00 to $15,000.00.[27] More importantly, patients with PE usually also have some comorbidity, such as pneumonia, femoral neck fracture, stroke, lung cancer, and others.[7,15] The occurrence of PE, along with comorbidities, can aggravate not only the patient's clinical outcome, but also the cost of hospitalization.

Some limitations of our study should be mentioned. An ecological study was conducted using secondary data that could be biased, mainly in relation to differences in the quality of information systems between regions of the country. As a result, both the number of PE cases and the number of deaths may be underreported, especially in the North and Northeast regions. Additionally, errors in data typing in the information systems, as well as the inclusion of suspected but unconfirmed cases, can compromise the quality of the data.

Taken together, our analyses showed increasing trends in the hospitalization rate and in the total and average cost for PE in Brazil and its regions. On the other hand, we identified a decreasing trend in the in-hospital mortality rate, while the average length of hospital stay showed a stationary trend. Additionally, we observed spatial variations in temporal trends between regions and states in Brazil. These findings therefore highlight the urgent need to develop regional and local strategies that promote improvements in hospital infrastructure, diagnostic services, and timely treatment of cases, so that there is a reduction in the time and cost of hospitalizations and, especially in the mortality rate due to PE in the country.

AUTHOR CONTRIBUTIONS

JAG, JEBB and CDFS: substantial contribution to the study design; data analysis and interpretation; drafting and revision of the manuscript; and approval of the final version to be published. CAOR, RFC, MBS, DSC, ALON, JPOA and GBAS: data collection and analysis and drafting and revision of the manuscript.

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ORIGINAL ARTICLE

Sleep health and the circadian rest-activity pattern four months after COVID-19

Mario Henríquez-Beltrán[1], Gonzalo Labarca[2,3], Igor Cigarroa[1], Daniel Enos[4], Jaime Lastra[4], Estefania Nova-Lamperti[2], Adriano Targa[5], Ferran Barbe[5,6]

1. Escuela de Kinesiología, Facultad de Salud, Universidad Santo Tomás, Chile.
2. Laboratorio de Inmunología Traslacional, Departamento de Bioquímica Clínica e Inmunología, Facultad de Farmacia, Universidad de Concepción, Concepción, Chile.
3. Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, Boston (MA) USA.
4. Facultad de Medicina, Universidad de Concepción, Concepción, Chile.
5. Translational Research in Respiratory Medicine (TRRM) Group, Hospital Universitari Arnau de Vilanova-Santa Maria, IRBLleida, Lleida, España.
6. Centro de Investigación Biomedica En Red de Enfermedades Respiratorias – CIBERES – Madrid, España.

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Study carried out at the Hospital Clínico Regional Dr. Guillermo Grant Benavente, Concepción, Chile, and the Complejo Asistencial Dr. Víctor Ríos Ruiz, Los Ángeles, Chile.

ABSTRACT

Objective: To describe the prevalence and severity of sleep disorders and circadian alterations in COVID-19 patients four months after the acute phase of the disease. **Methods:** This was a cross-sectional observational prospective study of patients with mild COVID-19, moderate COVID-19 (requiring hospitalization but no mechanical ventilation), or severe COVID-19 (with ARDS) four months after the acute phase of the disease. All patients underwent a home sleep apnea test and seven-day wrist actigraphy, as well as completing questionnaires to assess sleep quality and mental health. Differences among the three groups of patients were evaluated by ANOVA and the chi-square test. **Results:** A total of 60 patients were included in the study. Of those, 17 were in the mild COVID-19 group, 18 were in the moderate COVID-19 group, and 25 were in the severe COVID-19 group. Sleep quality, as assessed by satisfaction, alertness, timing, efficiency, and duration scale scores, was found to be impaired in all three groups, which also had a high prevalence of unhealthy sleep, as assessed by the Pittsburgh Sleep Quality Index. The prevalence of insomnia was increased in all three groups, as assessed by the Insomnia Severity Index. The home sleep apnea test showed that the overall prevalence of obstructive sleep apnea was 60%, and seven-day wrist actigraphy showed that total sleep time was < 7 h in all three groups. Changes in quality of life and in the circadian rest-activity pattern were observed in all three groups. **Conclusions:** Sleep-related symptoms, changes in the circadian rest-activity pattern, and impaired mental health appear to be common in COVID-19 patients four months after the acute phase of the disease, severe COVID-19 being associated with a higher prevalence of obstructive sleep apnea.

Keywords: Sleep apnea, obstructive; Sleep disorders, circadian rhythm; COVID-19.

INTRODUCTION

The current health emergency due to COVID-19 is the first pandemic of the 21st century.[1] It has spread across the world rapidly.[2,3] After the acute phase of the disease, current evidence indicates that clinical, physical, and mental health continues to be affected.[4-6] Novel research applies the term "long COVID-19 syndrome" to identify this subtype of patients with persistent symptoms during the recovery phase.[7] Previous studies have indicated that, after acute COVID-19 infection, the most common symptoms are anxiety, depression, fatigue, and impaired pulmonary function.[4] Moreover, other studies suggest that, during the recovery phase, COVID-19 patients report more posttraumatic stress symptoms and deterioration of preexisting psychiatric disorders.[6-9] However, most of the studies aiming to explore COVID-19 sequelae include clinical data, pulmonary function data, and health-related quality of life (HRQoL) data, excluding a comprehensive evaluation of sleep health and circadian rhythms.

The sleep-wake cycle is under a circadian rhythm, along with several other processes, including the control of body temperature and the secretion of hormones such as cortisol and melatonin.[10] COVID-19 and its associated context can, by affecting sleep, affect other circadian rhythms and sleep-related processes such as cognition and immune function.[8] Additionally, sleep disorders such as obstructive sleep apnea (OSA) can be linked to both processes.[11] Moreover, OSA has been linked to severe COVID-19 and worse outcomes during the recovery phase.[12] Therefore, it is necessary to investigate the relationship of sleep health and disruption of the circadian rest-activity pattern with the severity of COVID-19. The objective of the present study was to describe the prevalence and severity of sleep disorders and circadian alterations in COVID-19 patients four months after the acute phase of the disease.

METHODS

This was a cross-sectional observational prospective study including two hospitals in Chile (the *Hospital Regional Dr. Guillermo Grant Benavente* and the *Complejo Asistencial Dr. Víctor Ríos Ruiz*) and performed

Correspondence to:
Gonzalo Labarca. Division of Sleep and Circadian Disorders, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Avenue, Boston, MA, USA.
Tel.: 1 617 955-2145. Email: glabarca@bwh.harvard.edu
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in accordance with current guidelines for reporting observational studies.[13] The study protocol was approved by the institutional review boards of the Biobío Health Service and the Concepción Health Service (Code CEC-SSC: 07-20-26).

We included patients ≥ 18 years of age with an RT-PCR–confirmed diagnosis of SARS-CoV-2 infection between April and July of 2020. We included COVID-19 patients with varying degrees of disease severity, in accordance with the WHO definitions[3]: severe COVID-19—severe hypoxemia and medical records of ARDS in accordance with the Berlin definition[14]; moderate COVID-19—clinical or radiographic evidence of lower respiratory tract disease; and mild COVID-19—mild symptoms (e.g., fever, cough, and loss of taste or smell, without dyspnea). The patients with severe COVID-19 required ICU admission; those with moderate COVID-19 required hospitalization but no mechanical ventilation; and those with mild COVID-19 received clinical outpatient monitoring and supportive care. All of the patients included in the study were evaluated four months after the acute phase of COVID-19.

We excluded patients with previous respiratory comorbidities (asthma, COPD, and other respiratory diseases); patients receiving oxygen supplementation or noninvasive mechanical ventilation after hospitalization for COVID-19; and patients over 70 years of age. We also excluded patients who were lost to follow-up, those who were transferred to other hospitals or towns after discharge, and those with mental disability that might prevent them from completing the evaluations.

After giving written informed consent, all participants underwent physical examination and blood sample collection for further analysis. We collected data on demographics (age, sex, level of education, and place of residence), as well as on BMI (in kg/m^2), waist circumference (in cm), neck circumference (in cm), hip circumference (in cm), and comorbidities at baseline.

Sleep health

At baseline, the study participants completed a self-report questionnaire including information on their sleep habits and sleep-related symptoms, similar to that employed by Mazzotti et al.[15] Furthermore, the study participants completed the Spanish versions of the following questionnaires:

1. The satisfaction, alertness, timing, efficiency, and duration (SATED) scale.[16] A SATED scale score of 10 indicates good sleep health.
2. The Pittsburgh Sleep Quality Index (PSQI). The PSQI ranges from 0 to 21. A score of 0 indicates no sleep difficulties, and a score of 21 indicates severe sleep difficulties. Participants with PSQI scores = 5 were classified as healthy in terms of sleep quality, whereas those with PSQI scores > 5 were classified as unhealthy.[17]
3. The Epworth Sleepiness Scale (ESS). An ESS score > 10 was considered indicative of daytime sleepiness, and an ESS score of ≤ 10 was considered indicative of no daytime sleepiness.[17]
4. The Insomnia Severity Index (ISI). The ISI evaluates the presence and severity of insomnia. An ISI score > 7 was used in order to indicate insomnia.[18]
5. The STOP-Bang questionnaire. The STOP-Bang questionnaire was used in order to assess the risk of OSA. Scores of 0-2 were considered indicative of a low risk of OSA; scores of 3 and 4 were considered indicative of an intermediate risk of OSA; and scores of 5-8 were considered indicative of a high risk of OSA.[19-21]
6. The Morningness-Eveningness Questionnaire (MEQ). The MEQ was used in order to assess chronotypes. MEQ scores of 16-30 were considered indicative of an extreme evening chronotype; MEQ scores of 31-41 were considered indicative of a moderate evening chronotype; MEQ scores of 42-58 were considered indicative of an intermediate chronotype; MEQ scores of 59-69 were considered indicative of a moderate morning chronotype; and MEQ scores of 70-86 were considered indicative of an extreme morning chronotype.[22]

Evaluation of OSA and the circadian rest-activity pattern

OSA was evaluated by means of a home sleep apnea test (HSAT). The HSAT was performed in accordance with the American Academy of Sleep Medicine recommendations.[23] The HSAT was manually scored by one researcher, who was blinded to the clinical and questionnaire data. The HSAT was performed with an ApneaLink Air™ home sleep testing device (ResMed, San Diego, CA, USA) between August and November of 2020. We collected data on the following variables: respiratory disturbance index (RDI—apneas or hypopneas associated with 3% oxygen desaturation per hour), mean SpO_2, nadir SpO_2, total time with SaO_2 below 90%, and oxygen desaturation index ≥ 3%. OSA was defined as an RDI ≥ 5 events/h, and non-OSA was defined as an RDI of ≤ 4 events/h.[23]

Seven-day wrist actigraphy was performed with an ActTrust 2 actigraph (Condor Instruments, São Paulo, Brazil) between August and November of 2020. The data collected by the actigraph were extracted with the use of ActStudio software (Condor Instruments).[24,25] We examined the following parameters: time in bed (in min); total sleep time (TST, in min), defined as the number of minutes spent asleep during the time spent in bed; sleep onset latency (in min), defined as the number of minutes between bedtime and the first minute scored as sleep; sleep efficiency (in %), defined as the ratio between TST and time spent in bed; wake after sleep onset (in min), defined as the number of minutes awake after sleep onset; and arousals (in n).[26]

To describe the shape and consistency of the 24-h rest-activity pattern, activity counts of 30-s epochs were obtained, and nonparametric circadian rhythm analysis was performed.[27] We extracted the following data: interdaily stability (IS), which ranges from 0 to 1, representing the synchronization between

the internal rest-activity rhythm and the different zeitgebers; intraday variability (IV), which ranges from 0 to 2, representing the fragmentation of the rest-activity rhythm within each 24-h period; the most active 10-h period (M10); the least active 5-h period (L5); relative amplitude, which ranges from 0 to 1, representing the difference in magnitude of activity between active and rest phases (M10 − L5/M10 + L5); and the circadian function index, which ranges from 0 to 1 and is calculated as the average between IS, IV, and relative amplitude (IV values were inverted and normalized between 0 and 1). Additionally, we extracted the following variables through cosinor analysis: mesor, which represents the mean activity; amplitude, which represents the difference in magnitude of activity between the highest value of activity and the mean activity; and acrophase, which represents the time of peak activity.[28,29]

Evaluation of mental health

HRQoL was assessed by the 12-Item Short-Form Health Survey (SF-12), and the results were presented in the domains of physical health and mental health.[30] Quality of life was measured by the Hospital Anxiety and Depression Scale (HADS). Scores of 0-7 indicated normal quality of life, scores of 8-10 indicated borderline abnormal quality of life, and scores of 11-21 indicated abnormal quality of life.[31] Depression was measured by the Beck Depression Inventory. Scores of 0-13 indicated minimal depression, scores of 14-19 indicated mild depression, scores of 20-28 indicated moderate depression, and scores of 29-62 indicated severe depression.[32] Finally, fatigue was assessed by the Chalder Fatigue Scale.[33,34]

Statistical analysis

In this study, we hypothesized that the severity of COVID-19 was associated with a risk of OSA and unhealthy sleep. On the basis of a study by Perger et al.,[35] who reported undiagnosed OSA in 75% of patients with severe COVID-19, a baseline OSA prevalence of 25% from Chile,[36] a power of 90%, and a p value of 0.05 (type I error), the estimated sample size was 16 per group.

Quantitative variables with normal or non-normal distribution were expressed as means and standard deviations. Qualitative variables were expressed as absolute and relative frequencies. The normality of the data distribution was examined with the Shapiro-Wilk test. The between-group differences established by the clinical variables were evaluated by the chi-square test and one-way ANOVA (for parametric variables) or by the Kruskal-Wallis test or Fisher's exact test (for nonparametric variables). ANCOVA was performed to analyze sleep questionnaire data and HSAT results. BMI and age were used as covariates. Factors associated with a higher probability of OSA were identified by logistic regression analysis. The analysis was adjusted for sex, age (19-36, 37-46, 47-56, and 57-69 years), and nutritional status. The results of the analysis were presented as ORs and their respective 95% CIs. An OR > 1 indicated a higher probability of having OSA, and an OR of < 1 indicated a lower probability of having OSA. For all tests, a p value < 0.05 was considered statistically significant. All statistical analyses were performed with the IBM SPSS Statistics software package, version 25 (IBM Corporation, Armonk, NY, USA).

RESULTS

Sociodemographic data and comorbidities

A total of 60 COVID-19 patients were included in the study. Of those, 17 had mild COVID-19, 18 had moderate COVID-19, and 25 had severe COVID-19. Table 1 presents sociodemographic, anthropometric, and comorbidity data, by COVID-19 severity. The patients with severe COVID-19 were older than those with mild or moderate COVID-19. The prevalence of obesity was 64.7% in the moderate COVID-19 group and 64% in the severe COVID-19 group. Additionally, the prevalence of central obesity was high in the mild, moderate, and severe COVID-19 groups (66.7%, 82.4%, and 76.0%, respectively). The prevalences of diabetes mellitus, insulin resistance, and hypertension were highest in the moderate COVID-19 group (35.2%, 29.4%, and 47.0%, respectively).

Sleep health and the circadian rest-activity pattern in COVID-19 patients during the recovery phase

Table 2 shows the self-report data on sleep-related symptoms. Excessive daytime sleepiness and daytime tiredness were more prevalent in the mild COVID-19 group than in the moderate and severe COVID-19 groups, although the difference was not significant. In the moderate COVID-19 group, there was a high prevalence of difficulty falling asleep, difficulty maintaining sleep, and waking up too early. In the severe COVID-19 group, there was a high prevalence of difficulty maintaining sleep and waking up too early. The mean number of hours of sleep as reported by patients ranged from 6.4 h to 6.9 h.

The risk of OSA as assessed by the STOP-Bang questionnaire was higher in the severe and moderate COVID-19 groups (p = 0.038). The prevalence of OSA as assessed by the HSAT was 60% (27.8%, 64.7%, and 80.0% for the mild, moderate, and severe COVID-19 groups, respectively; Table 3). The logistic regression analysis showed that COVID-19 patients in the 57- to 69-year age bracket had a higher probability of having OSA than did those in the 19- to 36-year age bracket (OR = 22.709; p = 0.003). Neither nutritional status nor sex increased the probability of having OSA (Figure 1).

Sleep quality was found to be impaired in all three groups of COVID-19 patients. Mean SATED scale scores were 6.3 ± 3.0 in the mild COVID-19 group, 5.2 ± 2.3 in the moderate COVID-19 group, and 6.1 ± 2.2 in the severe COVID-19 group. Moreover, the PSQI showed that all three groups had a high prevalence of unhealthy sleep. An ESS score > 10 was found in

Table 1. Baseline characteristics of the study population (N = 60).[a]

Variable	COVID-19			p*
	Mild (n = 18)	Moderate (n = 17)	Severe (n = 25)	
Age, years	39.8 ± 13.8[a]	47.6 ± 11.3[a]	50.2 ± 10.6[b]	0.020
Sex				
Male	33.3%	64.7%	60.0%	0.121
Female	66.7%	35.7%	40.0%	
Level of education, no. of years of schooling				0.230
< 8 years	22.2%	29.4%	56.0%	
8-12 years	33.3%	17.6%	16.0%	
> 12 years	44.5%	52.9%	28.0%	
Living in a nonurban area	5.6%	17.6%	8.0%	
Anthropometry				
BMI	29.5 ± 5.1	31.3 ± 2.6	32.1 ± 5.9	0.238
Normal	16.7%	0%	8.0%	0.271
Overweight	44.4%	35.3%	28.0%	
Obesity	38.9%	64.7%	64.0%	
Hip circumference, cm	98.1 ± 13.4	104.6 ± 9.8	107.0 ± 13.2	0.072
Central obesity, n (%)	6 (33.3%)	3 (17.6%)	6 (24.0%)	0.557
Neck circumference, cm	40.1 ± 5.5	42.5 ± 3.9	42.8 ± 5.7	0.212
Waist circumference, cm	107.8 ± 8.8	106.6 ± 8.6	110.4 ± 10.4	0.415
Comorbidities				
Hypertension	11.1%	47.0%	36.0%	0.350
Diabetes mellitus	5.5%	35.2%	20.0%	0.030
Insulin resistance	0%	29.4%	4.0%	0.020
Smoking status				
Nonsmoker, n (%)	17 (66.6)	20 (52.9)	20 (58.8)	0.480
Current smoker, n (%)	4 (22.2)	1 (5.8)	3 (8.8)	0.240
Former smoker, n (%)	2 (11.1)	7 (38.8)	11 (32.3)	0.280
Smoking history, pack-years	5.6 ± 7.5	8.1 ± 9.3	8.6 ± 9.3	0.470

[a]Data expressed as %, n (%), or mean ± SD. *One-way ANOVA and the chi-square test, with ANOVA being adjusted for confounding variables (age, sex, and BMI). Different letters in the same row indicate significant differences between groups (one-way ANOVA and post hoc analysis with the Bonferroni test). A value of $p < 0.05$ was considered significant for all analyses.

38.9% of the patients in the mild COVID-19 group, in 47.1% of those in the moderate COVID-19 group, and in 36.0% of those in the severe COVID-19 group. The prevalence of insomnia as assessed by the ISI was increased in all three groups (50.0%, 82.4%, and 56.0% in the mild, moderate, and severe COVID-19 groups, respectively).

Actigraphy revealed a TST of < 7 h in all three groups (5 h 47 min and 54 s in the mild COVID-19 group, 6 h 04 min and 06 s in the moderate COVID-19 group, and 6 h 25 min and 30 s in the severe COVID-19 group). Sleep efficiency ranged from 86.3% to 87.4%. Circadian function was found to be impaired in all three groups. We found significant differences among the three groups regarding IV, which was higher in the moderate COVID-19 group than in the mild and severe COVID-19 groups (0.72 ± 0.11, 0.62 ± 0.09, and 0.64 ± 0.11, respectively). However, there were no significant differences among the three groups regarding the remaining variables. The acrophase was 15:33:05 (time) in the mild COVID-19 group, 15:44:00 (time) in the moderate COVID-19 group, and 15:17:33 (time) in the severe COVID-19 group.

Clinical and mental health

Table 4 shows the results related to fatigue, HRQoL, mood, and depression, by COVID-19 severity. We found significant differences between the moderate COVID-19 group and the other groups regarding HADS anxiety domain scores. The mean HADS anxiety domain score in the moderate COVID-19 group was 8.6 ± 3.8, and 47% of the patients in that group reported abnormal values, in comparison with 16.7% and 12% of those in the mild and severe COVID-19 groups, respectively. With regard to HRQoL, we found significant differences among the groups; mental health was found to be better in the mild COVID-19 group than in the moderate and severe COVID-19 groups. Furthermore, severe fatigue was found in all three groups (in 61.1% of the patients in the mild COVID-19 group, in 88.2% of those in the moderate COVID-19 group, and in 72.0% of those in the severe COVID-19 group).

DISCUSSION

The main findings of the present study are as follows: 1) Sleep health is severely impaired four

Table 2. Self-report data on sleep-related symptoms in the study population (N = 60).[a]

Variable	COVID-19			p*
	Mild (n = 18)	Moderate (n = 17)	Severe (n = 25)	
Excessive daytime sleepiness	52.9%	23.5%	24.0%	0.15
Falling asleep involuntarily during the day	52.9%	35.3%	28.0%	0.25
Dozing off while driving	5.9%	5.9%	8.00%	0.95
Difficulty falling asleep	41.2%	70.6%	36.0%	0.07
Difficulty maintaining sleep	47.1%	64.7%	56.0%	0.58
Waking up too early	35.3%	58.8%	52.0%	0.36
Taking a nap	17.6%	5.9%	24.0%	0.30
Daytime tiredness	58.8%	64.7%	48.0%	0.54
Heavy nocturnal sweating	47.1%	47.1%	52.0%	0.93
Observed apneas	11.8%	17.6%	20.0%	0.78
Morning headaches	47.1%	52.9%	36.0%	0.53
Number of hours of sleep (on weekdays)	6.9 ± 0.9	6.4 ± 1.4	6.7 ± 1.9	0.58
Number of hours of sleep (on weekends)	8.2 ± 1.5	6.7 ± 1.5	7.6 ± 2.4	0.09
Nocturia	41.2%	70.6%	64.0%	0.17
Apnea during the night	23.5%	35.3%	36.0%	0.66
Restless legs syndrome	47.1%	47.1%	52.0%	0.93
Severe snoring	23.5%	23.5%	28.0%	0.92
Taking sleeping pills	17.6%	35.3%	24.0%	0.48

[a]Data expressed as % or mean ± SD. *One-way ANOVA and the chi-square test. A value of $p < 0.05$ was considered significant for all analyses.

months after the acute phase of COVID-19. 2) The overall prevalence of OSA was 60%, being as high as 80% in the severe COVID-19 group. 3) With regard to the circadian rest-activity pattern, the moderate COVID-19 group had higher IV and lower circadian function index, M10, L5, IS, mesor, and amplitude, as well as worse sleep quality as assessed by the PSQI. Moreover, the moderate COVID-19 group had a higher prevalence of insomnia, an intermediate chronotype (as determined by the MEQ), and higher anxiety (as assessed by the HADS).

After the acute phase of COVID-19, all three groups had poor sleep quality, low TST values, and prevalent insomnia. With regard to SF-12 scores, the moderate and severe COVID-19 groups had lower quality of physical and mental health than did the mild COVID-19 group. Recent evidence has shown that patients with severe COVID-19 have similar risk factors for OSA.[37] We have previously shown that undiagnosed sleep-disordered breathing is associated with severe COVID-19 during the acute phase.[12] Current evidence suggests that OSA is an independent risk factor for severe COVID-19 presentations and an increased risk of hospitalization.[12]

The present study confirmed the physical and psychological consequences of COVID-19. The symptoms of the acute phase, four months after medical discharge, may be more significant than those thought to be essentially disorders associated with sleep. We investigated respiratory sleep disturbances, sleep quality disturbances, and sleep patterns in COVID-19 patients four months after discharge, providing prospective evidence of the relationship between sleep-disordered breathing and the severity of COVID-19. In addition, we found that all of the patients with COVID-19 in the present study had sleep disturbances, regardless of the severity of the disease. This evidence can contribute to a more precise profile of the sequelae of COVID-19 and to the development of comprehensive, long-term intervention programs covering these health problems.

