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HIGHLIGHT

Use of electronic cigarettes and hookah in Brazil: a new and emerging landscape. The Covitel study, 2022

Prevalence and associated factors of experimentation with and current use of water pipes and electronic cigarettes among medical students: a multicentric study in Brazil.

Prevalence, outcomes, and predictors of multidrug-resistant nosocomial lower respiratory tract infections among patients in an ICU

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.
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What happened to non-SARS-CoV-2 respiratory diseases during the pandemic?

Rosemeri Maurici[1,2,3]

Early reports of pneumonia of unknown cause associated with SARS and death in Wuhan, China, in December of 2019, did not size up with what was to come. The local outbreak was followed by an exponential spread of the disease. When the WHO declared the condition a pandemic in March of 2020, the disease had already been named (COVID-19) and its etiological agent had already been known (SARS-CoV-2).

Today, approximately 671 million cases and 7 million deaths after its beginning, COVID-19 is still considered as a global health emergency. However, much has changed in understanding the pathophysiological aspects, clinical manifestations, diagnosis, treatment, and prevention of the disease. Immeasurable advances have been achieved in the field of vaccines, in the development of molecular and serological testing technology, and in the evaluation of the treatment of the disease, with a view to mitigating its impact on people's lives. In addition to these aspects, the COVID-19 pandemic has also had an impact on the dynamics of health care, from primary care to the highest levels of complexity. Emergency care, hospitalization, and intensive care beds have been created and modified in view of the new reality.

In this sense, statistics and epidemiological data were disclosed in terms of the number of cases of COVID-19, number of deaths caused by the disease, daily moving averages, among others. In fact, even during the pandemic, other respiratory diseases did not disappear, and the question is inevitable: what happened to these diseases in terms of the dynamics of hospital admissions?

The paper by Resende de Albuquerque et al.[1] intends to answer this question by evaluating the indicators of hospitalization and deaths related to respiratory diseases other than COVID-19 during the first months of the pandemic in Brazil. The authors observed a 42% reduction in hospital admissions for these conditions, and for the two most prevalent chronic respiratory diseases, bronchial asthma and COPD, the reduction in hospitalization rates was approximately 46% and 45%, respectively. The second most important finding of the study[1] refers to the fact that, although the number of hospitalizations decreased, lethality increased by 60% when compared with the same indicator in the period before the pandemic.

These data do not refer to Brazil exclusively. In a Danish study, Bodilsen et al.[2] observed that hospital admissions for all groups of non-COVID-19 diseases decreased when compared with the periods prior to the pandemic, and, additionally, mortality rates were higher for conditions such as chronic respiratory diseases, cancer, pneumonia, and sepsis, especially during lockdown periods. Domingo et al.[3] also observed a significant reduction in hospital admissions mainly related to respiratory and cardiovascular diseases in Spain.

A few factors may be responsible for the scenario described by Resende de Albuquerque et al.[1] Initially, we can mention the exacerbations of chronic respiratory diseases, notably COPD and asthma, whose infectious agents (particularly viruses) are the major causes. The implementation of social distancing, use of masks, and hand hygiene with alcohol gel sanitizer incorporated into people's daily lives may have reduced the exposure of these individuals to COVID-19 and other respiratory viruses. Saeed et al.[4] believe that social distancing was one of the major factors responsible for this phenomenon.

The high demand for care of patients with COVID-19, overloading both emergency services and hospital beds and causing the collapse of health systems in some situations, may have, due to logistical reasons, prioritized the hospitalization of more severe cases, which had an impact on the increase in lethality of respiratory diseases other than COVID-19. Chronic patients themselves might have postponed the visit to an emergency department for fear of contamination with the SARS-CoV-2, configuring a delay in the pharmacological management of these conditions and, consequently, greater severity at admission. Ojetti et al.[5] highlight this fear as one of the major causes of delay in the search for care and increased mortality.

Finally, but not less important, we draw attention to the fact that health indicators and their reliability are directly related to the quality of records, that is, the accuracy of the information collected. In scenarios where health systems were overloaded, with a smaller number of professionals than what was ideal, associated with the impossibility of laboratory confirmation of all of the cases, COVID-19 overdiagnosis might have occurred and interfered with the quality of the records, leading to underreporting of chronic respiratory diseases.

Time series considering different epidemiological moments and, most importantly, the effect of vaccination for COVID-19 are desirable so that we can improve the understanding of the dynamics of SARS-CoV-2 infections and their repercussions on indicators of chronic respiratory diseases, especially aiming at supporting public health policies.

1. Departamento de Clínica Médica, Universidade Federal de Santa Catarina – UFSC – Florianópolis (SC) Brasil.
2. Programa de Pós-Graduação em Ciências Médicas – UFSC – Florianópolis (SC) Brasil.
3. Hospital Universitário – UFSC – Florianópolis (SC) Brasil.

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Better education and surveillance to approach the e-cigarette surge as a pandemic

Irma de Godoy[1]

"We are in the business of selling nicotine, a drug that causes addiction and effectively releases the stress mechanisms."

Alberto Addison Yeman, from the cigarette industry Brown & Williamson. Document 1802, from the secret file that was unveiled in 1963 – USA.[1]

Professor José Rosemberg, one of the best examples of human dignity, ethics, and solidarity, while fighting disease for many years and pursuing the right of the Brazilian population to live healthy lives, wrote the book "*Pandemia do Tabagismo: enfoques históricos e atuais*" in 2002."[1] We quote him, "No social habit or drug has expanded at the speed of tobacco. It was a real fever that took hold of everyone."[1] Nowadays, with the surge of e-cigarettes, we are seeing a remake of this dark era.

E-cigarettes have been the most used tobacco product among adolescents in the United States since 2014. In 2022, over 2.5 million youth, including 14.1% of American high schoolers, were current e-cigarette users.[2] Findings from the Global Youth Tobacco Survey in 17 European sites evaluating students aged 11-17 years showed that the prevalence of vape use doubled in some countries between 2014-2018, with rates between 7.6% and 18.5%.[3] A study in 73 countries showed that the prevalence of use (at least one day in the last 30 days) of water pipe among adolescents aged 12-16 years was 6.9%, and rates higher than 10% were found in Europe and Eastern Mediterranean.[4]

To achieve one of the most important declines in smoking worldwide, Brazilian institutions took strong actions, and the prevalence of smoking dropped from 34.8% in 1989 to 9.1% in 2021.[5] According to the 2019 Brazilian National Adolescent School-based Health Survey,[6] the total proportion of smokers among students aged 13 to 17 years was 6.8%, being higher among boys (7.1%) in comparison with girls (6.5%). When comparing the findings with data from the same survey in 2015,[7] a slight increase in the total proportion of smokers in the 13-17 year-old age group (from 6.6% in 2015 to 6.8% in 2019) can be observed due to the increase in the proportion of smokers among girls (from 6.0% in 2015 to 6.5% in 2019), although the prevalence of smokers among boys remained stable during the same period (7.1% in 2015 and 2019).[6,7]

Regarding electronic smoking devices, the resolution of the Brazilian National Health Surveillance Agency[8] prohibits selling, importing, and advertising of any devices for smoking, known as electronic cigarettes. Nevertheless, data from the Brazilian National Health Survey identified a prevalence of 0.64% of e-cigarette users, 70% of whom were between 15-24 years of age, and almost 90% of whom were not cigarette smokers.[9] The prevalence of water pipe use was estimated at 0.47%, an increase of 300% between 2013 and 2019, and approximately 80% of the users were in the 15-24 year-old age group.[9]

The real problem is not just the experimentation with e-cigarettes, but their continuous use, which can lead to an addiction that is difficult to overcome. In addition, the characteristics of e-cigarette and water pipe users and the tobacco industry propaganda reveal that the main objective is not smoking cessation, but rather to get the users hooked on nicotine and become dependent.

In this issue of the Brazilian Journal of Pulmonology, two important articles analyze the experimentation with and use of e-cigarettes and water pipes among people older than 18 years of age and medical students. Menezes et al.,[10] as part of a countrywide cross-sectional telephone-based study conducted in 2022, included 1,800 individuals from each of the five Brazilian geographic regions. It was found identical prevalence of lifetime use of e-cigarettes and hookah (7.3%; 95% CI: 6.0-8.9), which were higher among men, in those in the 18-24 year-old age group, and in those with a higher level of education. Martins et al.[11] evaluated 711 medical students in an online cross-sectional multicentric study in the five Brazilian geographic regions. Experimentation with and current use of water pipes were 42.6% and 11.5%, respectively, whereas those of e-cigarettes were 13.2% and 2.3%, respectively. A higher risk of experimentation was found among those with higher incomes and those who had smokers in their social group. Water pipe and e-cigarette experimentation was associated with an elevated risk of smoking cigarettes. The use of e-cigarettes to quit smoking was more commonly associated with dual use than with smoking cessation. Surprisingly, even among medical students, the knowledge about the health consequences of consumption of nicotine delivery products did not stop experimentation.

These studies reveal and reinforce some important findings. First, even with the prohibition of selling, importing, and advertising of these devices, the prevalence of use is increasing, mainly between well-educated and higher-income groups. In addition, nonsmokers represent most of the users, and tobacco industry advertisements

1. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.

have targeted this public. These findings add to the challenge of developing strategies to prevent this group of consumers from being hooked by the appeal of such devices and the industry strategies.

Although long-term health effects of inhaling liquid flavoring chemicals and nicotine need further investigations, there is clear evidence that the use of any nicotine product by young people is unsafe. Therefore, aggressive steps are needed in order to protect our children and youth from these products, which have great appeal, partly due to their innovative design, attractive taste and scent, and great ability to release nicotine, inducing nicotine dependence and being a gateway to smoking initiation.

The current Brazilian regulation prohibits commercialization of e-cigarettes and includes the adoption of additional measures to curb the illegal trade of these devices, such as increasing inspection actions and carrying out educational campaigns. However, maintaining surveillance on sales ban is a difficult task, even more so because of e-commerce, and people may obtain their e-cigarettes during international trips as well as from friends or family members.

To achieve success, we must work together, aligning and coordinating efforts across governmental agencies at national, state, and local levels, as well as across medical entities, educational institutions, and society.[12] Parents, teachers, health professionals, and communities must take actions such as: learn about the different shapes and types of e-cigarettes and the risks of all forms of e-cigarette use; develop, implement, and enforce tobacco-free policies; engage people in discussions about the dangers of e-cigarette use; and ask about e-cigarettes. In addition, when screening patients for the use of any tobacco products, health professionals must educate patients, especially if they are young, about the risks of all forms of tobacco product use, including e-cigarettes, and encourage patients to quit.

I finalize this editorial with the following quote:

"I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of protecting our children from a lifetime of nicotine addiction and associated health risks by immediately addressing the epidemic of youth e-cigarette use. The recent surge in e-cigarette use among youth, which has been fueled by new types of e-cigarettes that have recently entered the market, is a cause for great concern. We must take action now to protect the health of our nation's young people. KNOW THE RISKS. TAKE ACTION. PROTECT OUR KIDS."[12]

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Hyperdensities within the pulmonary arteries

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

A 55-year-old woman presenting with a two-year history of breast cancer and undergoing chemotherapy reported acute-onset severe chest pain and dyspnea. An unenhanced chest CT scan showed normal lungs and areas of increased density in the pulmonary arteries. An intravenous contrast-enhanced chest CT scan showed thrombi in pulmonary artery branches (Figure 1).

Pulmonary embolism (PE) is a common life-threatening condition that is associated with high morbidity and mortality. In patients with acute PE, however, nonspecific symptoms are common, and prompt recognition of PE can be challenging. Early diagnosis and prompt, appropriate treatment are essential to prevent further complications. Clinical findings alone are not sufficient to establish a diagnosis of PE, imaging therefore playing a critical role in the diagnostic workup of PE. CT angiography is the method of choice for the diagnostic imaging of PE and can safely exclude it. Pulmonary arterial filling defects on CT angiography play a critical role in establishing a diagnosis of PE. In addition, CT allows evaluation of the lung parenchyma, mediastinum, and pleural cavity with excellent spatial resolution, making it possible to assess alternative diagnoses.[1,2]

Unenhanced chest CT scans are commonly performed in patients presenting with nonspecific acute cardiopulmonary symptoms. Therefore, indirect signs of pulmonary thromboembolism are crucial in prompting the need for ancillary tests for a timely diagnosis.

Identification of indirect signs of PE is important in a variety of situations, especially when PE is not clinically suspected, and can be critical in preventing delayed diagnosis and complications. Unenhanced chest CT findings of thrombi in the pulmonary arteries have been described as an important CT sign of PE (particularly central PE), with the thrombi seen as hyperattenuating material on CT scans. The hyperdense appearance of the thrombus is due to increased hemoglobin concentration caused by decreased water content as the thrombus retracts, its attenuation value being raised above that of the regional blood pool. Despite being an important indirect sign of central PE, the presence of hyperdense material within the pulmonary arteries has limited diagnostic value for peripheral PE.[1,2]

Our patient initially underwent unenhanced CT, which showed hyperdense areas in the main pulmonary arteries. A contrast-enhanced CT scan was then performed, confirming the diagnosis of PE.

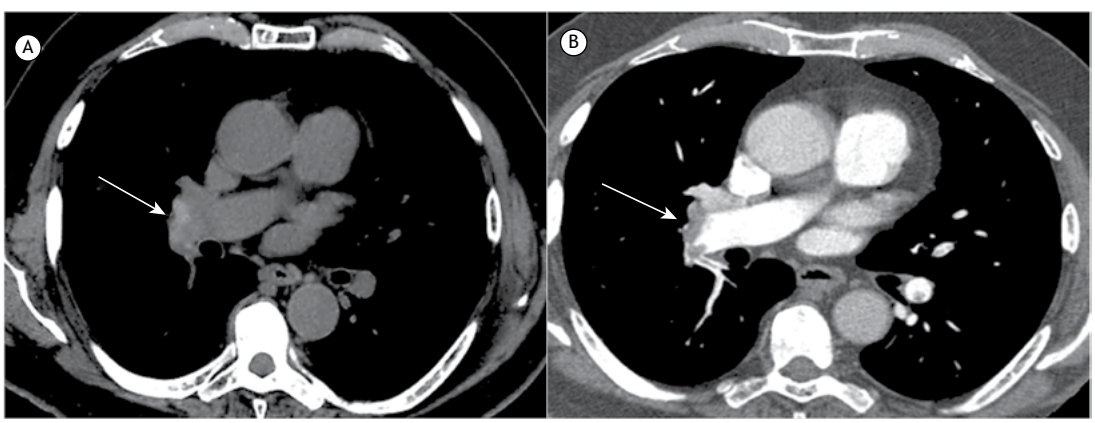

Figure 1. In A, unenhanced CT scan of the chest (mediastinal window) showing hyperdense material present within the right pulmonary artery (arrow). In B, chest CT angiography confirmed the finding to be a thrombus (arrow). Note also a small thrombus in a segmental branch of the left pulmonary artery (in B).

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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.

Fragility index and fragility quotient in randomized clinical trials

Marcos Vinicius Fernandes Garcia[1], Juliana Carvalho Ferreira[2,3,4], Pedro Caruso[2,3]

CLINICAL SCENARIO

In a randomized clinical trial (RCT) by Meyer et al.,[1] tenecteplase plus heparin was compared with placebo plus heparin in patients with pulmonary embolism. The primary outcome (death or hemodynamic decompensation) occurred in 13 of 506 patients (2.6%) in the intervention group as compared to 28 of 499 patients (5.6%) in the control group (OR = 0.44; 95% CI: 0.23-0.87; p = 0.02).

RCT ROBUSTNESS

RCTs are expensive and time consuming, and they generally have limited sample sizes; therefore, results can be dependent on few events. In the abovementioned RCT,[1] despite the large sample size, if only 3 more patients in the intervention group had experienced the outcome, the p-value would be greater than 0.05, which means that if 16 patients, rather than 13 patients, in the experimental group had experienced the primary outcome, the study would not be significant. This number indicating how many additional events in one of the groups would be required to turn a statistically significant trial into a statistically non-significant trial is called the fragility index (FI).

FI

The FI is calculated by changing the status of 1 patient in the group with the fewest number of events (control or experimental) from "non-event" (not experiencing the primary outcome) to "event" and then recalculating a two-sided Fisher's exact test until p becomes ≥ 0.05.[2] Table 1 illustrates the calculation of the FI for the abovementioned RCT.[1] Therefore, the FI is a measure of robustness of clinical trial results; the smaller the FI is, the less robust the trial is considered to be. Although the FI has no formal cutoff, it serves as an additional indicator of how easily the statistical significance of an RCT depends on a small number of events. Also, as a rule of thumb, if the number of patients lost to follow-up is greater than the FI, the trial should be considered less robust.

The fragility quotient (FQ) is the FI divided by the sample size, and a low FQ indicates a less robust trial. The FQ for the abovementioned RCT[1] would be 3/1,005 = 0.003, which is small and also indicates that the trial is not robust. FQ provides a way to assess the vulnerability of studies with regard to sample size, especially when sample sizes vary widely between studies addressing the same intervention.

FI USE AND LIMITATIONS

A large FI does not necessarily indicate a conclusive result, and a small FI does not indicate that the RCT results are trivial. There is no clear consensus on defining what a "fragile" study is, but FI and FQ can help clinicians make health decisions considering the fragility of RCT results.

Table 1. Example of calculation of the fragility index.[a]

Study sample (N = 1,005)	Death or hemodynamic decompensation	Neither death nor hemodynamic decompensation	p
Study outcome			0.02
Intervention group	13	493	
Control group	28	471	
First step of FI calculation			0.027*
Intervention group	14	492	
Control group	28	471	
Second step of FI calculation			0.043*
Intervention group	15	491	
Control group	28	471	
Third step of FI calculation			0.065*
Intervention group	16	490	
Control group	28	471	

FI: fragility index. [a]Adapted from Meyer et al.[1] *Fragility index steps and p-values were calculated using the "R package: fragility index."

1. Cleveland Clinic Foundation, Cleveland (OH) USA.
2. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Unidade de Terapia Intensiva, AC Camargo Cancer Center, São Paulo (SP) Brasil.
4. Methods in Epidemiologic, Clinical, and Operations Research-MECOR-program, American Thoracic Society/Asociación Latinoamericana del Tórax, Montevideo, Uruguay.

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The main limitation of the FI is that it applies only to RCTs with dichotomous outcomes. Another limitation is an FI equal to zero. While a trial uses chi-square analysis to calculate a p-value, FI is calculated using the Fisher's exact test, and therefore, an FI = 0 could occur in such trials when statistical significance was lost by simply changing the analysis from the chi-square test to the Fisher's exact test.

KEY MESSAGES

- The FI estimates the number of events needed to turn a statistically significant trial into non-significant. The smaller the FI is, the less robust the trial is.
- FI and FQ offer an alternative to the frequentist approach to RCT analysis and have been increasingly used in the critical appraisal of RCTs as an adjunctive tool for RCT interpretation.

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Getting the most out of the six-minute walk test

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

BACKGROUND

The six-minute walk test (6MWT) was introduced into clinical practice almost half a century ago. Gradually, it became the most widely used field exercise test in chronic respiratory disease. Despite advances in standardization,[1,2] there are some aspects of test performance and interpretation that should be carefully tempered by individual clinical judgment (Chart 1).

OVERVIEW

A 49-year-old woman presenting with a BMI of 34.2 kg/m^2, antiphospholipid syndrome, and two episodes of submassive pulmonary embolism developed chronic thromboembolic pulmonary hypertension . The six-minute walk distance (6MWD) increased from 198 m to 336 m after administration of riociguat. Over the next 6 months, she reported a decrease in exercise tolerance: her DL_{CO}, a ventilation-perfusion scan, and a transthoracic echocardiogram did not suggest disease progression. However, the 6MWD decreased by 72 m, i.e., approximately twice the recently estimated minimal clinically important difference of 33 m.[3] Given the conflicting results, she was referred for right heart catheterization, which confirmed hemodynamic stability. A review of the results of the latest 6MWT showed the following: a) a pronounced increase in the body weight (BMI, 41.2 kg/m^2); b) a shift from dyspnea to limiting "leg fatigue" associated with palpitations, lightheadedness, and limb paresthesia; and c) an SpO_2 of 99-100% on room air. Cardiopulmonary exercise testing revealed the negative effects of obesity, physical deconditioning, and dysfunctional breathing/hyperventilation. After aggressive weight loss (BMI, 30.7 kg/m^2), physical reconditioning, anxiety control, and breathing exercises, the 6MWD increased to 389 m, with marked symptom improvement.

Chart 1. Challenges to performing/interpreting the six-minute walk test: current recommendations and additional practical recommendations for clinical settings.

Points of concern	Standard recommendations	Practical recommendations
Test performance		
Less distance is walked a) up an inclined surface; b) to cover a short and tortuous track, because of slowing down to turn around and because of curves; c) on a treadmill.	The 6MWT should be performed along a flat, straight indoor course of at least 30 m (ideally 50 m) in length with a hard surface and little pedestrian traffic.	A long, unimpeded corridor might not be available in all settings. If a shorter track is used, this should be clearly stated. Track length should not change between interventions. Free-walking and treadmill tests are not interchangeable.
Large variability in walking speed depending on pre-test instructions. Given the maximal, all-out nature of many PFTs, patients may interpret it as a maximal test.	Patients should cover the longest possible distance in 6 min, walking along the hallway between markers. They are allowed to slow down, stop, and rest, but should resume walking as soon as possible.	It is critical that the patient understands the purpose of the test. Avoid walking alongside the patient. If clinically required (in order to improve safety or because of an unstable gait, for example), walk behind the patient.
Distance may increase across sequential tests as efficiency and pacing strategy improve, turning "positive" an ineffective intervention.	When the 6MWT is used in order to evaluate response to treatment or change over time, two baseline tests should be performed, with the longest distance being recorded.	Test repetition is usually not feasible in clinical settings: record whether/ when the patient had previous experience with the 6MWT. Test repetition is less critical in patients repeatedly exposed to the test, such as those undergoing cardiac or pulmonary rehabilitation.
Longer distance when the patient is continuously and actively encouraged; conversely, shorter distance with little/no encouragement.	Standardized phrases of encouragement. If the patients stops during the test, they should be reminded every 30 s to resume walking when possible.	Ensure tone consistency across examiners; avoid conversation with the patient; adhere strictly to standardized phrases.

Continue...▶

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.

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Chart 1. Challenges to performing/interpreting the six-minute walk test: current recommendations and additional practical recommendations for clinical settings. (Continued...)

Points of concern	Standard recommendations	Practical recommendations
Test performance		
The patient may lose the ability to self-pace if he/she is unaware of the time left for walking.	Every minute is signaled to the patients with standardized phrases of encouragement.	Keep a written description of the standard operating procedures for routine application by the assessors.
SaO_2 is critically dependent on metabolic demands: SpO_2 may vary widely in tandem with changes in pace, increasing rapidly upon exercise cessation.	Continuous monitoring of pulse oximetry is recommended. Plotting SpO_2 against time might provide patterns of desaturation (early vs. late exercise, stable vs. progressive).	Increased costs. More frequent detection of "severe" desaturation. Depending on the clinical context, it may trigger unnecessary interruption, artificially decreasing the 6MWD.
Hypoxemia increases ventilation and reduces O_2 delivery to leg muscles, both leading to high symptom burden and lower 6MWT	O_2 should be given at the standard rate when the patient is on long-term O_2 therapy. O_2 supplementation using the patient's carrier device leads to 12-59 m longer 6MWD.	The provision of supplemental O_2 and the carrying method should be kept constant across sequential assessments. If not, this should be clearly stated.
Many patients require walking aids for safety and/or to lessen exertional dyspnea.	Walking aids should be used when the patient regularly uses these devices. A wheeled aid increases the 6MWD by 2-46 m in comparison with no aid.	The walking aid should be kept constant on longitudinal assessments. If not, this should be clearly stated.
Exercise tolerance—particularly walking capacity—is influenced by a multitude of symptoms.	Dyspnea and subjective fatigue should be measured at the beginning and end of the 6MWT using the 0-10 Borg scale.	Record *all* reported symptoms and barriers to walking, as well as the number and duration of stops (if any), together with the reasons for the stops (and their severity).
Test interpretation		
Given the known effects of sex, age, and body dimensions on exercise capacity, there is a large between-subject variability in the 6MWD.	Use prediction equations representative of the local population. Prefer reference values generated from large samples of men and women, showing a wide age and height ranges.	Relatively large confidence intervals decrease the accuracy of equations at the extremes of age and height, particularly in elderly and short women. Apply a Bayesian approach to values close to the lower limit of normal.
Akin to bronchodilator "reversibility," the higher the pre-intervention 6MWD, the easier a given absolute threshold (in m) is reached. The opposite is true for relative changes (in %).[5]	Available evidence suggests an MCID of ~30-35 m for the 6MWD in adults with chronic respiratory disease. There is a relatively small amount of variability across patient groups.	MCIDs were established in moderate-to-severe lung disease patients exposed to selected interventions. The mean baseline distance ranged from 343 m to 403 m. Care should be taken when interpreting the 6MWT in different scenarios.
Less room for improvement after interventions when the patient walks close to the fastest possible walking speed.[5]	Despite this caveat, jogging is not allowed, because of the abrupt increase in metabolic/ventilatory demands and due to safety concerns.	The 6MWT may lose sensitivity to functional improvement after interventions in those who are already walking at the fastest allowed speed.
More work is performed when a larger body mass is displaced against gravity; conversely, obesity is known to decrease exercise tolerance.	The six-minute walk work is the product of distance and body weight, which may provide a better estimate of the total work required to perform the 6MWT than distance alone.	Additional studies are needed to better characterize the utility of the six-minute walk work in adults with chronic respiratory disease and its sensitivity to change over time.
The nature and severity of the symptoms limiting walking capacity may vary over time.	The symptoms reported in previous tests should be available for longitudinal comparison.	Special attention should be given to the locus of symptom limitation/concurrent symptoms in longitudinal assessments.

6MWT: six-minute walk test; PFT: pulmonary function test; 6MWD: six-minute walk distance; and MCID: minimal clinically important difference.

The 6MWT is a self-paced test of functional walking capacity that neither provides a metric of physical performance/fitness nor gives the causes of exercise limitation.[1,2] These considerations should not prevent the reader from seeking information beyond the 6MWD. For instance, in the case reported here, a more careful consideration of the ancillary findings (obesity progression, patient symptoms, and supra-normal SpO_2 on room air suggesting deconditioning and hyperventilation) in light of other data indicating disease stability might have avoided a futile invasive procedure (right heart catheterization). Continuous monitoring of SpO_2 improves the yield of oximetry in predicting mortality and hospitalization in patients with COPD.[4] Paradoxically, however, it can have undesirable consequences, such as early exercise interruption and slowing down at a "critically low" SpO_2 that could be faced in daily life without major implications. Patients experiencing the long-term consequences of disabling dyspnea and self-restraint are less likely to walk faster after an effective intervention; that is, they "can," but "won't." In fact, the test is notoriously more sensitive to interventions in (usually younger) patients with pulmonary arterial hypertension than in older patients with COPD.[2,3]

CLINICAL MESSAGE

Although the 6MWT provides limited information regarding the underlying mechanisms of exercise intolerance, it can be clinically useful to assess (a) functional capacity; (b) the severity of walking-induced hypoxemia, including the need for exertional O_2 supplementation; (c) the symptoms contributing to impaired exercise tolerance; and (d) potentially meaningful changes in walking capacity over time, either spontaneous changes or changes secondary to interventions. Akin to exercise-based evaluations that are more elaborate, all subjective and objective data should be interpreted in light of the clinical context and the limitations of the method (Chart 1).

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ORIGINAL ARTICLE

Periostin as an important biomarker of inflammatory phenotype T2 in Brazilian asthma patients

Danielle Cristiane Baldo[1,2], José Gustavo Romaldini[1], Marcia Margaret Menezes Pizzichini[3], José Eduardo D. Cançado[1], Alessandra Dellavance[2], Roberto Stirbulov[1]

1. Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo (SP), Brasil.
2. Grupo Fleury, Pesquisa e Desenvolvimento, São Paulo (SP), Brasil.
3. Programa de Pós-Graduação em Ciências Médicas, Universidade Federal de Santa Catarina, Florianópolis (SC), Brasil.