In our study, we explored different parameters of circadian rest-activity rhythms. In the group of patients with moderate COVID-19, we found significant fragmentation of the rest-activity rhythm, as assessed by IV. This finding can be explained by the high prevalence of comorbidities in the moderate COVID-19 group. Circadian and sleep disorders have been associated with harmful health outcomes in non-COVID-19 patients, including cardiometabolic and cognitive disorders.[37] Interruptions in the sleep-wake cycle can influence circadian rhythms and homeostasis.[38]

Recent evidence indicates that people who recover from COVID-19 continue to experience symptoms for months (long COVID-19 syndrome). In the present study, the prevalence of sleep disorders was found to be high. To our knowledge, this is the first study to describe sleep health after acute COVID-19. Moreover, we found symptoms associated with mental health (depression and anxiety), fatigue, and impaired HRQoL.[6]

Our study showed a high prevalence of poor sleep quality and insomnia in all three groups of patients with COVID-19, as well as a decrease in the number of hours of sleep (which were below the recommended for optimal health).[39] In addition, our study showed a low quality of life in the physical and mental health

Table 3. Sleep questionnaire data and home sleep apnea test results in the study population (N = 60).[a]

Variable	COVID-19			p*
	Mild (n = 18)	Moderate (n = 17)	Severe (n = 25)	
Sleep questionnaires				
SATED scale score	6.3 ± 3.0	5.2 ± 2.3	6.1 ± 2.2	0.470
PSQI score	8.5 ± 4.2[a]	12.3 ± 4.4[b]	9.3 ± 4.5[a]	0.049
Healthy sleep (≤ 5)	16.7%	11.8%	12.0%	0.883
Unhealthy sleep (> 5)	83.3%	88.2%	88.0%	
ESS score	7.5 ± 5.5	9.2 ± 5.2	8.2 ± 5.1	0.511
Nonsleepy (≤ 10)	61.1%	52.9%	64.0%	0.768
Sleepy (> 10)	38.9%	47.1%	36%	
ISI	8.2 ± 6.9	12.9 ± 6.2	9.4 ± 6.1	0.082
Without insomnia	50%	17.6%	44.0%	0.108
With insomnia	50%	82.4%	56%	
STOP-Bang questionnaire score	2.2 ± 1.7[a]	3.5 ± 2.2[a]	3.6 ± 1.6[b]	0.047
No risk of OSA	27.8%	0%	4.0%	0.038
Low risk of OSA	27.8%	41.2%	16.0%	
Intermediate risk of OSA	33.3%	35.3%	48.0%	
High risk of OSA	11.1%	23.5%	32.0%	
MEQ score	54.1 ± 8.7	55.2 ± 7.9	59.5 ± 7.4	0.208
Home sleep apnea test				
RDI	7.3 ± 10.2	12.2 ± 10.5	12.6 ± 9.5	0.779
0-4 events/h (non-OSA)	72.2%	35.3%	20.0%	0.002
≥ 5 events/h (OSA)	27.8%	64.7%	80.0%	
Obstructive apneas, events/h	1.79 ± 2.87	1.41 ± 2.70	2.89 ± 5.53	0.686
Central apneas, events/h	2.3 ± 4.5	3.8 ± 7.8	2.1 ± 3.5	0.595
Hypopnea index, events/h	4.92 ± 7.16	6.91 ± 8.59	7.12 ± 5.18	0.747
ODI ≥ 3%	7.2 ± 11.7	11.2 ± 11.9	11.6 ± 9.7	0.489
Snoring events	608.6 ± 950.8	966.8 ± 1,591.9	958.7 ± 1,207.2	0.499
T90%	2.4 ± 5.6	7.5 ± 14.6	12.1 ± 22.0	0.352
Mean SpO_2	95.2 ± 1.2[a]	93.9 ± 1.5[b]	93.6 ± 1.8[b]	0.041
Nadir SpO_2	85.8 ± 7.6	83.9 ± 5.6	82.4 ± 5.6	0.475
Actigraphy				
Time in bed, min	400.9 ± 101.0	410.1 ± 96.2	434.5 ± 99.4	0.445
Total sleep time, min	347.9 ± 105.3	364.1 ± 96.3	385.5 ± 90.6	0.399
Sleep onset latency, min	2.0 ± 1.5	2.1 ± 1.7	2.2 ± 2.3	0.965
Sleep efficiency, %	87.4 ± 5.7	86.3 ± 8.4	86.9 ± 6.2	0.912
WASO, min	42.2 ± 20.0	42.9 ± 19.2	47.2 ± 26.0	0.759
Arousals	7.7 ± 3.9	7.1 ± 3.6	7.3 ± 4.3	0.948
Circadian rhythm				
CFI	0.73 ± 0.06	0.71 ± 0.05	0.73 ± 0.06	0.520
M10	6,371.0 ± 1,170.3	6,024.0 ± 1,237.6	6,227.1 ± 1,629.6	0.794
L5	79.9 ± 48.5	62.0 ± 27.3	69.6 ± 36.7	0.435
RA	0.98 ± 0.01	0.98 ± 0.01	0.97 ± 0.02	0.959
IS	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.428
IV	0.62 ± 0.09[a]	0.72 ± 0.11[b]	0.64 ± 0.11[a]	0.030
Mesor	3,012.5 ± 635.3	2,777.8 ± 785.4	2,789.8 ± 701.7	0.593
Amplitude	2,417.7 ± 682.5	2,162.7 ± 585.2	2,416.0 ± 688.8	0.441
Acrophase	15:33:05	15:44:00	15:17:33	

SATED: satisfaction, alertness, timing, efficiency, and duration; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; OSA: obstructive sleep apnea; MEQ: Morningness-Eveningness Questionnaire; RDI: respiratory disturbance index; ODI: oxygen desaturation index; T90%: total time with SaO_2 below 90%; WASO: wake after sleep onset; CFI: circadian function index; M10: the most active 10-h period; L5: the least active 5-h period; RA: relative amplitude; IS: interdaily stability; and IV: intraday variability. [a]Data expressed as mean ± SD or %. *One-way ANOVA and the chi-square test. Different letters in the same row indicate significant differences between groups (one-way ANOVA and post hoc analysis with the Bonferroni test). ANCOVA was performed to analyze sleep questionnaire data and home sleep apnea test results. BMI and age were used as covariates. A value of $p < 0.05$ was considered significant for all analyses.

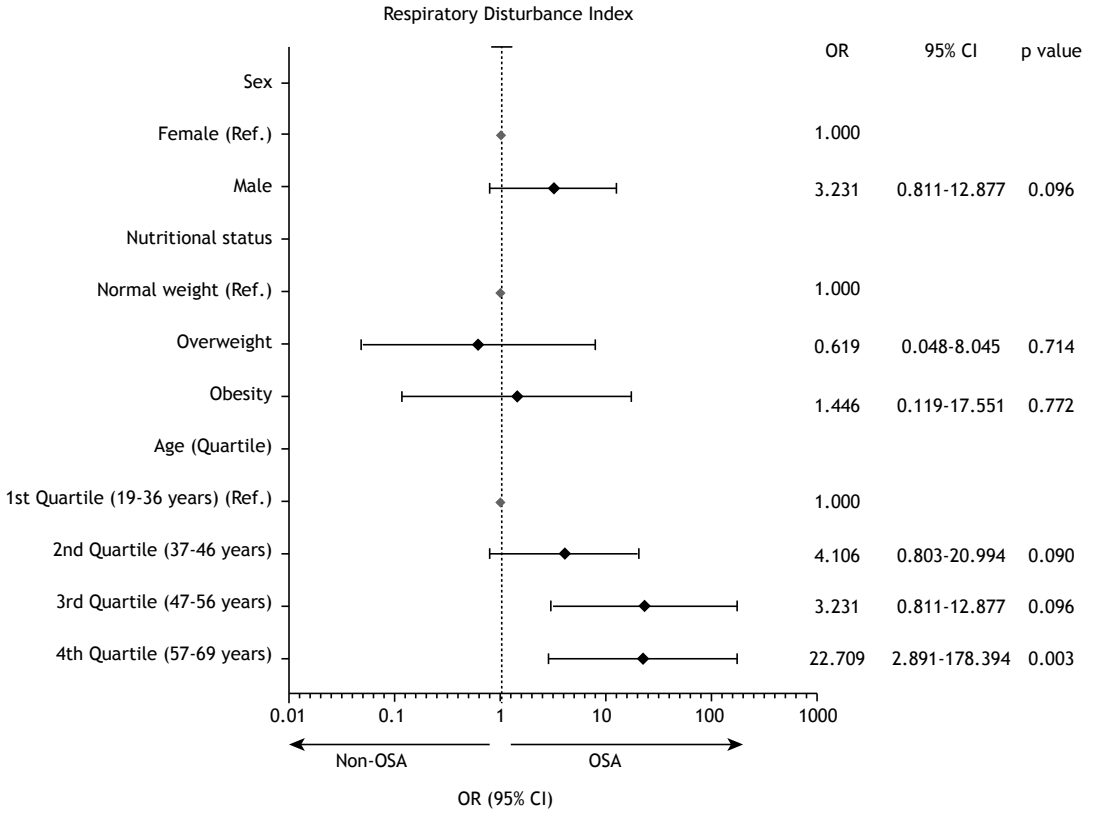

Figure 1. Logistic regression analysis of the probability of obstructive sleep apnea (OSA) in COVID-19 patients four months after the acute phase of the disease. The results were presented as ORs and their respective 95% CIs. The analysis was adjusted for sex, age, and nutritional status. An OR > 1 indicated a higher probability of having OSA, and an OR of < 1 indicated a lower probability of having OSA. A value of $p < 0.05$ was considered statistically significant.

domains of the SF-12, as well as a high prevalence of severe fatigue.

Previous studies have evaluated the risk of sequelae after COVID-19, focusing on clinical parameters, pulmonary function tests, and quality of life parameters.[3-6] Our study opens up another dimension to explore during the recovery phase of COVID-19 infection (i.e., sleep health), and our results are relevant to current clinical practice.

One of the limitations of the present study is that the sample size was small (60 patients). Future studies exploring COVID-19 symptoms in larger cohorts should include sleep health in their evaluations. Another limitation is the lack of a control group, meaning that we were unable to compare the effects of COVID-19 severity on the study variables.

We found a high prevalence of sleep-related symptoms in the group of patients with moderate COVID-19. Future studies investigating such patients should examine the psychological and sleep sequelae of COVID-19. The patients with moderate COVID-19 in the present study had worse sleep quality and higher anxiety than did those with mild or severe COVID-19. This might be due to the high prevalence of insulin resistance, diabetes mellitus, and hypertension in the moderate COVID-19 group. It has recently been shown that a high burden of comorbidities is associated with low sleep quality and high anxiety.[39,40]

Yet another limitation is that we used subjective measures of different sleep parameters. However, the prevalence of sleep disorders in the present study was high in all three groups of patients.

In conclusion, our findings show several sleep-related symptoms, as well as changes in the circadian rest-activity pattern, together with impaired mental health, in COVID-19 patients four months after the acute phase of the disease. Further studies are needed to confirm these findings and understand the underlying mechanisms.

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AUTHOR CONTRIBUTIONS

GL: study design and guarantor of the article; MH-B, JL, DE, IC, and EN-L: data extraction and analysis; GL, IC, and MH-B: statistical analysis; MH-B, IC, EN-L, GL, AT, and FB: drafting of the manuscript; GL, EN-L, AT,

Table 4. Health-related quality of life, mood, depression, and fatigue in the study population (N = 60).[a]

Variable	COVID-19			p*
	Mild (n = 18)	Moderate (n = 17)	Severe (n = 25)	
Mental health				
HADS-A score	5.6 ± 4.6[a]	8.6 ± 3.8[b]	5.6 ± 3.7[a]	0.042
Normal	77.8%	47.1%	72.0%	0.067
Borderline abnormal	5.6%	5.9%	16.0%	
Abnormal	16.7%	47.1%	12.0%	
HADS-D score	5.0 ± 4.6	5.9 ± 3.6	3.4 ± 2.9	0.096
Normal	72.2%	70.6%	84.0%	0.305
Borderline abnormal	11.1%	11.8%	16.0%	
Abnormal	16.7%	17.6%	0%	
BDI score	8.2 ± 9.4	12.1 ± 8.1	8.9 ± 6.8	0.308
No depression	77.8%	76.5%	72.0%	0.744
Mild depression	11.1%	5.9%	20.0%	
Moderate depression	5.6%	11.8%	8.0%	
Severe depression	5.6%	5.9%	0%	
Health-related quality of life				
SF-12, mental health score	50.26 ± 7.77[a]	40.37 ± 11.44[b]	41.21 ± 10.09[b]	0.005
SF-12, physical health score	45.0 ± 11.06	43.33 ± 12.44	49.86 ± 8.93	0.123
Fatigue				
Chalder Fatigue Scale score	4.4 ± 3.4	6.6 ± 2.3	5.1 ± 2.7	0.079
Total score	13.3 ± 10.2	19.8 ± 6.9	15.4 ± 8.0	0.079
Severe fatigue	61.1%	88.2%	72.0%	0.189

HADS-A: Hospital Anxiety and Depression Scale, anxiety domain; HADS-D: Hospital Anxiety and Depression Scale, depression domain; BDI: Beck Depression Inventory; and SF-12: 12-Item Short-Form Health Survey. [a]Data expressed as mean ± SD or %. *One-way ANOVA and the chi-square test. Different letters in the same row indicate significant differences between groups (one-way ANOVA and post hoc analysis with the Bonferroni test). A value of $p < 0.05$ was considered significant for all analyses.

and FB: critical revision of the manuscript for important intellectual content; MH-B, GL, IC, DE, JL, EN-L, AT, and FB: approval of the final version.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Sleep quality in COPD patients: correlation with disease severity and health status

Danielle Cristina Silva Clímaco[1,2], Thais C Lustosa[2], Marcus Vinícius de França Pereira Silva[2], Ozeas L Lins-Filho[2], Valesca Kehrle Rodrigues[3], Luiz de Albuquerque P de Oliveira-Neto[3], Audes Diógenes Magalhães Feitosa[4], Fernando José Pinho Queiroga Jr[3], Marília Montenegro Cabral[2], Rodrigo P Pedrosa[2,4]

1. Clínica de Pneumologia, Hospital Otávio de Freitas, Recife (PE) Brasil.
2. Laboratório do Sono e Coração, Pronto-Socorro Cardiológico Universitário de Pernambuco – PROCAPE – Universidade de Pernambuco, Recife (PE) Brasil.
3. Hospital Universitário Oswaldo Cruz, Recife (PE) Brasil.
4. Pronto-Socorro Cardiológico Universitário de Pernambuco – PROCAPE – Universidade de Pernambuco, Recife (PE) Brasil.

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Study carried out at the Hospital Universitário Oswaldo Cruz, Universidade de Pernambuco, Recife (PE) Brasil.

ABSTRACT

Objective: To evaluate clinical predictors of poor sleep quality in COPD patients with and without obstructive sleep apnea (OSA). **Methods:** Consecutive stable patients with COPD were evaluated for OSA by means of overnight polysomnography; for sleep quality by means of the Pittsburgh Sleep Quality Index (PSQI); and for disease impact by means of the COPD Assessment Test. COPD severity was graded in accordance with the 2020 GOLD guidelines. Predictors of poor sleep quality were evaluated by multivariate logistic regression analysis. **Results:** We studied 51 patients with COPD alone and 51 patients with COPD and OSA. Both groups had similar age (66.2 ± 9.2 years vs. 69.6 ± 10.7, p = 0.09) and airflow limitation (p = 0.37). Poor sleep quality was present in 74.8% of the study participants, with no significant difference between COPD patients with and without OSA regarding PSQI scores (p = 0.73). Polysomnography showed increased stage 1 non-rapid eye movement sleep and arousal index, as well as reduced sleep efficiency and stage 3 non-rapid eye movement sleep, in the group of patients with COPD and OSA (p < 0.05). Independent predictors of poor sleep quality were GOLD grade C/D COPD (OR = 6.4; 95% CI, 1.79-23.3; p < 0.01), a COPD Assessment Test score ≥ 10 (OR = 12.3; 95% CI, 4.1-36.5; p < 0.01), and lowest SaO_2 < 80% (p < 0.0001). **Conclusions:** Poor sleep quality is quite common in patients with COPD and is associated with severe COPD and poor health status, having a negative impact on overall quality of life. Despite changes in polysomnography, OSA appears to have no impact on subjective sleep quality in COPD patients.

Keywords: Pulmonary disease, chronic obstructive; Sleep Quality; Sleep apnea, obstructive; Health status.

INTRODUCTION

COPD is a common respiratory illness that is characterized by chronic airway obstruction and is associated with abnormal inflammatory responses in the lungs.[1] It has been associated with high morbidity, mortality, and health care costs. Changes in lung mechanics lead to the main clinical manifestations of dyspnea, cough, and chronic expectoration.[2,3]

COPD increases susceptibility to sleep disturbance. Patients may be predisposed to poor sleep quality due to upper and lower airway abnormalities. Patients with COPD and obstructive sleep apnea (OSA) may experience symptoms such as snoring, witnessed apneas, difficulty falling asleep, and fragmented sleep.[4] Nocturnal alterations in ventilation and respiratory symptoms can result in difficulty maintaining sleep, possibly causing daytime somnolence, cognitive changes, and altered immune function.[5] Severe disease has been associated with reduced sleep quality, including decreased total sleep time, decreased sleep efficiency, and sleep fragmentation.[6,7] Potential causes of disturbed sleep in patients with COPD include impaired lung function and hyperinflation, which are exacerbated during sleep.[8] Moreover, OSA may occur in 10-30% of patients with COPD. The co-occurrence of COPD and OSA has been associated with poor health outcomes.[9] Corticosteroid use and increased upper airway edema caused by rostral fluid shift in the supine position, with a consequent increase in neck circumference, may contribute to this co-occurrence. These effects together may increase the work of breathing, leading to increased arousability and sleep disturbance.[10]

Correspondence to:
Danielle Cristina Silva Clímaco. Hospital Otávio de Freitas, Serviço de Pneumologia. Rua Aprígio Guimarães, s/n, Tejipió, Recife, PE, Brasil.
Tel.: 55 81 3182-8500. E-mail: danielleclimaco@gmail.com
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Sleep quality is a major determinant of overall health status and quality of life. Although the importance of sleep in patients with COPD has been extensively studied, nighttime symptoms and their daytime consequences are often not reported by patients and may go unnoticed by physicians.[7]

We hypothesized that patients with COPD + OSA have poorer sleep quality than do those with COPD alone. Therefore, the objective of this study was to describe sleep quality, as measured by the Pittsburgh Sleep Quality Index (PSQI), in patients with COPD+ OSA and in those with COPD alone from three referral centers, as well as to evaluate clinical predictors of poor sleep quality and its possible associations with disease severity.

METHODS

For this cross-sectional study we recruited COPD patients from three referral centers. All patients were consecutively evaluated, constituting a convenience sample.

The study was approved by the local research ethics committee (Protocol no. 68781017.3.0000.5192) and was performed in accordance with the Declaration of Helsinki. All participants gave written informed consent.

We included patients in the 44- to 91-year age bracket with a confirmed diagnosis of COPD and without hospitalization in the past three months. COPD was defined on the basis of pulmonary function testing as an FEV_1/FVC ratio of < 0.70 and an FEV_1 of < 80% of the predicted value.[11] We excluded patients with respiratory diseases other than COPD, patients with previously diagnosed OSA, obese patients (i.e., those with a BMI > 40 kg/m^2), patients with neurological diseases, patients using home oxygen therapy, and patients who could not visit the sleep laboratory.

All patients underwent overnight polysomnography in a sleep laboratory with standard equipment (Alice 6; Philips Respironics, Murrysville, PA, USA), undergoing the following: electroencephalography, electrooculography, submental electromyography, electromyography of the left and right anterior tibial muscles, electrocardiography, inductance plethysmography with two thoracoabdominal bands, oronasal airflow measurement with a thermistor and a nasal pressure cannula, pulse oximetry, and body position monitoring. Sleep and sleep stages were determined by an experienced observer, in accordance with the recommendations of the American Academy of Sleep Medicine. Apnea was defined as an airflow reduction > 90% for more than 10 s, and hypopnea was defined as an airflow reduction > 30% associated with oxygen desaturation > 3% or arousal from sleep.[12] COPD + OSA was defined as an apnea-hypopnea index (AHI) ≥ 15 events/h.

COPD severity was graded as A, B, C, or D, in accordance with the 2020 GOLD guidelines.[2,13]

Sleep quality was evaluated with the PSQI[14] and the Epworth Sleepiness Scale.[15] The PSQI provides a sensitive and specific measure of sleep quality. A global PSQI ≥ 5 was adopted for identification of "poor" sleepers. COPD severity was graded on the basis of the COPD Assessment Test (CAT) score, the modified Medical Research Council dyspnea scale score, and the frequency of exacerbations in the past year, which is associated with disease severity in COPD patients.[16,17]

Statistical analysis

Normal distribution was evaluated with the Kolmogorov-Smirnov test, and the results were expressed as mean ± SD, median (IQR), or percentage, as appropriate. The two-tailed unpaired t-test or Mann-Whitney U test was used for independent variables, and the chi-square test was used for between-group comparisons. Univariate and multivariate logistic regression models were used to evaluate the presence of poor sleep quality and its predictors, which included age > 65 years, sex, GOLD grades C and D COPD, a CAT score ≥ 10, presence of hypertension and diabetes, a BMI > 25 kg/m^2, an AHI ≥ 15 events/h, and an Epworth Sleepiness Scale score > 10. A two-sided p-value of < 0.05 was considered significant. Data management and statistical analyses were performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

As can be seen in Figure 1, of the 115 COPD patients enrolled in the study, 13 were excluded from analysis, a total of 102 COPD patients therefore being included. The sample included 51 patients with COPD alone and 51 patients with COPD + OSA (mean age, 66.2 ± 9.2 years vs. 69.6 ± 10.7 years, p > 0.05). Their baseline clinical characteristics, spirometric classification, GOLD classification, sleep efficiency, and oxygen data as assessed by polysomnography are presented in Table 1. Polysomnography data showed increased stage 1 non-rapid eye movement sleep and arousal index, as well as reduced sleep efficiency and stage 3 non-rapid eye movement sleep, in the COPD + OSA group (p < 0.05).

There were more males in the COPD + OSA group than in the COPD group (72.5% vs. 47.1%, p < 0.01). All patients were using long-acting beta-adrenergic agonists and long-acting anticholinergic bronchodilators, and adherence to the inhaled medications was checked. Those with GOLD grade D COPD (with a history of two or more exacerbations) were also using inhaled corticosteroids. There was a significant difference between the COPD and COPD + OSA groups regarding the lowest SaO_2 as assessed by polysomnography (p = 0.0153).

Table 2 presents the associations between PSQI component and global scores for both groups. PSQI component scores showed no significant differences

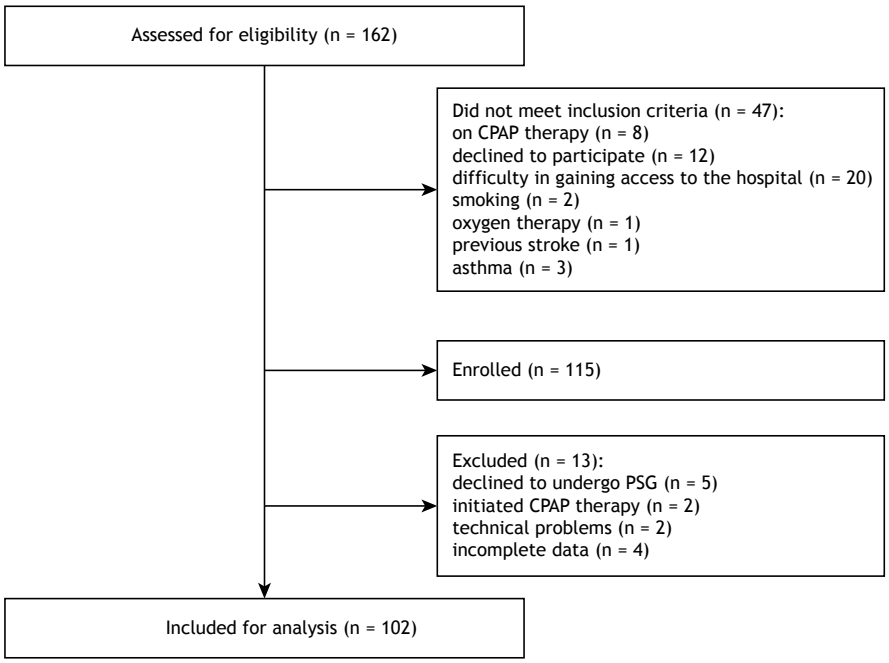

Figure 1. Flow chart of the study design. PSG: polysomnography.

between the groups. However, high PSQI global scores were observed in both groups.

Table 3 presents the results of the univariate and multivariate logistic regression analyses. GOLD grade C/D COPD and a CAT score ≥ 10 were independently associated with poor sleep quality (a PSQI ≥ 5), as was lowest SaO_2 < 80% ($p < 0.0001$). Sleep quality was not significantly associated with OSA, comorbidities, or BMI.

DISCUSSION

In the present study we demonstrated the negative impact of COPD on sleep quality in a large sample of patients from three referral centers. We found that 1) poor sleep quality was very common in patients with COPD, even if they did not have comorbid OSA; 2) OSA had no impact on poor sleep complaints in COPD patients; and 3) frequent exacerbations (GOLD grade C/D COPD) and severe COPD (a CAT score ≥ 10) were associated with poor sleep quality.

Sleep has major effects on breathing and gas exchange in patients with COPD. The efficiency of diaphragmatic contraction may diminish during sleep, leading to increased reliance on accessory muscles to maintain ventilation.[18,19] Additionally, nocturnal hypoxemia can occur in patients with COPD despite adequate oxygenation during wakefulness; it frequently occurs during rapid eye movement sleep, leading to ventilation-perfusion mismatch.[20] Moreover, the supine position contributes to worsening airflow obstruction, which exacerbates hyperinflation and hypoventilation.[21] These factors increase susceptibility to sleep disturbance. However, sufficient attention has not been given to the effects of COPD-related impairments on sleep quality.[10]

We also examined the impact of comorbid OSA on sleep quality in patients with COPD. Poor sleep quality, as measured by the PSQI, was noted, regardless of comorbidity with OSA. This is in accordance with data showing that individuals with COPD sleep poorly.[4,6] OSA was present in half of the sample, even though none of the participants had received a previous diagnosis of OSA, thereby suggesting a low awareness of OSA in this population. We found that COPD + OSA patients had more pronounced oxygen desaturation during sleep. Thus, treating OSA would prevent an increase in oxyhemoglobin desaturation and interference with sleep quality in patients with COPD. Silva Junior et al.[20] showed that 60% of patients with COPD without daytime hypoxemia had some sleep disorder; in addition, they found that an SaO_2 of 90-94% during wakefulness predicted sleep disorders.