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ABSTRACT

Objective: The aim of this study was to assess the laboratory performance of periostin associated with a panel of biomarkers to identify the inflammatory phenotype of Brazilian asthma patients. **Methods:** We evaluated 103 Brazilian individuals, including 37 asthmatics and 66 nonasthmatic controls. Both groups underwent analyses for serum periostin, eosinophil levels in the peripheral blood, the fraction of exhaled nitric oxide (FeNO), total serum IgE, urinary leukotriene E_4, and serum cytokines. **Results:** Higher levels of periostin ($p = 0.005$), blood eosinophils ($p = 0.012$), FeNO ($p = 0.001$), total IgE ($p < 0.001$), and IL-6 ($p \leq 0.001$) were found in the asthmatic patients than the controls. Biomarker analyses by the ROC curve showed an AUC greater than 65%. Periostin (OR: 12,550; 95% CI: 2,498–63,063) and IL-6 (OR: 7,249; 95% CI: 1,737–30,262) revealed to be suitable asthma inflammation biomarkers. Blood eosinophils, FeNO, total IgE, IL-6, TNF, and IFN-γ showed correlations with clinical severity characteristics in asthmatic patients. Periostin showed higher values in T2 asthma ($p = 0.006$) and TNF in non-T2 asthma ($p = 0.029$). **Conclusion:** The panel of biomarkers proposed for the identification of the inflammatory phenotype of asthmatic patients demonstrated good performance. Periostin proved to be an important biomarker for the identification of T2 asthma.

Keywords: Asthma; Biomarkers; Eosinophilia; Phenotype.

INTRODUCTION

Asthma is a chronic inflammatory disease characterized by hyperresponsiveness of the lower airways and variable airflow limitations that are reversible spontaneously or with treatment. Considered one of the most prevalent chronic diseases in the world, asthma is directly and indirectly responsible for various medical and productive losses,[1,2] with Brazil being one of the countries with the highest prevalence.[3,4]

The diagnosis of asthma is clinically based on the presence of compatible symptoms associated with variable airflow limitations and demonstrations of airway hyperresponsiveness.[5,6] Among asthma patients, there is a subgroup of individuals who have difficult-to-treat asthma. Although these patients use high doses of medication to control their symptoms, they exhibit attributes that hinder control, such as behavioral factors, low adherence, incorrect inhaler techniques, environmental or occupational exposure, and the presence of comorbidities.[7] A smaller subgroup of these patients have severe asthma. These individuals lack adequate symptom control, even when alternative diagnoses are excluded, comorbidities are treated, triggers are removed, and treatment adherence is satisfactory; they represent around 1 to 4% of the general population of asthmatics.[8,9]

Several immunobiological options are currently available for the treatment of severe asthma. For a target-specific approach among the existing options, the identification of the inflammatory phenotype is fundamental.[10] Among the inflammatory phenotypes, the most frequent is type 2 (T2) inflammation, which is characterized by the presence of type 2 T-helper cells (Th2) or innate immune cells (ILC-2) and manifests as airway and/or systemic eosinophilia.[11]

All immunobiological agents approved for use are directed to the treatment of T2 asthma, which can be identified through available biomarkers such as eosinophils in the peripheral blood (blood eosinophils) and total serum immunoglobulin E (total IgE), eosinophils in induced sputum (sputum eosinophils), and the fraction of exhaled nitric oxide (FeNO).[12] New biomarkers for the differentiation of T2 asthma have been proposed, such as serum periostin and urinary leukotriene E_4 (LTE_4).[13,14] There are also studies investigating the use of cytokines involved in the inflammatory pathways of Th1 and Th17 cells, such as IL-6, TNF, and IFN-γ, as biomarkers for non-T2 asthma.[15-17]

The 2021 Global Initiative for Asthma (GINA) guidelines recommend the identification of at least one of the following findings for the establishment of T2 asthma: (1) blood eosinophils ≥ 150 cells/μL and/or (2) FeNO ≥ 20 ppb and/or (3) sputum eosinophils ≥ 2% and/or (4) allergy-induced asthma and/or (5) the need for maintenance therapy with oral corticosteroids (OC). If necessary, the values of eosinophils in the blood and

Correspondence to:
Danielle Cristiane Baldo. Av. Santo Amaro, 4584 - Brooklin, CEP 04702-000, São Paulo, SP, Brasil.
Tel.: 55 (11) 98553-1348. E-mail: danielle.baldo@grupofleury.com.br.
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FeNO should be measured at least 3 times under the lowest possible dose of oral corticosteroids.[5]

Currently, the routine services of clinical laboratories are widely available for the quantification of total serum IgE and blood eosinophils, but lack methodologically-directed validation in the clinical context of asthma. There is also no service that provides quantifications of FeNO, periostin, and LTE_4 for use in clinical practice. The quantification of sputum eosinophils is an ideal test for asthma phenotyping; however, it is a complex and difficult-to-apply technique in the clinical routine.[18] The availability and accessibility of other biomarkers are essential, not only aiming at the replacement of less useful biomarkers but also for the complementation of information on the inflammatory phenotype of patients. In this sense, a more complete panel of biomarkers may be useful.[12,19,20] To this end, it is crucial that clinical laboratories validate these trials in the clinical context of asthma to determine the analytical performance of tests for this purpose.

In view of the above, the aim of the present study was to evaluate the analytical performance of a panel of biomarkers to identify the inflammatory phenotype in a group of asthmatic patients in Brazil.

METHODS

This cross-sectional, observational, analytical study was duly registered in Plataforma Brasil under CAAE No. 73640917.8.0000.5479 and approved by the Research Ethics Committees of the Irmandade da Santa Casa de Misericórdia de São Paulo and Fleury Group. All participants signed a free and informed consent form.

The present study included Brazilian individuals aged above 18 years old from two different centers: patients diagnosed with severe asthma according to the international criteria described in the ATS/ERS guidelines,[21] who were followed up at the severe asthma outpatient clinic of the Irmandade da Santa Casa de Misericórdia de São Paulo, and patients with nonsevere asthma and control individuals, employees of the Fleury Group company, who volunteered to participate through an internal communication of the research project. The sample size was estimated following the CLSI (Clinical & Laboratory Standards Institute) EP09-A3 guideline, which determines a minimum requirement of 40 samples for user-conducted verification.

Patients and controls were recruited from February 2019 to May 2021. The patients were instructed not to discontinue ongoing treatment since the assessment was not interventional and did not address a specific treatment. For inclusion in the nonsevere asthma group, patients previously diagnosed by a specialist, who had asthma attacks during adulthood, and who did not meet the criteria for severe asthma by clinical history and the medications used for symptom control were accepted. The control group was determined by sex pairing with the asthma group.

All study participants (patients and controls) were evaluated regarding obesity (BMI calculation), allergy to inhalant antigens (detection of specific IgE against house dust, mites, grass pollen, animal epithelium and proteins, and/or fungi), and whether they had any of the following comorbidities: sleep apnea, bronchiectasis, atopic dermatitis, chronic urticaria, nasal polyposis, chronic rhinosinusitis, vocal cord dysfunction, or autoimmune diseases.

Asthmatic patients were evaluated concerning the history of the disease (late-onset asthma was defined as the onset of symptoms in adulthood), the drugs in use for categorization of the treatment stage according to GINA, asthma control through the Asthma Control Test (ACT), and pulmonary function by analyzing the values of forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) of predicted (prior to bronchodilator use) spirometry (Koko® PFT Spirometer, nSpire Health Inc, Longmont, CO, USA) results, performed according to the quality and reproducibility criteria of ATS/ERS.[22] T2 asthma was defined when patients presented with both biomarkers: blood eosinophil values ≥ 150 cells/μL and FeNO ≥ 20 ppb.

Quantifications of total and specific IgE were conducted using automated immunofluorimetry and electrochemiluminescence platforms, and the results were expressed as kilo units per liter (kU/L). Blood eosinophil levels, expressed as cells per microliter (cells/μL), were determined by fluorescent flow cytometry and impedance, with confirmation of counts and morphological analysis performed by microscopy when applicable.

The quantification of serum periostin was carried out by enzyme-linked immunosorbent assay (ELISA) using the Human Periostin/OSF-2 kit (R&D Systems Inc, Minneapolis, MI, USA), and the results were expressed as nanograms per milliliter (ng/mL). FeNO quantification tests were performed according to the ATS/ERS recommendations[23] using a NIOX-MINO® device (Circassia AB, Uppsala, Sweden) and expressed as parts per billion (ppb). LTE4 quantification was conducted by competitive ELISA with the Leukotriene E4 ELISA Kit (Cayman Chemical, Ann Arbor, MI, USA). The LTE4 results were normalized by the serum creatinine concentration in the sample and expressed as picograms per milligram of creatinine (pg/mg Cr). As for the inflammatory cytokines IL-6, TNF, and IFN-γ, they were quantified using the BD™ Cytometric Array Human methodology (CBA) (BD Biosciences, San Diego, CA, USA) and expressed as picograms per milliliter (pg/mL). IL-6 was evaluated in the asthmatic patients and controls, and TNF and IFN-γ were analyzed only in asthmatic patients.

The distributions of the numerical variables were assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. In cases of nonparametric data distribution, the Mann-Whitney test was used for two-group comparisons, and the Kruskal-Wallis test was used for three-group comparisons. For categorical variables, frequency interactions were analyzed by Fisher's chi-square or exact test. The ROC curve was used to measure test performance as a discriminator of asthmatics and controls. The inference of the

predictor variables of the inflammatory phenotype was performed by bivariate log regression using the linear regression method.

The analyses were conducted using the IBM SPSS Statistics software (version 20.0), and the graphs were generated using the GraphPad PRISM software (version 5.01).

It was not possible to quantify all variables for all samples due to volume limitations or unavailability; however, this loss did not significantly impact any variable. The final sampling in each analysis is detailed in the Tables and Figures below.

RESULTS

Data collection was performed in 103 individuals, 37 (36%) of whom were asthmatic patients and 66 (64%), nonasthmatic controls. Of the 37 asthmatic patients, 15 (40.5%) were severe asthmatics who were followed up at the Severe Asthma Outpatient Clinic of the Irmandade da Santa Casa de Misericórdia de São Paulo, while 22 (59.5%) were patients with nonsevere asthma who were employees of the Fleury Group. The demographic data of the patients are shown in Table 1.

Comparative analysis of biomarkers in the asthma patients and control subjects

In order to evaluate the analytical methods used for biomarker quantification, the values obtained from the asthmatic patients were compared to those of the controls. Figure 1 illustrates the results obtained in this analysis, as well as the statistical significance found in each comparison. Higher values of blood eosinophils ($p = 0.012$), FeNO ($p \leq 0.001$), IgE ($p \leq 0.001$), periostin ($p = 0.005$), and IL-6 ($p \leq 0.001$) were observed in the asthmatic patients compared to the controls; however, there was no difference in LTE_4 values ($p = 0.353$).

Verification of the analytical performance of the biomarkers

In order to establish the cutoff points of optimal analytical performance regarding the methods evaluated in the context of asthma, biomarkers that presented significantly higher levels in asthmatic patients were evaluated by ROC curve analysis to assess sensitivity and specificity. Samples with missing data were excluded from the analyses. The results showed a statistically significant curve for all biomarkers analyzed, with an area under the curve (AUC) greater than 65%. The obtained curves are represented in Figure 2.

Table 2 describes the results of the ROC curve, as well as the cutoff points of best analytical performance for each biomarker, including sensitivity when specificity was above 90%.

Binary logistic regression analysis was performed to determine whether the association of biomarkers would contribute to better sensitivity in the clinical context of asthma. To that end, the biomarkers were categorized according to the cutoff points established as positive (above the cutoff point) and negative (below the cutoff point). Periostin (OR: 12,550; CI 95%: 2,498-63,063) and IL-6 (OR: 7,249; 95% CI: 1,737-30,262) were significant asthma predictors, whereas the other biomarkers were not.

Analysis of the interference of comorbidities on biomarker values

In order to analyze the interference of comorbidities on the biomarker values, the control group was stratified regarding the presence of allergies, obesity, and the presence of one or more comorbidities associated with worse prognoses in asthma (sleep apnea, bronchiectasis, atopic dermatitis, chronic urticaria, nasal polyposis, chronic rhinosinusitis, allergic rhinitis, or vocal cord dysfunction). None of the comorbidities was associated with high biomarker values (Table S1)

Comparative analysis of biomarkers in asthmatic patients according to clinical characteristics and phenotypes

In order to assess the association between the biomarker values and the patients' clinical data, the asthma group was analyzed separately regarding the clinical variables studied.

Table 1. Demographic data stratified by group.

Variables	Asthmatics (n = 37)	Controls (n = 66)
Sex (% women)[a]	27 (73%)	49 (74%)
Age (years)[b]	39 (33.5 - 54.0)	33 (27.8 - 38.3)
BMI (kg/m^2)[b]	28 (23 - 33)	25 (23 - 29)
Allergy (specific IgE)[a]	30 (81%)	26 (39%)
Other comorbidities[a]	19 (51%)	23 (35%)
Late-onset (adult asthma)[a]	15 (41%)	-
ACT[b]	20 (16 - 23)	-
Exacerbations (previous year)[a]	9 (24%)	-
FVC (% of predicted)[b]	90 (73 - 100)	-
FEV_1 (% of predicted)[b]	80 (55 - 92)	-
Steps 4 and 5 GINA treatment[a]	17 (46%)	-
Use of OC[a]	5 (14%)	-

BMI: Body mass index (kilograms per square meter); IgE: Immunoglobulin E; ACT: Asthma control test; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in the first second; GINA: Global Initiative for Asthma; OC: Oral corticosteroids. [a]Number of cases (%); [b]Median (Interquartile range 25 - 75).

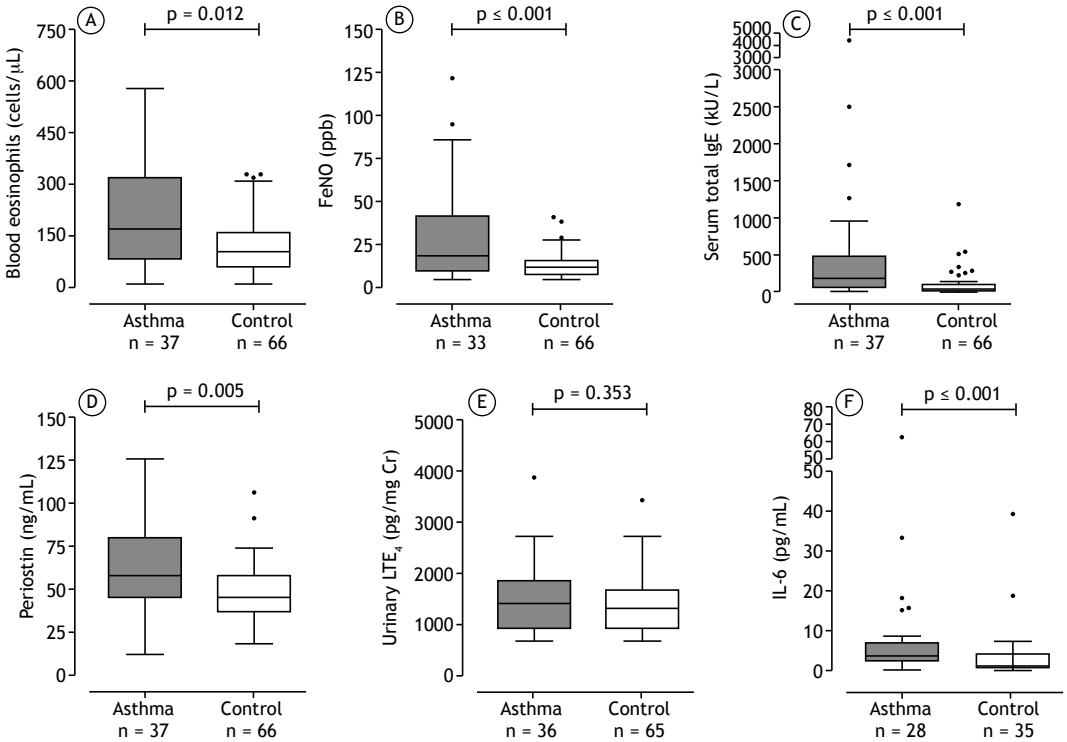

Figure 1. Biomarkers in asthmatic and control patients. Vertical boxes represent the interquartile intervals 25 - 75. The centerlines represent the medians and the stems indicate the lower and upper limits. Dots represent outliers. FeNO: Fraction of exhaled nitric oxide; LTE_4: Urinary leukotriene E_4; IL: Interleukin; IgE: Immunoglobulin E.

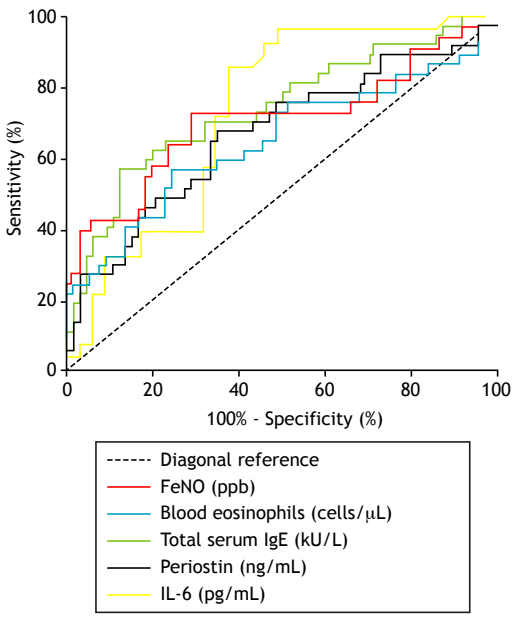

Figure 2. Receiver operator characteristic (ROC) curve based on the values of the biomarkers in the clinical context of asthma. Each biomarker has its own estimated curve.

Patients with more severe asthma (in higher levels of treatment according to GINA) presented higher values of IL-6 (p ≤ 0.001) and IFN-γ (p = 0.007) and lower levels of blood eosinophils (p = 0.030) than the nonsevere asthma patients. In the categorical assessment regarding asthma control, no differences were found in biomarker levels in uncontrolled (ACT < 20) and controlled asthma (ACT ≥ 20) or in asthmatics using oral corticosteroids. As for the variables concerning airflow limitations, lower percentages (≤ 80%) of FVC were associated with higher values of IL-6 (p = 0.002) and IFN-γ (p < 0.001). Similarly, lower percentages (≤ 80%) of FEV_1 also correlated with higher values of IFN-γ (p = 0.045).

Allergic asthma, defined as the presence of specific IgE, presented significantly higher values of FeNO (p = 0.008) and lower values of IFN-γ (p = 0.044). As for late-onset asthma, significantly lower FeNO values were found (p = 0.038). The stratification of patients according to the obesity phenotype (BMI ≥ 30) revealed significantly higher total IgE values in obese patients (p = 0.033) (Figure 3).

In the classification of asthma patients using the parameters FeNO ≥ 20 ppb and blood eosinophils ≥ 150 cells/μL for the establishment of T2 asthma,[5] periostin presented significantly higher levels in T2 asthma (p = 0.006), but not LTE_4 (p = 0.893) or IL-6 (p = 0.593). TNF showed lower values in T2 asthma (p = 0.029) (Figure 4).

DISCUSSION

The primary objective of the present study was to validate the use of a panel of biomarkers in clinical practice and to determine the analytical performance of

already used and new tests to identify the inflammatory phenotype of asthma. This is of paramount importance to physicians and patients, especially in the context of severe asthma, in which the identification of the inflammatory phenotype is fundamental for the implementation of target-specific therapy.[6] In view of this objective, the analytical performance (sensitivity and specificity) of the isolated trials was verified, as well as the benefits of offering a test panel with more information on the pathophysiological characteristics of patients.

Table 2. Results of ROC curve analysis and analytical performance of biomarkers considering cutoff points with specificity above 90%.

Variables	AUC	Standard Error	p-value	95% confidence interval		Cutoff point	Analytical performance	
				Lower limit	Upper limit		Sensitivity	Specificity
FeNO (ppb)	0.707	0.062	≤0.001	0.586	0.828	>27	42.4%	93.9%
Blood eosinophils (cells/μL)	0.649	0.061	0.012	0.530	0.769	>275	29.7%	92.4%
Total IgE (kU/L)	0.741	0.053	≤0.001	0.637	0.845	>265	40.5%	90.9%
Periostin (ng/mL)	0.669	0.058	0.005	0.555	0.782	>75	27.0%	97.0%
IL-6 (ng/mL)	0.731	0.064	0.001	0.605	0.857	>6	32.1%	91.4%

FeNO: Fraction of exhaled nitric oxide; IgE: Immunoglobulin E; IL: Interleukin.

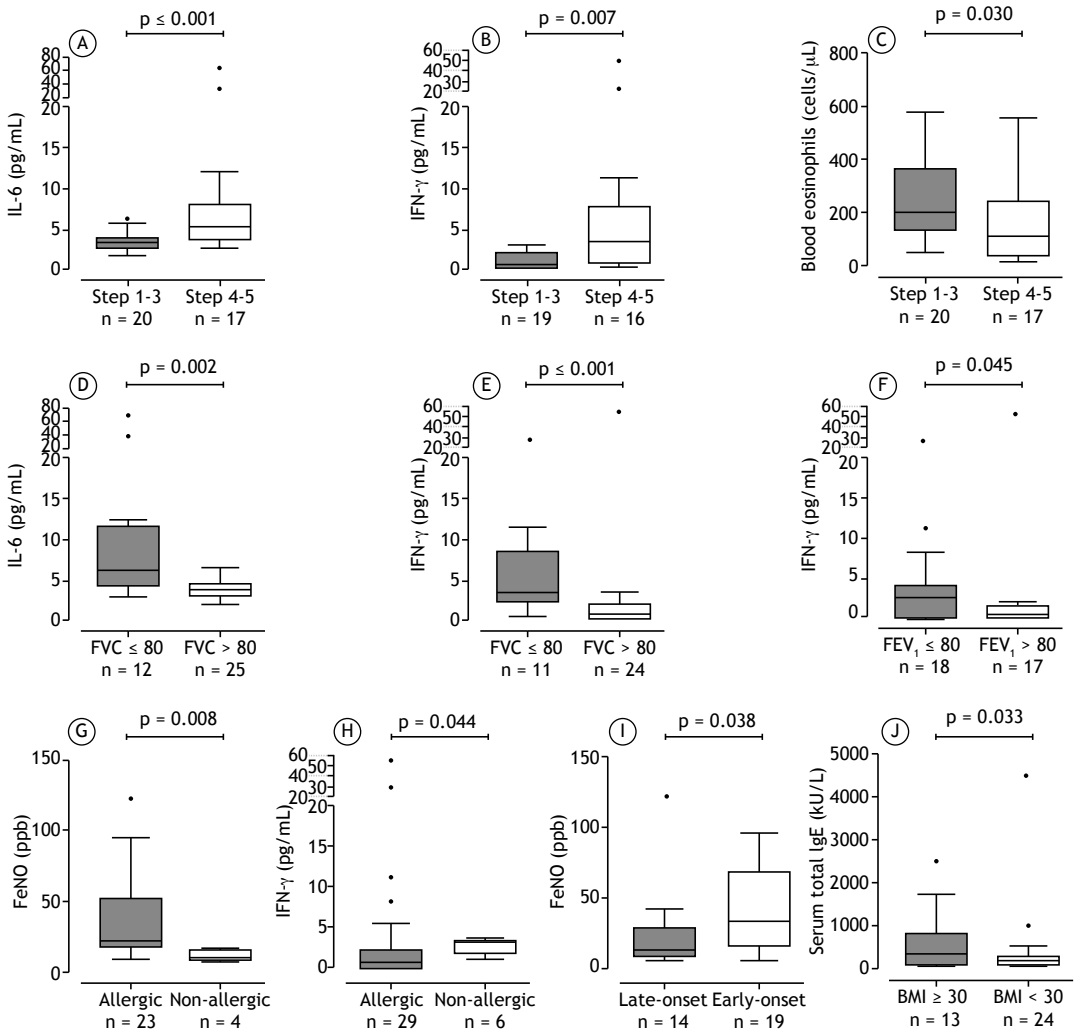

Figure 3. Biomarkers in asthmatic patients according to their clinical characteristics. Vertical boxes represent the interquartile intervals 25 - 75. The centerlines represent the medians and the stems indicate the lower and upper limits. Dots represent outliers. FeNO: Fraction of exhaled nitric oxide; IL: Interleukin; IFN-γ: Interferon-gamma; FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second; BMI: Body mass index. (a - c) Treatment steps according to GINA.

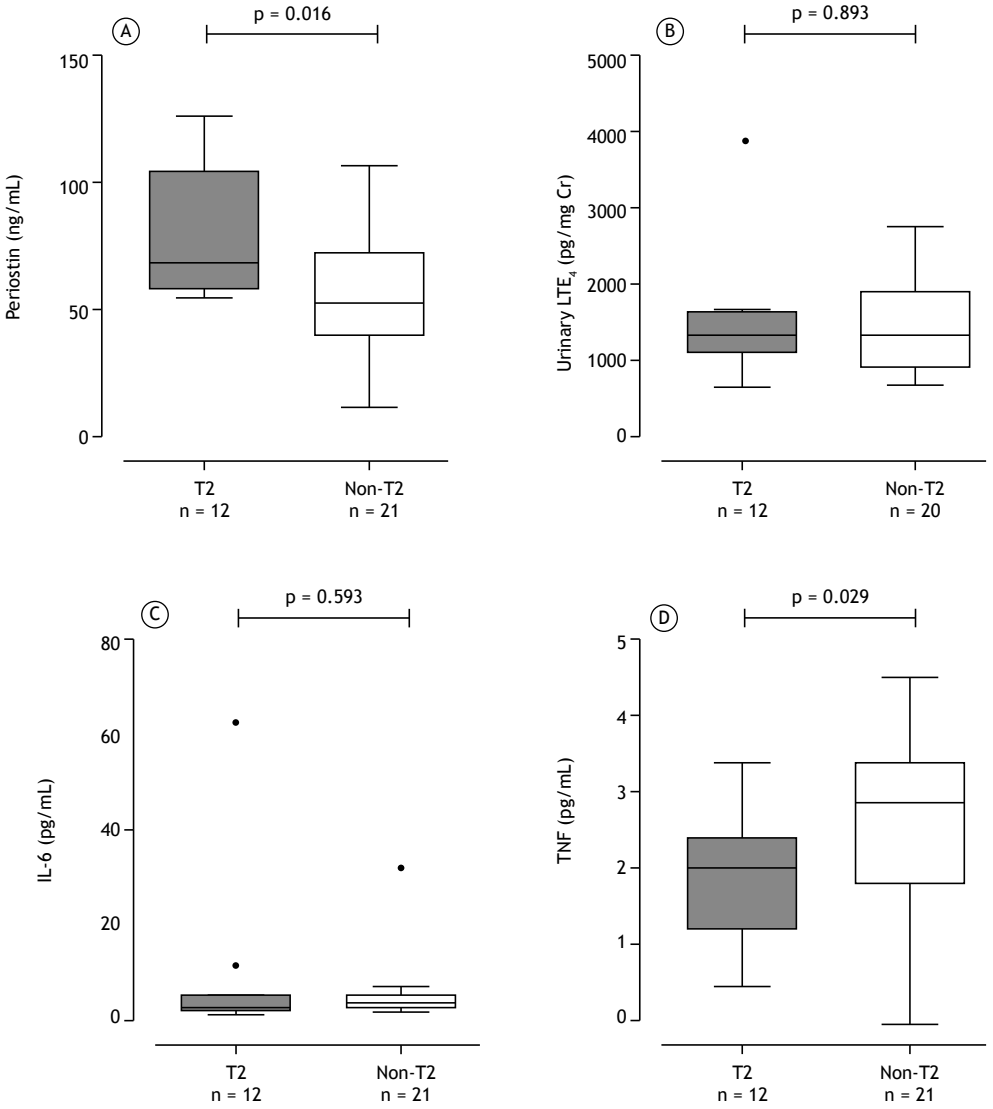

Figure 4. Biomarkers in asthmatic patients according to the inflammatory phenotype T2. Vertical boxes represent the interquartile intervals 25 - 75. The centerlines represent the medians and the stems indicate the lower and upper limits. Dots represent outliers. LTE_4: Urinary leukotriene E_4; IL: Interleukin; TNF: Tumor necrosis factor.

Corroborating some studies in the literature,[19,24] the values of blood eosinophils and total IgE were higher in asthmatic patients than in the controls. These biomarkers are currently widely used in clinical practice and assist in the identification of eosinophilic and allergic inflammatory phenotypes. However, targeted analytical validation is not performed in the clinical context of asthma by laboratories. Lower levels of blood eosinophils were found in asthmatic patients undergoing GINA treatment steps 4 and 5, a possible effect of high doses of inhaled corticosteroids and the use of systemic corticosteroids by these patients, resulting in eosinophilic suppression.[25] A previously described albeit poorly studied finding was higher total IgE levels in obese patients.[26]

FeNO is also an important biomarker not only for identifying the inflammatory phenotype but also as a predictor of the response to treatment with anti-IL-4/IL-13.[27] One of the ways of determining FeNO is by using a portable device that is easy to handle[28] in clinical practice. With the approval of this method by ANVISA, it became possible to use this biomarker during the management of asthma patients in Brazil. This study corroborated findings in the literature regarding the increased values of this biomarker in the clinical context of asthma and shed light on its analytical characteristics for national validation. The correlation between FeNO and allergic and early-onset asthma has also been previously described in the literature,[5,29] reinforcing the relationship between FeNO and T2 asthma.

Two biomarkers that are not currently used routinely in clinical practice were also evaluated: serum periostin and urinary LTE_4; both are related to T2 asthma,[14,30] although urinary LTE_4 often shows controversial results in the literature.[31] Periostin is a matricellular protein

involved in different biological functions[32] that has been identified in asthma in the process of airway tissue remodeling.[33] Its expression is induced by IL-13, a cytokine that plays a key role in T2 asthma response and is involved in airway hyperresponsiveness.[13] Periostin is used as a biomarker of T2 asthma, and its role in the identification of good responders to corticosteroids[34] and anti-IL-13[35] has already been described. This study not only corroborated the increase in periostin values in the clinical context of asthma but also reinforced its complementary role in the predictive value of the disease when compared to the controls and its high levels in patients with elevated blood eosinophils and FeNO (T2 asthma). Regarding urinary LTE_4, no differences were observed between the values obtained in the controls or regarding clinical characteristics.

Another investigated biomarker, IL-6, presented higher values in asthmatic patients than the controls and even higher values in non-T2 asthma patients. Similar to the other biomarkers, IL-6 may be elevated in different clinical conditions, such as COVID-19,[36] by its known participation in chronic inflammatory processes.[37] In this study, higher IL-6 values were also predictors of asthma and related to steps 4 and 5 of GINA treatment and lower percentages of FVC, which directly reflect a possible relationship with the severity of the disease. Higher values of IFN-γ were also observed in patients in higher stages of treatment, with lower FVC and FEV_1, and in nonallergic asthma, showing possible immunological activation mediated by Th1 cells.[16] The TNF cytokine also presented higher values in non-T2 asthma, a fact that reinforces the identification of other pathophysiological pathways in these patients.

The data obtained with the ROC curves revealed cutoff points with a better balance between specificity and sensitivity in asthma. These points are higher than those indicated by GINA[5] but closer to the cutoff, with solid clinical applications such as FeNO ≥ 25 ppb for indication of treatment with anti-IL-4/IL-13[27] and blood eosinophils ≥ 300 cell/μL with anti-IL-5/anti-IL-5-receptor.[38,39] The modest sensitivity found was expected since all the evaluated biomarkers, with the exception of IL-6, are increased in eosinophilic asthma, which represents most, but not all cases of the disease.[40] Regarding specificity, this cohort showed that the presence of comorbidities associated with difficulty controlling asthma did not significantly affect biomarker levels. However, the number of patients analyzed was a limitation; further studies are needed to support this finding.

Finally, an important limitation of this study was the absence of induced sputum collection, one of the most important tests for the identification of the inflammatory phenotype. With the COVID-19 pandemic, procedures capable of releasing aerosols from respiratory material, such as nebulization during the collection of induced sputum, have been prohibited outside emergency contexts. Thus, future studies with the addition of induced sputum tests may strengthen our findings. In addition, access to a larger sample of individuals with severe asthma and patients of other centers in Brazil is crucial to better evaluate the clinical applicability of this panel, as well as outcomes related to the response to treatment. It is possible that the lack of differences regarding the levels of biomarkers and uncontrolled patients was due to the small number of severe patients.

The use of a panel of biomarkers as a single test, with technical laboratory information regarding the validation of each examination in the clinical context of asthma, is a fundamental approach to assist clinicians and patients in individualized and effective treatment. The biomarkers already consolidated in clinical practice, together with new ones, offered jointly, could provide reliable and accurate information for the determination of the inflammatory phenotype of asthma, allowing for targeted interventions that could foresee severe symptoms and complications related to the disease.

AUTHOR CONTRIBUTIONS

Study conception and design: DCB and RS; acquisition of data: DCB and JGR; data analysis and interpretation: DCB and RS; writing the manuscript: DCB; critical revision of the manuscript: DCB, JGR, MMMP, JEDC, AD, and RS; final approval of the manuscript: RS.

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ORIGINAL ARTICLE

Characteristics of individuals with moderate to severe asthma who better respond to aerobic training: a cluster analysis

Tiago C Endrigue[1], Adriana C Lunardi[1], Patrícia D Freitas[1], Ronaldo A Silva[1], Felipe A R Mendes[1], Andrezza França-Pinto[1], Regina M Carvalho-Pinto[2], Celso R F Carvalho[1]

1. Departamento de Fisioterapia, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Divisão de Pneumologia, Instituto do Coração – InCor – 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, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To determine the characteristics of individuals with asthma who are responsive to aerobic training. **Methods:** This post hoc analysis of pooled data from previous randomized controlled trials involved 101 individuals with moderate to severe asthma who underwent aerobic training. Participants underwent a maximal cardiopulmonary exercise test and completed the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire before and after a 24-session aerobic training program. Better and worse responders to aerobic training were identified by cluster analysis. **Results:** Two clusters were identified according to the improvement in peak VO_2 after aerobic training (better and worse responders). Characteristics of the better responder group were being older, being female, having higher BMI, and having higher cardiac reserve at baseline when compared with the worse responder group. Also, better responders had worse clinical control, worse quality of life, and lower physical capacity at baseline. After training, worse responders, in comparison with better responders, showed half the improvement in Δpeak VO_2 (7.4% vs. 13.6%; 95% CI, −12.1 to −0.92%; $p < 0.05$) and worse asthma control. A weak, negative, but significant association ($r = -0.35$; $p < 0.05$) was observed between clinical control and aerobic fitness only in the better responder group. Both groups showed significant improvement in quality of life. **Conclusions:** Obese individuals with worse exercise capacity, clinical control, and quality of life showed improvement with aerobic training. Moreover, worse responders also improved with training, but to a lesser extent.

Keywords: Asthma; Exercise therapy; Cluster analysis; Status Asthmaticus; Quality of Life; Rehabilitation.

INTRODUCTION

Asthma is defined as a heterogeneous disease, usually characterized by chronic airway inflammation.[1] Asthma leads to systemic inflammation, exercise-induced bronchospasm, and development of comorbidities. In addition, this condition promotes increased levels of anxiety and depression and reduced physical activity levels, leading to a reduction in the physical capacity of these individuals.[2] However, the increase in exercise capacity by means of physical training at moderate intensity in individuals with asthma improves immune responses and reduces airway inflammation.[3] Exercise also decreases exercise-induced bronchoconstriction[3] and corticosteroid use.[4] In addition, physical training in individuals with moderate to severe asthma improves clinical asthma control[5,6] and health factors related to the individual's quality of life[3,7]; conversely, the association between physical fitness and clinical control is still poorly understood.

It remains unknown who would most benefit from a physical training program[8] and whether there would be a certain subgroup of individuals who do not respond to a specific training program.[9] Pulmonary rehabilitation is an expensive and time-consuming program. Ambrosino and Clini[10] stated the importance of knowing the predictors of a successful pulmonary rehabilitation program in individuals with COPD to optimize the use of financial resources in this field. The response to a pulmonary rehabilitation program is multidimensional.[11] For example, COPD responders to pulmonary rehabilitation presented with more severe dyspnea symptoms, greater number of hospitalizations, more severe anxiety and depression symptoms, greater BMI, worse health condition, and worse exercise performance prior to the intervention.[11] Another study demonstrated that obese individuals with COPD with better lung function and worse physical activity levels at baseline benefited more from a pulmonary rehabilitation program.[12]

Correspondence to:
Celso R F Carvalho. Departamento de Fisioterapia, Faculdade de Medicina, Universidade de São Paulo, Avenida Dr. Arnaldo, 455, Sala 1210, CEP 01246-903, São Paulo, SP, Brasil.
Tel.: 55 11 3061-7317. E-mail: cscarval@usp.br
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Despite the well-known benefits of improving exercise capacity in individuals with asthma, the factors determining those who respond to a pulmonary rehabilitation program have been exclusively reported in individuals with COPD. Although these factors could be obvious and may be applied to other chronic pulmonary diseases, determining these factors is mandatory due to the specific characteristics and impact on the lives of patients with asthma. So far, there is no information on which individuals with asthma respond to aerobic training or pulmonary rehabilitation programs. Therefore, this study aimed to determine the characteristics of individuals with moderate to severe asthma who respond to aerobic training and the relationship between that response with changes in clinical control, quality of life, and exercise capacity.

METHODS

This was a post hoc analysis of pooled data from previous randomized controlled trials.[3,6,13] These trials involved individuals with moderate to severe asthma who had previously participated in a pulmonary rehabilitation program in our center and underwent aerobic training (Chart 1).[3,6,13] There was no overlap of individuals among the studies. All individuals were followed at the same university hospital. The research ethics committee of the institution approved the clinical studies (CAAE no. 0121/10; no. 07137512.9.0000.0068; and no. 18178013.9.0000.0068).[3,6,13] All of the participants completed the aerobic training program between 2015 and 2019. Cardiopulmonary exercise test (CPET) variables, asthma clinical control, and quality of life were evaluated before and after the intervention.

Individuals aged 20-60 years and with a diagnosis of asthma (severity level in accordance with the criteria established by the Global Initiative for Asthma)[1] in each of the studies, based on the level of treatment needed to control exacerbations and symptoms, were included in the present study. Individuals should have had medical follow-up for at least six months, using optimized medical treatment for asthma, and clinical stability (no need to change medications, no visits to the emergency room, and no hospitalizations within 30 days at least).

Exclusion criteria were having other chronic lung disease, cancer, cardiovascular disease, or musculoskeletal dysfunction that could interfere with the assessments and/or physical exercises. In addition, those who were pregnant, current or former smokers (≥ 10 pack-years), unable to understand the instructions given by researchers, or participating in another research protocol were also excluded.

All individuals underwent a 24-session aerobic training program. Training parameters were determined by assessing VO_2 during a pre-rehabilitation CPET, and they were similar among the studies (Chart 1). Before and after the intervention, pulmonary function was assessed via spirometry,[14] and FEV_1 and FVC were analyzed using the predicted values for the Brazilian population.[15] Clinical control was assessed using the Brazilian-Portuguese version of the 7-item Asthma Control Questionnaire (ACQ-7).[16] The questions on the ACQ-7 are related to symptoms, activity limitations, dyspnea, wheezing, and use of rescue bronchodilators in the last week.[16] The last item on the ACQ-7 refers to a question that assesses FEV_1 (in % of the predicted

Chart 1. Aerobic training protocols performed by the patients included in the studies during 24 sessions.

Study	Session duration	Intensity	Progression	Ergometer
França-Pinto et al.[6]	30-35 min	60% of peak VO_2 in the first 2 weeks and then progression to 70% of peak VO_2	If the individual had no symptoms in 2 consecutive sessions, intensity was increased by 5% of HR up to a maximum of 80%	Treadmill
Freitas et al.[10]	60 min	50-60% of peak VO_2 in the first 2 weeks	If the individual had no symptoms, intensity was increased by 5% of HR every 2 weeks, up to a maximum of 75%	Treadmill, cycle ergometer, or elliptical ergometer
Silva et al.[19] Continuous training group	40 min	60% of peak VO_2 in the first 2 weeks and then progression to 70% of peak VO_2	If the individual had no symptoms in 2 consecutive sessions, intensity was increased by 5% of HR, up to a maximum of 80%	Cycle ergometer
Silva et al.[19] Interval training group	40 min, with cycles of 30 seconds of activity, alternating with 30 seconds of recovery	In the first 2 weeks, periods of high-intensity (80% of maximum work rate) with low-intensity intervals	In the 3rd and 4th weeks, intensity reached 100% of maximum work rate. If the individual had a reduction in symptoms, intensity was increased by 5% of the load	Cycle ergometer

value, pre-bronchodilator). This questionnaire contains seven items on a 7-point scale (0 = no limitation and 6 = maximum limitation). Higher scores indicate worse clinical control. A score of 1.5 or greater is considered uncontrolled asthma.[17] A change of 0.5 point in the ACQ-7 score is considered clinically effective.[18] In addition, the health-related quality of life in asthma was assessed by the Brazilian-Portuguese version of the Asthma Quality of Life Questionnaire (AQLQ).[19] The AQLQ contains 32 items and is divided into four domains: activity limitations, symptoms, emotional function, and environmental exposure. Higher scores indicate better quality of life. A change of 0.5 point in the AQLQ score is considered clinically effective.[20]

Exercise capacity was assessed via a maximal CPET to the limits of tolerance performed either on a treadmill[3] or on a cycle ergometer.[6,13] The protocols used were previously established for treadmill[21,22] and cycle ergometer.[23] The comparison between predicted VO_2max values obtained on two ergometers was corrected according to the equation[24]:

$$VO_2max = 45.2 - 0.35 \times age - 10.9 \times sex - 0.15 \times weight + 0.68 \times height - 0.46 \times exercise\ mode$$

where VO_2max is in $mL \cdot kg^{-1} \cdot min^{-1}$; age, in years; sex (male = 1; female = 2); weight, in lb; height, in inches; and exercise mode (treadmill = 1; cycle ergometer = 2). That was required due to the difference between the energy expenditure assessed on the two ergometers.[25] The CPET variables were VO_2 at baseline, in mL/min; anaerobic threshold (AT), in $mL \cdot kg^{-1} \cdot min^{-1}$; and peak exercise, in % predicted.[24] In addition, V_e, maximum HR, and respiratory exchange ratio (RER) were recorded at the end of the test.

Data were analyzed for normality using the Kolmogorov-Smirnov test. Cluster analysis was performed in two steps.[26] Initially, a hierarchical analysis using Ward's method automatically determined the number of clusters. Subsequently, the k-means algorithm analysis was used to group the individuals into the clusters. Cluster analysis was performed including the following variables: age; FEV_1 (% predicted); BMI; pre-intervention VO_2AT; pre-intervention peak VO_2; (post/pre-intervention) ΔAQLQ score; (post/pre-intervention) ΔACQ-7 score; and post/pre test Δpeak VO_2. The t-test was used to compare the clusters. The z-test was used to compare proportions between the clusters. Pearson's tests were used to analyze the correlation between ΔVO_2 and ΔACQ-7 in both clusters. The Statistical Package for the Social Sciences, version 12.0 (SPSS Inc., Chicago, IL, USA) and the SigmaStat software, version 3.5 (Systat Software Inc., Chicago, IL, USA) were used. The significance level was set al 5% ($p < 0.05$).

RESULTS

This study involved 101 individuals with asthma who completed an aerobic training program: 22 from the study by França-Pinto et al.,[3] 26 from the study by Freitas et al.,[6] and 53 from the study by Aparecido da Silva et al.,[13] allocated in two groups: interval training group and continuous training group.

Among all of the individuals included, 55 (54.5%) were obese (BMI > 30 kg/m^2), 49 (48.5%) presented with moderate airway obstruction (Table 1), and 67 (66.3%) had uncontrolled asthma. Regarding the response to maximum CPET, 32 (31.7%) of the individuals presented limitations in the ventilatory system, as did 51 (50.5%) in the cardiovascular system and 65 (64.4%) in the peripheral muscle system.

After cluster analysis, the two groups were determined based on the improvement in peak VO_2 after aerobic training. The groups were classified as better or worse responders to aerobic training (Table 2). Before the intervention, the better responder group mostly consisted of females and older individuals with higher BMI and higher cardiac reserve in comparison with the worse responder group. In addition, the better responder group presented with worse clinical control and worse quality of life before training and lower physical capacity (peak VO_2 and VO_2AT) than did the

Table 1. Baseline clinical and anthropometric characteristics (N = 101).[a]

Characteristics	Values
Female	86 (85)
Age, years	43.0 (36.5-51.0)
Body mass, kg	76.5 (67.8-86.4)
BMI, kg/m^2	30.3 (25.8-34.7)
Uncontrolled asthma[b]	67 (66)
Pulmonary function	
FEV_1, % predicted	74.5 (62.5-87.0)
FEV_1/FVC	0.70 (0.63-0.78)
Clinical control	
ACQ-7, score	1.90 (1.00-2.57)
Quality of Life (AQLQ)	
Activity limitations	3.84 (2.73-4.75)
Symptoms	4.42 (3.16-5.60)
Emotional Function	4.00 (2.40-5.40)
Environmental exposure	3.75 (2.25-5.00)
AQLQ, total score	4.04 (2.94-5.25)
CPET	
Peak VO_2, $mL*min^{-1}$	1,608 (1,324-1,886)
$mL*kg^{-1}*min^{-1}$	21.6 (16.8-26.6)
Peak VO_2/predicted VO_2max, %[c]	83.9 (71.1-92.8)
VO_2AT, $mL*min^{-1}$	1,010 (806.8-1,127)
$mL*kg^{-1}*min^{-1}$	13.5 (10.3-15.8)
Peak RER	1.16 (1.07-1.22)
Ventilatory reserve, %	25.1 (13.8-47.0)
Cardiac reserve, %	14.37 (5.94-22.7)

ACQ-7: 7-item Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; CPET: cardiopulmonary exercise test; VO_2AT: anaerobic threshold oxygen consumption; and peak RER: respiratory exchange ratio at peak effort. [a]Values are expressed as n (%) or median (IQR). [b]Uncontrolled asthma: ACQ-7 score ≥ 1.5.[18] [c]Scott et al.[34]

worse responder group. In contrast, pulmonary function (FEV_1 and FEV_1/FVC ratio) and ventilatory reserve were similar between the groups. After the training program, the better responder group showed twice the improvement in Δpeak VO_2 when compared with the worse responder group. Only the better responder group showed a clinically significant improvement on clinical asthma control (a decrease ≥ 0.5 in the ACQ-7 score), which was associated with aerobic power improvement (Figure 1).

Both groups had a clinically significant improvement in health-related quality of life (an increase ≥ 0.5 in AQLQ score) after the intervention (Table 2). Cardiac and respiratory reserves, VO_2AT, and peak VO_2 after the CPET were similar between the groups.

DISCUSSION

Our results showed the characteristics of individuals with moderate to severe asthma who significantly responded to aerobic training. Females and older individuals with a higher BMI, as well as with worse aerobic capacity, clinical control, and quality of life, had a good response to aerobic training. Although these results seem intuitive, this is the first study to investigate such clinical characteristics. In addition, it was observed that both groups showed clinically significant improvement in health aspects related to quality of life.

Several systematic reviews have investigated the benefits of physical exercise in improving exercise capacity, quality of life, and symptoms in individuals with asthma.[27-29] However, limited information regarding which individuals with asthma benefit more from aerobic training is available. In this study, there was a predominance of females in the better responder group, and two explanations can support this finding. First, there is a higher prevalence of adult females with moderate to severe asthma.[30] Second, middle-aged females tend to be more sedentary, to be overweight/obese, and to present worse physical conditioning even when they do not have asthma.[31,32] This may also explain the differences in age between the groups. However, we do not believe that our results establish a priority for physical training in female individuals with asthma. Instead, the priority should be on individuals having low physical conditioning, obesity, and clinically uncontrolled disease.

Table 2. Comparison of baseline characteristics and effect of aerobic training between clusters.

Characteristic	Group		95% CI of the difference between groups
	Better responder (n = 67)	Worse responder (n = 34)	
Anthropometric			
Female	67 (100)	19 (56)	0.29-0.59
Age, years	44.7 (38.3-51.0)	39.6 (29.0-50.0)	−9.29 to −0.96
Pre BMI, $kg*m^{-2}$	32.9 (29.7-36.2)	25.3 (21.7-28.4)	−9.62 to −5.59
Pulmonary function			
Pre FEV_1, % predicted	73.6 (60.8-87.8)	76.3 (63.0-86.0)	−10.2 to 4.94
Pre FEV_1/FVC	0.69 (0.61-0.78)	0.72 (0.63-0.81)	−0.08 to 0.03
Clinical control			
ACQ-7, pre score	2.14 (1.46-2.57)	1.43 (0.57-2.14)	−1.10 to −0.32
ΔACQ-7, score	−0.59 (−0.96 to −0.04)	−0.18 (−0.57 to 0.14)	0.09-0.73
Clinical improvement	39 (58)	9 (26)	0.11-0.53
Quality of life			
Pre AQLQ, total score	3.79 (2.73-4.84)	4.52 (3.56-5.84)	0.18-1.27
ΔAQLQ, total score	0.73 (0.01-1.50)	0.68 (0.09-1.31)	−0.51 to 0.41
Clinical improvement	34 (51)	20 (59)	−0.29 to 0.13
CPET			
Pre peak VO_2, $mL*kg^{-1}*min^{-1}$	18.5 (16.0-21.0)	27.7 (26.5-30.2)	7.80-10.68
Pre peak VO_2, $mL*min^{-1}$	1,466 (1,253-1,623)	1,888 (1,717-2,113)	291.5-551.3
Δpeak VO_2, $mL*kg^{-1}*min^{-1}$	2.38 (0.90-3.98)	1.78 (0.00-3.90)	−1.73 to 0.53
Δpeak VO_2/pre peak VO_2, %	13.6 (4.57-22.5)	7.14 (0.00-13.8)	−12.1 to −0.92
Pre VO_2AT, $mL*kg^{-1}*min^{-1}$	11.6 (9.75-12.7)	17.2 (14.9-20.0)	4.27-6.86
ΔVO_2AT, $mL*kg^{-1}*min^{-1}$	1.43 (0.00-3.15)	1.27(−1.40 to 3.00)	−1.58 to 1.27
Pre ventilatory reserve, %	27.1 (14.8-47.5)	21.1 (4.06-39.4)	−0.19 to 0.07
Δventilatory reserve, %	−9.84 (−19.1 to 0.00)	-9.83 (-14.3-0.00)	−0.07 to 0.07
Pre cardiac reserve, %	17.4 (11.0-23.7)	8.37 (−1.55 to 16.3)	−0.14 to −0.04
Δcardiac reserve, %	−2.59 (−9.49 to 3.57)	−2.14 (−5.37 to 1.10)	−0.03 to 0.04

Pre: pre-intervention; ACQ-7: 7-item Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; CPET: cardiopulmonary exercise test; and VO_2AT: anaerobic threshold oxygen consumption. [a]Values are expressed as n (%) or median (IQR).

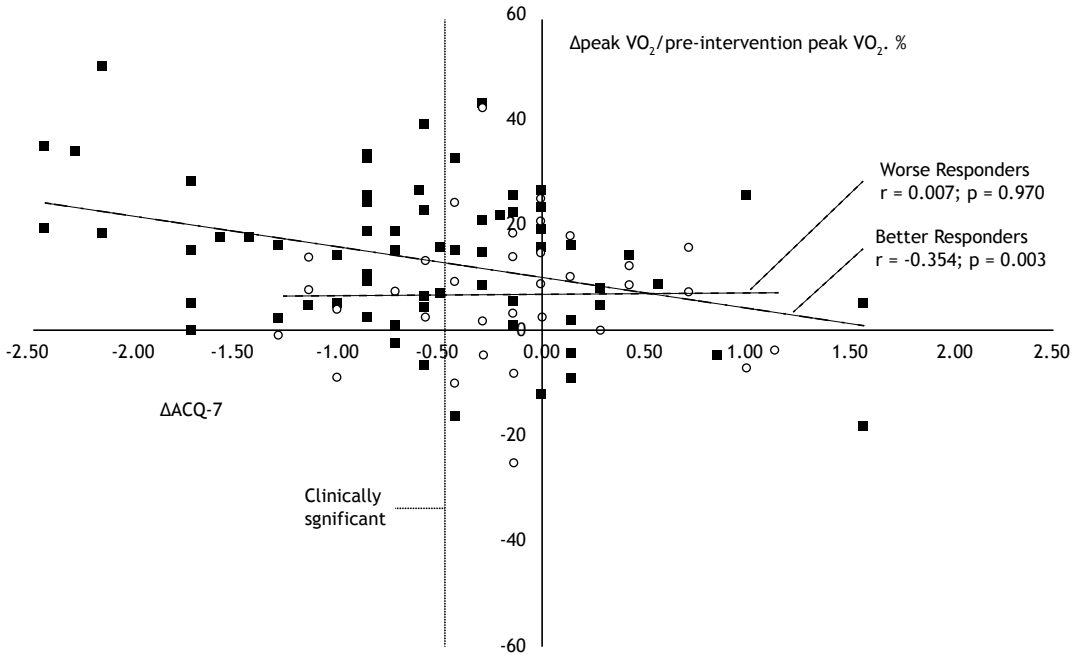

Figure 1. Linear correlations* between clinical control variation[a] (7-item Asthma Control Questionnaire [ΔACQ-7] score) and exercise capacity variation,[a] (Δpeak VO_2/pre-intervention peak VO_2, in %) in a sample of 101 individuals with moderate to severe asthma who underwent an exercise training program (intervention) and categorized as better or worse responders to the intervention. The dotted line shows the minimum 0.5-point reduction in the ACQ-7 score as a clinically significant improvement. The dashed lines show a linear association in the better responder group (black) and poor responder group (grey). [a]Post-intervention minus pre-intervention. *Pearson's correlation coefficient.

Previous studies reported that nonobese individuals with controlled asthma[3,5] and obese individuals with uncontrolled asthma[6] improve their aerobic conditioning and quality of life after a physical training program. These findings support our results, because we found no differences regarding quality of life between the groups after a physical training program. However, the better responder group showed twice the improvement in aerobic capacity (Δpeak VO_2) than did the worse responder group. This improvement cannot be associated with differences among the training programs, because exercise intensity was similarly established based on a CPET in all studies, regardless of the training modality (continuous or interval training).[13] Likewise, we believe that using a treadmill for half of the sample instead of a cycle ergometer did not interfere with the results since all of the participants improved their aerobic capacity. Our results indicated that individuals with moderate to severe asthma with low AT and aerobic power had a greater increase in their physical conditioning after aerobic training.

Individuals with uncontrolled asthma before training mostly benefit from controlling asthma symptoms and present a clinically significant change (> 0.5 point in ACQ-7).[5,6,17] Obesity and poor clinical control of asthma have been associated with worse physical conditioning[30]; therefore, it is more common to identify individuals who have more than one factor associated with exercise response. We consider that aerobic training prescription for individuals with asthma should be recommended for those who have poor asthma control, despite having optimized pharmacological treatment (inclusion criteria of all patients in the present study). In addition, our results support that the benefits of exercise training should be analyzed differently in individuals with and without asthma control in future studies. This approach may improve our understanding of the effects of physical training in this population.

Three theories have been suggested to explain how the improvement in aerobic capacity in individuals with asthma reduces symptoms and improves asthma control: improvement in ventilatory capacity,[27] improvement in pulmonary function,[28] and reduction in pulmonary and systemic inflammation.[3,6] Our results showed that individuals with asthma had reduced ventilatory reserve at baseline (25% on average) in comparison with the general population (approximately 50%) and close to the cutoff value to establish a ventilatory limitation (< 20%).[23] Furthermore, we observed that individuals with asthma had reduced aerobic capacity and cardiac reserve, strongly suggesting that they were physically unfit before exercise training. Thus, our results reinforce that exercise training improves aerobic fitness in individuals with asthma, demanding an increase in ventilatory capacity.

In this study, only the better responder group showed a linear association between improvements in physical conditioning and clinical control. A possible explanation for this association is that improving aerobic fitness improves aerobic capacity, reduces ventilation in

activities of daily living, and reduces asthma symptoms. Previous randomized and controlled studies also suggested that training improves immune response,[3,6] but a systematic review suggested that there was no effect in the immune response of asthma patients.[28] However, that review included patients with different levels of asthma severity and clinical control that might have interfered with data analysis. Furthermore, not all individuals included in our study were evaluated for pulmonary and systemic inflammation, making this type of analysis impossible.