In the present study, patients with GOLD grade C/D COPD and most of the symptomatic patients (i.e., those with a CAT score ≥ 10) had higher PSQI scores. This is in agreement with previous reports stating that poor sleep quality in patients with COPD is related to poorer health status, disease that is more severe, and impaired ability to perform activities of daily living.[8,22-24]

The results of a study involving 480 COPD patients showed that higher PSQI scores were associated with an increased risk of exacerbations during the study's 18-month follow-up period.[25] The patients with high PSQI scores had a shorter time to symptom-based exacerbation and a higher risk of hospitalization. Moreover, chronic sleep deprivation and poor sleep

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

Variable	Total	Group		p
		COPD	COPD + OSA	
	(N = 102)	(n = 51)	(n = 51)	
Age, years		66.2 ± 9.1	69.6 ± 10.7	0.1546*
Males	59 (57.8)	24 (47.1)	35 (68.6)	0.0359†
Hypertension	40 (39.2)	23 (45.1)	17 (33.3)	0.3106†
Diabetes mellitus	80 (78.4)	43 (84.3)	37 (72.5)	0.2287†
Spirometric data				
FEV_1, L		1.1 ± 0.2	1.3 ± 0.4	0.0717‡
FEV_1, % predicted		44.6 ± 0.2	46.6 ± 0.2	0.2872‡
FVC, L		2.0 ± 0.6	2.2 ± 0.8	0.0943‡
FVC, % predicted		35.5 ± 15.4	61.5 ± 0.2	0.0902‡
FEV_1/FVC, % predicted		55.3 ± 15.6	57.2 ± 14.4	0.2639‡
Spirometric classification				
Mild	26 (25.5)	12 (23.5)	14 (27.5)	
Moderate	36 (35.3)	14 (27.5)	22 (43.1)	0.1091†
Severe	40 (39.2)	25 (49.0)	15 (29.4)	
mMRC score				
< 2	61 (59.8)	31 (60.8)	30 (58.8)	1.000†
≥ 2	41 (40.2)	20 (39.2)	21 (41.2)	
CAT score				
< 10	22 (21.6)	11 (21.6)	11 (21.6)	0.8098†
≥ 10	80 (78.4)	40 (78.4)	40 (78.4)	
GOLD A/B COPD	65 (63.7)	35 (68.6)	30 (58.8)	
GOLD C/D COPD	37 (36.3)	16 (31.4)	21 (41.2)	0.4101†
FEV_1, % predicted				
< 40	43 (42.2)	25 (49.0)	18 (35.3)	0.3734*
41-59	34 (33.3)	15 (29.4)	19 (37.2)	
> 60	25 (24.5)	11 (21.6)	14 (27.5)	
PSG data				
Sleep efficiency, %				
< 85	79 (77.4)	39 (76.5)	40 (78.4)	1.0000†
> 85	23 (22.6)	12 (23.5)	11 (21.6)	
Median SaO_2, %				
≥ 90	93 (91.2)	48 (47.1)	45 (44.1)	0.4851†
< 90	9 (8.8)	3 (2.9)	6 (5.9)	
Lowest SaO_2, %				
≥ 90	17 (16.7)	10 (9.8)	7 (6.9)	
80-89	63 (61.8)	36 (35.3)	27 (26.5)	0.0153*
< 80	22 (21.5)	05 (4.9)	17 (16.6)	
Stage 1 sleep, %		9.8 ± 6.0	20.7 ± 14.6	< 0.0001‡
Stage 2 sleep, %		52.7 ± 12.9	49.1 ± 12.9	0.0619 ‡
Stage 3 sleep, %		20.3 ± 9.5	15.7 ± 9.5	0.0127‡
REM sleep, %		15.2 ± 8.57	14.4 ± 7.6	0.3219‡
Arousal index, events/h		19.5 ± 12.2	37.6 ± 21.2	< 0.0001‡
Sleep efficiency, %		73.0 ± 16.2	68.0 ± 17.0	< 0.0001‡
AHI, events/h		6.8 ± 4.3	34.1 ± 20.2	< 0.0001‡
ODI, events/h		5.1 ± 7.4	23.4 ± 21.6	< 0.0001‡

OSA: obstructive sleep apnea; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test; PSG: polysomnography; REM: rapid eye movement; AHI: apnea-hypopnea index; and ODI: oxygen desaturation index. [a]Data presented as mean ± SD or n (%). *Chi-square test. **Chi-square test with Yates' correction. ‡t-test.

quality have been reported to impact immune function and increase susceptibility to infections.[26] Furthermore, frequent sputum production has been associated with nocturnal sleep disturbances and poor sleep quality.[27] In our study, patients with GOLD grade C/D COPD represent those with frequent exacerbations and more unstable respiratory symptoms, which negatively impact sleep quality. Consequently, poor sleep quality

Table 2. Pittsburgh Sleep Quality Index component and global scores for the group of patients with COPD alone and for that of those with COPD and obstructive sleep apnea.[a]

PSQI components	Group		p
	COPD (n = 51)	COPD + OSA (n = 51)	
Subjective sleep quality	1 (1-2)	1 (1-2)	0.59
Sleep latency	1 (0-2)	1 (0-2)	0.27
Sleep duration	1 (1-2)	1 (1-2)	0.98
Sleep efficiency	1 (0-3)	1 (0-2)	0.84
Sleep disturbances	1.5 (1-2)	1 (1-2)	0.41
Use of sleep medications	0 (0-1)	0 (0-0)	0.35
Daytime dysfunction	0 (0-1)	0 (0-2)	0.17
Global PSQI score	7.5 (5.0-11.0)	7.0 (4.0-11.0)	0.73
PSQI ≥ 5[b]	39 (78)	38 (75)	0.68

PSQI: Pittsburgh Sleep Quality Index; and OSA: obstructive sleep apnea. [a]Data presented as median (IQR), except where otherwise indicated. [b]Data presented as n (%).

Table 3. Unadjusted and adjusted ORs for associations between clinical variables and sleep quality in patients with COPD and obstructive sleep apnea and in those with COPD alone.

Variable	Univariate analysis			Coefficient		Multivariate analysis		
	OR (95% CI)		p	(β)	SE	OR (95% CI)		p
Age > 65 years	0.52	(0.20-1.33)	0.17					
Female sex	1.10	(0.45-2.74)	0.82					
GOLD C/D COPD	6.47	(1.80-23.40)	< 0.01	1.53	3.25	4.64	(1.18-18.28)	0.02
CAT score ≥ 10	12.32	(4.16-36.50)	< 0.01	2.30	5.70	9.92	(3.22-30.54)	< 0.01
Hypertension	0.76	(0.30-1.92)	0.57					
Diabetes	0.54	(0.20-1.47)	0.22					
BMI > 25 kg/m^2	1.05	(0.43-2.58)	0.90					
Lowest SaO_2 < 80% (PSG)	0.20	(0.05-0.82)	0.04	1.00	0.27	4.45	(3.91-4.96)	< 0.0001
OSA (AHI > 15 events/h)	0.78	(0.32-1.94)	0.60					
ESS score > 10	1.57	(0.60-1.20)	0.36					
Constant				−2.53	0.07	0.08	(0.01-0.50)	0.07

CAT: COPD Assessment Test; PSG: polysomnography; OSA: obstructive sleep apnea; AHI: apnea-hypopnea index; and ESS: Epworth Sleepiness Scale.

may be a marker for an exacerbating COPD phenotype and indicate a need for closer follow-up. On the other hand, promoting better sleep quality may reduce the risk of exacerbations and improve survival.

Comorbidities may worsen prognosis in patients with COPD. OSA has a high incidence, and patients with comorbid COPD + OSA may have a poorer prognosis than those with either COPD or OSA alone.[23] Reduced exercise tolerance may lead to obesity and muscle weakness, which may contribute to greater upper airway collapse. These factors may also contribute to the occurrence of both COPD and OSA.[9,28-30] Kapur et al.[12] described the negative impact of OSA on sleep and quality of life. Our study demonstrated that patients with COPD sleep poorly regardless of whether or not they have OSA. Current concepts about OSA endotypes (such as arousal threshold and reduced pharyngeal dilator function) and phenotypes (such as insomnia complaints, tiredness, and daytime sleepiness) play an important role in the different clinical manifestations and the subjective complaints related to sleep.[31] This variability in the clinical expression of OSA may have influenced our findings regarding sleep quality. Therefore, it is essential to identify OSA in order to prevent its negative effects on sleep quality in patients with COPD, as well as to predict disease complications and guide clinical management.[32]

One possible limitation of the present study is that depression, anxiety, or other psychological aspects of COPD were not assessed, and they might have an impact on disease control and sleep quality. Another limitation is the cross-sectional design of our study, which allows us to infer an association, but not causality, between COPD severity and poor sleep quality. The absence of a control group without COPD is yet another limitation of the study. However, the strength of our study lies in the large sample size, use of a strict protocol, performance of complete polysomnography, and detailed characterization of patients with COPD.

In the present study, OSA had no impact on worsening sleep problems (PSQI scores), although there were changes in polysomnography. Nocturnal symptoms related to COPD and frequent awakenings have the potential to impact quality of life.[5] Therefore,

we believe that it is important to shed light on this topic and identify predictors of poor sleep and their relationship to clinical outcomes.

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AUTHOR CONTRIBUTIONS

DCSC: study conception and design, and analysis and interpretation of data; TCL and MVFP: study conception and design; OLLF: writing and reviewing of the manuscript, study conception, and analysis and interpretation of data; VKR, LAPON, and ADMF: study conception and design, analysis and interpretation of data, and final approval of the version to be submitted; FJPQJ: study conception and design, writing of the manuscript, and final approval of the version to be submitted; MMC: study design, writing of the manuscript, and final approval of the version to be submitted; and RPP: study conception and design, and final approval of the version to be submitted.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Impact of microvascular invasion on 5-year overall survival of resected non-small cell lung cancer

Andreia Salarini Monteiro[1], Sérgio Ricardo de Carvalho Araújo[2], Luiz Henrique Araujo[3], Mirian Carvalho de Souza[2]

1. Seção de Cirurgia Torácica, Instituto Nacional de Câncer, Rio de Janeiro (RJ), Brasil.
2. Divisão de Pesquisa Populacional, Instituto Nacional de Câncer, Rio de Janeiro (RJ), Brasil.
3. Divisão de Pesquisa Clínica, Instituto Nacional de Câncer, Rio de Janeiro (RJ), Brasil.

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Study carried out at the Instituto Nacional de Câncer (INCA), Rio de Janeiro, RJ, Brasil.

ABSTRACT

Objectives: Non-small cell lung cancer (NSCLC) is an incidental and aggressive type of cancer. Although curative treatment can be offered, the recurrence rate is relatively high. Identifying factors that have a prognostic impact may guide changes in the staging system and recommendations for adjuvant therapy. The aim of this study was to evaluate the impact of microvascular invasion on the 5-year overall survival (OS) of patients with resected NSCLC treated at a reference cancer center. **Methods:** This retrospective, observational cohort study included patients diagnosed with early-stage NSCLC (clinical stages I-IIIA), treated with curative-intent surgery at the Brazilian National Cancer Institute between 2010 and 2016. **Results:** The dataset comprised 91 surgical patients, mostly females and white, with a mean age of 62 years (range between 29-83). Cases were distributed as stages I, II, and III in 55%, 29%, and 16%. Adenocarcinoma was the predominant histological subtype (67%), and microvascular invasion was present in 25% of the patients. The 5-year OS probability was 60% (95% CI, 48.3-68.9). Among all characteristics, advanced stages (p = 0.001) and the presence of microvascular invasion (p< 0.001) were related to a worse 5-year OS. After adjusting for age group and pathological stage, the presence of microvascular invasion was associated with a 4-fold increased risk of death (HR 3.9, 95% CI, 1.9-8.2). **Conclusion:** The presence of microvascular invasion was an independent factor related to worse survival and, therefore, should be routinely assessed in resected specimens.

Keywords: non-small cell lung cancer, thoracic surgery, survival analysis, microvascular invasion.

INTRODUCTION

Lung cancer is the most frequent malignancy among men and the third most frequent among women, with an estimated 2 million new cases worldwide in 2020.[1] The five-year overall survival (OS) is considered low (10-20%), especially when compared to other frequent malignant tumors, such as colon (60-69%), prostate (70-100%), and breast cancer (85%).[2] The extent of the disease at diagnosis influences both the treatment decision and the prognosis. In less than 20% of cases, the diagnosis is performed when the tumor is still localized, a fact that greatly limits the number of patients who can be treated primarily with curative-intent surgery.[3,4] It is estimated that this percentage will rise in upcoming years as a result of the increased use of lung cancer screening.[5] Even though curative treatment can be offered, the recurrence rate is relatively high (30-70%) and, in most cases (80%), it occurs within the first 2 years of follow-up.[6]

Some characteristics have been associated with a better prognosis, including non-advanced disease stages, good performance status (PS), the absence of weight loss (< 5% of body weight), and being of the female sex.[7,8] The identification of factors that impact the prognosis can guide changes in the staging system and recommendations for adjuvant therapy, improving the quality of treatment and the outcome.[7] The description of microvascular invasion, determined by the presence of malignant cells within the vessel lumens, has been associated with lower disease-free survival and OS of operated patients for over a decade. Some authors have proposed adjuvant therapy in the presence of this finding, even in the absence of lymph node involvement or advanced primary tumors,[7] as is already practiced in other cancer types.

The aim of the present study was to evaluate the impact of microvascular invasion on the 5-year overall survival (OS) of patients with resected non-small cell lung cancer (NSCLC) treated at the Brazilian National Cancer Institute (INCA).

METHODS

Study Design

This was a retrospective, observational cohort study of patients diagnosed with early-stage NSCLC (clinical

Correspondence to:
Luiz H. Araujo. Instituto Nacional de Câncer (INCA), Rua André Cavalcanti, 37, 5º andar, prédio anexo, Centro, CEP 20231-050, Rio de Janeiro, RJ, Brasil.
Tel.: 55 21 3207-6650. Fax: 55 21 3207-6566. E-mail: luiz.lima@inca.gov.br
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stages I-IIIA) treated with curative-intent surgery at INCA between January 2010 and December 2016. The exclusion criteria were: ages less than 18 years, prior treatment at other institutions, other malignant tumors in the preceding 5 years, and atypical lung cancer histological subtypes: sarcomatoid carcinoma, mucoepidermoid carcinoma, neuroendocrine tumors, and salivary gland tumors. Hospital medical records were the primary source for data collection. Patient screening was carried out using the hospital database system and the thoracic surgery database. A list of all potentially eligible patients was provided by the institution's cancer registry.

An electronic clinical research form was created to annotate all relevant information, including patient and tumor characteristics and the outcomes. Former smoker status was defined as patients who had quit smoking at least 1 year before diagnosis. The Eastern Cooperative Oncology Group PS scale was used.[9] The maximum standardized uptake value (SUVmax) was selected to determine tumor avidity through F18-fluorodeoxyglucose (FDG) positron emission tomography (PET). Staging was established according to the seventh edition of the UICC/IASLC/AJCC (Union for International Cancer Control/International Association for the Study of Lung Cancer/American Joint Committee on Cancer).[10] Pathological surgical reports were standardized as an institutional routine protocol during the study period, including systematic reports of microvascular invasion. Briefly, the surgical specimens were fixed in 10% formalin and embedded in paraffin. Serial sections were stained with hematoxylin-eosin (H&E), and microvascular invasion was defined as the presence of intravascular cancer cells within the blood vessels. The analysis was exclusive for blood vessel invasion, and lymphatic invasion was not routinely annotated.

Statistical Analysis

In order to describe the study population, tables including absolute and relative frequencies were elaborated. Descriptive statistics (minimum, maximum, mean, median, and standard deviation) were calculated for age and tumor SUV. The staging group was used as a single variable instead of each TNM descriptor for the survival analysis. To estimate the probability of 5-year OS, the Kaplan-Meier estimator was used. OS was defined as the time interval between the date of surgery and death. The log-rank hypothesis test was used to determine the existence of differences between the estimated survival curves. Variables that presented p-values lower than 0.20 in this test were included in Cox proportional risk models. Those that represented less than ten patients were not shown or analyzed, as was the case for other histological subtypes. All the analyses were conducted using the Stata 15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX, USA: StataCorp LLC).

Ethical Considerations

This research project was approved by the local Research Ethics Committee at INCA. A waiver for informed consent was also approved since no interventions were planned.

RESULTS

Patient and Sample Characteristics

From January 2010 to December 2016, a total of 3,489 patients were diagnosed with lung cancer at INCA. Among these, 207 were NSCLC patient cases that had undergone surgical resection (6%). Thirty-six patients were excluded from the study analysis due to disease stage (IIIB or IV), 45 due to histological subtype, 20 had other malignancies in the past 5 years, 2 underwent prior treatment at other institutions, and 13 had insufficient pathological records to determine the status of microvascular invasion (Figure 1).

Ninety-one patients were included in the study, most of whom were females and white, with a mean age of 62 years (range between 29-83). Approximately 85% had a history of smoking, and in 70%, the smoking load was greater than 40 pack-years. The PS was 0 or 1 in all cases, with 64% classified as mildly symptomatic (PS of 1). Seventy-nine patients were staged using PET-CT, and the mean SUVmax was 10. The cases were distributed as stages I, II, and III in 55%, 29%, and 16%. Adenocarcinoma was the predominant histological subtype (67%), and microvascular invasion was present in 25% of the patients (Table 1). The occurrence of microvascular invasion was associated with a more advanced pathological nodal stage ($p< 0.001$) and staging group ($p = 0.003$). Surgical resections included lobectomy in 75 cases (82%), while pneumectomy was performed in 9 (10%), bilobectomy in 5 (5%), and segmentectomy or wedge in 1 case each. Chemotherapy was performed in 48 patients, 10 (11%) as neoadjuvant and 38 (42%) as adjuvant treatment.

Survival Analysis

The median follow-up was 83 months (95% CI, 54-97 months), and the probability of 5-year OS was estimated at 60% (95% CI, 48.3-68.9). There was no difference in survival between age groups ($p = 0.211$), men and women ($p = 0.683$), and between white and non-white individuals ($p = 0.618$). Smoking history, as well as higher smoking loads, did not interfere in the 5-year OS ($p = 0.997$ and $p = 0.456$, respectively). There were no statistically significant differences in 5-year OS according to the PS ($p = 0.188$), the SUVmax ($p = 0.588$), tumor size ($p = 0.093$), and histological subtype ($p = 0.878$). Among all the analyzed characteristics, only advanced stages ($p = 0.001$) and the presence of microvascular invasion ($p< 0.001$) were related to a worse probability of survival at 60 months (Table 2).

As the disease stage becomes more advanced, the likelihood of long-term survival decreases. The greatest difference in 5-year OS was observed in stage IIIA when compared to the other stage groups and was more pronounced after the first year of follow-up (Figure 2). Patients whose tumors presented microvascular

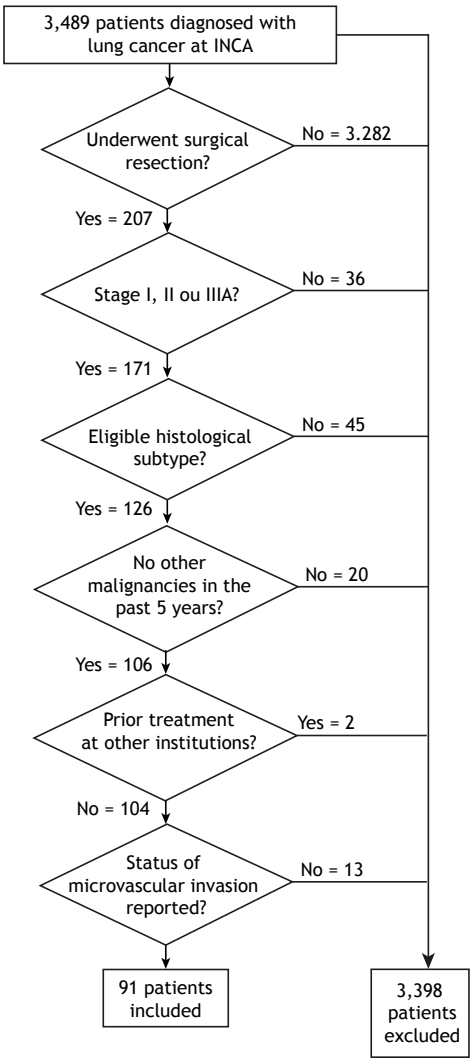

Figure 1. Flow diagram of patient enrollment and analysis.

invasion evolved with lower rates of survival compared to those without microvascular invasion. Again, the magnitude of the difference was mainly observed after the second year of follow-up (Figure 3).

The results obtained with the Cox model, adjusted for age group, pathological stage, and presence of microvascular invasion, indicated that patients aged 60 years or older had twice the risk of death at 60 months when compared to younger patients (HR 1.9, 95% CI, 0.9-3.9). Individuals with pathological stage IIIA disease also presented a higher risk of death at 60 months when compared to those with stage I tumors (HR 2.8, 95% CI, 1.2-6.5), while no difference was observed between stages I and II (HR 0.8 95% CI, 0.3-1.8). The presence of microvascular invasion increased the risk of death 4-fold in relation to patients without microvascular invasion (HR 3.9, 95% CI, 1.9-8.2). The magnitude of the risk caused by the presence of microvascular invasion increased and maintained statistical significance after the adjustment in the complete model (Table 3).

DISCUSSION

The present study was carried out to evaluate the influence of microvascular invasion on the survival of patients undergoing surgery to treat lung cancer. We analyzed a total of 91 locally operated patients and observed a lower 5-year OS rate associated with the presence of microvascular invasion. A 4-fold increased risk of death was estimated, even after adjustment for age and pathological stage.

While surgery represents the greatest chance of cure, less than 20% of NSCLC cases are resectable at diagnosis.[4] The identification of prognostic factors could allow for more customized treatment decisions, for instance, to help define whether adjuvant chemotherapy is required.[11] The presence of microvascular invasion is considered a strong negative prognostic indicator, regardless of the histological subtype.[7,12-15] In 2011, a meta-analysis concluded that the risk of recurrence in patients with microvascular invasion was 4 times higher compared to patients without microvascular invasion, and the risk of death was 2 times greater.[7] In addition, microvascular invasion has also been related to an increased risk of late recurrence.[13,16]

In 2014, another meta-analysis showed that the presence of lymphovascular invasion increased the risk of recurrence and death, even at stage I.[17] Microvascular and lymphatic invasion have been described as a single pathological factor (lymphovascular invasion), but the two findings seem to have different weights.[11] Hishida et al. (2013) analyzed 1,039 patients operated on at stages T1A-3N0M0 and found microvascular and lymphatic invasion in 34% and 20%, respectively.[18] According to the authors, patients with recurrence and microvascular invasion had more distant metastases than those with lymphatic invasion alone, indicating that microvascular invasion had a worse impact on the prognosis.[18] Miyoshi et al. (2009) noted a worse prognosis in patients with microvascular and pleural invasion within the same pathological stage, suggesting that prospective studies should be carried out to evaluate adjuvant chemotherapy for stage I cancer with microvascular or pleural invasion.[19,20] In the present study, lymphatic invasion was not systematically annotated; only microvascular invasion was assessed.

The authors of the United States National Comprehensive Cancer Network (NCCN) consensus recommended that adjuvant chemotherapy be considered in high-risk patients, even at stage IB (eighth edition of the staging system).[21] High-risk features include poorly-differentiated tumors, microvascular invasion, wedge resection alone, tumors larger than 4 cm, visceral pleural involvement, and unknown lymph node status.[21] Of note, the eighth edition of the staging system, which was published in December 2016 and is currently in use worldwide, should not be replaced with the ninth edition until 2024.[22]

The fact that one-fifth of cancer patients submitted to curative-intent surgery, with free margins and without lymph node involvement, may still recur indicates that it

Table 1. Distribution of patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016.