Before training, individuals in both groups showed lower AQLQ scores in our study than in previous studies.[5,7,33,34] Better responders to aerobic training had AQLQ scores even lower than did worse responders. After training, both groups showed clinically significant improvement, and previous studies support our findings.[5,7,33,34] There was no association between improved aerobic power and quality of life. One hypothesis for this finding would be the multifactorial aspect of quality of life. The AQLQ has several domains (activity limitations, symptoms, emotional function, and environmental exposure) that can be modified by exercise training, regardless of the physical conditioning obtained by each individual.[20]

This study has limitations. First, this was a post hoc analysis of pooled data from previous randomized controlled trials, not a prospective study. However, this limitation is mitigated by the number of patients and variables evaluated, and all individuals underwent physical training in the same research center using similar exercise intensity. Furthermore, we believe no other center has such a large number of individuals undergoing physical training, based on CPET results, being assessed regarding asthma clinical control and quality of life. Second, most individuals in this study were females; however, this was expected due to the higher prevalence of asthma in female individuals, and the fact that females seek medical care more regularly than do males.[30] Furthermore, females with asthma have a high prevalence of obesity and uncontrolled asthma. However, our female patients had a wide distribution of obese and nonobese individuals with controlled and uncontrolled asthma. Third, the effect on inflammatory mediators was not included, because only two studies assessed this outcome,[6,13] making it impossible to include it in the statistical analyses. Additionally, muscle strength could be associated with a patient's response to the physical training program, and the improvement in peripheral muscle response could also add important information; however, this variable was not evaluated by any of the studies herein included. Finally, exercise limitation was categorized as cardiac, ventilatory, and peripheral muscle systems, which can be considered a simplified way to understand individual limitations of the patients. However, this analysis has been considered in individuals with asthma[35] and in other populations.[23] In addition, we did not use these physiological responses to determine the main reason by which patients would necessarily interrupt the test. Instead, this analysis was secondarily used to understand the major limitation in each cluster.

The results of this study show that obese individuals with poor exercise capacity, clinical control, and quality of life obtained greater benefits from an aerobic training program. Therefore, individuals with these characteristics should be primarily referred to aerobic training programs in order to reduce asthma symptoms. Better and worse responders to aerobic training had similar improvements in their quality of life.

AUTHOR CONTRIBUTIONS

TCE, ACL, PDF, and CRFC: study conception and design. TCE and ACL: data analysis and drafting of the manuscript. PDF, RAS, FARM, and AFP: data collection and critical revision of the manuscript. RMCP and CRFC: critical and final revision of the manuscript. All authors approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

The authors declare they have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The database is available in the repository: https://zenodo.org/record/6326209#.YyospqTMK5c

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ORIGINAL ARTICLE

Diagnostic performance of cryobiopsy guided by radial-probe EBUS with a guide sheath for peripheral pulmonary lesions

Hui Chen[1], Xuechan Yu[1], Yiming Yu[1], Lin Zheng[2], Qidong Zhuang[1], Zhongbo Chen[1], Zaichun Deng[1]

1. Department of Pulmonary and Critical Care Medicine, The Affiliated Hospital of Medical School, Ningbo University, Jiangbei District, Ningbo, Zhejiang Province, China.
2. Department of Microbiology, The Affiliated Hospital of Medical School, Ningbo University, Jiangbei District, Ningbo, Zhejiang Province, China.

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Study carried out in the Department of Pulmonary and Critical Care Medicine, The Affiliated Hospital of Medical School, Ningbo University, Jiangbei District, Ningbo, Zhejiang Province, China.

ABSTRACT

Objective: Transbronchial lung cryobiopsy (TBCB) has developed rapidly and has become one of the research hotspots of lung biopsy technology. The present study sought to evaluate the efficacy of TBCB guided by radial-probe EBUS (RP-EBUS) and a guide sheath (GS) without fluoroscopy for peripheral pulmonary lesions. **Methods:** In this retrospective study, McNemar's test was used in order to compare TBCB and transbronchial forceps biopsy (TBFB) in terms of diagnostic performance. A multivariate logistic regression model was designed to explore the association between predictive variables and the diagnostic yield of TBCB. **Results:** A total of 168 patients underwent GS-guided RP-EBUS. Of those, 157 had lesions that were visible and 11 had lesions that were not. Of those 157 patients, 24 were excluded because of missing data or an unclear final diagnosis. Therefore, 133 patients underwent RP-EBUS-GS–guided TBFB and TBCB. The pooled diagnostic yield of RP-EBUS-GS–guided TBCB without fluoroscopy was 71.5% (103/144). In 133 patients, the diagnostic yield of TBCB was significantly higher than that of TBFB (77.4% vs. 59.4%; $p < 0.05$). Multivariate analysis indicated that lesion size and site were independently associated with the diagnostic yield of TBCB (OR = 2.8, $p = 0.03$ and OR = 4.1, $p = 0.01$, respectively), although cryoprobe size was not. There was no significant difference between the 1.1-mm cryoprobe and the 1.9-mm cryoprobe in terms of diagnostic performance (78.4% vs. 76.8%; $p > 0.05$). **Conclusions:** GS-guided RP-EBUS is regarded as a practical option for guiding cryobiopsy, although it may not be able to replace fluoroscopy. Peripheral pulmonary lesions not located in the upper lobes or larger than 30 mm are significantly associated with a higher diagnostic yield of cryobiopsy.

Keywords: Bronchoscopy; Lung neoplasms; Biopsy.

INTRODUCTION

In recent years, because of the widespread use of chest CT in physical examination, more cases of peripheral pulmonary lesions (PPLs) have been found.[1] PPLs can often go undiagnosed by liquid biopsy, sputum cultures, and sputum smears, a lung biopsy therefore being necessary, especially in cases of suspected malignancy. Since the 1990s, interventional pulmonology has developed rapidly.[2] Most PPLs can be diagnosed by nonsurgical biopsy, including transbronchial forceps biopsy (TBFB), CT-guided transthoracic needle biopsy, and transbronchial lung cryobiopsy (TBCB).[3,4]

The cryoprobe is a novel biopsy tool that allows tissue to be obtained in a 360° manner laterally from the tip of the probe. In recent years, it has been increasingly used in lung biopsy. One meta-analysis demonstrated that the pooled diagnostic yield of TBCB was as high as 77% (95% CI, 71-84%).[5] Previous studies have focused on the 1.9-mm cryoprobe, with patients undergoing fluoroscopy-guided TBCB or TBCB without the assistance of a guide sheath (GS).[5-7] In addition, some single-center studies have analyzed the factors that may affect the efficacy of cryobiopsy. However, controversy remains as to whether the size of the cryoprobe is an independent factor.[3,4,8] In particular, there is a lack of studies comparing the new 1.1-mm cryoprobe and the traditional 1.9-mm cryoprobe in terms of diagnostic efficiency. Therefore, the objective of our study was to evaluate the performance of TBCB guided by radial-probe EBUS (RP-EBUS) with a GS (RP-EBUS-GS–guided TBCB) without fluoroscopy for the diagnosis of PPLs.

METHODS

This was a retrospective observational study conducted between May of 2017 and March of 2022 in the Department of Pulmonary and Critical Care Medicine of the Affiliated Hospital of Medical School, Ningbo University, located in Ningbo, China. A total of 225 patients who had

Correspondence to:
Zhongbo Chen and Zaichun Deng. Department of Pulmonary and Critical Care Medicine, The Affiliated Hospital of Medical School, Ningbo University, 247, Renmin Road, Jiangbei District, Ningbo, Zhejiang Province, 315020, China.
Tel.: 86 13777125910 and 86 13777121526. E-mail: leonczb@163.com and dengzaichun@nbu.edu.cn
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unexplained PPLs and who had originally planned to undergo cryobiopsy were enrolled in the study. Patients presenting with endobronchial lesions were excluded, as were those for whom lesion-related data were missing and those in whom diagnosis was uncertain. Therefore, 133 patients undergoing RP-EBUS-GS–guided TBFB and TBCB were analyzed in this study. Figure 1 shows a flow chart of the patient selection process. All procedures were performed in accordance with the 2019 Chinese expert consensus on the standardized procedure and technique of transbronchial cryobiopsy.[9] This study was approved by the Research Ethics Committee of the Affiliated Hospital of Ningbo University (Protocol no. XJS20210612), and written informed consent was obtained from all participants. Clinical information regarding patient characteristics was based on patient medical records.

In this study, a standard bronchoscope (BF-1TQ290/BF-1T260; Olympus Corporation, Tokyo, Japan; distal end outer diameter, 5.9 mm; working channel, 3.0/2.8 mm), a radial probe (UM-S20-20R; Olympus Corporation; outer diameter, 1.7 mm), a GS (K-203/201; Olympus Corporation; outer diameter, 2.55/1.95 mm), and a 1.9-mm cryoprobe (AS Medizintechnik GmbH, Tuttlingen, Germany) were used in combination. A thin bronchoscope (BF-P260F/BF-F260/BF-260; Olympus Corporation; distal end outer diameter, 4.0/5.5/4.9 mm; working channel, 2.0 mm) was used in conjunction with a radial probe (UM-S20-17S; Olympus Corporation; outer diameter, 1.4 mm), a GS (K-201; Olympus Corporation; outer diameter, 1.95 mm), and a 1.1-mm cryoprobe (AS Medizintechnik GmbH). Because the K-203 GS was 2 cm longer than the 1.9-mm cryoprobe, we trimmed the distal end of the GS so that the tip of the probe was at least 1 cm out of the GS (Figure 2). The K-201 GS required no modification to be used with the 1.1-mm cryoprobe.

All procedures were performed by expert bronchoscopists. For each lesion, cytological samples were obtained by brushing, whereas histological samples were obtained by TBFB and TBCB. Rapid on-site cytopathological evaluation was performed as routinely described. The bronchoscope was advanced to the target bronchus by following the route designed prior to performing the procedure. The radial probe in the GS was inserted into the working channel of the bronchoscope and advanced without fluoroscopic guidance. After detection of a low-echo area, the position of the ultrasound probe was adjusted until the maximum image area was reached. The probe was then removed, whereas the GS was kept in place for subsequent sampling. If PPLs were invisible on RP-EBUS, TBCB and TBFB were not performed, and only local washing was performed.

First, small biopsy forceps were inserted into the GS for sample collection. To ensure tissue volume, five samples were collected from each lesion.[10] For TBCB, after PPLs were located by means of RP-EBUS, the cryoprobe was inserted into the GS and activated

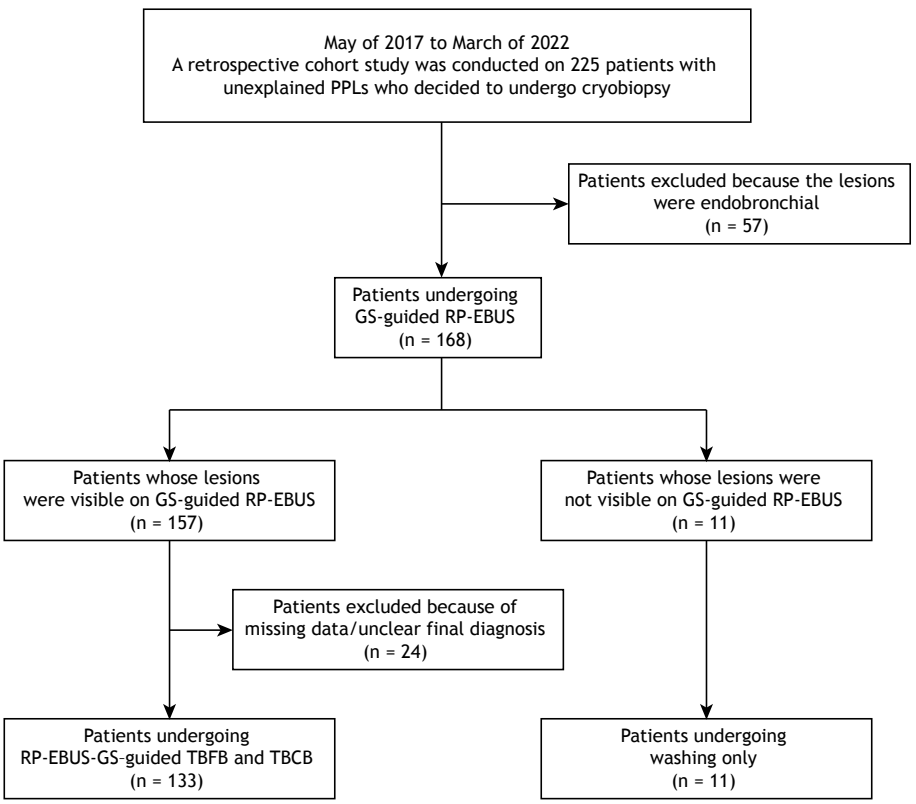

Figure 1. Flow chart of the study. PPLs: peripheral pulmonary lesions; GS-guided RP-EBUS: radial-probe EBUS performed with a guide sheath; TBFB: transbronchial forceps biopsy; and TBCB: transbronchial lung cryobiopsy.

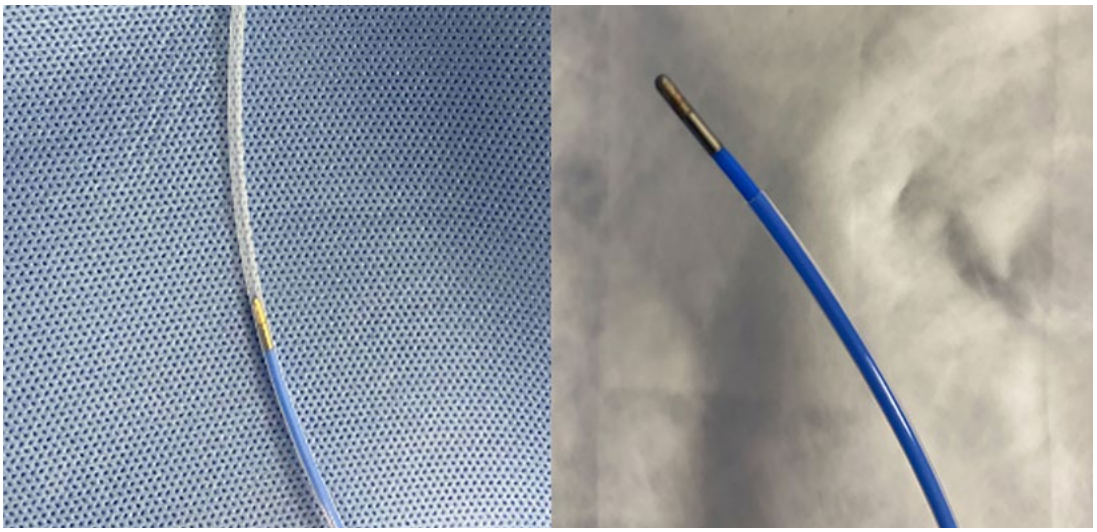

Figure 2. Modified guide sheath.

with carbon dioxide to a pressure of 50 bar for 4 s.[9] Then, tissues at the tip of the cryoprobe were removed together with the bronchoscope. Another bronchoscope was immediately inserted in order to assess the degree of airway bleeding upon removal of the first bronchoscope. If no effective samples were obtained, the freezing time was increased by 2 s for rebiopsy. To reduce the risk of bleeding and pneumothorax, TBCB was performed no more than three times per site. A chest X-ray was performed to look for evidence of pneumothorax and other complications after each procedure.

Bronchoscopy results were categorized as diagnostic or nondiagnostic. Specimens showing clear malignant features were considered true positives. For a benign diagnosis, if the pathological or microbiological diagnosis of the sample was consistent with the final clinical diagnosis, the procedure was considered diagnostic. Any lesions without pathological findings or suspicious findings were considered negative cases. All nondiagnostic biopsy samples underwent another diagnostic test (repeat bronchoscopy, CT-guided biopsy, surgery, or a follow-up CT scan six months later) in order to confirm the clinical diagnosis. In the analysis of pooled diagnostic yield, the lesions that were not visible were categorized as undiagnosed by histological biopsy.

Descriptive statistics are presented as frequency, proportion, and mean ± standard deviation. McNemar's test was used in order to analyze the diagnostic yield of TBCB and TBFB samples. Univariate and multivariate logistic regression models were used in order to analyze factors affecting the diagnostic yield of TBCB. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed with the IBM SPSS Statistics software package, version 26 (IBM Corporation, Armonk, NY, USA).

RESULTS

A retrospective cohort study was conducted on 225 patients who had unexplained PPLs and who had originally planned to undergo cryobiopsy. Lesions were excluded if they were endobronchial (in 57 patients). Thus, 168 patients underwent GS-guided RP-EBUS. Of those, 157 had lesions that were visible on RP-EBUS and 11 had lesions that were not visible on RP-EBUS. Of the 157 patients whose lesions were visible on RP-EBUS, 24 were excluded because of missing data or an unclear final diagnosis. Therefore, 133 patients (86 males and 47 females) undergoing RP-EBUS-GS–guided TBFB and TBCB were enrolled in the univariate and multivariate logistic regression analyses. The mean age was 59.1 ± 13.2 years. Approximately half of the patients had nodules, with the other half having lesions ≥ 30 mm in size. Most of the lesions were not located in the upper lobes (in 102 patients; 76.7%), and only 31 patients (23.3%) had lesions that were located in the upper lobes. Of the 133 patients enrolled in the analyses, 99 (74.4%) were enrolled as cases of concentric probe orientation (toward the center), with only 34 (25.6%) being enrolled as cases of eccentric and adjacent orientation (toward the side). A 1.9-mm cryoprobe was used in 82 (61.7%) of the study participants, and a 1.1-mm cryoprobe was used in 51 (38.3%). The characteristics of the patients and target lesions are described in Table 1.

In this study, the pooled diagnostic yield of RP-EBUS-GS–guided TBCB without fluoroscopy was 71.5% (103/144). For the 133 patients who underwent RP-EBUS-GS–guided TBFB and TBCB, the diagnostic yield of TBCB was as high as 77.4%, which was significantly higher than that of TBFB (59.4%; $p < 0.05$). In order to show the performance of TBCB and TBFB more clearly, the lesions were divided into ten groups on the basis of five different factors (lesion size, lesion site, final diagnosis, probe orientation, and cryoprobe size), which are shown in Table 2. The data show that the diagnostic yield of TBCB was higher than that of TBFB in all groups. However, there was no statistically significant difference when the lesions were ≥ 30 mm in size and malignant.

Table 3 shows five factors that may affect the diagnostic yield of TBCB. Univariate and multivariate analyses indicated that lesion size and lesion site were independently associated with the diagnostic yield of TBCB (OR = 2.8, p = 0.03 and OR = 4.1, p = 0.01, respectively). However, there was no significant difference between the 1.1-mm cryoprobe and the 1.9-mm cryoprobe in terms of diagnostic performance (78.4% vs. 76.8%; p > 0.05).

In our study, most of the cases of bleeding were categorized as grade 0 or 1; that is, bleeding that can stop on its own or that requires suction to clear. Only a few of the patients who underwent TBCB with a 1.9-mm cryoprobe had grade 2 bleeding requiring wedging, cold saline solution lavage, and regional instillation of epinephrine (5 mL; 1:10,000),[9] without the need for further intervention (bronchial blocker or surgical intervention). Pneumothorax occurred in only 4 patients and was managed by closed thoracic drainage. Of the 4 cases of pneumothorax, 3 were caused by the 1.9-mm cryoprobe and 1 was caused by the 1.1-mm cryoprobe.

DISCUSSION

Various techniques such as robot technology, electromagnetic navigation, virtual bronchoscopy, and RP-EBUS have been used in order to diagnose PPLs, and these techniques have improved diagnostic efficiency.[11-13] Nevertheless, the application of these technologies plays a role in guiding the bronchoscope to locate the lesion. In some cases, even if the lesion can be located, it is still difficult to obtain effective pathological samples because the volume and quality of the samples are determined by biopsy methods, such as TBFB, TBCB, and needle aspiration.[14] Therefore, there is a need to improve biopsy techniques in order to address the diagnostic dilemma of PPLs.

Table 1. Characteristics of the patients and target lesions.[a]

Characteristic	Result
Sample, N	133
Patient characteristics	
Age, years[b]	59.1 ± 13.2
Sex	
Male	86 (64.7)
Female	47 (35.3)
Target lesion characteristics	
Lesion size, mm	
<30	60 (45.1)
≥30	73 (54.9)
Lesion site	
Upper lobe	31 (23.3)
Other	102 (76.7)
Probe orientation	
Toward the side	34 (25.6)
Toward the center	99 (74.4)
Cryoprobe size	
1.9 mm	82 (61.7)
1.1 mm	51 (38.3)
Final diagnosis	
Benign lesion	93 (69.9)
Malignant lesion	40 (30.1)

[a]Data expressed as n (%), except where otherwise indicated. [b]Data expressed as mean ± SD.

Cryobiopsy is a novel biopsy tool. For eccentrically and adjacently oriented lesions, our results show that the diagnostic yield of TBCB is significantly higher than that of TBFB, a finding that is consistent with the literature.[15] In the present study, the diagnostic yield of TBCB was higher than that of TBFB in all groups. It is well recognized that cryobiopsy samples are preferred for molecular testing and immunohistochemical analysis, being superior in terms of tissue volume when compared with forceps biopsy samples.[5,16] In one patient in the present study, the sample obtained by TBFB was limited, without any evidence of malignancy. However, the sample obtained by TBCB showed suspicious tumor cell clumps. Therefore, TBCB samples were used for further immunohistochemical analysis to confirm the diagnosis. Various staining methods and biomarker analyses led us to conclude that the patient had poorly differentiated lung squamous cell carcinoma (Figure 3). Therefore, it is evident that the higher quality of cryobiopsy samples allows morphological diagnosis and biomarker analysis, especially for malignancies with minimal histological heterogeneity. Cryobiopsy avoids repeat procedures and contributes to precision medicine against lung cancer.

The GS has been reported to play an important role in ensuring accurate and consistent cryobiopsy.[14,17,18] However, in most centers, cryobiopsy is performed without the assistance of a GS. In this study, a 1.9-mm cryoprobe was housed within a K-203 GS for sampling. Because the GS was 2 cm longer than the 1.9-mm cryoprobe (which was 1,050 mm long), the GS had to be modified in order to be used for cryobiopsy in our study. Herath et al. trimmed the GS by 3 cm from the distal end to enable contact with the lesion.[17] The 1.1-mm cryoprobe used in the present study was compatible with the K-201 GS (outer diameter, 1.95 mm). In order to make the procedure smoother, all instruments should be selected and measured preoperatively, including the radial probe, the cryoprobe, and the GS.

Some studies have shown that the diagnostic performance of TBFB for PPLs is just as good with fluoroscopy as it is without it.[19,20] Therefore, it is reasonable to assume that it is possible to forgo fluoroscopy during cryobiopsy. In this study, we demonstrated the utility of RP-EBUS-GS–guided TBCB without fluoroscopy in evaluating PPLs. The pooled yield of 71.5% is at least good, even if it is inferior to that of TBCB with fluoroscopy, which is of 97%.[4] In addition, there are reports that cryobiopsy without fluoroscopy can increase the risk of pneumothorax.[4,21] In this study, the incidence of pneumothorax was only 3%, which might be due to the use of a GS in the whole process of cryobiopsy. Therefore, although GS-guided RP-EBUS may not replace fluoroscopy in

Table 2. Comparison of diagnostic yield between transbronchial forceps biopsy and transbronchial lung cryobiopsy.[a]

Variable	Group		p*
	TBFB	TBCB	
All	59.4 (79/133)	77.4 (103/133)	<0.01
Lesion size, mm			
< 30	43.3 (26/60)	68.3 (41/60)	<0.01
≥ 30	72.6 (53/73)	84.9 (62/73)	0.09
Lesion site			
Upper lobe	51.6 (16/31)	61.3 (19/31)	0.51
Other	61.8 (63/102)	82.4 (84/102)	<0.01
Probe orientation			
Toward the side	50.0 (17/34)	70.6 (24/34)	0.04
Toward the center	62.6 (62/99)	79.8 (79/99)	<0.01
Final diagnosis			
Benign lesion	63.4 (59/93)	80.6 (75/93)	<0.01
Malignant lesion	50.0 (20/40)	70.0 (28/40)	0.057
Cryoprobe size			
1.9 mm	61 (50/82)	76.8 (63/82)	0.01
1.1 mm	56.8 (29/51)	78.4 (40/51)	0.02

TBFB: transbronchial forceps biopsy; and TBCB: transbronchial lung cryobiopsy. [a]Data presented as % (n/N). *McNemar's test.

Table 3. Multivariate logistic regression model for the diagnostic yield of transbronchial lung cryobiopsy.[a]

Category	Group	Diagnostic yield	Univariate analysis		Multivariate analysis		
			X^2	p	B	OR (95% CI)	p
Lesion size, mm	< 30	68.3 (41/60)	5.2	0.04	0	1	0.03
	≥ 30	84.9 (62/73)			1.1	2.8 (1.1-6.9)	
Lesion site	Upper lobe	61.3 (19/31)	6	0.02	0	1	0.01
	Other	82.4 (84/102)			1.4	4.1 (1.5-11.3)	
Probe orientation	Toward the side	70.6 (24/34)	1.2	0.34	0	1	0.56
	Toward the center	79.8 (79/99)			0.3	1.3 (0.5-3.6)	
Final diagnosis	Benign lesion	80.6 (75/93)	1.8	0.26	0	1	0.12
	Malignant lesion	70.0 (28/40)			−0.7	0.5 (0.2-1.2)	
Cryoprobe size	1.9 mm	76.8 (63/82)	0.05	0.84	0	1	0.22
	1.1 mm	78.4 (40/51)			0.6	1.9 (0.7-5.0)	

[a]Data presented as % (n/N).

determining the precise site for cryobiopsy, it is also safe and effective.

Previous single-center studies have reported several factors that can affect the diagnostic yield of cryobiopsy, such as probe orientation, lesion site, and lesion size.[22,23] On the basis of previous reports and clinical experience, we discussed five factors that can affect the yield of cryobiopsy. Univariate and multivariate analysis indicated that PPLs that were not located in the upper lobes were significantly associated with a higher diagnostic yield of cryobiopsy (OR = 4.1; 95% CI, 1.5-11.3; p = 0.01). PPLs in the upper lobes are notoriously difficult to be accessed with bronchoscopes.[22,24] We also encountered such difficulties. In addition, the size of the lesions was a significant factor affecting the diagnostic yield of cryobiopsy, a finding that is consistent with those of a report providing the largest data series of TBCB.[4]

In this study, the diagnostic yield of TBCB performed with a 1.1-mm cryoprobe was not significantly higher than that of TBCB performed with a 1.9-mm cryoprobe (78.4% vs. 76.8%; p = 0.84), a finding that is consistent with those of Lonny et al.[8] Some studies have reported that the 1.1-mm cryoprobe is a dramatic improvement over the 1.9-mm cryoprobe in diagnosing specific lesions (such as ground-glass nodules, lesions located in the upper lobe, and lesions near the pleura),[25-27] the diagnostic yield of the 1.1-mm cryoprobe therefore being higher than that of larger probes. Previous studies have suggested that when an ultrathin cryoprobe and a GS are used for cryobiopsy, it is no longer necessary to remove *en bloc* the bronchoscope from the patient in tissue sampling, and this is beneficial to repeat biopsy and early monitoring of bleeding.[5,28] However, the fact that the GS used in conjunction with the ultrathin cryoprobe is also thinner means that the samples might be too big to be taken out.[26] It is necessary to determine the appropriate activation time because the area of the samples increases with increasing activation time.[8] However, in the present study, the number of enrolled

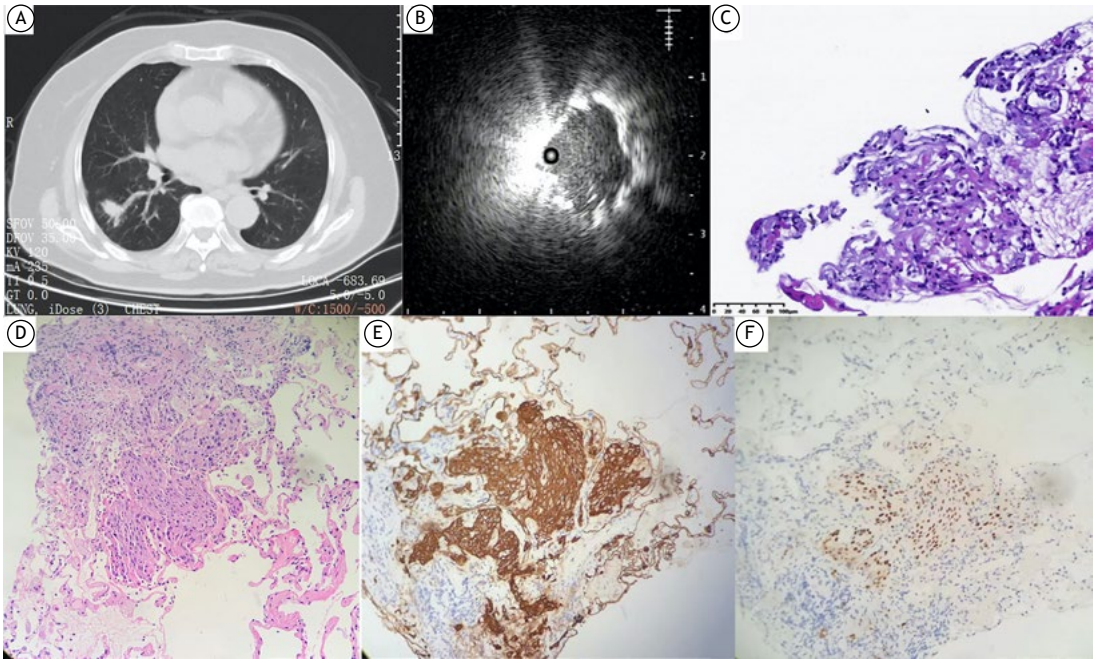

Figure 3. A patient with poorly differentiated lung squamous cell carcinoma underwent transbronchial forceps biopsy (TBFB) and transbronchial lung cryobiopsy (TBCB) guided by radial-probe EBUS and a guide sheath. In A, solitary peripheral pulmonary nodule (of 2.0 cm in size) in the dorsal segment of the right lower lobe. In B, radial-probe EBUS showing an eccentric lesion, with no surrounding vessels. In C, TBFB showing no features of suspected malignancy (H&E; magnification, ×200). In D, TBCB showing suspicious tumor cell clumps (H&E; magnification, ×200). In E, immunohistochemistry showing strong and diffuse positivity for cytokeratins. In F, immunohistochemistry showing strong and diffuse positivity for p40.

patients undergoing TBCB with a 1.1-mm cryoprobe was relatively limited, being insufficient for a more detailed comparison between the 1.1-mm cryoprobe and the 1.9-mm cryoprobe.

Our study has some limitations. First, because of the retrospective design, the study may have a bias on patient and lesion characteristics. Second, the number of enrolled patients undergoing TBCB with a 1.1-mm cryoprobe was small, further studies therefore being needed.

Cryobiopsy is a safe and effective method for diagnosing PPLs. Moreover, GS-guided RP-EBUS is considered a practical option for guiding the procedure, although it may not be able to replace fluoroscopy. PPLs not located in the upper lobes or larger than 30 mm are significantly associated with a higher diagnostic yield of cryobiopsy, and the 1.1-mm and 1.9-mm cryoprobes have similar diagnostic performance.

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AUTHOR CONTRIBUTIONS

ZD and ZC equally contributed to the study. ZC: study conception and design; administrative support; data collection, analysis, and interpretation; drafting of the manuscript; and final approval of the version to be published. HC: study conception and design; data collection, analysis, and interpretation; drafting of the manuscript; and final approval of the version to be published. ZD: administrative support; drafting of the manuscript; and final approval of the version to be published. YY: provision of study materials/patients; data collection, analysis, and interpretation; drafting of the manuscript; and final approval of the version to be published. LZ: provision of study materials/patients; data collection; drafting of the manuscript; and final approval of the version to be published. QZ: data collection, analysis, and interpretation; drafting of the manuscript; and final approval of the version to be published. XY: data collection; drafting of the manuscript; and final approval of the version to be published.

CONFLICTS OF INTEREST

None declared.

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Effects of a home-based pulmonary rehabilitation program with and without telecoaching on health-related outcomes in COVID-19 survivors: a randomized controlled clinical study

Hülya Şahın[1], İlknur Naz[2], Gülistan Karadeniz[3], Onur Süneçlı[4], Gulru Polat[3], Ozlem Ediboğlu[3]

1. Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, Pulmonary Rehabilitation Unit, Izmir, Turkey.
2. Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Izmir Katip Celebi University, Izmir, Turkey.
3. Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Chest Diseases, Izmir, Turkey.
4. Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, Department of Physiotherapy and Rehabilitation, Izmir, Turkey.

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ABSTRACT

Objective: To compare the effects of a home-based pulmonary rehabilitation (PR) program with and without telecoaching on health-related outcomes in COVID-19 survivors. **Methods:** A total of 42 COVID-19 patients who completed medical treatment were randomly divided into two groups: the study (telecoaching) group (n = 21) and the control (no telecoaching) group (n = 21). Both groups participated in an 8-week home-based PR program including education, breathing exercises, strength training, and regular walking. The study group received phone calls from a physiotherapist once a week. Both groups of patients were assessed before and after the program by means of the following: pulmonary function tests; the modified Medical Research Council dyspnea scale; the six-minute walk test; extremity muscle strength measurement; the Saint George's Respiratory Questionnaire (to assess disease-related quality of life); the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36, to assess overall quality of life); and the Hospital Anxiety and Depression Scale. **Results:** In both groups, there were significant improvements in the following: FVC; the six-minute walk distance; right and left deltoid muscle strength; Saint George's Respiratory Questionnaire activity domain, impact domain, and total scores; and SF-36 social functioning, role-physical, role-emotional, and bodily pain domain scores ($p < 0.05$). Decreases in daily-life dyspnea, exertional dyspnea, and exertional fatigue were significant in the study group ($p < 0.05$), and the improvement in SF-36 social functioning domain scores was greater in the study group ($p < 0.05$). **Conclusions:** A home-based PR program with telecoaching increases social functioning and decreases daily-life dyspnea, exertional dyspnea, and exertional fatigue in COVID-19 survivors in comparison with a home-based PR program without telecoaching.

Keywords: COVID-19; Exercise; Telerehabilitation; Dyspnea; Fatigue.

(ClinicalTrials.gov identifier: NCT04791072 [https://www.clinicaltrials.gov/])

INTRODUCTION

COVID-19, a highly contagious respiratory disease, has spread rapidly worldwide, posing a devastating threat to health, economy, and lifestyle.[1,2] COVID-19 predominantly affects the respiratory system. Although most patients are asymptomatic, the disease can show clinical progress ranging from upper respiratory tract symptoms to life-threatening severe pneumonia.[3] Flu-like symptoms such as fever, dyspnea, fatigue, cough, expectoration, sore throat, and headache are common in infected individuals.[4] Patients with COVID-19, whether hospitalized or not, continue to have multiple symptoms, particularly dyspnea and fatigue, even approximately 3 months after the onset of symptoms. This indicates the presence of a "post-COVID-19 syndrome" and highlights the unmet health care needs of patients with mild or severe COVID-19.[5]

Long-term treatment of critically ill patients in the ICU or inpatient ward, bed rest, continuous quarantine, and social distancing lead patients to be inactive for extended periods,[6] resulting in a decrease in muscle mass and strength; changes in muscle fibers; remodeling of muscle tissue; fatigue; and inflammation.[7] The unpredictability of the disease state, the uncertainty of effective treatment methods, and being afflicted with a deadly disease cause stress. Anxiety, depression, and stress disorder are quite common and severe in patients hospitalized for COVID-19.[8]

In patients with COVID-19, pulmonary rehabilitation (PR) facilitates patient follow-up, strengthens health management, and helps patients recover and return to society more quickly and safely.[9] Telehealth practices are the most appropriate method because of the risk of transmission and because they allow social distancing

Correspondence to:
Hulya Sahin. Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital, Pulmonary Rehabilitation Unit, Yenişehir, Gaziler Cd No:331 D:28, 35170 Konak, Izmir, Turkey.
Tel.: 90 232 433- 3333, extension 2141. E-mail: drhdogan@yahoo.com
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during the COVID-19 pandemic.[10] Pulmonary telerehabilitation has been shown to be as beneficial as conventional PR in patients with chronic respiratory diseases such as COPD, interstitial lung disease, and bronchiectasis, with no safety issues.[11] Studies have described different methods of delivering PR, such as over the phone, through mobile phone applications, through videoconferencing, and through websites.[11] Although home-based programs and telerehabilitation applications are commonly used in the management of COVID-19, there is inadequate information on the best strategy for PR. The objective of the present study was to evaluate whether adding telecoaching to a home-based PR program would have any impact on the effectiveness of the program. To that end, we compared the effects of PR with and without telecoaching on dyspnea, exercise capacity, peripheral muscle strength, quality of life, and psychological symptoms in COVID-19 survivors.

METHODS

Study setting and participants

This was a randomized controlled study conducted between February of 2021 and July of 2021. The study was approved by the Research Ethics Committee of the Dr. Suat Seren Chest Diseases and Thoracic Surgery Training and Research Hospital (Protocol no. E-49109414-604.02) and registered at https://clinicaltrials.gov (NCT04791072). All participating patients gave written informed consent. The inclusion criteria were as follows: having been diagnosed with COVID-19; having stayed in the ICU or ward for more than 10 days with or without the need for invasive mechanical ventilation (IMV); having received noninvasive mechanical ventilation (NIMV); having received high-flow oxygen therapy; and having completed medical treatment. COVID-19 patients who received outpatient pharmacological treatment before hospitalization, those who experienced dyspnea for the first time ever because of the disease, and those in whom dyspnea continued despite treatment were also included.[12]

An effort was made to include post-acute COVID-19 patients (i.e., those with persistent symptoms at 4 weeks after the onset of symptoms).[13] Patients who were past the post-acute phase, those who had orthopedic problems, those who were receiving treatment for active cancer, and those who declined to participate were excluded from the study. In addition, patients with cardiac and thromboembolic complications were excluded from the study because of their ongoing medical treatment and the potentially harmful effects of exercise.[14]

The G*Power software, version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany), was used in order to determine the required sample size for the study. It was calculated that at least 21 participants were needed in each group to obtain a power of 80%, with an effect size of 0.80 and a type I error of 0.05, to identify intergroup differences.[15]

Procedure

The flow chart of the study is shown in Figure 1. The patients referred to our PR unit were divided into two groups (the study [telecoaching] group and the control [no telecoaching] group) by means of a randomization program.[16] Breathing exercises, as well as exercises focusing on lower and upper extremity strengthening, were prescribed to both groups by a physiotherapist as part of a home-based PR program. All patients were asked to keep an exercise diary to evaluate their compliance with the program. Although the control group was not contacted, the study group was contacted every Monday by a physiotherapist to collect information about their adherence to the program; a motivational speech was made, and the importance of the program was emphasized. During the phone calls, the physiotherapist talked to the patients about the problems that they experienced when doing the exercises and suggested solutions. One researcher, who was blinded to which group the patients were in, entered the data and performed all statistical analyses.

Outcomes

A detailed anamnesis was obtained from the patients, and their demographic and clinical characteristics were recorded. The Charlson Comorbidity Index was calculated for all patients before SARS-CoV-2 infection.[17] Patients were asked whether they had received mechanical ventilation or high-flow oxygen therapy during hospitalization. The respiratory system was evaluated by a pulmonologist, and the cardiovascular system was evaluated by a cardiologist. Chest X-ray and CT findings were reported by a radiologist at our hospital. Functional assessment was performed in person (in our PR unit) for both groups before and after PR.

The primary outcome of this study was the six-minute walk distance (6MWD). Secondary outcomes included the following: respiratory function; upper and lower extremity muscle strength; perception of dyspnea; quality of life; and psychological symptoms (anxiety and depression).

Exercise capacity

Exercise capacity was determined by the six-minute walk test. Patients were asked to walk as far as possible along a 30-m straight corridor for a period of 6 min.[18]

Upper and lower extremity muscle strength

Upper and lower extremity muscle strength was tested against the resistance of the assessing physiotherapist, being graded from 0 (no contraction) to 5 (normal strength). The movement pattern required for each measurement was explained to the patient and demonstrated. The patient was asked to perform the movement in the entire range against gravity. If the patient was able to complete the movement through the full available range against gravity, the joint was placed at the appropriate angle, and resistance was applied gradually. Appropriate feedback and encouragement

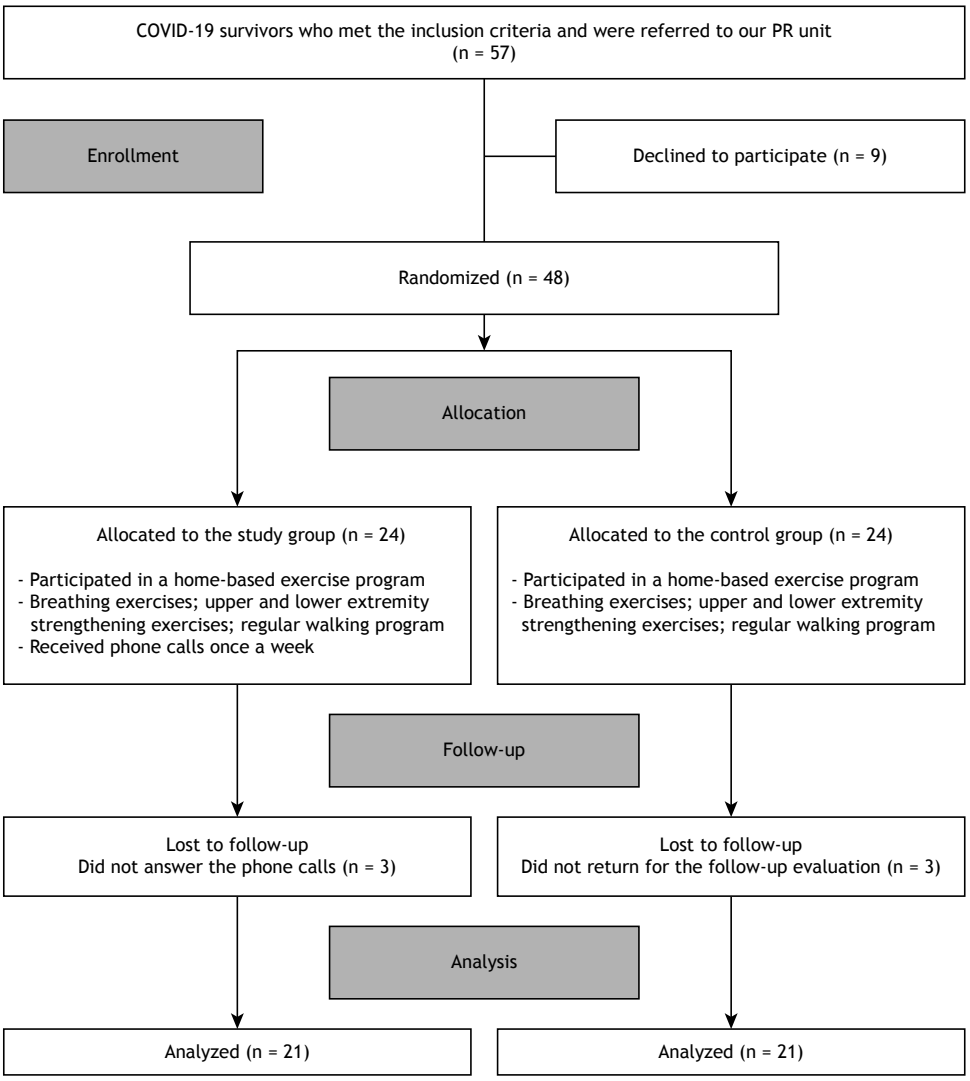

Figure 1. Flow chart of the study. PR: pulmonary rehabilitation.

were given during measurement to promote greater effort. Measurements were made on each patient, first on the right side and then on the left side.

The biceps and deltoid muscles were evaluated for upper extremity muscle strength, and the quadriceps muscle was evaluated for lower extremity muscle strength.[19]

Respiratory function

A body plethysmograph (Zan 500; nSpire Health, Inc., Longmont, CO, USA) was used in order to evaluate respiratory function. The following parameters were assessed and recorded: FEV_1, FVC, and FEV_1/FVC.

Dyspnea

The modified Medical Research Council (mMRC) dyspnea scale,[20] consisting of five grades, was used in order to determine the severity of dyspnea, with 0 being the best grade and 4 being the worst grade. The modified Borg scale,[21] with a scoring system ranging from 0 to 10, was used in order to evaluate dyspnea and fatigue on exertion, with 0 being the best score and 10 being the worst score.

Psychological symptoms

The Hospital Anxiety and Depression Scale, consisting of 14 questions, was used in order to determine the psychological status of patients. A score of 0-7 indicated a normal status; a score of 8-11 indicated a borderline status; and a score > 11 indicated anxiety or depression.[22]

Quality of life

The Saint George's Respiratory Questionnaire (SGRQ) was used in order to determine disease-specific quality of life. High scores indicated worsening of the disease and an increase in symptoms.[23] The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) was used in order to measure the overall quality of life. A higher score translated to a better quality of life.[24]

Home-based PR program

Our home-based PR program was explained to all patients in detail by a physiotherapist in our PR unit. All patients were asked to keep an exercise diary. The home-based program included breathing exercises, strength training, and a regular walking program. Table 1 summarizes the program. Bronchial hygiene techniques were taught to the patients in need by means of pulmonary auscultation. Breathing exercises included pursed-lip breathing, diaphragmatic breathing, and thoracic expansion exercises. Strengthening exercises were performed with free weights for the biceps and deltoid muscles (in the upper extremity) and the quadriceps and gastrocnemius muscles (in the lower extremity). In addition, for the lower extremities, squat and calf-raise exercises were given, with each exercise being repeated 8-10 times per set, 1-2 sets per day, 5-7 days per week. All strengthening exercises were started without weight. During the program, half a kilogram of weight was added to every 6 periods of exercise on the basis of a modified Borg scale score of ≤ 3. All patients were given an exercise booklet. A 2-min break was given between exercises for resting. Patients participated in a walking exercise program for a total of 20-30 min in an outdoor environment without a slope or in an indoor environment with good ventilation and a slope. The exercise was adjusted according to the target HR and the modified Borg scale score.[25,26] The exercise duration was increased when dyspnea and fatigue perception scores were ≤ 3 on the modified Borg scale. The patients were instructed to keep their oxygen saturation above 90% and their HR below 124 bpm in order to perform the exercise within safe limits and avoid cardiopulmonary complications.[26]

The patients were reevaluated 8 weeks after completing the home-based exercise program, and telecoaching was added to the study group. Respiratory function, perception of dyspnea, psychological symptoms, and quality of life were evaluated by the same pulmonologist, and exercise capacity, muscle strength, and compliance with the program were evaluated by the same physiotherapist. The exercise diary kept by the patients was used in order to evaluate their compliance with the program.

Statistical analysis

All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). The normality of the data was evaluated by the Shapiro-Wilk test and histograms. Descriptive statistics were reported as mean ± standard deviation, median (interquartile range), or proportion. Results were reported by comparing post-intervention and baseline values. The independent sample t-test or the Mann-Whitney U test was used in order to compare baseline characteristics, and two-way ANOVA with Bonferroni correction was used in order to compare variables before and after treatment in each group. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Of the 57 patients who met the inclusion criteria, 9 declined to participate in the study. The remaining 48 patients were randomized into study (telecoaching) and control (no telecoaching) groups. Of those 48 patients, 3 (all of whom were in the study group) did not answer the phone calls. A total of 3 controls were unable to return to our PR unit for the follow-up evaluation: 2 moved to another city, and 1 had a vertigo attack. Therefore, 6 patients (3 from each of the two groups) were excluded from the analysis. A total of 42 COVID-19 patients therefore completed the study. Of those, 21 were in the study group and 21 were in the control group (Figure 1). The baseline values for those who withdrew from the study were similar to those for those who remained in the study ($p > 0.05$).

The rate of compliance with the exercise program was 90% in the study group and 70% in the control group. After receiving feedback from study and control group patients at the end of the program, we determined that they did their breathing exercises fully but failed to comply with the walking program.

The demographic and physical characteristics of the patients in the study and control groups were similar ($p > 0.05$), the exception being that the control group comprised older patients ($p = 0.009$). The number of patients with bilateral radiological findings was higher in the study group ($p = 0.048$). In addition, 2 of the patients in the study group had nodules, and 1 had pleurisy, which was not present in the control group. The number of patients receiving home oxygen therapy was higher in the control group ($p = 0.044$). The hospital and ICU length of stay, the number of patients who received IMV or NIMV, and the number of

Table 1. Home-based pulmonary rehabilitation program for COVID-19 survivors.

Breathing exercises	• Techniques: diaphragmatic breathing, pursed-lip breathing, thoracic expansion exercises • Frequency: 8-10 repetitions per set, 1-2 sets per day, 5-7 days per week
Strength training	• Intensity: perceived fatigue of ≤ 3 on the modified Borg scale • Frequency: 8-10 repetitions per set, 1-2 sets per day, 5-7 days per week • Progression: Weights were increased when perceived dyspnea and fatigue were ≤ 3 on the modified Borg scale.
Walking program	• Intensity: Fatigue was targeted at ≤ 3 on the modified Borg scale. • Frequency: 3-5 days per week, 20-30 min per day • Progression: Walking speed and increased duration targeting a score of ≤ 3 on the modified Borg scale for perceived dyspnea and fatigue.

patients who received high-flow oxygen therapy were similar in both groups (p > 0.05; Table 2).

Table 3 provides a between-group comparison of outcome measures before and after the home-based PR program. In the study and control groups, there was a significant increase in the following: FVC (in % of predicted); 6MWD; right and left deltoid muscle strength; SGRQ activity domain, impact domain, and total scores; and SF-36 social functioning, role-physical, role-emotional, and bodily pain domain scores (p < 0.05). Daily-life dyspnea (as measured by the mMRC scale), exertional dyspnea and fatigue (as measured by the modified Borg scale), lower extremity muscle strength, and SF-36 role-physical and bodily pain domain scores decreased significantly, although only in the study group (p < 0.05). Figure 2 shows the changes in the 6MWD, mMRC scale scores, exertional dyspnea, and exertional fatigue before and after PR in the study and control groups.

Right and left biceps muscle strength increased, although only in the control group (p < 0.05). No significant changes were observed in FEV_1 (in % of predicted), FEV_1/FVC, anxiety scores, or depression scores (p > 0.05; Table 3).

The results of the two-way ANOVA comparing the study and control groups showed that the improvements in daily-life dyspnea, exertional dyspnea, exertional fatigue, and SF-36 social functioning domain scores were significantly greater in the study group (p < 0.05; Table 4).

DISCUSSION

In the present study, COVID-19 survivors participated in an 8-week home-based exercise program, with telecoaching being added to the study group. We found that the 6MWD, FVC, and quality of life significantly improved in both groups. Upper and lower extremity muscle strength significantly increased in the telecoaching group, whereas, in the control group, only upper extremity muscle strength increased. Daily-life dyspnea, exertional dyspnea, and exertional fatigue decreased significantly, although only in the telecoaching group. When the two groups were compared in terms of the benefits of the program, the improvement in daily-life dyspnea, exertional dyspnea, exertional fatigue, and social functioning was significantly greater in the telecoaching group than in the control group. No side effects were observed in either group during the program.

Given the elevated risk of hospital spread, rehabilitation should be provided through telemedicine, with minimal contact. This can be provided to COVID-19 patients through remote consultation (telecoaching) or online training (telerehabilitation). In this study, telecoaching was preferred because of the easy and widespread use of mobile phones.

In our study, ground-glass opacity was the most common radiographic finding. Bilateral findings were more common in the study group than in the control group (73% vs. 42%). In our study, there was no difference between the two groups in terms of the

Table 2. Comparison of sociodemographic and clinical characteristics between study and control group patients.[a]

Variable	Group		p
	Study (n = 21)	Control (n = 21)	
Male	13 (68.4)	15 (78.9)	0.714*
Age, years	57.67 ± 8.42	63.67 ± 7.90	0.009†
BMI, kg/m^2	29.98 ± 6.37	28.75 ± 3.51	0.352†
Smoking status			0.203*
Current smoker	1 (5.3)	0 (0.0)	
Former smoker	8 (42.1)	13 (68.4)	
Never smoker	10 (52.6)	6 (31.6)	
Smoking history, pack-years	36.33 ± 21.73	37.50 ± 23.40	0.913†
Presence of comorbidity	14 (73.7)	13 (68.4)	0.721*
CCI	0 [0-1]	1 [0-1]	0.488
Radiological finding			
Bilateral	14 (73.6)	8 (42.1)	0.048
Unilateral	8 (42.1)	11 (57.8)	0.330
Pleural effusion	1 (5.2)	0 (0.0)	-
Ground-glass opacity	14 (73.6)	16 (84.2)	0.633
Nodule	2(10.5)	0 (0.0)	-
Hospital LOS, days	12 [5-15]	11 [8-14]	0.975‡
ICU LOS, days	0 [0-11]	2.5 [0-9]	0.638‡
NIMV	6 (31.6)	9 (47.4)	0.319*
IMV	2 (10.5)	3 (15.8)	0.631*
HFOT	3 (15.8)	5 (26.3)	0.473*
HOT	9 (47.4)	15 (78.9)	0.044*

CCI: Charlson Comorbidity Index; LOS: length of stay; NIMV: noninvasive mechanical ventilation; IMV: invasive mechanical ventilation; HFOT: high-flow oxygen therapy; and HOT: home oxygen therapy. [a]Values expressed as n (%), mean ± SD, or median [IQR]. *Pearson's chi-square test. †Independent sample t-test. ‡Mann-Whitney U test.