Characteristics	Microvascular invasion					Total	
	Absent		Present		p-value		
	N	%	N	%		N	%
Total	68	74.7	23	25.3	-	91	100.0
Age group							
< 60 years	22	32.4	10	43.5	0.334	32	35.2
≥ 60 years	46	67.6	13	56.5		59	64.8
Sex							
Male	30	44.1	10	43.5	0.957	40	44.0
Female	38	55.9	13	56.5		51	56.0
Race							
White	41	60.3	16	69.6	0.427	57	62.6
Non-white	27	39.7	7	30.4		34	37.4
Smoking status							
Never smoked	11	16.2	3	13.0	0.500	14	15.4
Current or former smoker	57	83.8	20	87.0		77	84.6
Smoking load							
< 40 pack-years	18	31.6	5	25.0	0.898	23	29.9
40-59 pack-years	17	29.8	7	35.0		24	31.2
≥ 60 pack-years	22	38.6	8	40.0		30	39.0
Performance Status (PS)							
0	27	39.7	6	26.1	0.240	33	36.3
1	41	60.3	17	73.9		58	63.7
Maximum SUV							
< 10	38	64.4	8	40.0	0.056	46	58.2
≥ 10	21	35.6	12	60.0		33	41.8
Tumor size							
pT1	21	30.9	4	17.4	0.157	25	27.5
pT2	37	54.4	11	47.8		48	52.7
pT3	8	11.8	6	26.1		14	15.4
pT4	2	2.9	2	8.7		4	4.4
pN							
pN0	61	89.7	12	52.2	< 0.001	73	80.2
pN1	2	2.9	8	34.8		10	11.0
pN2	5	7.4	3	13.0		8	8.8
Pathological stage							
IA	21	30.9	2	8.7	0.003	23	25.3
IB	24	35.3	3	13.0		27	29.7
IIA	8	11.8	7	30.4		15	16.5
IIB	8	11.8	3	13.0		11	12.1
IIIA	7	10.3	8	34.8		15	16.5
Histological subtype							
Adenocarcinoma	46	67.6	15	65.2	0.191	61	67.0
Squamous cell carcinoma	20	29.4	5	21.7		25	27.5
Other	2	2.9	3	13.0		5	5.5

Abbreviations: N, number of patients; SUV, standardized uptake value; pN, pathological staging nodal descriptor.

is possible to improve the way NSCLC is currently staged and treated. There is a need for better stratification of these cases so that more aggressive treatments can be offered to subgroups with a higher chance of recurrence. The identification of poor prognostic factors will allow for different strategies, not limited to treatment but also follow-up. An example would be to monitor these high-risk patients with shorter intervals between consultations, with more frequent or additional imaging tests, perhaps even including magnetic resonance of the brain for patients at risk of distant metastasis. Greater knowledge of prognostic factors is essential to discuss improvements in patient care, to become increasingly customized and efficient.

The definitive answer to how microvascular invasion should be used in clinical practice requires a large,

Table 2. Probability of overall survival at 60 months in patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016.

Characteristics	5-y OS	$CI_{95\%}$	log-rank p-value
Global	59.4	(48.3-68.9)	n.a.
Age group			
< 60 years	67.8	(48.1-81.3)	0.211
≥ 60 years	54.9	(41.1-66.8)	
Sex			
Male	59.4	(42.4-72.9)	0.683
Female	59.5	(44.3-71.8)	
Race			
White	62.6	(48.5-73.8)	0.618
Non-white	53.9	(35.2-69.4)	
Smoking status			
Never smoked	64.3	(34.3-83.3)	0.997
Current or former smoker	58.7	(46.6-68.9)	
Smoking load			
< 40 pack-years	69.3	(46.1-84.0)	0.456
40-59 pack-years	47.1	(25.5-66.1)	
≥ 60 pack-years	59.1	(39.2-74.4)	
Performance Status (PS)			
0	69.3	(50.3-82.2)	0.188
1	53.8	(39.7-65.9)	
Maximum SUV			
< 10	62.9	(46.3-75.6)	0.588
≥ 10	60.6	(42.0-74.9)	
Tumor size			
pT1	59.4	(37.6-75.8)	0.093
pT2	67.4	(51.6-79.0)	
pT3	42.9	(17.7-66.0)	
pN			
pN0	67.5	(55.1-77.1)	0.001
pN1	15.0	(1.0-45.7)	
pN2	37.5	(8.7-67.4)	
Pathological stage			
I	68.9	(53.5-80.0)	0.001
II	61.0	(39.6-76.9)	
IIIA	25.0	(6.9-48.8)	
Histological subtype			
Adenocarcinoma	61.3	(47.5-72.4)	0.878
Squamous cell carcinoma	58.6	(36.6-75.3)	
Microvascular invasion			
Absent	70.8	(58.0-80.4)	< 0.001
Present	26.1	(10.6-44.7)	

Abbreviations: 5-y OS, 5-year overall survival; CI, confidence interval; SUV, standardized uptake value; pN, pathological staging nodal descriptor.

properly-designed clinical trial that systematically analyzes microvascular invasion and other pathological risk factors to assess adjuvant treatment. Additionally, microvascular invasion should be routinely studied in trials evaluating novel adjuvant therapies, such as immunological checkpoint blockade and targeted therapies. Such clinical trials require a multicenter effort, which was beyond the scope of the present study. In order to assess the impact of microvascular invasion on the current staging group, the data collected herein was inserted into the IASLC database to construct the ninth edition of the TNM. These data will hopefully contribute to proving the role of microvascular invasion in NSCLC staging.

One limitation of this study was the relatively small sample size, which influenced the power to make inferences regarding potentially relative prognostic factors, including older age and symptomatic patients.

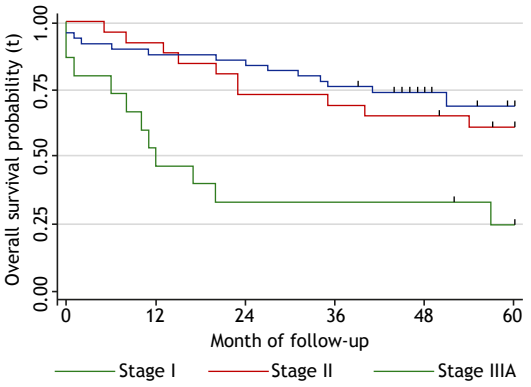

Figure 2. Overall survival probability curves of patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016, according to pathological stage.

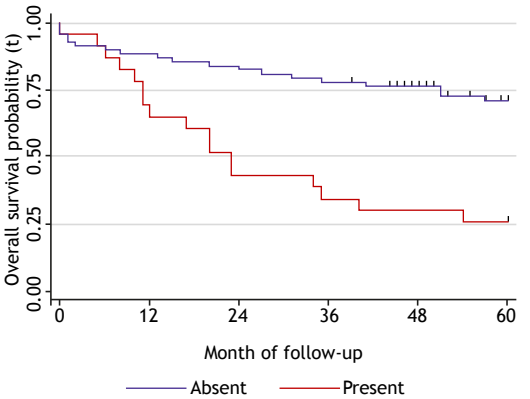

Figure 3. Overall survival probability curves of patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016, according to the presence of microvascular invasion.

Table 3. 60-month risk of death in patients with non-small cell lung cancer treated surgically at INCA from 2010 to 2016.

Characteristics	Hazard Ratio (HR)					
	Crude			Adjusted		
	HR	$CI_{95\%}$	p-value	HR	$CI_{95\%}$	p-value
Age group						
< 60 years	1.0			1.0		
≥ 60 years	1.6	(0.8-3.3)	0.217	1.9	(0.9-3.9)	0.101
Pathological stage						
I	1.0			1.0		
II	1.3	(0.6-2.9)	0.521	0.8	(0.3-1.8)	0.555
IIIA	4.0	(1.8-8.8)	0.001	2.8	(1.2-6.5)	0.017
Microvascular invasion						
Absent	1.0			1.0		
Present	3.7	(1.9-7.1)	< 0.001	3.9	(1.9-8.2)	< 0.001

Abbreviations: CI, confidence interval.

However, the number of resected patients reflects the reality of how lung cancer presents in late stages at tertiary reference centers in the public healthcare system. Since microvascular invasion was systematically assessed in the pathology routine, tumor slides were not reviewed by the research investigators. As a consequence, contemporary prognostic factors such as tumor spread through air spaces[23] and histological patterns[24] were not reviewed. Also, a significant amount of data on tumor differentiation grade was missing, a fact that impacted the analysis.

Another limitation of the present study was that the seventh edition of the staging system was used in the analysis. This was because it was originally used when the cohort was treated. Also, the current analysis was based on real-world data, thus lacking the quality control of a clinical trial. However, all patients were treated at the same institution, a reference cancer center in South America with solid expertise in lung cancer care and research. Importantly, long-term follow-up was achieved thanks to strong patient adherence.

Considering that NSCLC is one of the most incidental and aggressive types of cancer, with high mortality rates, even at early stages, the identification of prognostic factors is of utmost relevance and should enable healthcare providers to offer more appropriate treatment to each patient. The presence of microvascular invasion was an independent factor related to a worse prognosis and, therefore, should be routinely assessed in resected specimens.

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Clinical, radiological, and transbronchial biopsy findings in patients with long COVID-19: a case series

Bruno Guedes Baldi[1], Alexandre Todorovic Fabro[2], Andreia Craveiro Franco[3], Marília Helena C Machado[3], Robson Aparecido Prudente[3], Estefânia Thomé Franco[3], Sergio Ribeiro Marrone[4], Simone Alves do Vale[3], Talita Jacon Cezare[3], Marcelo Padovani de Toledo Moraes[2], Eloara Vieira Machado Ferreira[5], André Luis Pereira Albuquerque[1], Marcio Valente Yamada Sawamura[6], Suzana Erico Tanni[3]

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Departamento de Patologia e Medicina Legal, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo – USP – Ribeirão Preto (SP) Brasil.
3. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.
4. Disciplina de Radiologia, Departamento de Dermatologia e Radioterapia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.
5. Disciplina de Pneumologia, Departamento de Medicina, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.
6. Instituto de Radiologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

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Study carried out at the Hospital das Clínicas, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.

ABSTRACT

This brief communication demonstrates the correlation of persistent respiratory symptoms with functional, tomographic, and transbronchial pulmonary biopsy findings in patients with COVID-19 who had a long follow-up period. We report a series of six COVID-19 patients with pulmonary involvement who presented with persistent dyspnea within 4-15 months of discharge. We performed transbronchial biopsies, and the histopathological pattern consistently demonstrated peribronchial remodeling with interstitial pulmonary fibrosis. Therefore, lung biopsy may be useful in the approach of patients with long COVID-19, although the type of procedure, its precise indication, and the moment to perform it are yet to be clarified.

(Brazilian Registry of Clinical Trials–ReBEC; identifier: RBR-8j9kqy [http://www.ensaiosclinicos.gov.br])

Keywords: COVID-19; COVID-19/pathology; Pulmonary fibrosis; Respiratory function tests; Biopsy.

The prevalence of pulmonary involvement in severe acute COVID-19 is high, and there is a concern regarding the occurrence of lung sequelae in the long term.[1,2] However, the risk, prevalence, and severity of post-COVID-19 pulmonary fibrosis over time are still uncertain.[1,3] There is still a low number of histopathological reports regarding pulmonary lesions, and they are mostly based on explants and autopsies.[4-10] Additionally, pathological reports of interstitial lung disease secondary to COVID-19 in the long term are even scarcer.

Patients with COVID-19 may present three major lung histopathological patterns: epithelial lesions and diffuse alveolar damage (DAD); vascular injuries; and interstitial fibrosis. These patterns may coexist in the same patient during the natural history of the disease.[9,11] The most common histopathological pattern described in acute and severe cases is DAD. Progressive phases of DAD include an early exudative pattern with edema and hyaline membrane formation, a transition to an organizing phase, followed by a fibrosing stage later.[9,12]

A better understanding of the pulmonary sequelae of the lung lesions in the long term is warranted for determining a more targeted and optimized therapeutic proposal. The aim of this study was to report pulmonary histopathological findings obtained from transbronchial biopsy in a series of COVID-19 patients who had long follow-up periods.

We included six patients with a confirmed diagnosis of COVID-19 by a positive RT-PCR from a nasal swab specimen who presented with persistent respiratory symptoms and interstitial lung abnormalities on CT scans within 4 months of discharge at least and suspected of having post-COVID-19 pulmonary fibrosis. All patients were followed at the Hospital das Clínicas of the *Universidade Estadual Paulista* (UNESP, São Paulo State University).

This study was approved by the institutional research ethics committee (CAAE n. 31258820.5.1001.5411) and registered with the Brazilian Registry of Clinical

Correspondence to:
Suzana Erico Tanni. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Rubião Junior, CEP 18600-000, Botucatu, SP, Brasil.
Tel.: 55 14 3880-1171. Fax: 55 14 3882-2238. E-mail: suzanapneumo@gmail.com
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Trials (identifier, RBR-8j9kqy). Bronchoscopy with transbronchial biopsy[13] was performed after a multidisciplinary discussion based on the presence of symptoms or lung function impairment and persistence of interstitial lung abnormalities on CT scans. The lung samples (average size = 3.8 mm^2) were evaluated by an experienced pulmonary pathologist. The final diagnosis was defined by a multidisciplinary team, mainly based on the combination of clinical, tomographic, and histopathological features. We selected patients who were neither on immunosuppressive treatment nor using systemic corticosteroids after discharge. The following variables were collected from all of the patients before the biopsy procedure: baseline dyspnea index (BDI); post-bronchodilator spirometry; $D_{L_{CO}}$; TLC; Pa_{O2} on room air; SpO_2 on room air; six-minute walk distance (6MWD); and Saint George's Respiratory Questionnaire (SGRQ) score. All patients signed the informed consent form.

Figure 1 shows CT scans of the study subjects before and after discharge, whereas Figure 2 shows the histopathological findings from the biopsy samples of the patients.

Patient 1: a 62-year-old female, former smoker with diabetes mellitus experienced COVID-19 symptoms for 15 days before hospitalization and was discharged 25 days later without oxygen supplementation. Maximal oxygen supplementation (MOS) during the use of mechanical ventilation was $F_{I_{O2}}$ = 90% and $Pa_{O2}/F_{I_{O2}}$ < 100. Fifteen months after discharge, she presented with dyspnea (BDI = 7); SGRQ score = 32.2; and reduced $D_{L_{CO}}$ (57%). Spirometry, SpO_2, Pa_{O2}, and 6MWD (440 m) were unremarkable. There was improvement from chest CT results obtained at hospital admission (Figure 1A) to those obtained at 15 months after discharge (Figure 1B), demonstrating subtle peripheral and posterior ground-glass opacities (GGO). Histopathological analysis of biopsy samples showed focal septal thickening by prominent extracellular matrix deposition associated with architectural distortion of the bronchial smooth muscle layer (Figures 2A and 2B).

Patient 2: a 69-year-old female with systemic arterial hypertension (SAH), diabetes mellitus, and dementia experienced COVID-19 symptoms for 15 days before hospitalization and was discharged 9 days later. MOS flow with nasal prong was 4 L/min. Seven months after discharge, the patient reported persistent dyspnea (BDI = 7). Post-bronchodilator spirometry, SpO_2, and Pa_{O2} were unremarkable. However, TLC (75%), $D_{L_{CO}}$ (52%), 6MWD (389 m/78.8% of predicted), and SGRQ score (15.7) were reduced. CT scans at hospital admission and at 7 months after discharge are presented in Figures 1C and 1D, respectively, and there was tomographic improvement in the follow-up, although there were residual pulmonary abnormalities. Pulmonary histopathological analysis demonstrated mild hyaline peribronchial remodeling with septal extension and focal septal thickening by prominent extracellular matrix deposition (Figures 2C and 2D).

Patient 3: a 65-year-old female with hypothyroidism experienced COVID-19 symptoms for 14 days before hospitalization and was discharged 8 days later. She used a nasal prong (O_2 flow = 4 L/min). Six months after discharge, she still reported dyspnea (BDI = 9), and 6MWD was 502 m. Spirometry, SpO_2, and Pa_{O2} were unremarkable. $D_{L_{CO}}$ was mildly reduced (62%), and the SGRQ score was 30.8. Comparing CT scans at hospital admission and at 6 months after discharge, there were improvements, demonstrating subtle scattered GGO (Figures 1E and 1F, respectively). Pulmonary histopathological findings highlighted prominent peribronchial remodeling with extensive extracellular matrix deposition (Figure 2E). The architectural distortion of the bronchial smooth muscle layer was highlighted (Figure 2F).

Patient 4: a 44-year-old female with asthma and SAH started having COVID-19 symptoms 7 days before hospitalization and was discharged 14 days later. She used a non-rebreathing mask with a maximum O_2 flow of 6 L/min. Four months after discharge, she presented with dyspnea (BDI = 8) and an SGRQ score of 40.3. Spirometry, TLC, $D_{L_{CO}}$ (76%), SpO_2, and Pa_{O2} were unremarkable. In comparison with CT scans obtained at hospital admission (Figure 1G), only residual lesions were identified on CT obtained at 4 months after discharge (Figure 1H). Histopathologically, the architectural distortion around hyaline peribronchial remodeling promoted focal simile-desquamative reaction (Figure 2G). Note the disarray and hypertrophy of the bronchial smooth muscle layer (Figure 2H).

Patient 5: an 85-year-old male with SAH experience COVID-19 symptoms for 7 days before hospitalization and was discharged 16 days later. He used a nasal prong with MOS of 2 L/min. Ten months after discharge he still presented with reduced quality of life (SGRQ score = 62.0) and 6MWD (226 m/43.4% of predicted). He was unable to perform spirometry. SpO_2 and Pa_{O2} were normal. The comparison of CT scans at admission and at 10 months after discharge revealed improvements, the latter showing residual pulmonary lesions only (Figures 1I and 1J, respectively). Histopathological analysis was compatible with prominent peribronchial remodeling with extensive extracellular matrix deposition and small calcification (Figures 2I and 2J).

Patient 6: a 44-year-old female with a history of hysterectomy presented with COVID-19 symptoms for 7 days before hospitalization and was discharged 21 days later. MOS with non-rebreathing mask was 10 L/min. Seven months after discharge, she reported persistent dyspnea (BDI = 7), and her SGRQ score was 41.7. Spirometry suggested a restrictive pattern. SpO_2 and Pa_{O2} were normal, and 6MWD was reduced (375 m/69.0% of predicted). Follow-up CT scanning demonstrated an improvement in comparison with that at hospital admission (Figures 1K and 1L, respectively), showing residual pulmonary lesions only. Pulmonary histopathological analysis was compatible with peribronchial remodeling with extensive extracellular matrix deposition (Figures 2K and 2L).

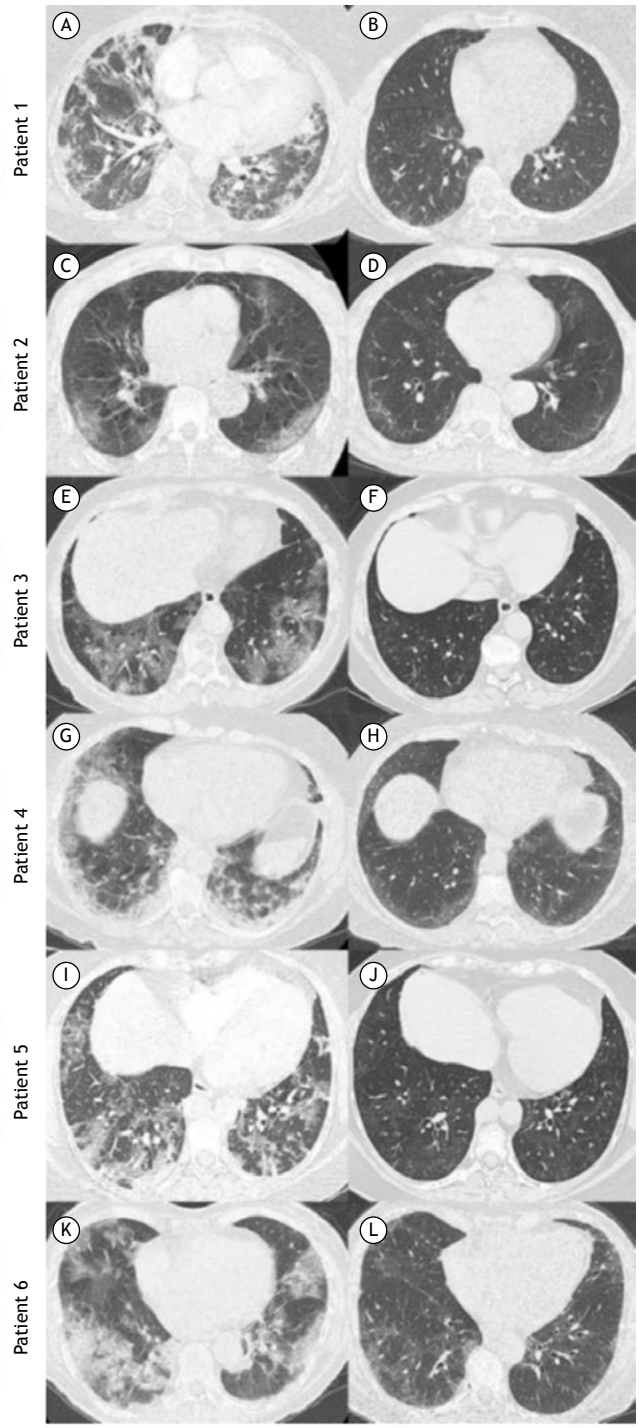

Figure 1. Chest CT scans of the patients studied. Patient 1: in A, a scan during the acute phase showing bilateral ground-glass opacities (GGO), consolidations, and parenchymal bands; in B, a scan after 15 months of follow-up showing subtle peripheral and posterior GGO. Patient 2: in C, a scan during the acute phase showing bilateral and peripheral GGO; in D, a scan after 7 months of follow-up showing subtle GGO with subpleural curvilinear lines and small dilated bronchioles in the right lower lobe. Patient 3: in E, a scan during the acute phase showing bilateral GGO and crazy-paving pattern; in F, a scan after 6 months of follow-up showing subtle scattered GGO. Patient 4: a scan during the acute phase showing bilateral and peripheral GGO and consolidations; in H, a scan after 4 months of follow-up showing subtle bilateral and peripheral GGO. Patient 5: in I, a scan during the acute phase showing bilateral GGO; in J, a scan after 10 months of follow-up showing subtle GGO and mosaic attenuation in the lung parenchyma. Patient 6: in K, a scan during the acute phase showing bilateral GGO and consolidations; in L, a scan after 7 months of follow-up showing bilateral GGO with some dilated bronchioles.

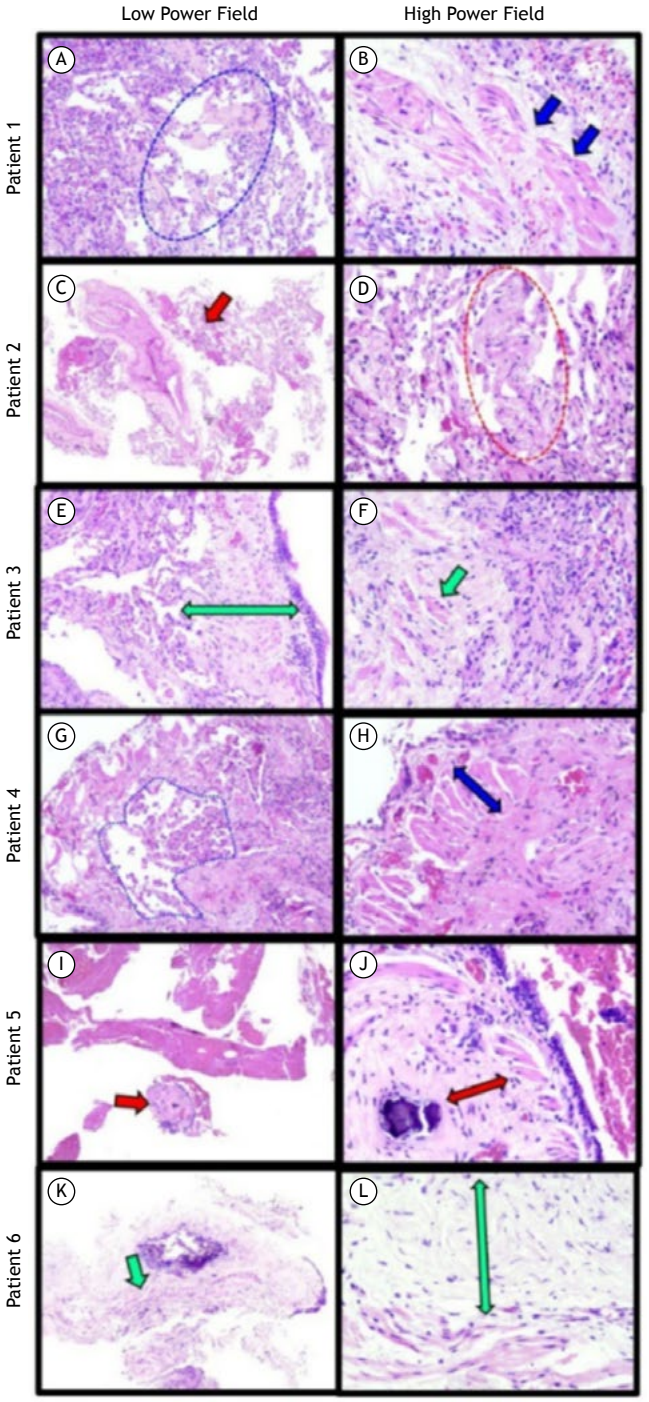

Figure 2. Histopathological panel of transbronchial biopsy samples collected from the patients studied (H&E; low power field, ×4, and high power field, ×40). All of the patients showed hyaline peribronchial remodeling with septal extension. Patient 1: focal septal thickening by prominent extracellular matrix deposition (blue dashed ellipse in A) associated with architectural distortion of the bronchial smooth muscle layer (blue arrows in B). Patient 2: mild hyaline peribronchial remodeling with septal extension (red arrow in C). Note the focal septal thickening by prominent extracellular matrix deposition (red dashed ellipse in D). Patient 3: prominent peribronchial remodeling with extensive extracellular matrix deposition (double green arrow in E). The architectural distortion of the bronchial smooth muscle layer is highlighted (green arrow in F). Patient 4: the architectural distortion around hyaline peribronchial remodeling promoted focal simile-desquamative reaction (area enclosed by blue dashed line in G). Note the disarray and hypertrophy of the bronchial smooth muscle layer (double blue arrow in H). Patient 5: prominent peribronchial remodeling (red arrow in I) with extensive extracellular matrix deposition (double red arrow in J) and small calcification. Patient 6: prominent peribronchial remodeling (green arrow in K) with extensive extracellular matrix deposition (green arrow in L).