Table 3. Comparison of pre- and post-rehabilitation outcome measures.[a]

Variable	Study group (n = 21)					Control group (n = 21)					F	p‡
	Before PR	After PR	Δ	F	p†	Before PR	After PR	Δ	F	p†		
PFT												
FEV_1 (% predicted)	85.05 ± 4.44	89.63 ± 4.96	4.57 ± 2.41	3.586	0.066	80.00 ± 4.44	84.68 ± 4.96	4.68 ± 2.41	3.753	0.061	0.603	0.443
FVC (% predicted)	83.94 ± 3.76	90.94 ± 4.11	7.01 ± 2.72	6.619	0.014	77.47 ± 3.76	83.57 ± 4.11	6.10 ± 2.72	5.035	0.031	1.476	0.232
FEV_1/FVC	83.47 ± 3.92	86.76 ± 4.05	3.28 ± 2.73	1.445	0.237	86.15 ± 3.92	86.84 ± 4.05	0.68 ± 2.73	0.063	0.804	0.234	0.632
mMRC scale	2.63 ± 0.33	1.21 ± 0.300	1.42 ± 0.24	33.38	< 0.001	2.31 ± 0.33	1.84 ± 0.30	0.474 ± 0.24	3.710	0.062	0.143	0.708
Six-minute walk test												
6MWD	378.1 ± 28.9	440.9 ± 25.8	62.8 ± 15.1	17.222	< 0.001	325.1 ± 28.9	381.7 ± 25.8	56.6 ± 15.1	14.013	0.001	1.671	0.204
ΔDyspnea (mBORG)	2.368 ± 0.38	1.368 ± 0.31	1.00 ± 0.31	10.09	0.003	2.051 ± 0.38	2.158 ± 0.31	0.10 ± 0.31	0.112	0.740	0.336	0.565
ΔLeg fatigue (mBORG)	2.158 ± 0.27	1.263 ± 0.29	0.89 ± 0.30	8.862	0.005	1.789 ± 0.27	1.787 ± 0.29	0.02 ± 0.01	0.001	0.998	0.934	0.340
Muscle strength												
Right biceps	4.737 ± 0.12	4.947 ± 0.03	0.211 ± 0.12	3.097	0.087	4.572 ± 0.12	5.00 ± 0.037	0.421 ± 0.12	12.387	0.001	0.298	0.589
Left biceps	4.737 ± 0.12	4.947 ± 0.03	0.211 ± 0.12	3.064	0.089	4.522 ± 0.12	5.00 ± 0.037	0.474 ± 0.12	15.51	< 0.001	0.664	0.421
Right deltoid	4.422 ± 0.15	4.895 ± 0.07	0.474 ± 0.12	13.75	0.001	4.474 ± 0.15	4.842 ± 0.07	0.368 ± 0.120	8.321	0.007	0.062	0.805
Left deltoid	4.474 ± 0.14	4.895 ± 0.11	0.421 ± 0.11	14.58	0.001	4.368 ± 0.14	4.632 ± 0.11	0.263 ± 0.11	5.696	0.001	0.250	0.620
Right quadriceps	4.737 ± 0.09	5.00 ± 0.03	0.263 ± 0.08	8.654	0.006	4.842 ± 0.09	4.947 ± 0.03	0.105 ± 0.08	1.385	0.247	0.610	0.440
Left quadriceps	4.737 ± 0.09	5.00 ± 0.00	0.105 ± 0.13	7.627	0.009	4.842 ± 0.09	5.00 ± 0.00	0.001 ± 0.01	2.746	0.106	0.610	0.440
SGRQ												
Symptoms	40.78 ± 6.19	35.25 ± 5.23	−5.52 ± 3.61	2.340	0.135	36.55 ± 6.19	31.38 ± 5.23	−5.202 ± 3.61	2.070	0.159	0.229	0.635
Activity	62.56 ± 4.85	49.06 ± 6.32	−13.49 ± 4.70	8.244	0.007	65.19 ± 4.85	52.95 ± 6.32	−12.24 ± 4.70	6.783	0.013	0.148	0.703
Impact	41.46 ± 5.69	30.05 ± 5.77	−11.41 ± 3.42	11.07	0.002	47.24 ± 5.69	33.3 ± 5.77	−13.86 ± 3.42	16.34	< 0.001	0.516	0.477
Total	47.77 ± 4.97	36.67 ± 5.45	−11.09 ± 2.87	14.94	<0.001	50.91 ± 4.97	39.03 ± 5.45	−11.88 ± 2.87	17.14	< 0.001	0.200	0.657
SF-36												
Physical functioning	52.36 ± 6.25	66.84 ± 6.97	14.47 ± 6.08	5.653	0.023	52.89 ± 6.25	59.47 ± 6.95	6.579 ± 6.08	1.168	0.287	0.004	0.953
Social functioning	32.23 ± 6.22	68.42 ± 6.10	36.18 ± 6.13	34.79	< 0.001	44.07 ± 6.22	57.23 ± 6.10	13.15 ± 6.13	4.601	0.039	1.812	0.187
Role-physical	15.78 ± 6.90	50.00 ± 8.84	34.21 ± 9.11	14.08	0.001	22.36 ± 6.90	43.42 ± 8.84	21.05 ± 9.11	5.333	0.027	0.454	0.505
Role-emotional	24.36 ± 7.12	50.63 ± 8.57	26.26 ± 8.78	8.937	0.005	27.94 ± 7.21	47.10 ± 8.57	19.15 ± 8.78	4.755	0.036	0.123	0.728
General health	57.89 ± 5.53	62.63 ± 5.81	4.737 ± 4.34	1.187	0.283	53.94 ± 5.53	57.36 ± 5.81	3.421 ± 4.34	0.619	0.436	0.254	0.617
Mental health	63.57 ± 4.72	69.21 ± 5.76	5.631 ± 3.63	2.395	0.130	58.10 ± 4.72	64.0 ± 5.76	5.895 ± 0.11	2.624	0.068	0.672	0.418
Bodily pain	48.94 ± 7.32	78.15 ± 5.22	29.21 ± 6.03	23.45	< 0.001	59.47 ± 7.32	73.50 ± 5.22	14.02 ± 6.03	5.408	0.026	1.033	0.316
Vitality	50.00 ± 4.98	62.63 ± 5.76	12.63 ± 4.72	7.134	0.011	47.10 ± 4.98	53.15 ± 5.76	6.05 ± 4.72	1.638	0.209	0.169	0.684
HADS												
Anxiety	6.263 ± 1.04	5.105 ± 1.10	1.15 ± 0.070	2.263	0.141	7.158 ± 1.04	7.737 ± 1.10	0.57 ± 0.45	0.566	0.457	0.370	0.547
Depression	5.895 ± 0.98	6.00 ± 1.10	0.10 ± 0.58	0.033	0.857	7.260 ± 0.09	7.158 ± 1.10	0.10 ± 0.58	0.033	0.857	0.968	0.332

PR: pulmonary rehabilitation; PFT: pulmonary function testing; mMRC: modified Medical Research Council; 6MWD: six-minute walk distance; mBORG: modified Borg scale; SGRQ: Saint George's Respiratory Questionnaire; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; and HADS: Hospital Anxiety and Depression Scale. [a]Data presented as mean ± standard error of the mean. Repeated-measures ANOVA. †Within-group differences. ‡Comparison of baseline values in the groups.

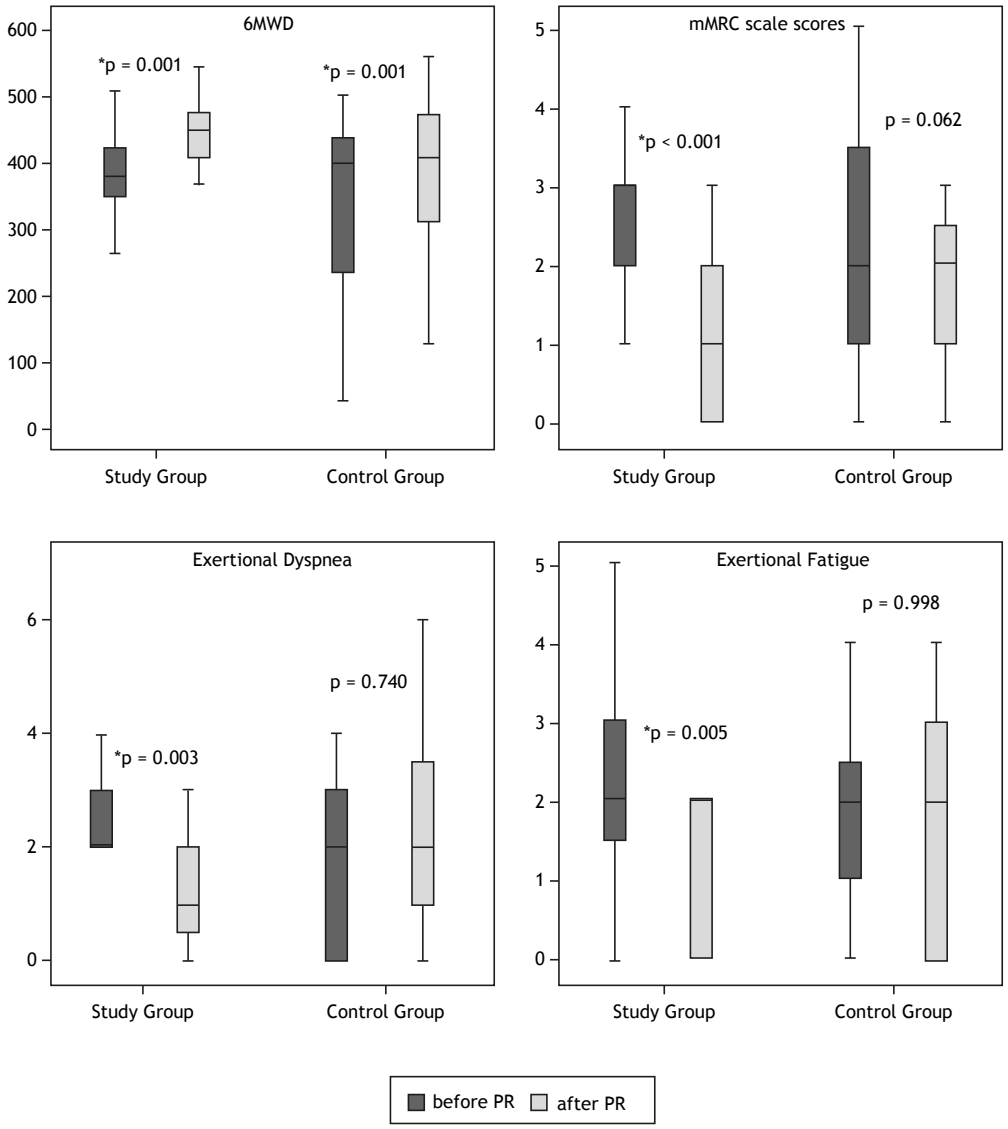

Figure 2. Changes in the six-minute walk distance (6MWD), modified Medical Research Council (mMRC) scale scores, exertional dyspnea, and exertional fatigue before and after pulmonary rehabilitation (PR) in the study (telecoaching) and control (no telecoaching) groups.

length of stay in the ward/ICU or the use of IMV and NIMV. Although the two groups were similar in terms of the number of patients receiving high-flow oxygen therapy, the number of patients receiving home oxygen therapy was higher in the control group. It is known that oxygen therapy has positive effects on functional recovery and quality of life.[27] Therefore, the improvement in functional parameters and quality of life despite a lower rate of compliance with the program in the control group might be due to the high number of patients receiving oxygen therapy in this group.

In our study, the patients in the study group were younger than were those in the control group. Although this is not a limitation, given that our study was a randomized controlled study, when we evaluate the effect of age on the results, the respiratory, functional, and psychological values measured before the program were similar between the two groups. The gains might appear to be higher if the baseline physical functions were worse in the older group. Therefore, we do not think that the younger patients in the study group inflated the results. However, compliance with telerehabilitation might be higher in younger patients, and this might explain why the improvement was greater in the study group.

It has been shown that PR increases exercise capacity, increases muscle strength, improves the quality of life, and reduces dyspnea.[3] In a study investigating the effect of telerehabilitation, there was no improvement in the respiratory function of COVID-19 survivors who had a perception of dyspnea of 2-3 on the mMRC scale after discharge.[28] In our study, a significant increase

Table 4. Group effect, time effect, and group-time effect on the outcome variables.

Variable	Group effect		Time effect		Group-time effect[a]		Partial η^2	Statistical power
	F	p	F	p	F	p		
PFT								
FEV_1 (% predicted)	2.257	0.142	7.339	0.010	0.001	0.976	0.001	0.050
FVC (% predicted)	1.745	0.195	11.60	0.002	0.054	0.817	0.001	0.056
FEV_1/FVC	0.068	0.796	1.055	0.311	0.453	0.505	0.012	0.100
mMRC scale	0.143	0.708	17.05	< 0.001	7.420	0.010	0.171	0.755
Six-minute walk test								
6MWD	2.257	0.142	31.152	< 0.001	0.083	0.775	0.002	0.059
Dyspnea (mBORG)	0.281	0.599	4.039	0.052	6.163	0.018	0.146	0.676
Leg fatigue (mBORG)	0.055	0.816	4.431	0.042	4.431	0.042	0.110	0.535
Muscle strength								
Right biceps	0.298	0.589	13.93	0.001	1.544	0.221	0.041	0.228
Left biceps	0.664	0.421	16.18	< 0.001	2.394	0.131	0.062	0.325
Right deltoid	0.001	0.997	21.73	< 0.001	0.340	0.564	0.009	0.088
Left deltoid	1.208	0.279	19.25	< 0.001	1.025	0.318	0.028	0.167
Right quadriceps	0.107	0.745	8.486	0.006	1.558	0.220	0.041	0.229
Left quadriceps	0.610	0.440	9.763	0.004	0.610	0.440	0.017	0.118
SGRQ								
Symptoms	0.274	0.604	4.406	0.043	0.004	0.949	0.001	0.050
Activity	0.203	0.655	14.99	< 0.001	0.036	0.851	0.001	0.054
Impact	0.347	0.559	27.16	< 0.001	0.255	0.616	0.007	0.078
Total	0.150	0.701	32.05	< 0.001	0.038	0.847	0.001	0.054
SF-36								
Physical functioning	0.170	0.683	5.980	0.019	0.841	0.365	0.023	0.145
Social functioning	0.002	0.966	32.34	< 0.001	7.045	0.012	0.164	0.733
Role-physical	0.001	0.998	18.37	< 0.001	1.042	0.314	0.028	0.168
Role-emotional	0.001	0.998	13.36	0.001	0.327	0.571	0.009	0.086
General health	0.386	0.538	1.761	0.193	0.046	0.832	0.001	0.055
Mental health	0.584	0.450	5.016	0.031	0.003	0.960	0.001	0.050
Bodily pain	0.137	0.713	25.69	< 0.001	3.169	0.083	0.081	0.410
Vitality	0.816	0.372	7.805	0.008	0.968	0.332	0.026	0.160
HADS								
Anxiety	1.549	0.221	0.283	0.598	2.546	0.119	0.066	0.342
Depression	0.792	0.379	0.001	0.998	0.065	0.800	0.002	0.057

PFT: pulmonary function testing; mMRC: modified Medical Research Council; 6MWD: six-minute walk distance; mBORG: modified Borg scale; SGRQ: Saint George's Respiratory Questionnaire; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; and HADS: Hospital Anxiety and Depression Scale. [a]Group-time effect is also known as comparison of Δ values. Repeated-measures ANOVA.

in FVC values was observed in both the study and control groups.

In one study, exercise capacity significantly increased following the telerehabilitation provided to COVID-19 patients after discharge, and dyspnea significantly decreased.[29] Similarly, in our study, there was an increase in the 6MWD and a decrease in the perception of dyspnea in the study group. In the control group, the 6MWD increased, and the perception of dyspnea did not decrease.

In one study, lower extremity muscle strength exercises were included in the telerehabilitation exercise program, and it was observed that muscle strength increased at the end of the program.[9] In our study, both upper and lower extremity muscle strength exercises were given. Although lower and upper extremity muscle strength increased in the study group, only upper extremity muscle strength increased in the control group. The higher increase in lower extremity muscle strength in the study group might be due to greater compliance with the walking program, as well as to peripheral strengthening.

Telerehabilitation provided to COVID-19 survivors improves the quality of life of patients.[30] In our study, there was an improvement in all parameters except for SGRQ symptoms domain scores in both groups. There was an improvement in most SF-36 domains in the study group, whereas, in the control group, fewer SF-36 domains were found to have improved. Anxiety and depression scores did not change in either group. This result suggests that COVID-19 survivors with symptoms of anxiety and depression should seek professional psychological support.

In our study, the rate of adherence to the telerehabilitation program was 90%. As expected, compliance with the program was higher in the telecoaching group. This rate is close to that reported elsewhere (88%).[9] In a study in which only breathing exercises were prescribed to elderly COVID-19 patients,

the respiratory function, 6MWD, and quality of life of the patients improved.[31]

In our study, the follow-up evaluation revealed that the patients in the control group performed breathing exercises and peripheral muscle strength exercises but failed to walk regularly. The increase in muscle strength in the upper extremities of control group patients might be due to increased use of upper extremities in daily life. The lower extremity muscle strength of control group patients may not have increased because they did not adhere to the walking program.

The relatively small number of patients participating in the study prevented us from making further between-group comparisons. The evaluation of upper and lower extremity muscle strength, the evaluation of health-related and disease-specific quality of life, and the examination of psychological symptoms are some of the strengths of the present study.

In conclusion, a home-based PR program increases exercise capacity, muscle strength, and quality of life in COVID-19 survivors. Adding telecoaching to the program results in more significant improvements in daily-life dyspnea, exertional dyspnea, exertional fatigue, and social functioning. Providing COVID-19 survivors with a home-based exercise program (and telecoaching, if possible) reduces the negative effects of the disease.

AUTHOR CONTRIBUTIONS

HŞ: conception and planning of the study; and drafting of the manuscript. İN: data analysis; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. OS: patient follow-up; editing of the data; and implementation of the program. GK: critical revision of the manuscript for important intellectual content. GP and ÖE: data collection.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Hospital admission and mortality rates for non-COVID-19 respiratory diseases in Brazil's public health system during the covid-19 pandemic: a nationwide observational study

Diogo de Azevedo Resende de Albuquerque[1], Marcelo Dantas Tavares de Melo[1], Thiago Lins Fagundes de Sousa[2], Paulo Garcia Normando[1], Juliana Góes Martins Fagundes[2], Jose de Arimateia Batista Araujo-Filho[3]

1. Faculdade de Medicina, Universidade Federal da Paraíba, João Pessoa (PB) Brasil.
2. Faculdade de Medicina da Universidade de São Paulo, São Paulo (SP), Brasil.
3. Hospital Sírio-libanês, São Paulo (SP), Brasil.

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Study carried out at the Universidade Federal da Paraíba, João Pessoa, PB, Brasil.

ABSTRACT

Objective: To assess the influence of the COVID-19 pandemic on hospital admissions (HA), intra-hospital deaths (HD), and intra-hospital lethality rates (HL) related to respiratory diseases (RD) other than COVID-19 in Brazil. **Methods:** This observational time-series study was conducted through comparative analyses of the HA, HD, and HL related to non-COVID-19 RD registered between March and December 2020 by the Brazilian Unified Public Health System on the DataSUS Tabnet platform, using as reference the values recorded in the same period of 2019 and those projected by linear regression methods for 2020, considering the period from 2015 to 2019. The adopted statistical significance level was 5% ($p < 0.05$). **Results:** Compared to 2019, in 2020, there was a 42% decrease in HA and a 7.4% decrease in total HD related to non-COVID-19 RD, followed by a 60% increase in HL associated with this group of diseases. The HA and HL registered in 2020 differed significantly from the projected trend for that year by linear regression ($p < 0.05$). Of note, a significant reduction in hospitalizations due to asthma (-46%), chronic obstructive pulmonary disease (-45%), bronchiectasis (-54%), pneumonia (-46%), and acute bronchitis (-73%) was observed. **Conclusions:** During the first 8 months of the pandemic, there was a decline in HA and an increase in HL related to non-COVID-19 RD in Brazil, which can hypothetically reflect logistical challenges and delays in the management of this group of diseases.

Keywords: Pulmonary disease, COVID-19, non-COVID-19, Hospitalization, Mortality.

INTRODUCTION

Brazil is considered one of the most affected countries in the world by COVID-19. The record of the first case of the disease was February 26, 2020, and the first death was registered on March 17 of the same year, both in the state of São Paulo. Within 24 days, the virus had already spread across the country. Since then, the number of cases in Brazil has fluctuated according to the natural history of the disease, based on waves of infection.[1] In July 2020, Brazil faced the first peak of the disease, with more than 1,000 deaths per day, and ranked as the second country in the world in the number of cases and deaths by COVID-19, currently reaching more than 22 million confirmed cases and more than 650,000 deaths due to the virus.[2]

Some of the restrictions adopted during the first year of the COVID-19 pandemic in Brazil included quarantines, restrictions regarding public and private gatherings, and the closure of schools, public workplaces, and private businesses. Moreover, it was necessary to expand hospital beds in intensive care units and wards and suspend appointments, complementary exams, and elective procedures, as well as direct most of the resources to care for patients infected with the disease.[3-5] In this context, populational studies have registered changes in the hospitalization patterns of other conditions, such as cancer[6,7] and cardiovascular diseases (CVD),[8] but also respiratory diseases, with reduced hospital admissions for chronic obstructive pulmonary disease (COPD) and asthma. The authors of a Korean study hypothesized that the decline in hospitalizations was due to the decrease in the transmissibility of other viruses, such as influenza, as a result of the measures to contain the advance of COVID-19, reducing the incidence of such diseases.[11] For instance, the pattern of CVD showed a relative decrease in hospital admissions; however, it was associated with an increase in the mortality rate of CVD patients in that period.[8-10] This paradigm shift was also extended to other non-COVID-19-related diseases.[12]

In light of the above, the aim of the present study was to investigate the changes in hospital admission and mortality rates related to non-COVID-19 respiratory diseases during the first 10 months of the COVID-19

Correspondence to:
Marcelo Dantas Tavares de Melo. Centro de Ciências Médicas, Universidade Federal da Paraíba - Jardim Universitário, S/N. CEP 58051-900, Campus I, Castelo Branco, João Pessoa, PB – Brasil.
Tel.: +55 (83) 99846-4272. E-mail: marcelot@alumni.usp.br

pandemic in Brazil using nationwide and population-based healthcare registries.

METHODS

This observational time-series study included hospital admissions (HA), intra-hospital deaths (HD), intra-hospital lethality rates (percentage of deaths among admissions) (HL), and the in-hospital and outpatient procedures performed through the Brazilian public health system (SUS) between March and December of 2015 to 2020. Data were extracted in March 2021 by accessing the SUS Hospital Information System (SIH/SUS) and the SUS Outpatient System (SIA/SUS), both available on the DataSUS Tabnet platform. It is noteworthy that these are public and anonymous data, in compliance with Article I of Resolution 510/2016 of the National Research Ethics Commission.[13]

The selection of the outpatient and in-hospital procedures was based on the codes of the Management System of the SUS Table of Procedures, Medicines, and Orthotics, Prostheses, and Materials (SIGTAP). The in-hospital and outpatient performance of each selected procedure were recorded, considering all related procedure codes, and grouped according to similarity as laboratory tests, imaging exams, respiratory function tests, and blood gases, as shown in Table S1.

Data on the records of secondary diagnoses related to respiratory pathologies were selected based on the Morbidity List of the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) and included the number of admissions and intra-hospital deaths and the intra-hospital lethality rates. The listed diseases on the DataSUS Tabnet platform are categorized according to their pathophysiological similarity as acute, chronic, other, and restrictive. Acute respiratory diseases: acute pharyngitis and tonsillitis; acute laryngitis and tracheitis; acute bronchitis and bronchiolitis; Influenza [flu]; pneumonia; other acute upper airway infections. Chronic respiratory diseases: chronic sinusitis; chronic diseases of the tonsils and adenoids; emphysema, bronchitis, and other chronic obstructive lung diseases; asthma; bronchiectasis. Other respiratory diseases: pneumoconiosis; other diseases of the nose and sinuses; other diseases of the upper respiratory tract; other diseases of the respiratory system. These data are available in Table S2.

Statistical analysis

A descriptive analysis of the number of outpatient and inpatient consultations was performed in terms of absolute numbers and percentages regarding the total number of consultations. Data were analyzed based on the conducted procedures (type of procedure) and the federative region (Midwest, Northeast, North, Southeast, and South) and state (including the 26 states and the Federal District). The number of non-COVID-19 respiratory hospitalizations and deaths were evaluated quantitatively, and as a percentage of the total, and segmented by pathology (disease category) (Table S2); the nature of the service (elective or urgent), age group (0 to 19 years old, 20 to 59 years old, and 60 years old or above), race, and sex (Table S4), and the federative region and state (Tables S5 and S6).

Statistical analyses were performed both for the groups (e.g., laboratory tests and acute respiratory diseases) and the components of each of the respective categories (e.g., biopsy and bronchoalveolar lavage for laboratory tests). Thus, it was possible to assess each of the procedures/pathologies individually, as well as in general, by category.

The values recorded between 2019 and 2020 and the corresponding percentage variation between them were compared, showing a percentage decrease or increase in that period. However, it is noteworthy that the annual variation cannot be directly attributed to the pandemic; therefore, it is necessary to assess the trend established in previous years to better understand the possible changes related to the pandemic.

In the interval from 2015 to 2019, the number of procedures, hospitalizations, deaths, and the estimated mortality rate for the year 2020 in the period from March to December were calculated using linear regression. Based on these estimated values, it was possible to determine whether the data showed a trend of growth or decrease for the year 2020 and compare them with the actual values found. In this sense, it is possible to assess both the historical trend and the statistical variations that occurred in previous years.

Since linear regression is subject to Gaussian error, Student's t-test was used to compare the projected values with those registered in 2020, rejecting the null hypothesis with a p-value less than 0.05 (95% confidence interval). The programs Microsoft® Excel® and Scilab® 6.1.0 were used to conduct the statistical analyses.

RESULTS

From March to December of 2015 to 2020, the number of hospital admissions totaled 5,764,727, and the number of deaths was 482,193. Considering the previous and the first year of the COVID-19 pandemic (2019 and 2020, respectively), a total of 102,504,443 procedures were identified, 132,593 of which were related to in-hospital procedures and 102,371,850 to outpatient procedures. In the same period, we evaluated the differences in the numbers of hospitalizations for non-COVID-19 acute, chronic, and other respiratory diseases, demonstrating a reduction in the absolute number of hospitalizations for such conditions, with an increase in intra-hospital mortality, as shown in Figure 1.

Regarding the data related to outpatient and in-hospital procedures surveyed between the years 2015 and 2020, from March to December,

and considering the projections for 2020 that were calculated using data from 2015 to 2019 through linear regression, a growing trend was observed in the number of procedures (dotted lines in Figure 2) for the year 2020. However, the data extracted from DataSUS showed a decrease in the number of procedures performed in 2020 compared to the calculated trend and the previous year, as shown in Figure 2A. In the same way, based on the number of hospitalizations and intra-hospital deaths recorded, considering all the surveyed diseases and the projections for 2020 (dotted lines), it can be noted that there was a significant reduction in the number of hospitalizations and deaths; this discrepancy was accentuated when comparing the values expected for 2020 (according to the calculated trend) and those extracted from the DataSUS platform, as shown in Figure 2B.

A significant increase in the intra-hospital lethality rate was also noticed in 2020 when compared with the numbers recorded in previous years, presenting a different behavior from the previously analyzed criteria (procedures, hospitalizations, and deaths), as shown in Figure 2. The projected rate for 2020 was 8.23% ($p < 0.005$) versus 12.89% of the actual intra-hospital mortality rate registered that year.

The number of procedures performed from March to December, considering the years 2019 and 2020, is shown in Table 1. There was a 15% decrease in the total number of procedures, with a 15% reduction in outpatient procedures and a 5% decrease in in-hospital procedures. Furthermore, we observed a 65% reduction in respiratory function tests, a 91% increase in chest CT scans, and a 33% increase in blood gas tests performed. Unfortunately, there is no way to differentiate whether the reason for requesting tests, such as chest tomographies and blood gases, was related to COVID-19.

These obtained data were compared with the trend in the number of procedures estimated for the year 2020 (March to December), showing a significant difference ($p = 0.02$) of 2,974,340 procedures between the total number estimated and performed. There was also a significant difference between the total number of imaging tests performed and estimated for 2020 ($p = 0.001$), of 3,194,339, with chest radiography being the one with the highest absolute disparity, with 3,794,046 tests performed below the estimated number (15,745,559). On the other hand, an increase in the number of performed chest CT scans (1,447,082) was observed compared to the estimated value (819,941), reflecting a difference of 627,141 more expected exams, both with statistical significance ($p < 0.05$).

Comparing the number of hospitalizations due to respiratory tract involvement from March to December 2020 with the same period of the

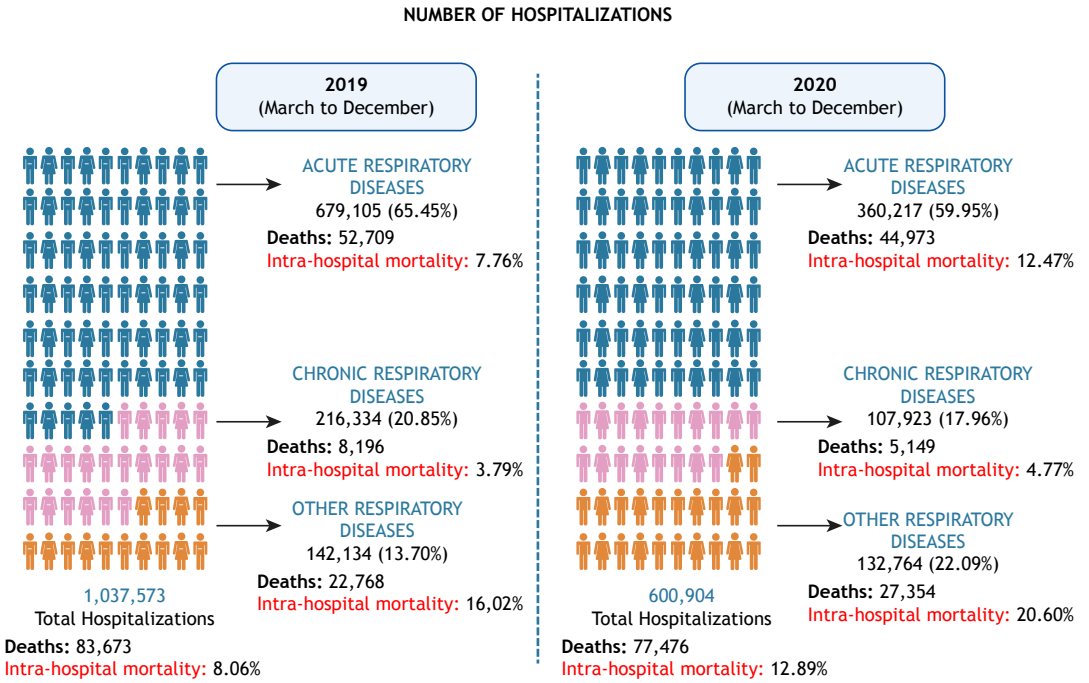
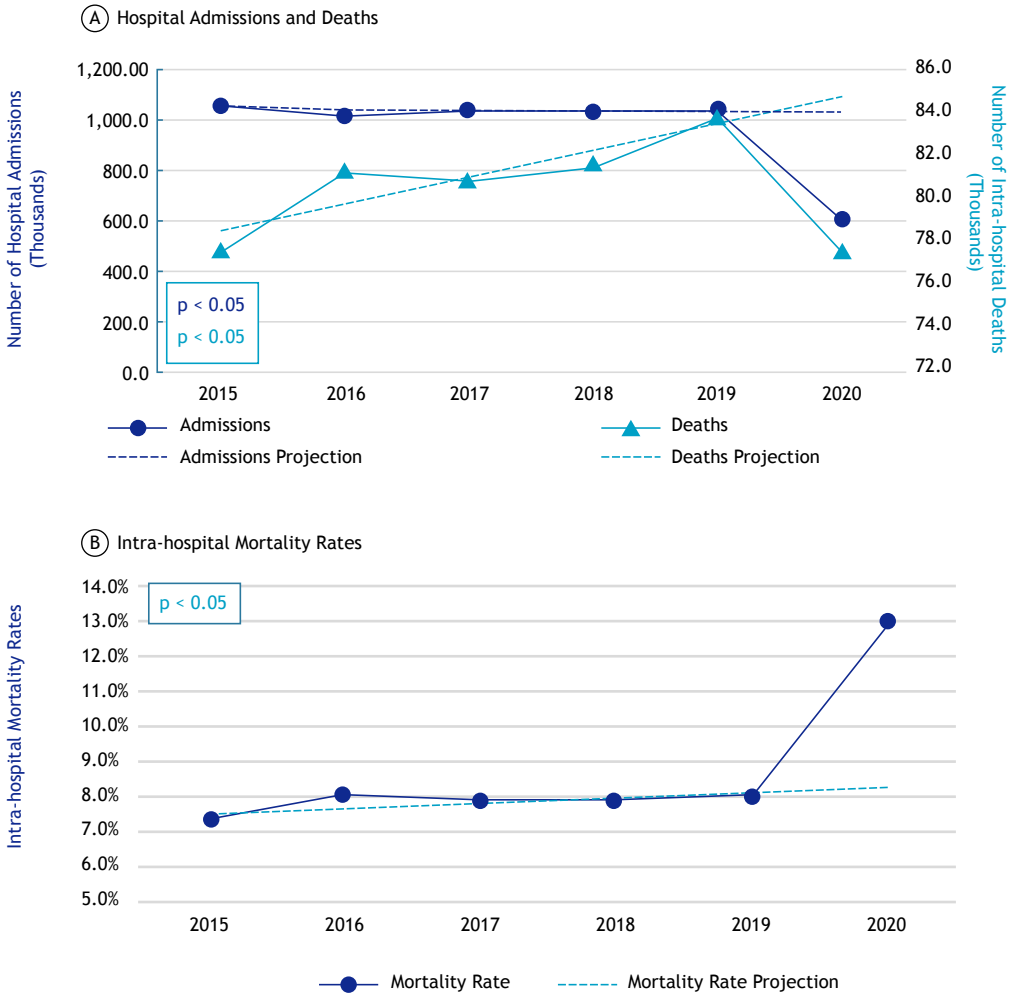


Figure 1. Descriptive analysis of the number of hospitalizations, deaths, and the intra-hospital mortality rates from March to December of 2019 to 2020 to assess the possible impacts of the new coronavirus pandemic on respiratory diseases. Acute respiratory diseases: acute pharyngitis and acute tonsillitis; acute laryngitis and acute tracheitis; acute bronchitis and acute bronchiolitis; Influenza [flu]; pneumonia; other acute upper airway infections. Chronic respiratory diseases: chronic sinusitis; chronic diseases of the tonsils and adenoids; emphysema, bronchitis, and other chronic obstructive lung diseases; asthma; bronchiectasis. Other respiratory diseases: pneumoconiosis; other diseases of the nose and sinuses; other diseases of the upper respiratory tract; other diseases of the respiratory system. Schematic generated using the BioRender web-based software.



[1] Temporal Intervals: March to December of respective years
[2] Projections calculated by linear regression, Student's distribuition

Figure 2. Analysis of the trend in A) number of hospitalizations and deaths and B) intra-hospital mortality rates, from March to December of 2015 to 2020. P-value calculated based on the difference between the projected values and those registered in 2020 using Student's t distribution. Graphs generated using the BioRender web-based software.

previous year, there was a 42% reduction in the total number of hospitalizations, as listed in Table S3. A considerable decrease in hospitalizations for Chronic Respiratory Diseases (-50%) and Acute Respiratory Diseases (-47%) was noted, with emphasis on Acute Inflammatory Diseases, which dropped by 70%, while Airway Infections reduced by only 44%, mainly due to the 37% increase in hospitalizations classified as Influenza [flu], which compensated for the process of retraction in the number of hospitalizations for acute airway infections.

Based on the trend analysis of the estimated number of hospitalizations for the year 2020 (March to December), in general, the values recorded on DataSUS were well below the absolute values calculated statistically for that year, except for influenza (expected value of 14,349 and reported value of 22,341, representing an increase of 7,992 hospitalizations) and other respiratory diseases (expected value of 113,494 and reported value of 120,339, representing an increase of 6,845 hospitalizations). It is noteworthy that all estimated values showed statistical significance ($p < 0.05$).

Considering the absolute number of deaths due to non-COVID-19 RD, a decrease in the total number of deaths between March and December of 2019 and 2020 was observed, from 83,673 deaths in 2019 to 77,476 in 2020, representing a 7% reduction. However, when analyzing deaths due to influenza, other acute infections of the upper airways, and other respiratory diseases individually, there was an increase in the number of deaths from 2019 to 2020, representing a 194% (1,164), 84% (166), and 20% (4,586) increase in mortality, respectively.

Table 1. Statistical analysis of the number of procedures in the months from March to December, comparing the years 2019 and 2020.

	March to December 2019	March to December 2020	% difference	Estimated number of procedures	(CI > 95%)	p-value
Laboratory tests						
Biopsy	2,164	1,874	-13%	2,123	2,292 - 1,954	0.0011
Bronchoalveolar Lavage	4,254	2,810	-34%	4,253	7,972 - 533	0.0405
Total	6,418	4,684	-27%	6,376	10,104 - 2,647	0.0001
Imaging exams						
Bronchography	6	6	0%	5	51 - 0	0.4469
Bronchoscopy	18,882	11,433	-39%	19,051	21,692 - 16,409	0.0002
Scintigraphy	3,949	1,725	-56%	3,854	2,783 - 4,925	0.0005
Thoracic MRI	12,576	13,289	6%	12,363	7,891 - 16,834	0.1302
Thorax X-ray	15,652,349	11,951,513	-24%	15,745,559	14,861,700 - 16,629,416	0.0000
Thorax CT	758,520	1,447,082	91%	819,941	747,732 - 892,148	0.0000
Tracheoscopy	15,385	10,291	-33%	16,284	15,917 - 16,651	0.0000
Chest ultrasound	18,238	9,623	-47%	22,086	14,061 - 30,110	0.0010
Video thoracoscopy	906	817	-10%	974	807 - 1,139	0.0040
Total	16,480,811	13,445,779	-18%	16,640,118	15,688,098 - 17,592,137	0.0001
Respiratory function tests						
Spirography	75,061	20,187	-73%	74,574	70,898 - 78,248	0.0000
Spirometry	10,087	2,514	-75%	6,909	0 - 15,697	0.0222
Respiratory function	307,189	112,967	-63%	325,002	312,167 - 337,836	0.0000
Total	392,337	135,668	-65%	406,485	389,782 - 423,186	0.0000
Blood Gases (Total)	1,658,394	2,206,684	33%	1,714,176	1,362,836 - 2,065,516	0.0013
Grand Total	18,537,960	15,792,815	-15%	18,767,155	17,551,319 - 19,982,990	0.0002

MRI: magnetic resonance imaging; CT: computed tomography.

In the trend analysis, in turn, there was a lower number of deaths than the generalized estimate, with the exception of cases related to influenza (591 cases estimated versus 1,765 registered, difference: +199%), other acute upper airway infections (202 cases estimated versus 363 registered, difference: +80%), and other respiratory diseases (22,416 cases estimated versus 27,354 registered; difference: +22%). It is important to note that the estimated values for acute respiratory diseases (total), influenza, other acute infections of the upper airways, other respiratory diseases, chronic respiratory diseases, and the overall total also differed statistically from the registered values ($p < 0.05$), as shown in Table S3.

DISCUSSION

The impacts of the pandemic can be analyzed in different ways, from the acute results, with the reallocation of material and human resources for treatment, to the change in the entire healthcare system, aiming at a management task force. These factors supposedly justify the higher intra-hospital lethality rate when compared to the predicted value for that year, despite the reduction in the number of hospitalizations for non-COVID-19 respiratory diseases. In other words, the overload of the healthcare system due to coronavirus infection probably reduced the availability of hospital beds for patients with non-COVID-19 RD, a fact that may have implied restricting hospitalizations for more severe cases of this class of diseases, thus influencing intra-hospital mortality. According to Table 1, it can be noted that the impact of such reallocation was considerable on diagnostic methods for respiratory diseases. There was a significant reduction in the number of biopsies and bronchoalveolar lavages, as well as in pulmonary function assessment methods. This fact was due to the hindrance of their performance on account of the closure of pulmonary function laboratories throughout the country. If, on the one hand, there was a reduction in performance in these sectors, with the pandemic, there was a significant increase in chest tomographies and blood gas analyses due to greater availability and the need to classify COVID-19 according to Berlin criteria, which include lung involvement.[14]

Attention is drawn to the significant reduction in the hospitalization of patients for respiratory diseases other than COVID-19. This drop, which in total reached 42%, also occurred in hospitalizations for asthma (-46%), COPD (-45%), bronchiectasis (-54%), pneumonia (-46%), and acute bronchitis (-73%), as can be seen in Table S3. Several hypotheses have been raised, including the fact that greater environmental isolation and the use of masks can contribute to the reduction of chronic disease exacerbations, given that viral infections are associated with the exacerbation of such diseases, including COPD and asthma. In addition, the temporal pattern of chronic disease exacerbations shows a correlation between respiratory viral infections and exacerbations of chronic obstructive pulmonary disease.[15-17] The use of masks, social distancing,

and the increase in hygiene care could contribute to the decrease in viral infections. However, this is not the only valid hypothesis; the reduction in the performance of diagnostic methods also contributed to diagnostic errors and the non-classification of hospital admissions.

When evaluating the total number of deaths due to respiratory diseases, there was an overall reduction, with an increase in the number of deaths by influenza. This fact seems to be due to the lower number of hospitalizations for respiratory diseases. Nevertheless, in terms of lethality, there was a general increase of 60% in 2020 compared to 2019. The rise in mortality and morbidity due to non-COVID-19 diseases was noticed in other countries;[18] however, the root cause remains unclear. The overwhelmed medical systems (as observed in Italy, the United States, Brazil, and India) and the disruption of standards of care have been reported as some of the leading causes of the increase in mortality and morbidity, although with low levels of certainty.[18] We believe this fact is related to the logistical challenges observed worldwide to guarantee the access of patients with chronic RD to specialized centers for treatment during the first year of the pandemic.

Some limitations of this study deserve consideration. The Brazilian national healthcare system has 2 branches, SUS and the supplementary health sector, which includes private healthcare plans, health insurance, and private health professionals. In order to minimize the heterogeneity of the presented data, this study intentionally disregarded patients from the supplementary health sector (approximately 30% of Brazil's population). In this context, it is important to highlight the limitations of DataSUS data (SIA and SIH/SUS). The data referring to the last six months before data collection could have been updated, including the period from October to December 2020. In addition, sporadic updates, fluctuations regarding the seasonality of respiratory diseases, and failure to update by the health department may occur. Therefore, there is no way to certify that all data is consolidated, regardless of the year. Case underreporting and errors in disease classification or diagnosis involving respiratory and viral diseases may also have occurred, especially during the first wave of the pandemic, due to the limited availability of confirmatory tests. It is also noteworthy that, based on the central limit theorem, it was assumed that the data were normal over time, given that the data for each year consists of the totalization of several random variables. Since DataSUS does not provide fully individualized data, it is impossible to thoroughly verify the homoscedasticity of the data. Finally, these results should be interpreted with caution. Additional studies are needed to clarify whether our observations represent a significantly higher mortality rate adjusted for disease severity or merely reflect the increased self or primary care management of less severe conditions.

In conclusion, a decline in HA and an increase in HL related to non-COVID-19 RD were registered during the first 8 months of the COVID-19 pandemic in Brazil. From our point of view, this can hypothetically reflect logistical challenges and delays in the management of this group of diseases. Such measures serve as an alert for the development of public policies, through hospital bed management and medical education, for the correct diagnosis and appropriate indications for hospitalization in each case, ensuring that there is no delay in treatment and worsening of mortality.

AUTHOR CONTRIBUTIONS

DARA and MDTM: study conception and planning; DARA, MDTM, TLFS, PGN, JGMF, and JABA: data collection, processing, and interpretation; PGN: statistical analysis and data tabulation; DARA, MDTM, TLFS, JGMF, and JABA: writing and review of the preliminary and final versions of the manuscript; DARA, MDTM, and TLFS: approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Antifibrotic therapy in idiopathic pulmonary fibrosis candidates for lung transplantation undergoing pulmonary rehabilitation

Monica Pruss Pereira[1], Gisele Branchini[1], Fernanda Bordignon Nunes[1], Stephan Altmayer[2], Guilherme Moreira Hetzel[3], Iveth Romero[1], Adalberto Sperb Rubin[2], Juliessa Florian[4], Douglas Zaione Nascimento[1,4], Guilherme Watte[1,2]

1. Programa de Pós-Graduação em Patologia, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.
2. Serviço de Pneumologia, Pavilhão Pereira Filho, Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS) Brasil.
3. Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.
4. Serviço de Transplante Pulmonar, Pavilhão Pereira Filho, Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS) Brasil.

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ABSTRACT

Objective: To investigate the impact of pulmonary rehabilitation (PR) on functional outcomes and health-related quality of life (HRQoL) in idiopathic pulmonary fibrosis (IPF) patients placed on a lung transplant waitlist and receiving antifibrotic therapy (AFT). **Methods:** This was a retrospective observational study of consecutive IPF patients receiving AFT with either pirfenidone or nintedanib (the AFT group) and undergoing PR between January of 2018 and March of 2020. The AFT group and the control group (i.e., IPF patients not receiving AFT) participated in a 12-week PR program consisting of 36 sessions. After having completed the program, the study participants were evaluated for the six-minute walk distance (6MWD) and HRQoL. Pre- and post-PR 6MWD and HRQoL were compared within groups and between groups. **Results:** There was no significant difference between the AFT and control groups regarding baseline characteristics, including age, airflow limitation, comorbidities, and oxygen requirement. The AFT group had a significant increase in the 6MWD after 12 weeks of PR (effect size, 0.77; $p < 0.05$), this increase being significant in the between-group comparison as well (effect size, 0.55; $p < 0.05$). The AFT group showed a significant improvement in the physical component of HRQoL at 12 weeks (effect size, 0.30; $p < 0.05$). **Conclusions:** Among IPF patients undergoing PR, those receiving AFT appear to have greater improvements in the 6MWD and the physical component of HRQoL than do those not receiving AFT.

Keywords: Idiopathic pulmonary fibrosis; Lung transplantation; Rehabilitation.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a progressive and irreversible lung disease that is currently the second most common indication for lung transplantation worldwide.[1] The prognosis of IPF is poor, with a mean life expectancy of 2-5 years after the diagnosis has been made. The course of IPF is irreversible, and most patients experience episodes of acute pulmonary exacerbation, with recurrent hospitalizations being required for respiratory support and symptom control in many cases.[2] Additionally, progressive hypoxia and impaired exercise tolerance lead to reduced health-related quality of life (HRQoL).[3]

There are currently two antifibrotic therapies (AFTs) that have been shown to slow the progression of IPF, reduce the decline in FVC, and decrease all-cause mortality: pirfenidone and nintedanib.[4,5] However, these AFTs do not improve dyspnea, exercise tolerance, or HRQoL.[6] On the other hand, pulmonary rehabilitation (PR) has been shown to improve these functional outcomes (and HRQoL) significantly, and therefore remains a central component in the management of IPF.[7-9] Although most studies have found that AFT does not have a significant impact on functional outcomes, whether or not patients receiving AFT have a better functional response to PR than do those not receiving AFT has yet to be extensively investigated, particularly in Brazil.

The objective of the present study was to investigate the impact of PR on functional outcomes and HRQoL in IPF patients placed on a lung transplant waitlist and receiving AFT.

METHODS

This was a retrospective observational study performed at a referral center for lung transplantation in the city of Porto Alegre, Brazil. Consecutive patients diagnosed with IPF and undergoing PR between January of 2018 and March of 2020 while on a waiting list for lung transplantation were included in the study. Cases were defined as those using either pirfenidone or nintedanib prior to starting PR, and controls were defined as those who were not on any AFT before starting PR. A multidisciplinary team of pulmonologists, radiologists, pathologists, and generalists discussed imaging and histopathological findings in order to rule out secondary causes of fibrotic lung disease.

Correspondence to:
Guilherme Watte. Serviço de Pneumologia, Pavilhão Pereira Filho, Irmandade Santa Casa de Misericórdia de Porto Alegre, Avenida Independência, 75, CEP 90020-160, Porto Alegre, RS, Brasil.
Tel.: 55 51 3228-2789. E-mail: g.watte@gmail.com
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Selected cases underwent surgical lung biopsy. IPF was diagnosed on the basis of HRCT findings and surgical lung biopsy findings in selected patients, in accordance with the 2011 or 2018 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/*Asociación Latinoamericana de Tórax* guidelines, with the latter being used for patients with a more recent diagnosis.[10,11] During PR, demographic, histopathological, clinical, and functional data were obtained.

Patients with clinically significant resting hypoxemia (resting SpO_2 ≤ 88%) were prescribed long-term oxygen therapy. Data were retrospectively reviewed from patient medical records, including pre- and post-PR data (when available). Completion of a PR program was defined as participation in at least 36 sessions[12] and all post-PR evaluations, including a six-minute walk test (6MWT) and an HRQoL questionnaire.[13,14] This study was approved by the local institutional review board (Protocol n. 04453412.7.0000.5335) with waiver of consent.

The PR program consisted of medical appointments with the PR team every two months and included psychiatric evaluation, nutritional counseling, social assistance, and monthly educational lectures.[12] The physical training component of the program was administered by two physical therapists, with three sessions per week for a total of 36 sessions. During physical training, patients performed an initial warm-up, followed by muscle strengthening and aerobic exercises. The warm-up consisted of breathing exercises (respiratory cycle) and arm raising. Muscle strengthening was based on arm and leg exercises performed with an initial load of 30% of a one-repetition maximum test, with a set of ten repetitions per exercise. The load was increased by 0.5 kg every seven sessions depending on exercise tolerance.[12] Aerobic exercises were performed on a treadmill at 70% of the speed achieved on the 6MWT, the speed being progressively increased every 6 min for a total of 30 min of exercise. The speed was increased by 0.3 km/h every seven sessions. The exercises were interrupted if patients reported dyspnea or leg fatigue, as assessed by a modified Borg scale score > 4, or if SpO_2 reached 92%. When patients presented with an SpO_2 of < 92%, exercise intensity was reduced and oxygen flow was increased in an attempt to sustain exercise effort and encourage patients to tolerate dyspnea. At the end of each session, patients performed stretching exercises for all of the major muscle groups involved. During PR, all patients received continuous oxygen therapy as prescribed and were constantly monitored by pulse oximetry so that SpO_2 was maintained at ≥ 92%. The modified Borg scale was used in order to assess dyspnea and leg discomfort.

Patient medical records were reviewed for treatment with pirfenidone or nintedanib before PR, and those patients who were using either drug before PR were included in the AFT group. The minimum dose was 267 mg (2 tablets) three times per day for pirfenidone and 100 mg twice per day for nintedanib. Patients in whom AFT had been discontinued 12 weeks before PR were included in the control group.[15]

Pulmonary function tests were performed in accordance with the American Thoracic Society/European Respiratory Society technical procedures and acceptability and reproducibility criteria.[16,17] All pulmonary function tests were performed in our pulmonary function laboratory, which is certified by the Brazilian Thoracic Association. In addition to administering the pulmonary function tests, the same physical therapists administered the 6MWT, in accordance with the American Thoracic Society recommendations,[13] and the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36),[14] in order to evaluate HRQoL.

Our primary outcome was to evaluate the impact of PR on functional outcomes and HRQoL using the 6MWT and SF-36, respectively. Pre- and post-PR six-minute walk distance (6MWD) and HRQoL were compared within groups and between groups, with post-PR 6MWD and HRQoL being compared between AFT and control group patients. Data were presented as absolute and relative frequencies, mean ± standard deviation (95% confidence interval), or median (interquartile range). The normal distribution of the data was evaluated with the Shapiro-Wilk test. Comparisons of proportions were made with the chi-square test for categorical variables and the Student's t-test for continuous variables. For within-group differences, the effect size was calculated in accordance with Cohen,[18] by dividing the difference between the mean values at baseline and at follow-up by the pooled standard deviation of both values. For between-group differences, the effect size was calculated in accordance with Carlson & Smith,[19] by using the pooled pretest standard deviation for weighting the differences of the pre-post-means.[20] Effect sizes were classified as small (0.2), medium (0.5), or large (0.8). A two-sided p-value of 0.05 was considered statistically significant. All analyses were performed with the Stata statistical software package, version 15 (StataCorp LP, College Station, TX, USA).

RESULTS

A total of 32 patients with IPF were included in the present study. Of those, 16 were in the AFT group and 16 were in the control group. Most of the patients were male, were 60 years of age or older, had a history of smoking (26-30 years of smoking), and were on long-term oxygen therapy (Table 1). There were no differences between the AFT group and the control group regarding FEV_1, FVC, or the FEV_1/FVC ratio (Table 1). There was no significant difference in the 6MWD between the AFT and control groups at study entry.

Tables 2 and 3 summarize the effects of PR on the 6MWD and HRQoL in the AFT and control groups. Although there was no significant change in the 6MWD after 12 weeks in the control group, there was an increase in the 6MWD in the AFT group (effect size,

0.77; $p < 0.05$). There was a significant difference in the pre- and post-PR 6MWD between the two groups, with an effect size of 0.554 ($p < 0.05$). The other parameters measured during the 6MWT (heart rate, oxygen saturation, dyspnea, and leg discomfort) were not significantly different at 12 weeks when they were compared either within groups or between groups.

With regard to the SF-36, almost all physical and mental components improved between the groups and within the AFT group before and after PR. A within-group improvement in the physical component was observed after PR in the AFT group (effect size, 0.30; $p < 0.05$), although not in the control group. However, the between-group difference in the physical component was not significant.

DISCUSSION

This study sought to evaluate the impact of PR on functional outcomes and HRQoL in IPF patients placed on a lung transplant waitlist and receiving AFT in comparison with those not receiving AFT. We found that those who were receiving AFT had significant within- and between-group improvements in the 6MWD after 36 sessions (12 weeks) of PR, along with a significant within-group improvement in physical functioning, as assessed by the SF-36.

A PR program includes training to improve muscle strength, aerobic training to improve endurance, and patient education, involving a multidisciplinary team of generalists, physical therapists, nutritionists, and psychologists.[7,21] The effects of PR include improved exercise tolerance, decreased dyspnea, increased exercise duration, increased 6MWD, and, consequently, improved HRQoL.[9,12,22] PR is safe and has a low risk of adverse events in patients with IPF, with a recommended duration of 12 weeks at specialized centers.[23]

Dyspnea is one of the predominant symptoms in patients with IPF and worsens HRQoL when associated with muscle weakness, thus contributing to the development of depression.[24] Hypoxemic patients with advanced disease can have high exertional oxygen requirements to participate in aerobic training, and oxygen therapy at rest or during exercise is essential to improve dyspnea, which can be minimized by means of PR.[25,26] In this study, although there was no significant change in SaO_2 or in dyspnea as assessed by the modified Borg scale, the study participants reported a significant improvement in the physical component of HRQoL as assessed by the SF-36, which is a surrogate for better physical performance at the end of 36 sessions of PR.

Despite the positive effects of AFT on lung function and survival, AFTs are not known to improve HRQoL or dyspnea. For this reason, PR has become an important adjuvant in the management of patients with IPF, particularly those on a lung transplant waitlist. However, there is a lack of studies investigating whether AFT can have an adjuvant effect on functional parameters and, consequently, HRQoL when associated with PR, given that AFT and PR both slow disease progression. Thus, our findings suggest that the use of AFT can increase the beneficial effects of PR on functional outcomes in these patients. One explanation for this is that patients who are not on AFT have a more rapid

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

Variable	Group		p
	Control (n = 16)	AFT (n = 16)	
Male sex	13 (81.3)	12 (75.0)	1.000
Age, years	60 ± 9	63 ± 5	0.373
BMI, kg/m^2	25.9 ± 1.42	27.8 ± 4.54	0.113
FEV_1, L	1.70 ± 0.46	1.68 ± 0.40	0.919
FEV_1, % predicted	55 ± 13	55 ± 14	0.953
FVC, L	1.98 ± 0.64	1.93 ± 0.54	0.818
FVC, % predicted	51 ± 14	49 ± 14	0.694
FEV_1/FVC ratio	0.87 ± 0.08	0.88 ± 0.08	0.785
DL_{CO}, % predicted	39 ± 11	37 ± 5	0.591
PASP, mmHg	45.5 ± 11.5	45.0 ± 14.9	0.919
6MWD, m	429 ± 104	358 ± 100	0.164
Hypertension	7 (43.8)	4 (25.0)	0.458
Diabetes mellitus	2 (12.5)	2 (12.5)	1.000
Osteopenia	4 (25.0)	1 (6.3)	0.333
Ischemic heart disease	5 (31.3)	3 (18.8)	0.685
Former smoker	11 (68.8)	8 (50.0)	0.473
Smoking, years	26 [18-31]	30 [5-37]	0.817
Long-term oxygen therapy	12 (85.7)	13 (81.3)	1.000
Oxygen flow rate, L/min	5.00 ± 1.96	4.81 ± 1.42	0.765

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

Table 2. Effects of pulmonary rehabilitation on parameters measured during the six-minute walk test.[a]

Outcome	PR	Mean ± SD		Within-group comparison between pre- and post-PR values	Between-group comparison between pre- and post-PR values
		Pre-PR	Post-PR	Mean difference (95% CI); Effect size [18] *	Mean difference (95% CI); Effect size [19,20] *
Six-minute walk test					
6MWD, m	CG	429 ± 104	448 ± 107	18 (−17 to 55); 0.18	59 (11 to 105); 0.554**
	AFT	358 ± 100	435 ± 99	77 (43 to 111); 0.77**	
Post-PR HR, bpm	CG	120 ± 26	132 ± 22	12 (1 to 24); 0.49	2 (−16 to 18); 0.087
	AFT	115 ± 18	129 ± 21	14 (1 to 27); 0.71	
Post-PR SpO_2, %	CG	76 ± 6	76 ± 8	0 (−2.0 to 0.4); 0.00	−1.0 (−7.3 to 5.6); 0.110
	AFT	81 ± 11	80 ± 7	−1.0 (−2.7 to 1.1); 0.10	
Post-PR dyspnea, modified Borg scale score	CG	5 ± 3	4 ± 2	−1.0 (−2.0 to 2.8); 0.32	0.0 (−2.0 to 2.5); 0.000
	AFT	5 ± 3	4 ± 1	-1.0 (−2.7 to 1.0); 0.44	
Post-PR leg discomfort, modified Borg scale score	CG	2 ± 2	2 ± 2	0.0 (0.0 to 0.0); 0.00	0.0 (0.0 to 0.0); 0.000
	AFT	2 ± 2	2 ± 2	0.0 (0.0 to 0.0); 0.00	

[a]Data presented as mean ± SD or mean difference (95% CI). PR: pulmonary rehabilitation; CG: control group; and AFT: antifibrotic therapy group. *For within-group differences, the effect size was calculated in accordance with Cohen,[18] by dividing the difference between the mean values at baseline and at follow-up by the pooled standard deviation of both values. For between-group differences, the effect size was calculated in accordance with Carlson & Smith,[19] by using the pooled pretest standard deviation for weighting the differences of the pre-post-means.[20] **p < 0.05.