Few studies have described pulmonary histopathological findings in patients with COVID-19 after a long follow-up period. Most case series have detailed features during the acute phase and based their findings on lung tissue from autopsy or transplant.[4-10] To our knowledge, this is the first study that evaluated histopathological features obtained from transbronchial biopsies during the late stage of pulmonary involvement by COVID-19, 4-15 months after the acute infection. The main finding of our study was that the histological analysis of the six patients with long COVID-19 and persistent pulmonary abnormalities on HRCT demonstrated signs of bronchiolocentric interstitial pneumonia, most of them presenting with architectural distortion and peribronchial remodeling with extracellular matrix deposition.

Although all of the patients in our series showed tomographic improvements, dyspnea and pulmonary tomographic abnormalities still remained. Only one patient met the criteria for ARDS. However, the late functional and tomographic findings of this patient with ARDS were similar to that of the others. It is not completely clear, however, when the presence of irreversible post-COVID-19 pulmonary fibrosis is defined, and which patients may present tomographic and functional improvement over time. Additionally, it remains uncertain in which scenario after COVID-19 lung biopsy should be considered for histopathological analysis.[1,3,14,15]

Previous descriptions of pulmonary histopathological characterization of COVID-19 were mostly obtained from autopsy and explanted lungs.[1,5-7,9,10] The main patterns identified alone or in combination were exudative and organizing DAD, hemorrhage, thrombosis, intra-alveolar fibrin deposition, lymphoid infiltrates, and organizing pneumonia. However, in the fibrosing DAD phase, our group has already demonstrated a fibrotic phenotype with excessive extracellular matrix and collagen deposition and lung architectural distortion, corroborating other studies.[7-12] Likewise, some autopsy and explanted lung cases demonstrated interstitial and bronchiolar fibrosis, with collagen deposition, bronchial metaplasia, and pulmonary vascular remodeling. Some cases have demonstrated areas of microscopic honeycombing.[5-9] A recent case series reinforced the presence of diffuse interstitial fibrosis and areas of microscopic honeycombing in patients after a 4-month follow-up period.[8] Our findings demonstrated some similarities, as we predominantly identified bronchiolocentric interstitial pneumonitis. However, to our knowledge, no study has described histological features and their patterns after COVID-19 with pulmonary involvement during a long follow-up period, which would add for a better understanding of this process.

Patients with interstitial lung disease secondary to COVID-19 might need to be monitored for a longer time, preferably through a multidisciplinary approach.[3] Pulmonary lesions may persist in the long term after COVID-19, although a significant proportion of patients may present progressive functional and tomographic improvement during follow-up.[15]

Our study has limitations. First, there were a small number of patients included for robust conclusions. Second, transbronchial biopsy does not allow assessment of peripheral lesions, which may have histological patterns that are different from those identified. Third, all patients showed tomographic improvements at follow-up, and we cannot conclude that the pattern found here would be the same as those found in patients who remain stable or deteriorate during follow-up.

In conclusion, findings compatible with bronchiolocentric interstitial pneumonia were identified from transbronchial biopsies in patients with long COVID-19. Patients with pulmonary involvement secondary to COVID-19 that require biopsy during the follow-up period need to be better defined. Based on our series, transbronchial biopsy may be an initial step in the assessment of patients with post-COVID-19 pulmonary fibrosis in the presence of symptoms or lung function impairment and persistence of interstitial lung abnormalities on CT scans. Further studies are warranted to determine the histopathological patterns in a larger number of lung tissue samples obtained from transbronchial cryobiopsy or surgical biopsy, as well as in patients who remain stable or present worsening of pulmonary involvement associated with COVID-19. It will also be important to assess the indications for and responses to drug treatment in such scenarios, including the use of corticosteroids and antifibrotic drugs.

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AUTHOR CONTRIBUTIONS

BB, ATF, and SET: study conceptualization; clinical, radiological, and histological interpretation; and drafting the manuscript. RAP, ETF, ACF, MHCM, SAV, TJC, and MPTM: performance of all procedures and data collection. MVYS and SRM: radiological interpretation. EVMF, ALPA, MVYS, BB, ATF, and SET: revision of preliminary and final versions; and approval of the final version.

CONFLICT OF INTEREST

None declared.

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Stereotactic body radiotherapy versus surgery for early-stage non-small cell lung cancer: an updated meta-analysis involving 29,511 patients included in comparative studies

Gustavo Arruda Viani[1], André Guimarães Gouveia[2], Michael Yan[3], Fernando Konjo Matsuura[1], Fabio Ynoe Moraes[3]

1. Departamento de Imagens Médicas, Oncologia e Hematologia, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo – USP – Ribeirão Preto (SP) Brasil.
2. Departamento de Radioterapia, Américas Centro de Oncologia Integrado, Rio de Janeiro (RJ) Brasil.
3 Department of Oncology, Division of Radiation Oncology, Kingston General Hospital, Queen's University, Kingston (ON) Canada.

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ABSTRACT

Objective: To evaluate the efficacy of stereotactic body radiotherapy (SBRT) versus surgery for early-stage non-small cell lung cancer (NSCLC) by means of a meta-analysis of comparative studies. **Methods:** Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis of Observational Studies in Epidemiology guidelines, searches were performed on PubMed, MEDLINE, Embase, and Cochrane Library for eligible studies. The meta-analysis compared the hazard ratios (HR) for overall survival (OS), cancer-specific survival (CSS), and local control (LC). Subgroup and meta-regression analyses evaluated the association of extent of surgical resection, study publication year, tumor staging, propensity score matching, proportion of chemotherapy use, and proportion of pathological lymph node involvement with CSS and OS. **Results:** Thirty studies involving 29,511 patients were included (surgery group: 17,146 patients and SBRT group: 12,365 patients). There was a significant difference in favor of surgery vs. SBRT in the 3-year OS (HR = 1.35; 95% CI: 1.22-1.44; I^2 = 66%) and 3-year CSS (HR = 1.23; 95% CI: 1.09-1.37; I^2 = 17%), but not in the 3-year LC (HR = 0.97; 95% CI: 0.93-1.08; I^2 = 19%). In the subgroup analysis for OS, no significant difference between surgery and SBRT groups was observed in the T1N0M0 subgroup (HR = 1.26; 95% CI: 0.95-1.68; I^2 = 0%). In subgroup analysis for CSS, no significant difference was detected between the sublobar resection subgroup and the SBRT group (HR = 1.21; 95% CI: 0.96-1.53; I^2 = 16%). **Conclusions:** Surgery generally resulted in better 3-year OS and CSS than did SBRT; however, publication bias and heterogeneity may have influenced these findings. In contrast, SBRT produced LC results similar to those of surgery regardless of the extent of surgical resection. These findings may have important clinical implications for patients with comorbidities, advanced age, poor pulmonary reserve, and other factors that may contraindicate surgery.

Keywords: Carcinoma, Non-Small-Cell Lung/surgery; Radiosurgery; Meta-analysis.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the world, with 2,206,771 new cases and 1,796,144 deaths in 2020.[1] NSCLC represents nearly 87% of lung cancer diagnoses, and only 15% of patients present with early-stage disease.[2] The introduction of lung cancer screening into clinical practice, however, will result in more patients being diagnosed with early-stage disease.[3] In the National Lung Screening Trial, approximately 70% of lung cancer patients diagnosed by CT screening have stage I NSCLC.[3]

Currently, surgery is the standard of care for patients with operable early-stage (stages I or II) NSCLC.[4] However, NSCLC usually affects elderly patients. In one study with 27,844 NSCLC patients submitted to surgery, the median age was 67.2 years. In addition, in this population, the incidence of major complications was 9.1%.[5] Older age ($p < 0.001$) and diseases associated with smoking, such as coronary artery disease ($p = 0.011$) and peripheral vascular disease ($p \leq 0.001$), were predictors of morbidity and mortality after surgery.[5]

In the last years, encouraging outcomes with stereotactic body radiotherapy (SBRT) in inoperable NSCLC patients have driven the interest in a direct comparison between surgery and SBRT in medically operable patients.[6] A standard SBRT course for stage I NSCLC consists of 1-5 treatments over 1 to 2 weeks with a dose per fraction of 10-34 Gy.[7,8] The ablative dose per fraction used with SBRT increases patient convenience due to reduced treatment duration, while translating into a higher biologically effective dose (BED), which is likely to produce a better local tumor control rate.[9]

Correspondence to:
Gustavo Arruda Viani. Rua Dr. Rubem Aloysio Monteiro Moreira, 155, CEP 14021-686, Ribeirão Preto, SP, Brasil.
Tel.: 55 16 3402-6584. Fax: 55 16 3402-1744. E-mail: gusviani@gmail.com
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Early randomized trials comparing surgery and SBRT closed prematurely because of low patient accrual.[9] Consequently, several studies and meta-analyses comparing both modalities have been published.[10-14] However, previously published studies lacked methodological rigor, and some key clinical aspects were missing. Therefore, the present study aimed to perform a meta-analysis of studies comparing surgery and SBRT in early-stage NSCLC patients to explore clinical aspects and identify potential differences for guiding future relevant studies.

METHODS

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, electronic searches were performed in PubMed, Embase, SciELO, and Cochrane Library for eligible studies published before January 1, 2020. The following keywords or medical terms were used: ("non-small cell lung carcinoma" OR "non-small cell lung cancer" OR "non-small cell lung neoplasms" OR "lung adenocarcinoma" OR "lung squamous cell carcinoma" OR "large cell lung cancer") AND ("surgery" OR "lobectomy" OR "sublobar resection" OR "limited resection" OR "sublobectomy" OR "segmentectomy" OR "wedge resection") AND ("stereotactic ablative radiotherapy" OR "stereotactic body radiotherapy" OR "SBRT" OR "SABR"). Only articles in English were included, and reference lists of relevant studies were manually searched for potentially eligible articles.

Study inclusion

We included comparative studies of SBRT and surgery (lobectomy, segmentectomy, or wedge resection) in patients with early-stage (T1-3N0M0) NSCLC. Only studies using an SBRT schedule with a median BED ≥ 100 Gy10 were included in the final meta-analysis. Randomized and observational studies using propensity score analysis or other statistical adjustment methods to reduce bias were included in the meta-analysis. Meta-analyses previously published were additionally included in the quantitative synthesis. Studies without comparisons between SBRT/stereotactic ablative radiotherapy and surgery, case reports, and reviews were excluded.

Outcomes

The outcomes studied in the meta-analysis were 3-year overall survival (OS), cancer-specific survival (CSS), and local control (LC). Studies combining treatments in one of the comparative arms or studies with no data regarding 3-year OS, CSS, and LC were also excluded.

Data collection and quality assessment

Two reviewers (GAV and AGG) independently screened studies and extracted study data using a standardized method, discrepancies being settled by a third reviewer (FKM). The following information was collected: author, year of publication, study design, staging, SBRT dose, fractionation SBRT regimen, clinical characteristics (sex, age, histology, and follow-up), and clinical outcomes.

Statistical analysis

Meta-analysis of the outcomes was performed using ProMeta 3.[15] Hazard ratios (HRs) and respective 95% CIs were used to analyze dichotomous data. Data from survival curves were extracted according to the methods described by Tierney et al.[16] When calculations were not possible or not available, HRs were estimated using the Kaplan-Meier method. We used the iterative algorithm proposed by Guyot et al.[17] to find numeric solutions to the inverted Kaplan-Meier equations. Heterogeneity was estimated using the I^2 index and Cochran's Q statistic. In the presence of heterogeneity using the fixed-effect model, the random-effects model was selected to estimate the outcomes. Sensitivity analysis was conducted by stepwise removal of each included study. Subgroup analysis was performed by separating the studies by type of surgery (lobectomy, sublobar resection, or mixed surgical resection), T staging (T1N0M0, T1-2N0M0, or T1-3N0M0), surgical technique (video-assisted thoracic surgery [VATS] or mixed surgical technique), and use of propensity score matching (yes or no). Meta-regression analysis was performed to determine the effect of different publication years, proportion of chemotherapy use, and proportion of pathological lymph node involvement on CSS and OS. These variables were treated as continuous variables. Publication bias was evaluated using Egger test, and a p-value < 0.05 was considered significant.[18]

RESULTS

A total of 3,632 studies were initially identified. After excluding duplicates and irrelevant publications, 30 studies were selected for the meta-analysis (Figure S1). Three studies had different control groups (lobectomy or sublobar resection); these groups were counted twice as separate cohorts, generating a total of 33 cohorts for quantitative synthesis. Overall, there were 26 retrospective studies with propensity score matching, 1 randomized clinical trial, 1 retrospective study with adjustment for prognostic covariates, and 2 retrospective studies without adjustment for covariates.[9,19-47]

In total, 29,511 patients with early-stage NSCLC were included, 17,146 undergoing surgery and 12,365 being treated with SBRT. Lobectomy, mixed surgical resection, and sublobar resection were compared with SBRT in 11, 10, and 6 studies, respectively. In addition, 3 studies separately compared lobectomy and sublobar resection with SBRT. VATS was employed exclusively in 4 studies; in the remaining studies, both open thoracotomy and VATS were used (Table 1). The SBRT dose ranged from 45 to 60 Gy, in 3 to 12

fractions. Details of study design, number of patients, clinical characteristics, treatment characteristics, and outcomes in the studies included are described in Table S1. Table S2 shows a summary of the characteristics of the previous meta-analyses[10-14] in the literature and of the present meta-analysis.

Considering the studies using propensity score matching to improve treatment group balance, we found that 16 covariates were utilized to generate propensity score models. Age, sex, and educational status were the most common covariates used, whereas tumor staging, tumor location, histology, and PET were the least common (Figure S2). In total, 2 studies used more than 10 covariates in the propensity score model, whereas 9 studies used less than 8 covariates (Figure S3).

Table 1. Summary of the characteristics of all studies included in the meta-analysis.

Variable	Studies, n	Patients, n	Median (range)
Trials and comparative studies			
Randomized trial	1	58	
Retrospective, propensity score matching	26	24,917	
Retrospective, adjustment for prognostic covariates	1	340	
Retrospective, other	2	4,196	
Total		29,511	
SBRT		12,365	
Surgery		17,146	
Patients			
Age			
SBRT			73 (66-82)
Surgery			72 (65-82)
Female sex, %			
SBRT			42 (3-65)
Surgery			40 (3-62)
Histology, %			
Adenocarcinoma			
SBRT			47 (9-100)
Surgery			53 (14-100)
Squamous cell carcinoma			
SBRT			30 (0-46)
Surgery			31 (0-43)
SBRT			
Total dose, Gy			48 (45-60)
Fraction, n			4 (3-12)
Dose per fraction, Gy			14 (5-20)
Median BED > 100	30		
Follow-up period, months			
SBRT			31 (18-58)
Surgery			43 (16-58)
Clinical stage			
T1N0	4	3,334	
T1-2N0	21	24,757	
T1-3N0	4	620	
Stage I	1	800	
Type of surgery[a]			
Mixed	10	772	
Lobectomy	14	6,242	
Sublobar resection	9	10,132	
Surgical technique			
Mixed	26	16,951	
VATS only	4	195	
Chemotherapy, %			
SBRT			1 (0-16)
Surgery			8 (0-15)
Positive lymph node involvement			
SBRT			6.5 (1.0-75.7)
Surgery			11.0 (4.0-37.8)

SBRT: stereotactic body radiotherapy; BED: biologically effective dose; and VATS: video-assisted thoracic surgery.
[a]Three studies reported using both lobectomy and sublobar resection.

OS

Thirty studies, with a total of 29,511 patients, compared surgery with SBRT and reported the OS. After quantitative synthesis, the pooled 3-year OS was significantly higher in the surgery group than in the SBRT group (HR = 1.35; 95% CI: 1.22-1.44; I^2 = 66%); however, there was significant heterogeneity in the studies. When we pooled the data stratified by the extent of surgical resection, the 3-year OS remained higher in the surgery group in comparison with the SBRT group for all subgroups. Significant heterogeneity was noted in the lobectomy subgroup (I^2 = 66%; HR = 1.47; 95% CI: 1.28-1.69), but not in the mixed surgical resection (I^2 = 0%; HR = 1.28; 95% CI: 1.07-1.53) and sublobar resection subgroups (I^2 = 38%; HR = 1.24; 95% CI: 1.06-1.46; Figure 1).

Table 2 presents the results of further subgroup analyses. When we compared VATS and non-VATS procedures or studies that used and did not use propensity score matching, surgery was associated with significantly higher 3-year OS. However, when we stratified patients by T staging, the subgroup of studies including only T1N0M0 patients showed no significant difference in 3-year OS between surgery and SBRT groups (HR = 1.26; 95% CI: 0.95-1.68; I^2 = 0%), with no heterogeneity noted among the studies included. Moreover, in the meta-regression analysis, publication year, proportion of chemotherapy use, and proportion of pathological lymph node involvement had no significant associations with OS (Table 2).

CSS

Sixteen studies involving 11,387 patients reported the CSS at 3 years as an outcome. When compared with SBRT, surgery was associated with higher 3-year CSS (HR = 1.23; 95% CI: 1.09-1.37; I^2 = 17%), and no significant heterogeneity was detected (Figure 2). In a subgroup analysis stratified by the extent of surgical resection, only lobectomy alone was found to be significantly associated with improved CSS when compared with SBRT (Figure 2 and Table 3). When we assessed sublobar resection, there was no significant difference when compared with SBRT and no significant heterogeneity (HR = 1.21; 95% CI: 0.96-1.53; I^2 = 16%; Figure 2 and Table 3). In additional subgroup analyses, comparison between studies using VATS and no VATS, as well between studies using and not using propensity score matching showed significant benefits of surgery over SBRT regarding 3-year CSS (Table 3). However, in studies including T1N0M0 patients only, no significant differences between surgery and SBRT were observed (HR = 1.12; 95% CI: 0.86-1.46; I^2 = 0%), and there was no heterogeneity. In the meta-regression analysis, publication year, proportion of chemotherapy use, and proportion of pathological lymph node involvement had no relationship with 3-year CSS (Table 3).

LC

Nine studies involving 912 patients reported data on 3-year LC. Surgery and SBRT showed equivalent LC at 3 years (HR = 0.97; 95% CI: 0.93-1.08; I^2 = 19%) and no heterogeneity (Figure 3).

Publication bias

Publication bias was assessed using the method by Egger et al.[18] A statistical significance for publication bias for OS at 3 years was detected in favor of surgery (p = 0.027; Figure S4).

PROPENSITY SCORE MATCHING

When stratifying the studies by use of propensity score matching, we surprisingly found high heterogeneity (I^2 = 61%). The covariates used for model generation in propensity score matching showed substantial variability among the studies (Figure S2). Several studies did not incorporate clinically essential confounders such as tumor stage, tumor size, clinical performance status, and histology within the propensity score model (only 10% of the studies; Figure S2). Furthermore, the number of covariates used within the generation of the propensity score model was variable. Only 2 studies used more than 10 covariates, whereas 9 used less than 8 parameters (Figure S3). Although propensity score matching can minimize known confounding factors and improve the balance between two groups, it cannot truly ever eliminate them or replicate the results of a randomized study.

DISCUSSION

The present study is the largest meta-analysis examining oncologic outcomes of SBRT versus surgery in early-stage NSCLC. First, our analysis confirmed that surgery improved 3-year OS in comparison with SBRT, with a low degree of heterogeneity. The lobectomy subgroup also showed improved OS compared with the SBRT group; however, there was a high degree of heterogeneity in the pooled result. Second, when we stratified by the type of surgery (VATS or non-VATS), the 3-year OS was better than that in the SBRT group. There was no heterogeneity in the VATS subgroup, indicating that VATS did not compromise the treatment outcome. Third, studies that included only patients with T1N0M0 staging showed no significant differences in OS between surgery and SBRT groups, with no heterogeneity among the pooled studies. These findings failed to show a difference between the two treatments for patients in this population.

CSS is less sensitive to external variables than is OS. Our analysis shows that lobectomy is superior to SBRT for CSS in propensity score matching adjusted and unadjusted studies (neither subgroup showed significant heterogeneity). For patients staged as T1N0M0, there was no significant difference in CSS when comparing SBRT and lobectomy. Similarly, there was no difference in CSS when comparing SBRT and sublobar resection or mixed surgical resection. These findings may have important clinical implications for patients with comorbidities, advanced age, poor

Studies	SBRT	Surgery	HR (95% CI)
Lobectomy subgroup			
Albano et al.[43]	48	64	1.63 (1.12-2.43)
Boyer et al.[29]	468	468	1.80 (1.08-3.20)
Bryant et al.[45]	449	2986	1.38 (1.08-1.78)
Chang et al.[9]	31	31	1.18 (0.98-1.43)
Cornwell et al.[44]	37	37	1.53 (1.05-2.20)
Eba et al.[39]	21	21	1.51 (0.70-3.19)
Hamaji et al.[31]	41	41	2.56 (1.31-5.00)
Lin et al.[47]	45	45	1.00 (0.93-2.80)
Mokles et al.[34]	73	73	1.97 (0.99-3.92)
Rosen et al.[40]	1781	1781	2.00 (1.80-2.30)
Shirvani et al.[30]	251	251	1.00 (0.74-1.38)
Shirvani et al.[22]	99	99	1.41 (0.90-2.31)
Smith et al.[35]	300	300	1.30 (1.01-1.68)
Verstegen et al.[26]	64	64	1.33 (0.68-2.58)
Total subgroup	3706	6241	I^2 = 66%; 1.47 (1.48-1.69)
Mixed subgroup			
Crabtree et al.[20]	57	57	1.62 (0.93-2.80)
Crabtree et al.[28]	56	56	1.63 (0.88-2.97)
Dong et al.[46]	66	66	1.45 (0.54-3.87)
Kasteljin et al.[32]	53	53	1.71 (0.87-3.35)
Miyazaki et al.[42]	27	27	1.07 (0.70-1.10)
Palma et al.[21]	60	60	1.39 (0.93-2.07)
Robison et al.[24]	76	76	0.86 (0.44-1.69)
Van der Berg et al.[36]	197	197	1.07 (0.74-1.74)
Varlotto et al.[25]	77	77	1.28 (1.22-2.38)
Wang et al.[37]	35	35	1.40 (1.09-2.00)
Total subgroup	704	704	I^2 = 0%; 1.28 (1.07-1.53)
Sublobar subgroup			
Bryant et al.[45]	243	243	1.17 (0.90-1.53)
Ezer et al.[33]	362	362	0.98 (0.85-1.28)
Grills et al.[19]	55	55	2.35 (0.95-6.20)
Matsuo et al.[27]	53	53	1.49 (0.90-2.48)
Paul et al.[38]	201	201	1.68 (1.18-2.68)
Puri et al.[23]	5355	5355	1.55 (1.24-2.80)
Shirvani et al.[22]	112	112	1.22 (0.79-1.89)
Smith et al.[35]	243	243	1.01 (0.84-1.30)
Yerokum et al.[41]	1584	1584	1.30 (0.88-1.60)
Total subgroup	8206	8206	I^2 = 38%; 1.24 (1.06-1.46)

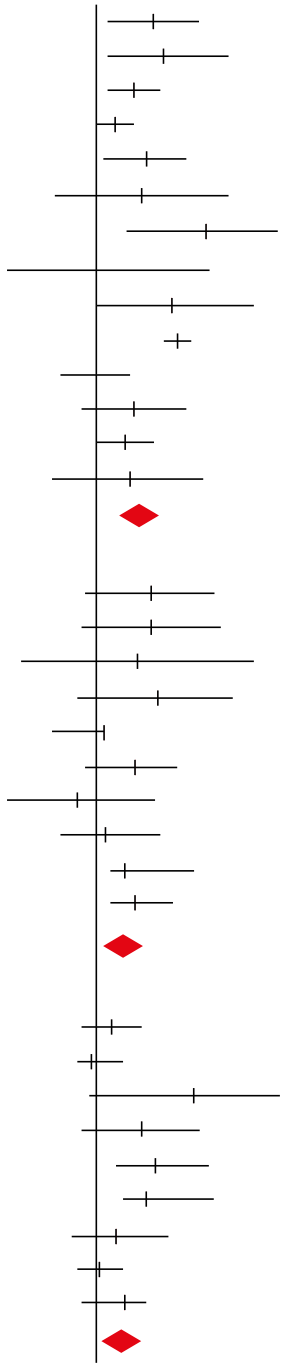

Figure 1. Analyses of 3-year (3y) overall survival comparing lobectomy, mixed surgical resection, and sublobar resection subgroups with the stereotactic body radiotherapy (SBRT) group. The 3y overall survival was significantly higher in all of the surgery subgroups (HR = 1.35; 95% CI: 1.22-1.44; I^2 = 66%). HR: hazard ratio.

pulmonary reserve, and other factors that may contraindicate surgery.

The American Society of Radiation Oncology has recently published a guideline that does not recommend SBRT outside of a clinical trial for patients who are at a low risk for lobectomy.[48] Our findings corroborate this recommendation. Both treatments, even when considering the publication bias in favor

Table 2. Subgroup analyses including categorical and continuous moderator variables for three-year overall survival.

Categorical moderator variable	Number of studies (patients)	HR (95% CI)	p	Heterogeneity	
				I^2, %	p
Type of surgery					
Lobectomy	7 (4,677)	1.47 (1.20-1.69)	<	66	0.0001
Mixed	4 (390)	1.28 (1.07-1.53)	0.001	0	0.658
Sublobar resection	5 (6,320)	1.24 (1.06-1.46)	0.007	38	0.114
			0.009		
VATS					
No	26 (16,951)	1.3 (1.2-1.4)	0.001	66	0.0001
Yes	4 (195)	1.7 (1.2-2.3)	0.002	0	0.528
Propensity score matching					
Yes	26 (24,917)	1.37 (1.23-1.54)	0.001	61	0.001
No	4 (4,594)	1.25 (1.01-1.54)	0.038	38	0.120
T staging					
T1	4 (3,334)	1.26 (0.95-1.68)	0.106	0	0.460
T1-2	21 (24,757)	1.33 (1.18-5.00)	0.0001	68	0.0001
T1-3	4 (620)	1.3 (1.2 -2.0)	0.048	0	0.40

Continuous moderator variable	Number of studies (patients)	Intercept	Slope	p
Publication year				
2010-2019	30 (29,511)	−3.8	0.01	0.916
Chemotherapy, %				
(median, 1-8)	12 (19,481)	0.75	−0.02	0.208
Pathological lymph node involvement, %				
(median, 6.5-11.0)	8 (8,969)	0.82	−0.042	0.279

HR: hazard ratio; VATS: video-assisted thoracic surgery; and T: tumor.

of surgery, had good OS and CSS outcomes, making the decision process complex and often dependent on patient desire.[49]

When we compared our meta-analysis results with those of previously published meta-analyses, three[11,12,14] of the five previous meta-analyses showed that surgery provides OS rates superior to those of SBRT. However, these analyses did not appraise publication bias or study heterogeneity. Our meta-analysis has explored study heterogeneity and publication bias, reinforcing the need for new studies with a more robust design, including clear inclusion and exclusion criteria, follow-up protocols, and statistical analyses that adjust for confounding variables, using methods such as propensity score matching and multivariable regression. Given the large sample size in the current study, it is unlikely that the inclusion of further observational studies comparing SBRT with surgery will significantly impact our findings.

Our meta-analysis does have limitations that warrant mention. Our analysis included only 1 small randomized trial, whereas the remaining 29 studies had a retrospective observational design. These are inherent limitations in the literature, although our quantitative synthesis improved the power in detecting the overall effect size. However, these results were significantly influenced by inter-study heterogeneity and publication bias, thereby presenting uncertainty to our pooled results. Similarly, a previous meta-analysis by Chen et al.[10] that reported on 16 comparative studies also found significant heterogeneity and publication bias. The authors identified favorable OS outcomes with surgery in comparison with SBRT (HR = 1.48; 95% CI: 1.26-1.72; $p < 0.001$), but high heterogeneity ($I^2 = 80.5\%$; $p < 0.001$).[10]

We also identified variations in the propensity score analysis for matching across a broad range of baseline variables, such as age, type of surgery, tumor size, histological subtype, tumor location, and others, in order to build two similar groups for comparison. Consequently, the readers must keep in mind that propensity score matching does not replicate randomized trial results, and that even after balancing, all sources of bias cannot be eliminated; unobserved confounders may exist. Lastly, we identified moderate heterogeneity in several of the quantitative syntheses by using random effects modeling.

FINAL CONSIDERATIONS

After pooling the data of 29,511 patients with early-stage NSCLC, surgery has shown to be superior to SBRT regarding OS and CSS outcomes, but no difference was found regarding LC. However, publication bias and heterogeneity may significantly have influenced these findings. Furthermore, there was no significant difference in OS between surgery and SBRT in the T1N0M0 subgroup analysis, the same happening when comparing the sublobar resection subgroup with the SBRT group regarding CSS. SBRT and surgery had similar LC regardless of the extent of surgical resection. Our analyses suggest equivalent outcomes for SBRT in subsets of patients with early-stage NSCLC, and SBRT seems to be a viable option for inoperable

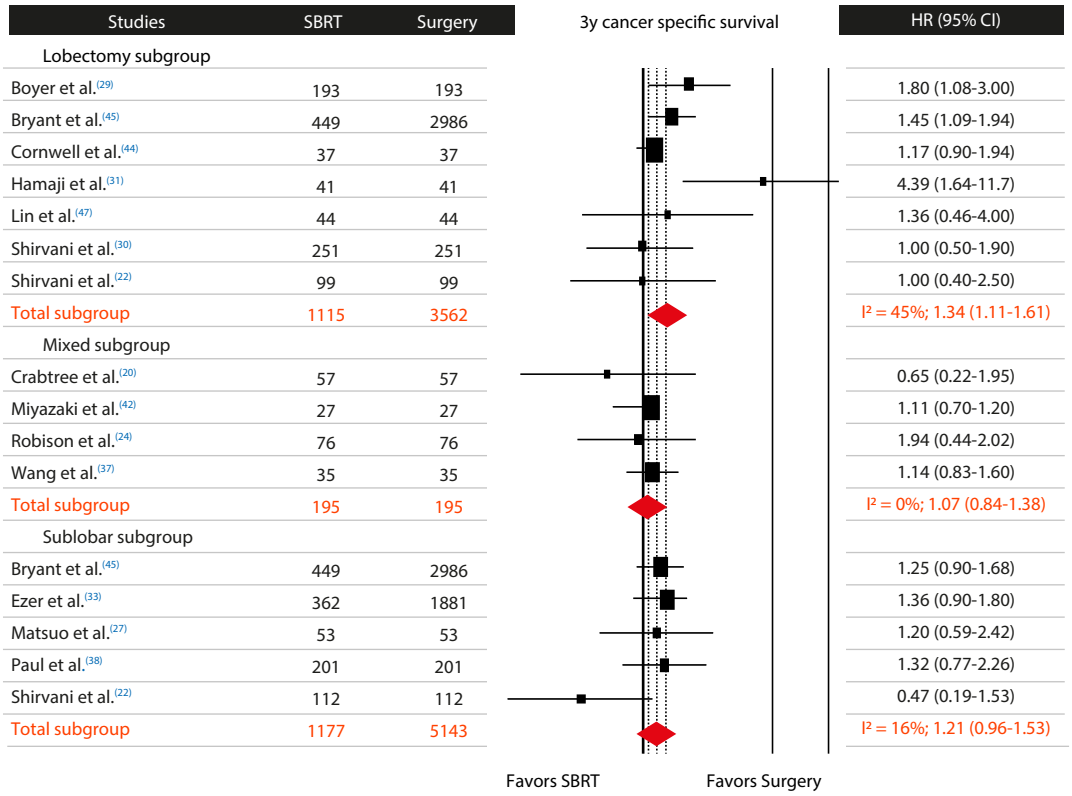

Figure 2. Analyses of three-year (3y) cancer-specific survival comparing lobectomy, mixed surgical resection, and sublobar resection subgroups with the stereotactic body radiotherapy (SBRT) group. The 3y cancer-specific survival was significantly higher in all of the surgery subgroups (HR = 1.23; 95% CI: 1.09-1.37; I^2 = 17%). HR: hazard ratio.

Table 3. Subgroup analyses including categorical and continuous moderator variables for three-year cancer-specific survival.

Categorical moderator variable	Number of studies (patients)	HR (95% CI)	p	Heterogeneity I^2, %	Heterogeneity p
Type of surgery					
Lobectomy	7 (4,677)	1.34 (1.11-1.61)	0.002	45	0.09
Mixed	4 (390)	1.07 (0.84-1.38)	0.573	0	0.77
Sublobar resection	5 (6,320)	1.21 (0.96-1.53)	0.112	16	0.309
VATS					
No	4 (195)	1.26 (1.02-1.54)	0.029	48	0.06
Yes	26 (16,951)	1.24 (1.06-1.44)	0.006	61	0.001
Propensity score matching					
Yes	26 (24,917)	1.15 (1.04-1.20)	0.017	15	0.295
No	4 (4,594)	1.40 (1.18-1.67)	0.0001	0	0.670
T staging					
T1	4 (3,334)	1.12 (0.86-1.46)	0.380	0	0.902
T1-2	21 (24,757)	1.27 (1.10-1.46)	0.001	30	0.145

Continuous moderator variable	Number of studies (patients)	Intercept	Slope	p
Publication year				
2010-2019	30 (29,511)	-102	0.05	0.447
Chemotherapy, %				
0-20%	12 (19,481)	0.54	-0.05	0.922
Pathological lymph node involvement, %				
0-22%	8 (8,969)	0.5	-0.02	0.833

HR: hazard ratio; VATS: video-assisted thoracic surgery; and T: tumor.

patients. These findings may have important clinical implications for patients with comorbidities, advanced age, poor pulmonary reserve, and other factors that may contraindicate surgery.

Studies	SBRT	Surgery	HR (95% CI)
Lobectomy subgroup			
Albano et al.[43]	48	64	0.88 (0.75-1.02)
Chang et al.[9]	31	27	0.97 (0.88-1.02)
Cornwell et al.[44]	37	37	0.92 (0.82-1.02)
Hamaji et al.[31]	41	41	0.79 (0.60-1.06)
Lin et al.[47]	45	45	1.45 (0.23-2.80)
Verstegen et al.[26]	64	64	3.68 (1.09-12.5)
Total subgroup	266	278	0.93 (0.85-1.01), p = 0.08
Mixed subgroup			
Crabtree et al.[28]	56	56	0.98 (0.22-1.95)
Dong et al.[46]	66	61	1.07 (0.70-1.20)
Total subgroup	122	122	0.98 (0.84-1.15), p = 0.809
Sublobar subgroup			
Grills et al.[19]	55	69	3.65 (0.98-13.6)
Total subgroup	55	69	3.65 (0.98-13.6), p = 0.06
Total I^2	443	469	I^2 = 19%; 0.97 (0.93-1.08)

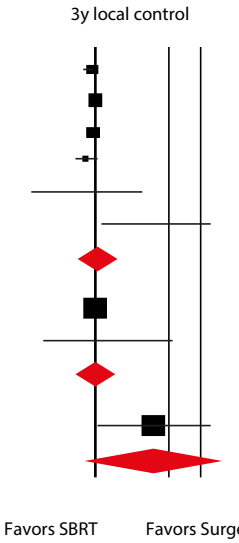

Figure 3. Analyses of 3-year (3y) local control comparing lobectomy, mixed surgical resection, and sublobar resection subgroups with the stereotactic body radiotherapy (SBRT) group. There were no significant differences between the surgery subgroups and the SBRT group (HR = 0.97; 95% CI: 0.93-1.08; I^2 = 19%). HR: hazard ratio.

AUTHOR CONTRIBUTIONS

GAV, AGG, and FYM: conception and planning of the study; interpretation of evidence; drafting and revision of preliminary and final versions; and approval of the final version. MY: interpretation of evidence; and drafting and revision of preliminary and final versions. FKM: conception and planning of the study; interpretation of evidence; and drafting and revision of preliminary and final versions.

CONFLICT OF INTEREST

None declared.

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Bronchoscopy simulation training in the post-pandemic world

Lais Meirelles Nicoliello Vieira[1], Paulo Augusto Moreira Camargos[1], Cássio da Cunha Ibiapina[1]

1. Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

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Study carried out at the Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

ABSTRACT

Bronchoscopy is an important procedure to examine the airways. It is traditionally taught by having trainees perform it in humans. This carries risks, albeit rarely, and causes stress to trainees. The objective of this study was to review bronchoscopy simulators, as well as their use in and impact on medical education, presenting perspectives on the use of simulators in the post-pandemic world. This review was based on articles published in English in 2000-2021 and retrieved from any of the following **databases:** MEDLINE (PubMed), Embase, SciELO, and Google Scholar. Bronchoscopy simulators have improved markedly over time, allowing the teaching/learning process to take place in a risk-free environment. Bronchoscopy simulation training is an interesting option for the evaluation of the airways, especially in the coming years, with the COVID-19 pandemic highlighting the need for continuing medical education.

Keywords: Bronchoscopy; Learning; Teaching; Students; Coronavirus.

INTRODUCTION

Bronchoscopy is an extremely important procedure performed by specialists such as pulmonologists, otolaryngologists, and surgeons. Appropriate training in performing bronchoscopy is essential because it is a complex procedure that requires mastery of cognitive and motor skills.[1] It is traditionally taught by the "see one, do one, teach one" approach, in which professionals in training perform the procedure directly in humans, under the guidance of experienced professionals.[1] This has long been an effective method for training bronchoscopists. However, complications may require repeated examinations, causing high levels of stress to learners.[2]

Technological advances have allowed the use of simulators, which have become an interesting alternative tool. Furthermore, the COVID-19 pandemic has posed numerous challenges. Given the reduction in the number of trainees in surgical procedures and the need to ration personal protective equipment (PPE), the use of simulators to train professionals in techniques such as bronchoscopy has become especially important.[3]

The objective of this study was to review the development of bronchoscopy simulators, as well as their use in and impact on medical education, presenting perspectives on the use of simulators in the post-pandemic world.

STUDY SELECTION PROCESS

We searched the MEDLINE (PubMed), Embase, SciELO and Google Scholar databases for articles published in English between 2000 and 2021. Articles were initially selected by title, then by abstract review prior to complete article review.

BRONCHOSCOPY SIMULATORS

The first study on simulation in bronchoscopy was conducted in 1999 in a swine model.[1] In that same year, a virtual reality simulator was developed, namely the PreOp Endoscopic Simulator® (HT Medical Systems; Rockville, MD, USA). In 2001, a study was conducted on simulator effectiveness in bronchoscopy training.[4] The AccuTouch® simulator (Immersion Medical; Gaithersburg, MD, USA) was developed and validated during this period.[5]

Several tools are currently being used. Bronchoscopy training in animal models is known as a wet lab simulation. Some advantages of this method are the similarity of the anatomy and the possibility of using a real bronchoscope. The disadvantages include ethical issues in the use of animals for human training, the cost of raising them, and the potential damage to the bronchoscopy equipment.[1]

Low-fidelity simulation consists of the use of inanimate airway models—which do not simulate resistance to scope or breathing movements and which and are not very realistic in anatomy—into which real bronchoscopes are inserted. There is a range of models, from simple, non-anatomical labyrinths to more modern simulators.[1,2] The non-anatomical labyrinth models provide training in the movement of the wrist and hands, and even bronchial tree models made of newsprint and vinyl glue are available. The most up-to-date models in this category, made of silicone and plastic-based materials,

Correspondence to:
Lais Meirelles Nicoliello Vieira. Faculdade de Medicina da Universidade Federal de Minas Gerais, Avenida Professor Alfredo Balena, 190, Santa Efigênia, CEP 30130-100, Belo Horizonte, Minas Gerais, Brasil.
Tel.: 31 3409-9660. E-mail: laisnicoliello@hotmail.com
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consist of a mannequin composed of a head, a larynx, a tracheobronchial tree, and a thorax, to which a panel is attached to visualize the procedure externally, like the Laerdal Airway Management Trainer® (Laerdal; Stavanger, Norway; Figure 1) and the Airway Larry® (Nasco; Fort Atkinson, WI, USA).[1] There is also the CLA Broncho Boy® model (CLA; Coburg, Germany), which has a detailed tracheobronchial tree at the level of the first segmental bronchi.[1]

Another class of low-fidelity simulators is produced by three-dimensional (3D) printers.[6] One study evaluated their performance in bronchoscopy training and found a significant improvement in examination speed and performance after training.[7] These are low-cost alternatives that allow the use of a real bronchoscope. However, the equipment can be damaged, and these systems do not provide much realism.

High-fidelity simulation is based on the use of computers for virtual projection of the airways, also known as virtual simulators. The first simulator is the PreOp Endoscopy Simulator® (HT Medical Systems; Rockville, MD, USA).[1] There is currently a new version of this simulator, designated the AccuTouch Endoscopy Simulator® (Figure 2) and consisting of a flexible scope and a computer with a monitor and software for simulating the procedure. The interface is a replica of the human face, with an access area in the nasal region for insertion of the scope. There is also hardware for detecting the movements performed by the machine operator, capable of simulating the mechanical resistance of a real examination, as well as coughing and the respiratory movements of the patient.[2] At the end of the examination, the equipment provides metrics related to the performance of the trainee, including procedure time, "red out" time, number of contacts with the bronchial walls, bronchial segments inspected, and use of the suction button, thus ensuring feedback.[2] In addition, it is possible to identify the anatomical structures explored because the device projects the location of the bronchoscope, injects aliquots of lidocaine, performs biopsies, and reproduces multiple clinical scenarios. This simulator was used in most of the studies reviewed here, with positive results.

Other available models include the Gi-Bronch Mentor® (Simbionix USA Corp; Cleveland, OH, USA) and Orsim® (Airway Limited; Auckland, New Zealand).[1] These are simulators that reproduce extreme anatomical reality, ensuring learners an environment conducive to their learning. However, despite the complexity of the imaging system, even the most up-to-date models reproduce the tactile sensitivity of the examination in a rudimentary way, and tactile sensitivity is important when learning how to perform a bronchoscopy.

With the improvement of virtual simulators, it has become possible to train skills with a high degree of realism, allowing beginners to learn from their mistakes before having direct contact with patients. Therefore, students can improve their performance in challenging situations, such as gaining access to the pediatric airway and performing a bronchoscopy in patients with COVID-19.[8]

Since bronchoscopy is an aerosol-generating procedure, it is necessary to implement strategies to mitigate contamination risks during the procedure, such as an acrylic casing during intubation and the use of disposable curtains to create a tent around the patient.[8] Thus, training with simulators eliminates the risk of infection in a pandemic environment.

VIRTUAL SIMULATORS IN THE EVALUATION OF BRONCHOSCOPISTS

Bronchoscopy teaching has not yet been standardized. At least 100 supervised procedures are recommended for the acquisition of basic competence.[9] However, this method has been questioned.

In a study conducted by Crawford & Colt,[9] pulmonology residents were asked to identify the bronchial segments using a virtual simulator. The bronchoscopists in training identified 71% of the

Figure 1. The Laerdal Airway Management Trainer® (Laerdal; Stavanger, Norway), a low-fidelity bronchoscopy simulator.

Figure 2. The AccuTouch Endoscopy Simulator® (Immersion Medical; Gaithersburg, MD, USA), a high-fidelity bronchoscopy simulator.

segments; 50% of the experienced bronchoscopists identified all segments; and beginners were not able to identify all necessary segments. This great variability indicated the need to review the assessment methods in the teaching of bronchoscopy.

Guidelines were updated, and it was recommended that the assessment of individual trainee improvement be performed with simulators. It was initially shown that the metrics provided by simulators allow the differentiation between beginners and experienced bronchoscopists.[4] However, it was later proposed that these metrics should not be used as the only assessment method, the accuracy of the software being questioned.[10]

In this context, two instruments were developed, namely the Bronchoscopy Skills and Tasks Assessment Tool (BSTAT) and the Bronchoscopy Step-by-Step Evaluation Tool (BSET).[11] The BSTAT provides a numerical score based on posture and knowledge of anatomy, as well as on tasks such as transbronchial biopsy and bronchoalveolar lavage. The BSET evaluates the handling of the bronchoscope at increasing levels of difficulty. A high correlation was found between the two instruments (0.86 for the BSTAT and 0.85 for the BSET), with clear differences between beginners and experts. However, there were no significant differences among intermediate-level trainees.[11]

In another study, based on video footage of trainees performing simulated bronchoscopy and evaluated by a checklist, it was possible to distinguish among beginners, intermediate users, and experts.[10] In yet another study, an automatic motion analysis system was used in order to analyze scope movements.[12] Deviations were found to be greatest for beginners and smallest for experienced operators, the motion analysis system therefore being able to distinguish among beginners, intermediate operators, and experts.[12] Table 1 summarizes the studies examining the role of virtual simulators in the evaluation of bronchoscopists in training.

The use of virtual simulators in bronchoscopy has become an important option for evaluating professionals in training because virtual simulators allow the assessment of objective metrics and individual improvement in a risk-free environment. This becomes relevant in the context of the COVID-19 pandemic, with virtual simulators allowing the assessment of the performance of learners without any risk of exposure to the coronavirus.

TRAINING ON VIRTUAL SIMULATORS

Virtual simulators allow the evaluation of bronchoscopy training by the equipment's own metrics. One study found evident improvement after training, both in dexterity, with fewer contacts with the bronchial walls ($p = 0.022$), and in efficiency, with a higher percentage of analyzed bronchi ($p = 0.029$).[4] Even a short introductory course with simulators showed significant improvement in resident

Table 1. Studies examining the role of virtual simulators in the evaluation of bronchoscopists in training.

Study	Objective	Population	Sample	Method	Result	Conclusion
Crawford et al.[9]	To evaluate specific technical skills by means of a virtual reality bronchoscopy simulator	Pulmonology residents	5	A prospective study evaluating the participants during identification of and insertion of the bronchoscope in five specific bronchial segments	Trainees identified 71% of the bronchi correctly. Of those who had performed more than 200 bronchoscopies, 50% explored all segments Beginners were unable to identify all segments	Great variability was observed, suggesting that these abilities do not correlate with the years of training or the number of bronchoscopies performed
Colt et al.[4]	To evaluate whether training beginners on a bronchoscopy simulator would allow the acquisition of basic skills, in comparison with experienced physicians, who received traditional training	Pulmonology and intensive care residents	5	A prospective study comparing a group of beginners receiving bronchoscopy simulator training and a group of experienced physicians who had performed more than 200 bronchoscopies	Beginners significantly improved their dexterity after training, equaling or even surpassing the performance of experts	The evaluation metrics provided by the simulator were able to distinguish among novice, intermediate-level, and expert bronchoscopists, suggesting that clinical skills are correlated with the simulator environment
Davoudi et al.[11]	To evaluate bronchoscopy abilities by means of two novel instruments: the BSTAT and the BSET	Medical students, pulmonology residents, intensive care residents, intensivists, and thoracic surgeons	22	A prospective cohort study in which two independent evaluators simultaneously scored participants during simulation bronchoscopy	A high correlation (0.86 for the BSTAT and 0.85 for the BSET) was found for both methods There were clear differences between beginners and experts	Both tools showed high reliability and simultaneous validity in distinguishing beginners from experts It was not possible to discriminate significantly among intermediate trainees
Konge et al.[10]	To explore the validity of an evaluation method for bronchoscopy simulation training	Medical specialists, resident physicians, and medical students	42	A prospective study that filmed the participants while they performed six simulated bronchoscopies, with increasing difficulty Their performance was scored by two blind evaluators using a checklist	High interexaminer reliability was found The evaluation method differentiated among the three groups in terms of their performance ($p < 0.001$)	The evaluation procedure differentiated among beginners, intermediate trainees, and experts
Colella et al.[12]	To evaluate whether there is a correlation between scope movements and operator experience by means of an automatic motion analysis system	Resident physicians and medical students	29	A prospective cohort study using an automatic motion analysis system to measure total scope deviation during simulation bronchoscopy	The deviations were greatest for beginners and smallest for more experienced trainees	The motion analysis system can discriminate among different levels of experience

BSTAT: Bronchoscopy Skills and Tasks Assessment Tool; and BSET: Bronchoscopy Step-by-Step Evaluation Tool.

performance (p = 0.017).[13] In another study, similar results were obtained, with a significant reduction in procedure time (p = 0.002) and improvement in general performance (p = 0.002).[14]

The effects of previous simulator training on performance in real patients have also been investigated. The use of simulated bronchoscopy has been found to increase the speed of skill acquisition, with improved BSTAT scores (p < 0.05).[15] Ost et al. found similar results; specifically, a reduction in the time needed to perform the procedure (p = 0.001) and an increased percentage of identified bronchi (p = 0.03).[5] Even a short training session with a bronchoscopy simulator has been found to improve pediatric endotracheal intubation, with reduced time needed for intubation (p < 0.001) and increased percentage of airway visualization (p = 0.004).[16]

In a meta-analysis published in 2017,[17] virtual bronchoscopy simulator training was evaluated by examining original articles published between 2000 and 2016. Eight studies were included, and the authors concluded that bronchoscopy simulator training improves technical skills and that simulators can be an important learning tool.[17] In a systematic review,[18] the structure of simulation training in bronchoscopy and assessment of competence in bronchoscopy training were investigated. The review showed that simulation in bronchoscopy is effective, as well as showing that the training must be structured, that practice in pairs contributes to increasing the use of simulators, and that it is important to assess learners through validated tools.[18] Table 2 summarizes the studies evaluating the impact of virtual simulators on bronchoscopy training.

The effectiveness of simulator training is a fact of recognized relevance in the post-COVID-19 era because it assures continuing education regardless of the stage of the pandemic, which is still ongoing. Thus, more evidence on the effectiveness of simulation bronchoscopy training helps educators make decisions, highlighting the need for further studies on the subject.

TEACHING METHODS IN BRONCHOSCOPY TRAINING

Given the relevance of bronchoscopy training on virtual simulators, new teaching methods have emerged in the past few years.

The effectiveness of bronchoscopy simulation training on a single day has been reported to be the same as that of training over one week (p > 0.36), a finding that suggests that bronchoscopy simulation training can be conducted in a format that best suits trainees and training centers.[19]

Self-training can also be considered, wherein learners follow the manufacturer instructions to train themselves. One study showed a significant improvement in BSTAT scores after four self-driven training sessions on a virtual simulator (p < 0,0001).[2] Veaudor et al.[14] obtained similar results with self-training residents, who acquired basic skills similar to those of experienced bronchoscopists (p = 0,002).

Evidence on the use of bronchoscopy simulators for training residents has increased. However, little is known about the impact of bronchoscopy simulation training on medical students, although some recent studies have investigated this issue.

One study found no difference in effectiveness between bronchoscopy simulation training of medical students in pairs and individually (p < 0.16).[20] Training in pairs was considered more effective because the same resources used individually can be used in pairs.[20]

Intubation using fiberoptic bronchoscopy simulators has been evaluated in medical students, with no significant difference in technical skills between beginners and experts after training.[21] The modeling example, in which trainees observe the procedure performed by the instructor during bronchoscopy simulation training, has also been evaluated.[22] After training, the modeling example group was found to be significantly better than the control group (p < 0.0001), a finding that demonstrates the effectiveness of this method.[22] Table 3 summarizes the studies examining bronchoscopy simulation training methods.

Thus, several studies have provided a well-established basis for the use of simulators in bronchoscopy training.

BRONCHOSCOPY SIMULATION AND COVID-19

Medical education has been profoundly affected by COVID-19. The number of professionals allowed in the examination room had to be reduced, thus limiting the training of residents. In addition, because of the need to manage medications and beds, many procedures were suspended, thereby affecting the learning process.[23]

Bronchoscopy is a procedure that generates aerosols, leading to potential exposure to the virus. Furthermore, in cases of medical emergencies, such as foreign body removal, airway obstruction, or atelectasis caused by mucus plugging, there may not be enough time to perform COVID-19 diagnostic tests on the patient. Such situations impel bronchoscopists to perform the procedure quickly and efficiently, minimizing the time of exposure to the virus and, consequently, the probability of infection.[24,25]

Recent studies have evaluated the transmissibility of SARS-CoV-2 among bronchoscopists and found a low risk of transmission.[26,27] However, it should be noted that strict adherence to the guidelines recommended by the WHO and other organizations was reported, with most procedures being performed in negative pressure rooms, with all professionals wearing PPE, with neuromuscular blockade to prevent coughing, with bronchoscopy under apnea, with the use of disposable bronchoscopes, and with a reduced number of health professionals.[28] These situations require

Table 2. Studies evaluating the impact of virtual simulators on bronchoscopy training.

Study	Objective	Population	Sample	Method	Result	Conclusion
Colt et al.[4]	To evaluate whether training beginners on a bronchoscopy simulator would allow the acquisition of basic skills, in comparison with experienced physicians, who received traditional training	Pulmonology and intensive care residents	5	A prospective study comparing a group of beginners receiving bronchoscopy simulator training and a group of experienced physicians who had performed more than 200 bronchoscopies	After training, beginners significantly improved their dexterity, with fewer contacts with the bronchial wall ($p = 0.022$), and precision, with more segments identified ($p = 0.029$), equaling or even surpassing the performance of experts.	Virtual simulator training was effective.
Colt et al.[13]	To evaluate an introductory one-day bronchoscopy simulation training course.	Pulmonology and intensive care residents	24	A multicenter prospective study evaluating pre-test and post-test trainees on the simulator	After training, the mean scores for the technical skill tests on the simulator improved significantly, from 43% to 77% ($p = 0.017$).	Virtual simulator training was effective.
Veaudor et al.[14]	To evaluate whether a self-driven training program on a high-fidelity simulator would allow beginner residents to acquire skills similar to those of experienced bronchoscopists	Pulmonology residents	34	A prospective cohort study comparing the performance of bronchoscopists trained on a high-fidelity simulator with that of experienced bronchoscopists	There was a significant reduction in mean procedure time ($p = 0.002$) and an improvement in overall performance ($p = 0.002$) among beginners, comparable to the general performance of experienced professionals.	The simulator was effective in bronchoscopy training.
Wahidi et al.[15]	To evaluate trainees performing bronchoscopy on real patients after receiving bronchoscopy simulator training.	Pulmonology residents	47	A multicenter prospective study comparing the performance of simulator-trained participants with that of participants who had received traditional training The BSTAT was used	The incorporation of simulated bronchoscopy increased the speed of acquisition of bronchoscopy skills, and there was a statistically significant improvement in the mean BSTAT scores of trainees ($p < 0.05$)	The use of simulators prior to performing bronchoscopy on real patients allows the improvement of bronchoscopy skills
Ost et al.[5]	To validate a virtual bronchoscopy simulator	Pulmonology and intensive care residents	28	A multicenter prospective cohort study evaluating participants performing bronchoscopy on real patients after receiving simulator training or traditional training	The participants who underwent simulation training significantly improved their abilities after 20 simulations, with a reduction in time ($p = 0.001$) and an increase in the number of bronchi inspected ($p = 0.03$) In addition, they obtained better results on real patients than did those who received traditional training	Bronchoscopy simulation training allowed faster acquisition of bronchoscopy skills in comparison with traditional training

Continue...▶

Table 2. Studies evaluating the impact of virtual simulators on bronchoscopy training. (Continued...)

Study	Objective	Population	Sample	Method	Result	Conclusion
Rowe et al.[16]	To evaluate the efficacy of a single short training session in pediatric endotracheal intubation on a bronchoscopy simulator	Pediatrics residents	20	A prospective study comparing the performance of residents on real patients before and after simulator training	After simulator training, there was a reduction in the time to complete intubation with a bronchoscope ($p < 0.001$), in the number of contacts with the mucosa ($p < 0.001$), and in the time spent to view the mucosa adequately ($p < 0.001$), as well as an increase in the percentage of airway visualization ($p = 0.004$)	Even a single short simulator training session improved the ability to perform pediatric endotracheal intubation with a bronchoscope
Sokouti et al.[17]	To conduct a systematic review of studies on virtual reality bronchoscopy simulator training	Database searching (MEDLINE/ PubMed, Scopus, and Google Scholar)	-	A meta-analysis including original articles published between 2000 and 2016 and examining virtual reality bronchoscopy simulator training in rigid and flexible bronchoscopy	Eight studies of virtual reality bronchoscopy simulator training were retrieved	Bronchoscopy simulation training improved technical skills and should be considered an important learning tool
Nilsson et al.[18]	To conduct an extensive bibliographic review of bronchoscopy simulation training	Database searching in July of 2016	-	Systematic review of studies of bronchoscopy simulation training, covering training structure, evaluation of skills, and inexpensive alternatives	It was reported that bronchoscopy simulation training should be structured, that practicing in pairs is feasible and allows for more efficient use of the equipment, and that the performance of trainees should be evaluated by validated tools	Bronchoscopy simulation training is effective

BSTAT: Bronchoscopy Skills and Tasks Assessment Tool.

Table 3. Studies examining bronchoscopy simulation training methods.

Study	Objective	Population	Sample	Method	Result	Conclusion
Bjerrum et al.[19]	To compare the efficacy of bronchoscopy simulation training on a single day with that of training distributed over one week	Pulmonology residents	20	A randomized study evaluating bronchoscopy simulation training on a single day vs. over one week Pre-test, post-test, and retention test performance was evaluated after four weeks	No interaction was found between groups and test scores ($p > 0.16$), except for the percentage of explored segments No major group effect was found for any of the evaluated measurements ($p > 0.36$)	Training can be conducted in a format that best fits the clinical practice of trainees and the availability of training centers
Veaudor et al.[14]	To evaluate the efficacy of self-driven bronchoscopy simulation training	Pulmonology residents	34	A prospective cohort study comparing the performance of beginner bronchoscopists receiving simulation training with that of experienced bronchoscopists	There was a significant reduction in the mean procedure time and a significant improvement in overall performance ($p = 0.002$) among beginners, comparable to the general performance of experienced professionals	Self-driven training on a bronchoscopy simulator was effective, allowing trainees to acquire basic skills similar to those of experienced bronchoscopists
Gopal et al.[2]	To evaluate the impact of bronchoscopy simulation training on the knowledge of anatomy and on the technical skills of medical students	Medical students	47	A prospective study in which two surgeons evaluated the performance of participants receiving bronchoscopy simulation training The BSTAT was used	After training, there was a significant increase in BSTAT scores ($p < 0.0001$), visualization of bronchial anatomy ($p < 0.0001$), and bronchoscopy navigational skills ($p < 0.0001$)	Self-driven bronchoscopy simulation training was effective in medical students
Bjerrum et al.[20]	To compare the effectiveness of bronchoscopy simulation training performed in pairs and individually	Medical students	36	A randomized study comparing bronchoscopy simulation training performed in pairs and individually, by means of a pre-test, a post-test, and a retention test three weeks later	The two groups showed significantly improved performance after simulation training ($p < 0.001$) There was no difference in the efficacy of acquiring bronchoscopy skills between the two groups ($p < 0.16$)	Training in pairs can be considered more effective because the same resources used individually can be used in pairs
Latif et al.[21]	To establish the time and number of attempts required to train beginners in fiberoptic bronchoscopy and intubation using simulators	Medical students	15	A prospective study in which participants received guidance from an experienced instructor and then started supervised training on a virtual simulator They returned after two months for a new evaluation	After training, the trainees' technical skills were compared with those of experts. In the evaluation performed after two months, a longer time was needed to view the anatomy; however, when this performance was compared with the pre-test performance, retention of knowledge was observed	Training in fiberoptic bronchoscopy and intubation on simulators was effective, with knowledge retention

Continue...▶

Table 3. Studies examining bronchoscopy simulation training methods. (Continued...)

Study	Objective	Population	Sample	Method	Result	Conclusion
Bjerrum et al.[22]	To evaluate the effectiveness of integrating modeling examples into bronchoscopy simulation training	Medical students	48	A randomized study evaluating the effectiveness of integrating modeling examples into bronchoscopy simulation training, by means of a pre-test, a post-test, and a retention test after three weeks	Both groups showed significant improvement after training However, the modeling example group was significantly better than the control group ($p < 0.0001$)	The use of modeling examples in bronchoscopy simulation training was effective

BSTAT: Bronchoscopy Skills and Tasks Assessment Tool.

experienced professionals who are able to perform the procedure quickly.

Koehler et al. developed a simulation model to visualize aerosol, droplet generation, and surface contamination using a fluorescent solution during a bronchoscopy simulation.[29] The authors found evidence of aerosol generation, droplet dispersion, and surface contamination; however, the proper use of PPE and safety strategies mitigated contamination risks.[29]

The changes imposed by COVID-19 require prior preparation from professionals performing bronchoscopy. Simulation allows professionals to state their concerns, discuss perceptions about the safety and comfort of both the team and the patient, and practice technical modifications to the procedure. The benefits of simulations are more clearly noted in emergency bronchoscopy situations, when previous training sessions have been reported to provide better communication and operational planning.[24]

In the COVID-19 era, simulation laboratories have gained importance in health sectors.[3] Bronchoscopy simulation allows the improvement of basic skills such as knowledge of anatomy, 3D spatial orientation, and motor coordination without putting patients at risk, as well as ensuring the continuation of the learning process regardless of the state of the pandemic. Lower levels of stress result in more efficient learning, ensuring effective performance in real situations.[2]

LIMITATIONS AND PERSPECTIVES

One of the difficulties in using virtual simulations is related to the cost. Low-fidelity simulator models cost between USD 2,000.00 and USD 3,000.00. The cost of developing and producing a simulator from 3D printing can range from USD 5.00 to USD 100.00.[6] On the other hand, virtual simulators can cost as much as USD 100,000.00. This problem can be solved by acquiring a single piece of equipment to be shared among different institutions.[9]

Another limitation is the absence or limited availability of pediatric simulators. Future simulators should incorporate multiple scenarios, allowing trainees to acquire decision-making ability and new skills, as well as basic proficiency.[17] However, because of the impact of the COVID-19 pandemic in 2020 and the uncertainty regarding how long the COVID-19 pandemic will last, simulation laboratories have become a necessity. Simulators guarantee the continuation of learning regardless of the state of the pandemic, providing training in daily clinical situations and in more difficult situations.

FINAL CONSIDERATIONS

Simulators in bronchoscopy training are useful and interesting tools to complement the conventional method of training. They allow trainees to practice in a risk-free environment and allow mistakes to be

made. Bronchoscopy simulation training meets the growing medical needs to ensure an effective teaching/learning process while ensuring patient safety. In addition, the COVID-19 pandemic has highlighted the importance of continuing education in a safe environment regardless of the state of the pandemic, allowing materials and supplies to be used in order to fight the virus.

Further studies on bronchoscopy simulation are needed in order to make this promising teaching tool more accessible. Its increased use in training centers by physicians and students alike will encourage other medical professionals to perform this procedure during and even after the COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

LMNV: literature review and drafting of the manuscript; PAMC and CCI: drafting of the manuscript and critical revision of the manuscript for important intellectual content; LMNV, PAMC, and CCI: final approval of the version to be published.

CONFLICTS OF INTEREST

None declared.

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How are we in Brazil with the treatment of alpha-1 antitrypsin deficiency?

Maria Vera Cruz de Oliveira Castellano[1], Paulo Henrique Feitosa[2]

TO THE EDITOR,

Recently, the Brazilian Journal of Pulmonary Medicine published a review article on alpha-1 antitrypsin deficiency (AATD),[1] which addresses the diagnosis and future prospects for reducing underdiagnosis in Brazil. However, the treatment is as important as the diagnosis, and, in this aspect, there is still a lot to be done.

AAT deficiency is a rare disease that is associated with early-onset pulmonary emphysema and various forms of hepatic disease, such as cirrhosis and neonatal liver disease.

Smoking has been shown to be a risk factor for the development of emphysema in individuals with AATD. Therefore, it is important to prevent smoking initiation, as well as promote smoking cessation in current smokers with AATD.[1]

The treatment for pulmonary disease associated with AATD is the same as that recommended for COPD, according to consensus and guidelines, and, when indicated, replacement therapy with AAT must be performed.

The discovery of the structure and function of the AAT protein (neutrophil protease inhibitor, potent anti-inflammatory, and immunoregulator) and its production from human plasma has allowed for replacement therapy to prevent the progression of emphysema.[2] The goal of treatment is to elevate serum AAT levels, maintain the concentration in the pulmonary interstitium above the "protective threshold", and slow the progression of emphysema. The concentration of anti-neutrophil elastase obtained from bronchoalveolar lavage fluid in patients with AAT deficiency after replacement therapy increases by 70% compared to baseline levels. This therapy was approved by the FDA in 1987 after studies evidenced its biochemical efficacy.[2]

Following diagnosis, it is important that the patient have access to replacement therapy. For this to occur, knowledge of pharmacological and technical aspects and its availability in countries as heterogeneous as Brazil are necessary.

Replacement therapy is indicated for non-smokers or former smokers over 18, with genetic variants of AAT compatible with deficiency, reduced serum AAT levels (< 116 mg/dL), and evidence of airflow limitation upon spirometry. Most patients with the PI*ZZ genotype or PI*Z null variants have serum levels < 57 mg/dL (nephelometry); it can be stated that serum levels < 20% of the normal value are suggestive of PI*ZZ deficiency.[3] Patients with other genetic variants may also present reduced serum AAT levels and an indication for replacement therapy. Heterozygous individuals (PI*MZ or PI*MS) usually are not candidates for AAT replacement since they do not have an increased risk of emphysema if non-smoking.[4]

The GOLD guidelines suggest that patients with an indication for AAT replacement are those with FEV1 of 35% to 65% of the predicted values (Evidence B).[5] The rationale for selecting this FEV1 range is that not all patients with AATD will progress with rapid loss of lung function, especially after smoking cessation. The American/European consensus[3] on AAT deficiency, after evaluating studies with mortality and FEV1 outcomes in patients who received replacement therapy compared to those who did not, concluded that the indication should occur with FEV1 between 31% and 65% of the predicted values. The Canadian guidelines[6] indicate AAT replacement for patients diagnosed with COPD (FEV1 between 25-80% of the predicted values) under maximal pharmacological and non-pharmacological therapy (*e.g.*, pulmonary rehabilitation) and justify this conclusion through the benefits of pulmonary density preservation, assessed by computed tomography (Evidence B) and decreased mortality (Evidence C).

In a cohort of 139 patients, pulmonary density was analyzed by computed tomography, and it was confirmed that treatment with AAT prevented the progression of emphysema in patients with AATD.[7] Another study[8] concluded that patients receiving AAT presented fewer exacerbations and lower levels of C-reactive protein, IL-6, IL-8, and TNFα.

The main objective of AAT replacement treatment is to contain the destruction of the lung parenchyma caused by the protease/antiprotease imbalance, which justifies, in some cases, the initiation of treatment in patients with mild to moderate degrees of airflow obstruction. It is important to remember that chest tomography to assess pulmonary density is more sensitive than spirometry for monitoring these patients. Moreover, it is essential that, in addition to spirometry, diffusion of carbon monoxide (DLCO), lung volumes, quality of life questionnaires, COPD assessment tests, and exacerbations are periodically evaluated to detect the benefits of replacement therapy and potential clinical worsening.

Treatment with intravenous AAT replacement has technical specifications and is recommended to be applied in Reference Centers, Primary Care Units, or Infusion Centers with trained staff. AAT must be transported and stored at low temperatures, and the recommended dose is 60 mg/kg of body weight weekly. Adverse reactions

1. Serviço de Pneumologia, Hospital do Servidor Público Estadual de São Paulo, São Paulo (SP), Brasil.
2. Serviço de Pneumologia, Hospital Regional da Asa Norte, Brasília (DF), Brasil.

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are rare and mild and include fever, dyspnea, tremors, and headache. There are no reports of hepatitis or HIV transmission upon AAT treatment.[9] The intravenous AATs are supplied as lyophilized powder or in liquid form. Instructions for reconstituting the lyophilized powder are labeled on the package insert and must be strictly followed. After reconstitution, the AAT injection must be given within three hours.

There are currently eleven countries in which AAT is provided through federal public protocols: Canada and the USA since 1988, Germany and Italy (1989), Spain (1994), Austria (2000), France (2006), Switzerland (2012), the Netherlands (2017), Denmark (2020), and Japan (2021). In most states in Brazil, treatment with AAT is obtained through legal action, with the exception of the Federal District, which has a protocol and has provided treatment in a specialized outpatient clinic since 2010. More reference centers are necessary to promote specialized diagnosis and treatment for patients with rare pulmonary diseases. There is no longer any doubt that severe AAT deficiency with emphysema requires enzyme replacement. We may discuss whether a higher dose than that recommended today would be more effective or what would be the FEV1 cut-off for starting replacement, but it is no longer appropriate to watch the patient's accelerated decline of pulmonary function and not perform AAT replacement. It is high time for CONITEC (National Commission for Technology Incorporation in the Unified Health System) to reassess its previous position; anyone with AATD will certainly be very grateful.

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One minute sit-to-stand test as an alternative to measure functional capacity in patients with pulmonary arterial hypertension

Monica C. Pereira[1], Layse N.G. Lima[1], Marcos M. Moreira[1], Felipe A.R. Mendes[2]

TO THE EDITOR,

The 6-minute walk test (6MWT) is a widely used approach to evaluate functional capacity in patients with Pulmonary Arterial Hypertension (PAH).[1] Despite its reproducibility and ease to perform, adequate space and standardized proceedings are required in order to guarantee its reliability.[2]

The 1-min sit-to-stand test (1-STST) has been proposed as an alternative to the 6MWT as a reliable method for individuals with various respiratory diseases.[3,4] It is an easy-to-apply and time-saving test, making it feasible to perform at home, in clinical care, or during pulmonary telerehabilitation.[4] Sit-to-standing is an ordinary movement that people are generally familiar with, in addition to being linked to the individual's autonomy.

A shorter STST (30 sec) was evaluated in patients with pulmonary hypertension (PH) and showed a good correlation with the 6MWT.[5] We aimed to investigate whether a longer version (1-STST) would correlate with the 6MWT and daily activity levels in patients with PAH.

A cross-sectional, observational study was carried out with a convenience sample of patients diagnosed with PAH. We recruited and included patients from the PH outpatient clinic of the State University of Campinas' (UNICAMP) teaching hospital between 2016 and 2018. All patients were required to be clinically stable, without any changes in therapy eight weeks prior. Patients with other lung diseases or orthopedic problems were not included. The institution's Research Ethics Committee approved the study (protocol No. 76543617.9.0000.5404/2017), and the patients signed an informed consent form before enrollment.

After collecting the patients' history and grading their functional class of dyspnea, the subjects underwent the 6MWT and 1-STST and had their steps counted by an accelerometer for seven days. All proceedings were carried out in one week, and the 6MWT and 1-STST were not performed on the same day. The 6MWT was conducted according to ATS Statement guidelines.[2] We analyzed the distance walked (6MWD, in meters and % predicted) and the patients' vital signs at the beginning and end of the test.

The 1-STST assesses the ability to perform physical exercises and the muscular strength of the lower limbs. The individual is asked to sit in a chair of standard height (46-48 centimeters) positioned against a wall. The knees and hips are to be flexed at 90 degrees, and the feet should be flat on the floor and hip-width apart. The patients' hands should rest on their hips, and no support is to be used. Over the course of one minute, the patient must sit and stand up from the chair repeatedly, as quickly as possible. The test starts following verbal command, and the patient is notified when 15 seconds remain. The number of repetitions performed is counted, and the modified Borg scale is used to assess dyspnea and fatigue.

The repetitions of the 1-STST and 6MWT were normalized for body weight.[6] Spearman's correlation coefficient (r) was used in the analysis of the 1-STST and 6MWT and the accelerometer variables. A p-value of less than 0.05 was considered significant. Correlation coefficients of ≥0.6 denoted a strong correlation, 0.4 to 0.6 a moderate correlation, and <0.4 a weak correlation. The Mann-Whitney U test was applied to compare the final Borg scores of the 1-STST and 6MWT using the SAS System software for Windows, version 9.4. (SAS Institute Inc., 2002-2012, Cary, NC, USA).

A total of twenty patients (mean age of 44.3 years, 80% female) took part in the study. The baseline characteristics and the results (tests, variables, and correlation analysis) are shown in Table 1. The mean number of repetitions in the 1-STST was 23.8, and the final Borg score was 4.5 (± 1.5). Meanwhile, the mean value for the 6MWD was 451 meters, and the final Borg score was 4.9 (± 2.0). The sit-to-stand repetitions correlated with the 6MWD and accelerometer variables. The 6MWD also showed a moderate correlation with the step counts and activity duration (Table 1).

Patients with PAH showed a lower number of repetitions in the 1-STST than healthy subjects,[7] in keeping with studies with patients with COPD.[12] Similarly, Kahraman et al. (2020) reported a mean of 12.23 ± 3.77 repetitions in a 30-second sit-to-stand test in patients with PH.[5]

The number of repetitions in the 1-STST showed a strong correlation with the 6MWD and a moderate correlation with the daily step counts and activity duration measured by the accelerometer. Some studies have shown correlations between the 1-STST and the 6MWD in patients with COPD[8] and PH.[5]

The 1-STST and 6MWT are both submaximal tests for assessing functional capacity. Nevertheless, there are

1. Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Cam-pinas, Campinas (SP), Brasil.
2. Universidade de São Paulo, São Paulo (SP), Brasil.

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Table 1. Descriptive data of the patients and correlation analysis results.

Clinical variables	PAH patients (N = 20)
Female / Male sex (n, %)	16 (80%)/ 4 (20%)
Age (years)	44.30 ± 13.20
BMI (kg/m^2)	26.90 ± 6.00
Comorbidities	14 (70%)
Hypertension	4 (20%)
Diabetes Mellitus	1 (5%)
Hypothyroidism	4 (20%)
IPAH / PAH long-term responders to calcium channel blockers / PAH-CD (n, %)	12 (60%) / 4 (20%) / 4 (20%)
FC I/ II / III (n) (%)	7 (35%) / 10 (50%) / 3 (15%)
1-STST	
Number of repetitions	23.80 ± 6.10
Final Borg score	4.50 ± 1.50
6MWT	
Walked Distance (m)	451.50 ± 96.40
Walked Distance (% predicted value) *	75.60 ± 16.70
SpO_2 baseline (%)	94.00 ± 2.80
Final SpO_2 (%)	87.80 ± 7.00
Final Borg score	4.90 ± 2.00
Echo variables	
SPAP (mmHg)	70 ± 27
TRV (m/s)	4 ± 1
Right ventricle diameter (mm)	40 ± 14
TAPSE (mm)	16 ± 3
Accelerometer	
Step counts / day	4,280 ± 2,352
Activity duration (min)	42 ± 19
Correlation analysis (1-STST versus 6MWT and accelerometer results)	
	r / **p-value**
6MWT	
Distance (m)	0.45 / 0.05
Distance (m/kg)	0.84* / <0.001
Distance (% predicted) ##	0.62 / 0.003
Accelerometer	
Step counts	0.59 / 0.006
Activity duration	0.58 / 0.007

Descriptive data expressed as absolute number and percentage or mean ± standard deviation. 6MWT: Six-Minute Walk Test; SPAP: Systolic Pulmonary Arterial Pressure; TRV: Tricuspid Regurgitation Velocity; TAPSE: Tricuspid Annular Plane Systolic Excursion; ## Enright and Sherril equation. * Correlation with 1-STST repetitions/kg.

some differences between the two, such as the ability of the 1-STST to evaluate lower limb muscle strength. Several studies have revealed a correlation between the 1-STST and lower limb strength.[8] Skeletal muscle strength in the upper and lower limbs is significantly reduced in patients with PH when compared to control subjects,[9] and among the mechanisms involved are increased muscle protein breakdown, switching from type I to type II fibers, and reduced capillary density and aerobic enzyme capacity.[10] Despite not measuring muscle strength in the present study, it is plausible to assume that the reduction in the number of repetitions in the 1-STST translates into a decrease in the muscular strength of the lower limbs.

We found moderate correlations of the 1-STST and daily step counts and activity duration. Such correlations have already been demonstrated in patients with COPD, although we did not identify studies in patients with PAH. Longer sit-to-stand tests assess exercise tolerance and muscle endurance, features that could have supported the association found herein.[4]

This small and single-centered study involved patients who were NYHA Class II and III. Thus, some differences may not have been identified, a fact that hinders generalization to all patients with PH. In spite of this limitation, the results allow us to consider the 1-STST as a promising complementary tool in the multidimensional assessment of exercise limitation

and to measure the functional capacity of individuals with PAH. However, further studies are needed to validate the 1-STST in this context.

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Tuberculosis: a deadly and neglected disease in the COVID-19 era

Ethel L Maciel[1,2], Jonathan E. Golub[3], Jose Roberto Lapa e Silva[1,4], Richard E. Chaisson[3]

TO THE EDITOR,

In 1993, the World Health Organization (WHO) declared Tuberculosis (TB) a global emergency. Since then, few advances have been made in the control of the disease, such as molecular diagnostic tools and new treatment-shortening regimens, but the overall lack of progress is mainly due to inadequate investments in the Research & Development of new products and strategies for TB prevention, diagnosis, and treatment.[1]

The United Nations' Sustainable Development Goals and the World Health Organization Global Plan to End TB state that funding for tuberculosis needs to approach the US$2-billion target a year to end the disease by 2030. However, this goal has never been reached, as noted by the Treatment Action Group (TAG) in its recent investment report, with US$772 million in 2017 coming the closest.[2]

In contrast, in 2020, the world faced a pandemic of enormous magnitude that changed the way we live our lives, substantially impacting global health and economic systems. Thus, the WHO declared COVID-19 a global health emergency within two months of the recognition of the first cases, and large economies quickly mobilized research funds to develop vaccines and drugs that could control the pandemic. The funding committed to combating COVID-19 exceeded US$21.7 trillion, according to data analysis available on the Devex funding platform.[3-5]

Although there is a marked difference in the magnitude of investments between the two diseases, the number of deaths was similar in 2020: 1.5 million with TB (including 214,000 among people living with HIV) and 1.8 million with COVID-19, as reported by the WHO. The 2021 death tolls are still being calculated, though it is likely that an excess of deaths will be seen regarding both diseases due to the more transmissible and virulent SARS-CoV-2 variants and, in the case of TB, to the impact of COVID-19 on access to health services resulting in delays in diagnosis.[6,7]

Thus, the discrepancy in funds that we are still facing is not related to the magnitude of the death toll in either disease but instead to where these deaths are occurring and which populations are affected. While COVID-19 has a widespread reach, affecting both rich and developing countries, TB remains a neglected disease, predominantly affecting the poorest countries and their more vulnerable populations.

In Brazil, as reported by TAG, funding for TB failed to reach 0.1% of the total allotted value for science and technology in all areas, which represents an expected US$35 million per year . Brazil invested only US$1,196,598 in 2019. In 2020, this funding increased, reaching a total of US$3,726,864, representing 11% of the US$35 million target. In the Transparency Portal of the Brazilian government, the total amount invested in the past ten years in TB research was only a little more than US$6 million.[2]

As demonstrated in Table 1, the amount provided for TB research in Brazil by the National Council for Scientific and Technological Development (CNPq), the main Brazilian research funding agency, was negligible. Most funding comes from financial management and agreement systems of the federal government (SICONV and GESCON). SICONV promotes financial transfers to states for the fulfillment of joint funding between CNPq and state research foundations, as well as parliamentary funds, while GESCON is the system that transfers funds to federal research institutions. It is possible that other transfers were not reported; however, Table 1 includes exactly what is informed and reported by the federal government.

On the other hand, funding for COVID-19 research in 2020, according to the Brazilian government, was in the order of US$100 million, a number that is still far short of what is desired, given the magnitude of the pandemic.[8]

In an editorial by R. E. Chaisson, M. Frick, and P. Nahid, two major differences in the response to the two pandemics are notable, considering that *Mycobacterium tuberculosis* was first described in 1882 and SARS-CoV-2 in 2019. First, there are currently only 15 TB vaccine candidates in the pipeline compared to 112 vaccines for COVID-19, and we have only one licensed vaccine in use for TB, the BCG vaccine (which stands for Bacillus Calmette-Guérin vaccine), whereas there are 25 licensed vaccines for COVID-19. Second, only a total of US$915 million was invested in TB research in 2020 compared to US$104 billion for COVID-19 in the same period,[9] *i.e.*, 113 times more than the amount spent by all funders on TB research in 2020 (US$915 million).

COVID-19 and tuberculosis are different diseases with distinct impacts on public health, demanding different actions from governments; however, it is also clear that, without appropriate investments, innovation for any disease control remains quite limited.

The lesson that can be learned from the rapid confrontation of the COVID-19 pandemic is that, with political will, the investments needed to control pandemic diseases can be achieved, as we are seeing around the

1. Rede Brasileira de Pesquisa em Tuberculose, Rio de Janeiro (RJ), Brasil.
2. Programa de Pós-Graduação em Saúde Coletiva, Vitória (ES), Brasil.
3. Centro de Pesquisa em Tuberculose, Faculdade de Medicina, Universidade Johns Hopkins, Baltimore (MD), EUA.
4. Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil.

Table 1. Amount invested in TB research from 2010 to 2020.

AGENCY	QUANT.	VALUE
CNPq	2	US$78,364.88
GESCON	2	US$199,874.00
SICONV	1	US$3,134,600.08
PROADI/SUS	2	US$31,689.80
UNODC	1	US$16,800,00
TOTAL	**8**	**US$3,461,328.76**
In progress	3	US$3,166,290.64

Source: Brazilian Federal Government Transparency Portal. Consider 1 US dollar equals five Brazilian reais.
CNPq - National Council for Scientific and Technological Development
GESCON - Management System for Inquiries and Rules for Government Funds
SICONV - System for Budget Execution of Federal Government Funds for States and Municipalities
PROADI/SUS - Program to Support Institutional Development of the Unified Health System
UNODC - United Nations Office on Drugs and Crime

developed world. Since tuberculosis is a problem of different dimensions, especially for the countries that make up the BRICS bloc, it is essential that these countries that sustain the greatest burden contribute to accelerating their research and innovation capabilities.

In addition, investments in science should reduce the burden of disease on the most vulnerable populations, such as people living in slums, deprived of their liberty, co-infected with HIV/AIDS, indigenous people, and the homeless, who have a greater risk of developing TB, with the aim of reducing social inequalities.[1,10]

Finally, we need to continue to fight for TB to be on the political agenda and to receive adequate funding, especially in the most burdened countries, such as Brazil, so that the goal of TB elimination can be achieved.

AUTHOR CONTRIBUTIONS

ELM, JEG, JRLS, and REC participated in the conception, planning, interpretation, and writing of this editorial letter. All authors approved the final version.

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The importance of asking the right question

Eduarda Seixas[1], Sónia Guerra[2], Marta Pinto[3,4], Raquel Duarte[3,5,6,7]

TO THE EDITOR,

In 2014, the World Health Organization adopted The End TB (tuberculosis) strategy, which "targets tuberculosis prevention, care, and control after 2015". The main goals were to reduce tuberculosis deaths by 95%, to reduce new cases of tuberculosis by 90% between 2015 and 2035, and to guarantee that no family will face ruinous costs due to tuberculosis by 2035.[1]

Contact investigation is an essential tool to find additional tuberculosis cases in the community, preventing the progression to active disease and helping initiate chemoprophylaxis in children and immunosuppressed patients. Active case finding has a better yield in detecting tuberculosis cases than passive case detection.[2-4]

Although Portugal has shown a reduction in the notification and incidence rate of tuberculosis in the past 10 years and achieved, in 2015, the goal of lowering the incidence of the disease (20 cases per 100,000 inhabitants per year), it is still one of the EU countries with the largest incidence rates of tuberculosis (16.5 cases/100,000 inhabitants).[5]

Tuberculosis outpatient centers are differentiated health units specialized in the approach of TB. These units are responsible for diagnosing, treating, and screening populations at high risk for the disease.

Usually, contact tracing is founded on forward tracing, which is based on finding contacts after infection which the index case may have infected. On the other hand, backward contact tracing identifies how the index case became infected. This strategy looks back in time and recalls where and when the exposure to the infectious organism occurred. This approach improves the number of traceable individuals and promotes the epidemiological understanding of high-risk settings, since transmission locations with a common origin are more likely to be identified.[6]

In this study, we used both contact tracing strategies to investigate and understand the differences between the number of contacts at risk identified by the patients.

All patients with pulmonary tuberculosis treated at a tuberculosis outpatient center in Gaia, Portugal, between March 2019 and March 2021 were analyzed. Only those with infectious tuberculosis (lung involvement) were included. The contagious period was considered the 3 months prior to symptomatic presentation, positive sputum smear, or X-ray with lung cavitation. If the diagnosis was established by a positive culture, the infectious time was considered as the 4 weeks before the sample was collected.[7]

Data collection was carried out by phone call inquiry, and all patients remotely consented to participate in the study. The data analysis was conducted using the IBM SPSS Statistics 25.0 software. Categorical variables were presented as frequencies and percentages, and continuous variables as means and standard deviations. The difference between the two questions regarding the number of contacts and the public places visited was evaluated using the T-test, with a p-value of 0.05 indicating statistical significance.

A total of 76 patients were eligible for the study; however, nineteen were excluded (6 died, 12 were uncontactable, and one was minor of age). This subgroup presented similar characteristics to the included patients: mean age of 50.9 years (SD ± 26.7 years), most were male (73.7%), and the majority had isolated pulmonary tuberculosis (78.9%), followed by disseminated tuberculosis (21.1%). Two patients were HIV positive (10.5%).

Our final sample included 57 patients, with a mean age of 45.1 years (SD ± 16.4 years), most of whom were male (68.4% versus 31.6% female patients). Regarding HIV infection, five were positive (8.8%). Most patients had pulmonary tuberculosis (n = 47, 82.5%), followed by the disseminated form of the disease (n = 6, 10.5%). Two patients had pleuropulmonary tuberculosis and two pulmonary tuberculosis, with local lymphatic dissemination. The majority of patients had drug-susceptible tuberculosis (96.5%).

When using forward contact tracing, the mean number of contacts identified per patient was 5.4 (SD ± 6.7), with a minimum of 0 contacts and a maximum of 40. Therefore, most patients had had contact with 2 (n = 10) or 4 (n = 10) individuals. The majority (78.9%) did not refer having been in public areas during the infectious period; the patients' mean number of public places visited during the contagious phase was 0.3 (SD ± 0.7).

Meanwhile, when using backward contact tracing, the patients identified a mean risk of contact with 11 people (SD ± 9.3) and 1.5 public spaces (SD ± 1.0), regarding their presence in public areas where other people had a risk of exposure.

1. Departamento de Pneumologia, Centro Hospitalar do Baixo Vouga, Aveiro, Portugal.
2. Departamento de Pneumologia, Centro Hospitalar Tondela-Viseu, Viseu, Portugal.
3. Unidade de Investigação Clínica da ARS Norte, Porto, Portugal.
4. Faculdade de Psicologia e de Ciências da Educação, Universidade do Porto, Porto, Portugal.
5. Instituto de Ciências Biomédicas de Abel Salazar, Universidade do Porto, Porto, Portugal.
6. Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal.
7. Serviço de Pneumologia, Centro Hospitalar de Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal.

There was a significant statistical difference (p - value < 0.001) between the number of contacted people and the public places visited, obtained by the two different questions made in the phone call inquiry.

In this study, the patients identified more at-risk contacts when the backward contact tracing strategy was used. This type of contact investigation can be applied routinely, enabling a greater and more expeditious identification of cases, thus preventing the emergence of more cases in the community.

Asking the right questions can make a difference in achieving the goals of the End TB strategy and, ultimately, end the global TB epidemic.

AUTHOR CONTRIBUTIONS

ES was involved in all aspects of the study, and contributed in the study design, data collection, data analysis and the interpretation of the results, and in the drafting and writing of the manuscript. SG contributed in data collection, the study design, and the drafting and writing of the manuscript. MP contributed in the interpretation of the results and supervised the writing of the manuscript. RD was the senior investigator of the study and was involved in all of its aspects: design, analysis, interpretation of the results, and supervised the writing of the manuscript. All authors have read and approved the final version of the manuscript.

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In-person and online application of the Bronchiectasis Health Questionnaire: are they interchangeable?

Adriano Luppo[1], Samia Z. Rached[2], Rodrigo A. Athanazio[2], Rafael Stelmach[2], Simone Dal Corso[1]

TO THE EDITOR,

Health-related quality of life questionnaires are patient-reported outcome measures that are widely used to evaluate the health status of patients with bronchiectasis. The Bronchiectasis Health Questionnaire (BHQ) was developed to assess health status using general and simple scoring systems to facilitate clinical use.[1] Aside from evaluating symptoms of patients with bronchiectasis, this simplified questionnaire eases the communication between patients and the multi-professional team by guiding specific conduct and assessing the efficacy of different interventions.[1] The validation of the BHQ was carried out in an in-person manner. However, testing its application in the online format is mandatory, mainly due to challenges related to in-person administration, such as the busy routine of patients, transportation barriers, and the lack of family support. In addition, remote administration is preferable during the COVID-19 pandemic because it contributes to social distancing and helps prevent the spread of the coronavirus.

The objective of the present study was to compare the in-person and online applications of the BHQ and evaluate which format is preferred by patients with bronchiectasis. The human research ethics committee of the two institutions where the study was carried out approved the study (Nove de Julho University, Protocol No.: 2,532,903 and University of São Paulo, Protocol No.: 2,574,759).

Bronchiectasis patients were recruited between October 2017 and December 2018 from a tertiary referral university hospital in São Paulo. The inclusion criteria were (1) clinical and tomographic diagnosis of bronchiectasis, (2) age ≥ 18 years old, and (3) clinical stability (*i.e.*, no coughing, high volume or thick consistency of pulmonary secretion, purulent pulmonary secretion, increased dyspnea, exercise intolerance, fatigue, or malaise in the four weeks prior to the study). As for exclusion criteria, the following were considered: (1) smoking or tobacco smoke loads > 10 pack-years, (2) associated pulmonary disease (asthma, chronic obstructive pulmonary disease, interstitial lung disease, or cystic fibrosis), (3) associated cardiovascular diseases, or (4) the inability to answer questionnaires. The sample size followed COSMIN standards, which consider a minimum sample of 50 participants optimal for reliability studies.[2]

After assessing the eligibility criteria, the participants completed a paper-based BHQ[1] and were submitted to the modified Medical Research Council[3] dyspnea scale in an in-person interview format during a routine medical appointment. After 14 days, the participants completed the BHQ online via the Google Forms platform sent by WhatsApp. Bronchiectasis severity was classified according to the E-FACED index and the Bronchiectasis Severity Index.[4-5]

Data were analyzed using the SPSS 22.0 software (IBM Corp., Chicago, IL, USA), and the Shapiro-Wilk test was used to assess data normality. The data were presented as mean ± standard deviation. The paired *t*-test was applied to compare the BHQ scores in the in-person and online applications, whereas the unpaired *t*-test compared basal characteristics among the included participants and those who were included but failed to participate due to technological issues. The in-person and online application reliability was analyzed using the intraclass correlation coefficient (ICC) model 2:1, adopting a 95% confidence interval (95%CI). ICC data was classified as poor (< 0.4), moderate (0.4 to 0.75), substantial (0.75 to 0.90), and excellent (> 0.90).[6] Cronbach's alpha was used to analyze internal consistency, and values between 0.75 and 0.95 were considered adequate. Ceiling or floor effects were present if ≥ 15% of the participants scored the minimum or maximum in the questionnaires.[6] The standard error of measurement (SEM) analyzed the level of agreement between the in-person and online administration formats. Significance was set at $p < 0.05$.

Thirteen out of 63 patients with bronchiectasis were excluded due to difficulties accessing the Google Forms platform. Therefore, the final sample consisted of 50 individuals (22 women). The clinical and functional characteristics of the excluded participants were similar to those of the included individuals (Table 1).

The BHQ scores obtained from the in-person and online application formats did not present significant differences. Reliability was considered substantial (ICC = 0.89; 95%CI: 0.82–0.94) and internal consistency was adequate (Cronbach's alpha = 0.94). The standard error of measurement was small (1.77 points), and no ceiling or floor effects were observed in either form of application.

Regarding the participants' preference regarding the mode of questionnaire administration, 26% reported no preference, whereas 74% stated that the online format was much better.

Our results show that both formats of the BHQ are valid and equivalent to assess the quality of life and symptoms of patients with bronchiectasis.

1. Programa de Pós-Graduação em Ciências da Reabilitação, Universidade Nove de Julho, São Paulo (SP), Brasil.
2. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP), Brasil.

Table 1. Characteristics of the included and excluded study participants.

Characteristics	Included (n = 50 / 28 women)	Excluded (n = 13 / 9 women)	p-value
Age, years old, mean (SD)	47.0 (14.0)	51.0 (13.0)	0.18
BMI, kg/m^2, mean (SD)	24.0 (4.0)	22.0 (5.0)	0.15
FVC, L, / mean (SD)	2.4 (0.9)	2.3 (0.8)	0.68
FVC % pred., mean (SD)	64.0 (17.0)	64.0 (18.0)	0.98
FEV_1, L, mean (SD)	1.4 (0.6)	1.4 (0.6)	0.93
FEV_1, % pred., mean (SD)	59.0 (14.0)	61.0 (12.0)	0.90
FEV_1/FVC, mean (SD)	60.0 (14.0)	61.0 (12.0)	0.68
O_2-dependent, n (%)	11 (10.9)	2 (15.3)	
Number of exacerbations/year, mean (SD)	1 (0.47)	1.2 (0.49)	0.20
mMRC, mean (SD)	2 (1.0)	1.7 (0.92)	0.19
E-FACED, mean (SD)	2.5 (1.8)	3.0 (1.4)	0.12
n per score mild/moderate/severe	34/10/2*	6/7/0	
BSI, mean (SD)	6.5 (4.0)	8.0 (4.0)	0.13
n per score low/intermediate/severe	15/21/10*	2/4/7	

SD: standard deviation, BMI: body mass index; kg/m^2: kilograms per square meter; FVC: forced vital capacity; FEV_1: forced expiratory volume in first second; L: liters; %: percentage; pred.: predicted value; n: number of patients; mMRC: modified Medical Research Council dyspnea scale; E-FACED: exacerbations, forced expiratory volume in first second, age, chronic colonization by *Pseudomonas aeruginosa*; BSI: Bronchiectasis Severity Index; BHQ: Bronchiectasis Health Questionnaire. *Four participants were not classified according to the BSI and E-FACED scores because they underwent a lobectomy.

These findings are in line with a study that compared the in-person and online application of the COPD Assessment Test (CAT) and the Clinical COPD Questionnaire (CCQ) in patients with COPD, showing adequate internal consistency and substantial reliability.[7] In our study, the SEM was used to evaluate the agreement between the two BHQ administration formats, and we found a narrow variation for this measure. In another study conducted with COPD patients, the authors observed good correlation, agreement, and reliability between in-person and online administration formats of CAT.[8] However, CAT scores were significantly higher in the face-to-face application (10.0 ± 7.4) than in the online format (8.6 ± 7.8). The assumption for this difference is that the online format was completed without supervision at the participants' homes, whereas the in-person format was filled out under supervision at the outpatient clinic.[8] A comparison performed between the in-person and online administration of the Asthma Quality of Life Questionnaire and Pediatric Asthma Quality of Life Questionnaire in patients with asthma showed that the online administration format was acceptable. Similar to our findings, the participants from these studies preferred the online over the in-person format.[9-10]

No ceiling or floor effects were found in the in-person or online administration formats, indicating that the online administration of the BHQ can also assess different responses to pulmonary rehabilitation or pharmacological interventions. The online BHQ format allows evaluating patients in their homes, with no need for displacement to medical offices or rehabilitation clinics.

This study had some limitations. The individuals were recruited from a single referral center for bronchiectasis in São Paulo. However, it receives patients from different regions of São Paulo and Brazil. Since this is a secondary study, randomization was not possible. Nonetheless, it was also not performed in other studies with COPD and asthma, and the results from previous studies were similar to those found herein.[7,9]

In conclusion, the in-person and online administration formats of the BHQ are equivalent and interchangeable. Both versions can be used to assess the quality of life of patients with bronchiectasis.

ETHICAL APPROVAL

All procedures followed the ethical standards of the institutional and national research committee and adopted the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards. Informed consent was obtained from all individuals included in the study (Certification No: 2,532,903 and 2,574,759).

DECLARATION OF CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Pulmonary vein stenosis after radiofrequency ablation

Antônio Carlos Portugal Gomes[1], Augusto Kreling Medeiros[1], Edson Marchiori[2]

A 49-year-old man underwent circumferential radiofrequency catheter ablation of the pulmonary veins to treat atrial fibrillation. The patient presented a favorable clinical course after the procedure. Nine months later, he underwent a chest radiography (Figure 1A), which revealed pulmonary opacities in the left upper lobe. The patient was asymptomatic. Chest computed tomography showed pulmonary opacities and interlobular septal thickening in the left upper lobe (Figure 1B), as well as tapering and filling defects in the pulmonary vein of the same lobe (Figure 1C) and stenosis of the ostium of the left inferior pulmonary vein (Figure 1D). The diagnosis of pulmonary vein stenosis (PVS) was confirmed. The patient remains under follow-up for disease monitoring.

Radiofrequency catheter ablation has become a widely used intervention in the treatment of atrial fibrillation. PVS is one of the most severe complications associated with this procedure. Most patients with significant PVS are asymptomatic or have few symptoms. Symptomatic patients usually present with dyspnea, cough, chest pain, and/or hemoptysis. The treatment of severe PVS depends on the symptoms and varies from no treatment to balloon dilatation or stent implantation. When such interventions fail, lobectomy may be necessary.[1,2]

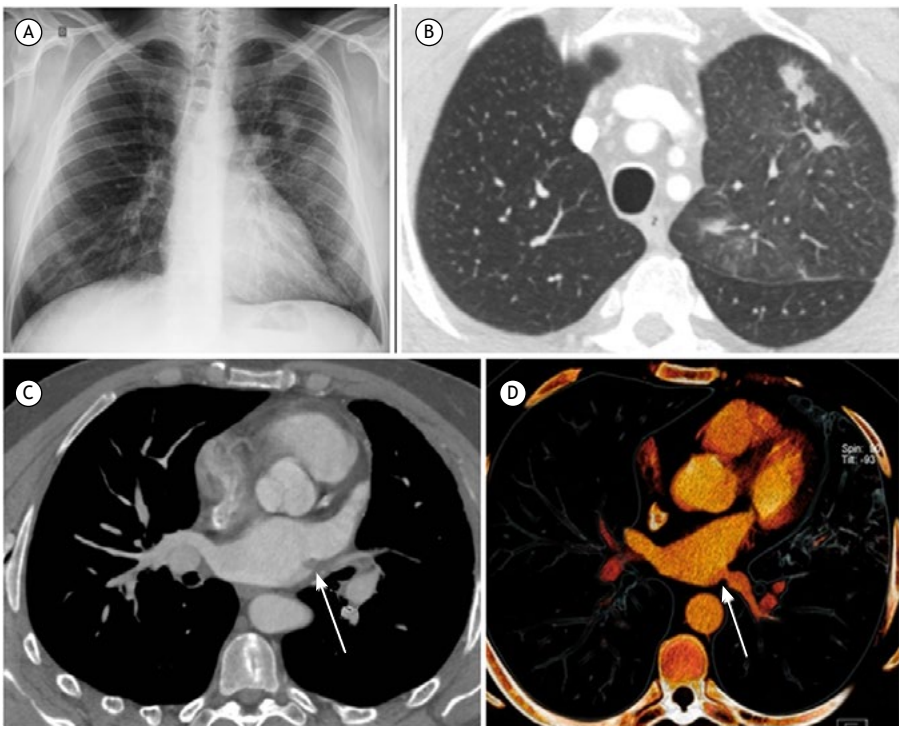

Figure 1. Chest radiography (A) showing pulmonary opacities in the left upper lobe. Axial chest computed tomography (B) demonstrating consolidations, some of which were nodular, ground-glass opacities, and interlobular septal thickening in the left upper lobe, compatible with pulmonary congestion. Axial images acquired at the level of the left atrium showing tapering and filling defects in the pulmonary vein of the left upper lobe (C) (arrow) and stenosis of the ostium of the left inferior pulmonary vein (D) (arrow).

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1. Medimagem/BP Medicina Diagnóstica, São Paulo (SP), Brasil.
2. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ), Brasil.

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On page 1 of the original publication, the correct affiliation of the author Antonio Marcos Vargas da Silva is number 8: Hospital Universitário de Santa Maria, Universidade Federal de Santa Maria, Santa Maria (RS) Brasil.

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