Table 3. Effects of pulmonary rehabilitation on health-related quality of life.[a]

Outcome	PR	Mean ± SD		Within-group comparison between pre- and post-PR values	Between-group comparison between pre- and post-PR values
		Pre-PR	Post-PR	Mean difference (95% CI); Effect size [18] *	Mean difference (95% CI); Effect size [19,20] *
SF-36					
Physical component summary	CG	33 ± 14	36 ± 17	3 (−5 to 10); 0.19	3 (−6 to 12); 0.134
	AFT	36 ± 15	41 ± 18	6 (0 to 12); 0.30**	
Mental component summary	CG	54 ± 18	61 ± 19	7(−3 to 18); 0.37	−4 (−19 to 10); 0.154
	AFT	56 ± 20	60 ± 27	3 (−8 to 15); 0.16	

[a]Data are presented as mean ± SD or mean difference (95% CI). PR: pulmonary rehabilitation; CG, control group; AFT: antifibrotic therapy group; and SF-36: Medical Outcomes Study 36-item Short-Form Health Survey. *For within-group differences, the effect size was calculated in accordance with Cohen,[18] by dividing the difference between the mean values at baseline and at follow-up by the pooled standard deviation of both values. For between-group differences, the effect size was calculated in accordance with Carlson & Smith,[19] by using the pooled pretest standard deviation for weighting the differences of the pre-post-means.[20] **p < 0.05.

decline in pulmonary function and therefore benefit less from PR than do those who are receiving AFT.

Our study has limitations. First, this was a single-center study involving a small sample of patients. This limits the generalization of our results and might have influenced some of the differences that we found between the groups. Second, this was a retrospective observational study rather than an interventional placebo-controlled trial, and it has all of the limitations inherent to this design. Therefore, potential confounding variables, including the placebo effect, could have contributed to the improvement observed herein, although there was no statistically significant difference in baseline demographics between the groups. Furthermore, our data pragmatically reflect real-world clinical practice and should be interpreted as such.

In this retrospective observational study conducted in a referral center for lung transplantation in Brazil, exploratory findings suggest that AFT is associated with improvements in the 6MWD after 36 sessions of PR. In addition, the group of patients receiving AFT while undergoing PR reported a positive within-group change in the physical component of HRQoL at the end of 12 weeks of PR.

AUTHOR CONTRIBUTIONS

MMPP, GB, SA, and GW: conceptualization; methodology; investigation; data curation; and drafting of the manuscript. JF, DZN, ASR, GMH, FBN, and IR: investigation; data curation; drafting of the manuscript; and reviewing and editing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Patient care in cystic fibrosis centers: a real-world analysis in Brazil

Elenara da Fonseca Andrade Procianoy[1,2], Norberto Ludwig Neto[2,3], Antônio Fernando Ribeiro[2,4]

1. Hospital de Clínicas de Porto Alegre – HCPA – Porto Alegre (RS) Brasil.
2. Grupo Brasileiro de Estudos de Fibrose Cística – GBEFC – São Paulo (SP) Brasil.
3. Hospital Infantil Joana de Gusmão, Florianópolis (SC) Brasil.
4. Hospital das Clínicas, Universidade Estadual de Campinas – UNICAMP – Campinas (SP) Brasil.

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ABSTRACT

Objective: To analyze the characteristics of cystic fibrosis (CF) care centers (CFCCs) in Brazil. **Methods:** A questionnaire was sent to the coordinators of all 51 registered CFCCs between May and September of 2021. **Results:** The response rate was 100%. Southeastern Brazil is the region where most of the CFCCs in the country are located (21 centers; 41%), followed by the southern and northeastern regions (11 centers each; 21.5%), the central-western region (6; 12%), and the northern region (2; 4%). A total of 4,371 patients with CF were cared for in Brazil during the study period, ranging from 7 to 240 patients per center (mean, 86 patients/center; median, 75 patients/center); 2,197 patients (50%) were cared for in centers in the southeastern region of the country, particularly in the state of São Paulo (33%), the remaining patients being treated in southern Brazil (1,014 patients, 23%), northeastern Brazil (665 patients, 15%), central-western Brazil (354 patients, 8%), and northern Brazil (141 patients, 4%). Overall, 47 centers (92%) reported having an incomplete multidisciplinary team; 4 (8%) lacked essential team members; 6 (12%) lacked a physical therapist; 5 (10%) lacked a dietitian; 17 (33%) lacked outpatient nursing care; 13 (25%) lacked outpatient social work services; 14 (27%) lacked a psychologist; and 32 (63%) lacked a clinical pharmacist. Seven CFCCs (14%) in the northern and northeastern regions of Brazil reported that the quality of newborn screening for CF was poor. All centers reported having difficulties in accessing CF medications. **Conclusions:** Brazilian CFCCs experience multiple problems, including inadequate staffing, infrastructure, testing, and medication supply. There is an urgent need to regulate the implementation of CF referral centers and an appropriate network structure for the diagnosis and follow-up of CF patients using optimal treatment recommendations.

Keywords: Cystic fibrosis; Neonatal screening; Quality of life; Genetic diseases, inborn; Lung diseases.

INTRODUCTION

Cystic fibrosis (CF) is a multisystem genetic disorder with a chronic and progressive course that mainly affects the respiratory and digestive systems, respiratory failure secondary to lung disease being the main cause of short life expectancy of patients.[1] The increasingly early diagnosis, currently made primarily through neonatal screening, and the improved effectiveness of treatment performed in specialist CF centers are associated with improved quality of life and increased survival in patients with CF.[2] New medications aimed at correcting the dysfunction of the CF transmembrane conductance regulator (CFTR), a protein affected in CF, are known as CFTR modulators and promise even better results.[1-7] Given the complexity of CF, several medical specialties are involved in patient care.

Better quality of life, better nutritional status, and longer survival in patients with CF are associated with routine specialist care provided in CF care centers (CFCCs). In accordance with international models, CF patients treated at CFCCs are routinely cared for by a multidisciplinary team, and this allows for more comprehensive and effective treatments.[1-7] The multidisciplinary team should be sufficiently trained and composed of health care professionals who take care of the various clinical aspects of CF in children, adolescents, and adults. In addition, such teams should provide guidance on proper bronchial hygiene therapy and pulmonary performance, as well as on the most adequate nutrition for each patient and on the care required for the use of all medications, catheters, and devices. Teams should also take care of the emotional and social aspects of CF in a standardized manner.[2,7] In addition to the multidisciplinary team, CFCCs should have an appropriate infrastructure of care and trained staff to meet the needs related to the diagnosis, follow-up, and treatment of CF.[7]

In Brazil, the 2001 National Neonatal Screening Program included screening for CF in all newborns from phase III implementation onwards. The Program stipulates that patients diagnosed with CF should be treated in the *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System), which is the national public health care system funded by federal taxes and

Correspondence to:
Elenara da Fonseca Andrade Procianoy. Avenida Carlos Gomes, 1111/1201, CEP 90480-004, Porto Alegre, RS, Brasil.
Tel.: 55 51 3331-4693. E-mail: efaprocianoy@gmail.com
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operated by state and municipal governments, in a specialist CF multidisciplinary outpatient clinic or in a CFCC that can provide appropriate patient counseling, monitoring, and treatment and also rely on a network of ancillary services.[8] A support hospital network with pediatric and adult ICUs, emergency departments, and inpatient units should be available. Patient care flow should follow current *Protocolos Clínicos e Diretrizes Terapêuticas* (PCDTs, Clinical Protocols and Therapeutic Guidelines) for the treatment of CF.[8] However, the Brazilian Ministry of Health provides neither a clear-cut, well-established, up-to-date definition of the composition and qualifications of CFCCs nor any standardization for delivery of care. In fact, state governments are responsible for the SUS accreditation of CFCCs, whereas CFCCs themselves are responsible for the organization of services and teams.

There are several CFCCs in Brazil. However, we are unaware of their characteristics and limitations in terms of personnel, infrastructure, and access to tests and medications. In the present analysis, we sought to understand and describe the status of Brazilian CFCCs critically in order to propose actions to adapt and standardize these centers so that a standardized delivery of care is achieved throughout the country.

METHODS

Data were provided by the coordinators of all CFCCs registered with both the *Grupo Brasileiro de Estudos de Fibrose Cística* (GBEFC, Brazilian CF Study Group) and CF patient associations. GBEFC is a nonprofit, non-governmental association consisting of various health care professionals specializing in the diagnosis and treatment of CF. GBEFC aims to disseminate knowledge on CF in Brazil, assisting health care professionals in the diagnosis of the disease; stimulate greater interest in CF on the part of health care professionals, hospitals, and public and private agencies in order to produce greater scientific knowledge through attendance at conferences and involvement in research; and discuss, develop, and update PCDT for CF in Brazil.

A questionnaire was sent via e-mail or mobile instant messaging to all coordinators of the CFCCs, including questions regarding the following: 1) total number of patients with CF at the CFCC; 2) CFCC address; 3) medical specialty of the coordinator and age of the patients receiving care; 4) whether or not the center infrastructure is appropriate (if no, give reasons); 5) whether or not the following medical specialties are part of the medical team or not: pediatric pulmonologist, pediatric gastroenterologist, adult pulmonologist, and adult gastroenterologist; 6) whether or not the following specialists are involved in multidisciplinary care: physical therapist, dietitian, nurse, social worker, psychologist, clinical pharmacist, and physical educator; 7) whether or not the CFCC is linked to a CF neonatal screening program; 8) whether the quality of CF neonatal screening at the CFCC is considered to be very good, good, or bad (if bad, give reasons); 9) whether or not genetic testing for CF is available at the CFCC, 10) whether or not the sweat test is available for CF diagnosis; 11) which technique is used for the sweat test (conductivity, Gibson-Cooke, or coulometric titration); 12) whether or not there are any complaints about the sweat test (if yes, explain), 13) whether or not the CFCC has access to the following medications: pancrelipase, dornase alfa, and inhaled tobramycin; and 14) whether or not there are any complaints about CF medications (if yes, explain). The questionnaire was sent between May and September of 2021. All data were entered into a Microsoft Excel spreadsheet to be processed and analyzed.

As most of the data are qualitative, we performed a descriptive analysis using absolute and relative frequencies. Quantitative data were expressed as means and/or medians.

RESULTS

A total of 51 CFCCs that met the inclusion criteria in Brazil, and all of the coordinators of these centers completed the questionnaire. Among the coordinators, 48 (94%) are pediatric or adult pulmonologists and 3 (6%) are pediatric gastroenterologists. Five states (Acre, Amapá, Roraima, Rondônia, and Tocantins), all of which are located in the northern region of Brazil, have no CFCCs. In the remaining Brazilian states, there is at least 1 CFCC per state. Southeastern Brazil is the region where most of the CFCCs are located (21 centers, 41%), followed by southern Brazil (11 centers, 21.5%), northeastern Brazil (11 centers, 21.5%), central-western Brazil (6 centers, 12%), and northern Brazil (2 centers, 4%). Of the 51 CFCCs, 40 (78%) are located in state capitals, whereas 11 (22%) are located in major inland cities; almost all CFCCs are affiliated with university hospitals. Thirty-four CFCCs (67%) care for more than 50 patients, whereas 17 centers (33%) care for less than 50 patients (Table 1).

Twenty-one CFCCs (41%) exclusively provide pediatric care however, the definition of pediatric age varies across centers: 0-12 years of age, 0-14 years of age, or 0-18 years of age. Nineteen CFCCs (37%) care for both children and adults, whereas 11 centers (22%) care for adults only. Adult CFCCs are located in the states of Ceará, Espírito Santo, Minas Gerais, Rio de Janeiro, São Paulo, Paraná, Rio Grande do Sul, and Santa Catarina, as well as in the Federal District of Brasília.

A total of 4,371 patients were being cared for in the 51 CFCCs during the study period. The number of patients cared for at each center varied widely, ranging from 7 to 240 patients (mean, 86 patients/center; median, 75 patients/center). Half of the patients (2,197 patients) were cared for in centers located in the southeastern region of Brazil, particularly in the state of São Paulo, where 33% (1,213) of all Brazilian patients with CF were treated, the remaining being

Table 1. Characteristics of cystic fibrosis care centers in Brazil (N = 51) between May and September of 2021.[a,b]

Type of cystic fibrosis care center			
	Pediatric center	21 (41)	
	Pediatric/adult center	19 (37)	
	Adult center	11 (22)	
Region	**Center/patient**	**Center per state/patient per state**	
North	2 (4)/141 (4)	Acre	-/-
		Amapá	-/-
		Amazonas	1/9
		Tocantins	-/-
		Roraima	-/-
		Rondônia	-/-
		Pará	1/132
Northeast	11 (21.5)/665 (15)	Alagoas	1/38
		Bahia	2/220
		Ceará	2/121
		Maranhão	1/25
		Paraíba	1/20
		Pernambuco	1/120
		Piauí	1/30
		Rio Grande do Norte	1/37
		Sergipe	1/54
Central-West	6 (12)/354 (8)	Federal District	2/138
		Goiás	2/116
		Mato Grosso	1/51
		Mato Grosso do Sul	1/49
Southeast	21 (41)/2,197 (50)	Espírito Santo	2/135
		Minas Gerais	6/560
		Rio de Janeiro	3/289
		São Paulo	10/1,213
South	11 (21.5)/1,014 (23)	Paraná	3/372
		Rio Grande do Sul	4/416
		Santa Catarina	4/226

[a]Values expressed as n (%) or n/n. [b]Total number of patients = 4,371.

treated in southern Brazil (1,014 patients, 23%), northeastern Brazil (665 patients, 15%), central-western Brazil (354 patients, 8%), and northern Brazil (141 patients, 4%). Based on population density estimates from the Brazilian Institute of Geography and Statistics in July of 2020,[9] the distribution of CF patients is proportional to the number of individuals in the southeastern, central-western, and northern regions of Brazil. However, in southern Brazil, there is a higher density of CF patients (23% of all Brazilian CF patients) and a lower population density (14% of the Brazilian population), whereas, in northeastern Brazil, there is a lower density of CF patients (15% of all Brazilian CF patients) and a higher population density (27% of the Brazilian population).

In addition, 3 CFCCs provide outpatient care only and are highly dependent on the local characteristics of the SUS to hospitalize patients if necessary.

All CFCCs have experienced difficulties. There were many complaints about the infrastructure of the centers, including (in order of frequency) lack of rooms for proper care, lack of places for patient segregation, lack of hospital beds for inpatient admission, inadequate care for adult patients (provided by pediatric teams in pediatric outpatient clinics), lack of a pediatric-to-adult transition program, delay in performing tests, and lack of basic tests, such as fecal elastase-1 to determine pancreatic insufficiency and pulmonary function tests (spirometry), among others (Chart 1).

In all CFCCs, the medical team providing care in a shared outpatient setting had at least one pediatric and/or adult pulmonologist, but only 29 centers (57%) had a gastroenterologist for simultaneous outpatient care. Three centers reported that the number of physicians was insufficient to meet patient demand. A common complaint was limited access to other medical specialties (e.g., endocrinology, psychiatry, and rheumatology), which were restricted to referral and back-referral processes between institutions or between services within the same institution.

Forty-seven CFCCs (92%) reported that they had a multidisciplinary team, but the team was usually incomplete; 4 CFCCs (8%) lacked essential

Chart 1. Major problems reported in cystic fibrosis care centers in Brazil, 2021.

- lack of rooms for proper care
- lack of places for patient segregation
- lack of hospital beds for inpatient admission
- inadequate care for adult patients (provided by pediatric teams in pediatric outpatient clinics)
- lack of a pediatric-to-adult transition program
- delay in performing tests
- lack of basic tests, such as fecal elastase-1 to determine pancreatic insufficiency and of pulmonary function tests (spirometry) to assess lung disease progression
- insufficient number of physicians to meet patient demand
- limited access to other medical specialties
- incomplete multidisciplinary team
- multidisciplinary team members shared with other services
- multidisciplinary team members replaced or assigned other duties
- irregular neonatal screening in some states
- sweat test not covered by the Brazilian public health care system for patients over two years of age
- high cost of supplies for the collection and analysis of sweat chloride
- lack of trained personnel to perform sweat tests
- irregular supply of medications, with frequent shortages and inefficient distribution

multidisciplinary team members. Six CFCCs (12%) lacked a physical therapist, 5 (10%) lacked a dietitian, 17 (33%) lacked outpatient nursing care, 13 (25%) lacked outpatient social work services, 14 (27%) lacked a psychologist, and 32 (63%) lacked a clinical pharmacist. Only 1 CFCC had a physical educator in the outpatient clinic. In addition to an incomplete team, all coordinators reported that the multidisciplinary team members were shared with other services or frequently replaced and assigned other duties. Throughout the COVID-19 pandemic, the diversion of health care professionals, especially adult pulmonologists and physical therapists, to care for COVID-19 patients was an aggravating factor that had a great impact on the care of adult CF patients.

All pediatric CFCCs reported being linked to CF neonatal screening centers. However, we have no information on neonatal screening in the northern states that do not have a CFCC. Seven CFCCs (14%) in the northern and the northeastern regions of Brazil reported that the quality of newborn screening for CF was poor, with a significant delay in collecting the second sample for immunoreactive trypsinogen testing and in communicating screening test results, as well as irregularities in the performance/quality of the screening-related sweat test. In the southern, southeastern, and central-western regions of Brazil, the quality of neonatal screening for CF was reported to be good or very good, with occasional problems related to the lack of materials and/or personnel. Genetic testing, which should complement the diagnosis, was not readily available in all regions through health services provided by the SUS.

At least one laboratory is accredited to perform the sweat test in each state, being often linked to the neonatal screening referral center, but not necessarily linked to the CFCC. However, the SUS subsidizes the sweat test only for patients up to 2 years of age. The technique utilized to collect and measure sweat chloride varied from center to center: 2 centers used conductivity measurements, 5 centers used manual titration (the Gibson-Cooke method), and the remaining centers were affiliated with laboratories that used coulometric titration. Major complaints about the sweat test included lack of coverage by the SUS for patients over 2 years of age, high cost of supplies for the collection and measurement of sweat chloride, lack of supplies, and lack of trained personnel.

All CFCCs reported having access to the medications listed in the 2017 CF PCDT,[10] namely pancrelipase, dornase alfa, and inhaled tobramycin. However, all centers complained about the irregular supply of medications, with frequent shortages and inefficient distribution. Several coordinators reported that the lack of patient adherence to treatment might be related to the irregular provision of medications.

DISCUSSION

This brief analysis of the status of Brazilian CFCCs reveals the different realities faced by patients with CF across the country and the presence of difficulties in 100% of the CFCCs. Standardization of delivery of care in CFCCs can be challenging in a country of continental dimensions such as Brazil, with a culturally and socially diverse population, limited financial resources, and considerable variability in public health policies among the different states and municipalities. Without proper resources, CFCCs are at risk of providing fragmented, non-comprehensive, non-standardized, ineffective care, thus increasing the financial burden on our health care system. We should therefore establish priorities and suggest improvements.

All of the 51 Brazilian CFCCs registered with the GBEFC and spread across the country strive to follow the recommendations for the provision of standardized multidisciplinary care to patients with CF. However, there are chronic problems in all centers: there are few physicians for many patients; centers lack specialists and medical specialties, thus making multidisciplinary teams incomplete; team members are shared with other services and are often assigned other duties; and

qualifications and training of health care professionals vary considerably. In addition, only a few centers are qualified to provide care to adult patients; most centers are located in state capitals, and patients need to travel long distances; the infrastructure of CFCCs is seriously inadequate; centers lack rooms for proper care; neonatal screening is not regularly performed; sweat testing is often discontinued, and patients have their diagnosis delayed; and centers lack tests to assess disease progression and hospital beds for inpatient admission. In short, health care professionals strive to provide proper care, and Brazilian patients with CF struggle to have access to effective treatment.

Patients are heterogeneously distributed across Brazilian CFCCs, with a large number of patients in the southeastern and southern regions of the country (68% of cases) and only a few in the northern region (4%). This distribution supports the variable incidence of CF previously reported in Brazil,[11] known to be related to regional ethnic characteristics and miscegenation as a result of the colonization/immigration process in the country. This great variability poses a challenge to physicians and managers of specialist CFCCs, as the health departments of each state are responsible for the planning and distribution of such centers, which should be in accordance with the rates of live births and the incidence of CF in the state in order to ensure an adequate operational flow to facilitate user access and care coverage while reducing unnecessary costs and/or inadequate use of existing resources. However, despite the publication of some of our data and of those from the *Registro Brasileiro de Fibrose Cística* (REBRAFC, Brazilian CF Registry), the results of neonatal screening are poorly disseminated at the national/state levels, whether regarding screening for CF or other diseases.

Brazilian CFCCs present a wide spectrum of issues, ranging from large centers with many patients but insufficient staff to meet the demand to small centers with few patients and many difficulties in implementing multidisciplinary care. Better planning of the distribution of patients across CFCCs might lead to better patient care and better organization of teams, obviating the need for patients to travel long distances. Currently, 78% of the CFCCs are located in state capitals, whereas the remaining centers are located in major inland cities, often affiliated with medical schools. According to data from the 2018 REBRAFC annual report, 43 registered patients were born in the northern states that do not have a CFCC.[12] These patients are probably being cared for in other states or have moved to another city to receive treatment.

Brazilian CF care teams are often incomplete, and team members are frequently replaced, negatively affecting the quality of care. These health care professionals do not have a specific contract to provide CF care and often need to assume multiple roles. Institutions have no financial incentives to support the implementation of CFCCs, which reveals little interest in maintaining large skilled teams to provide exclusive care to patients with CF. Moreover, the lack of specific resources hinders the availability not only of more expensive ancillary tests, especially the sweat test, but also of simple pulmonary function tests and fecal elastase-1 measurements to determine pancreatic insufficiency.

Despite the difficulties, Brazil as a whole shows an increasing number of patients with CF reaching adulthood (about 25% of patients are over 18 years of age), and the increasingly early diagnosis has been associated with neonatal screening. According to data from the 2018 REBRAFC annual report, 1,406 cases had been diagnosed through neonatal screening since 2009, accounting for almost 60% of all new diagnoses.[12] However, the quality of the process of neonatal screening and diagnostic confirmation unfortunately remains inadequate and highly variable. There are delays in communicating screening test results and, consequently, in confirming the diagnosis in some states, which is inconsistent with all the investment in early diagnosis. It is therefore essential to identify the difficulties and better organize the services. Improving the interaction between CF screening services and CFCCs may facilitate this process.

Performing the sweat test is another critical point. Because it is a high-cost test with a complex technique, it is poorly available and associated with quality problems. Reformulating the sweat test funding policies is of paramount importance.

All CFCCs reported an irregular supply of medications, with frequent shortages and inefficient distribution, even when considering the medications included in the 2017 CF PCDT. Access to other medications, vitamins, supplements, devices, oxygen, and other resources needed by patients with CF is even more problematic, substantially affecting patient adherence to treatment. The recent publication of a new CF PCDT,[13] more comprehensive and complete, includes ivacaftor, which is one of the novel CFTR modulators that may be helpful. However, it is still necessary to improve the administrative and organizational processes in the states and their respective public pharmacies.

Each CFCC should be committed to provide high-quality, humanized, comprehensive, well-coordinated care, aiming to grasp the full complexity of CF. The implementation of qualified, well-equipped, integrated centers can result in considerable savings to the SUS, especially when compared with the provision of fragmented, non-comprehensive care. Few Brazilian states have consolidated public policies on CF. In most states, we have enormous difficulties in regularizing CF-related services with health managers and secretaries due to the lack of documents that properly describe the necessary conditions for the implementation of these services. Therefore, there is a great need to regulate the implementation of CF referral centers in Brazil and to establish a network of appropriately trained and qualified centers to confirm

Chart 2. Required features of cystic fibrosis referral centers according to the Brazilian Cystic Fibrosis Study Group.

1. A multidisciplinary team of CF specialist health care professionals:
   a. Pediatric and/or adult pulmonologist and pediatric and/or adult gastroenterologist
   b. Physical therapist
   c. Dietitian
   d. Nurse
   e. Psychologist
   f. Clinical pharmacist
   g. Social worker
      i. The team should be trained and qualified to care for patients with CF
      ii. The ratio of 1 attending physician/50 patients is recommended
      iii. The recommended workload for each health care professional should be as follows: coordinating physician—96 h/week; pulmonologist—120 h/week; gastroenterologist—48 h/week; physical therapist—240 h/week; dietitian—96 h/week; nurse—240 h/week; psychologist—96 h/week; pharmacist—72 h/week; and social worker—96 h/week
      iv. An adult health care team should be available when the number of patients > 18 years of age in the center exceeds 20
      v. Appointments should be provided for patients every 2-3 months
      vi. The multidisciplinary team should be supported with training and continuing professional development
2. Access to other medical specialties, such as genetics, endocrinology, psychiatry, rheumatology, pediatric surgery, thoracic surgery, nephrology, otolaryngology, specialist pain management, and palliative care
3. Facilities should be appropriate due to the possibility of contamination/cross-infection between patients and have a sufficient number of rooms to allow adequate patient segregation
4. Own/affiliated laboratories for ancillary diagnostic tests:
   1. Quantitative sweat chloride measurement in accordance with international reference documents[14]
   2. *CF transmembrane conductance regulator* (*CFTR*) gene sequencing
5. Emergency care available 24 h/day
6. Availability of support hospital beds for inpatient admissions
7. Access to:
   1. Pulmonary function testing
   2. A microbiology laboratory with experience and resources to identify typical CF-associated pathogens
   3. Chest radiography, CT, pulmonary angiography, abdominal ultrasound, and bone densitometry
   4. Fecal pancreatic elastase-1 testing
   5. Clinical pathology laboratory capable of performing routine tests
8. Respiratory (flexible bronchoscopy) and digestive endoscopy

CF: cystic fibrosis.

the diagnosis of CF and follow-up of CF patients using established treatment recommendations. Therefore, GBEFC recommends that Brazilian CF referral centers be constituted in accordance with the features described in Chart 2.

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AUTHOR CONTRIBUTIONS

EFAP was responsible for data collection. All of the authors equally contributed to study conception and design; data analysis and interpretation; statistical analysis; drafting and critical revision of the manuscript; and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Prevalence and associated factors of experimentation with and current use of water pipes and electronic cigarettes among medical students: a multicentric study in Brazil

Stella Regina Martins[1], Alberto José de Araújo (*in memoriam*)[2], Fernando C Wehrmeister[3], Beatriz Martins Freitas[4], Rafaela Giunti Basso[5], Alfredo Nicodemos Cruz Santana[6,7], Ubiratan de Paula Santos[1]

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Comissão de Combate ao Tabagismo, Associação Médica Brasileira, São Paulo (SP) Brasil.
3. Programa de Pós-Graduação em Epidemiologia, Universidade Federal de Pelotas, Pelotas (RS) Brasil.
4. Curso de Medicina, Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo (SP) Brasil.
5. Internal Medicine Residency Program, Southeast Health, Dothan (AL) USA.
6. Hospital Regional da Asa Norte, Escola Superior de Ciências da Saúde, Brasília, Brasília (DF) Brasil.
7. Núcleo Avançado de Tórax, Hospital Sírio-Libanês, Brasília (DF) Brasil.

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ABSTRACT

Objective: To evaluate the prevalence of and factors associated with experimentation with and current use of water pipes and e-cigarettes among medical students. **Methods:** This was a cross-sectional multicentric study involving a convenience sample of students from medical schools in most Brazilian geographic regions. Information about experimentation with and current use of conventional cigarettes, water pipes, and e-cigarettes; beliefs and attitudes toward tobacco products; religiosity; and demographics were collected by means of an online structured questionnaire. We used descriptive statistics and logistic regression to analyze the association of those factors. **Results:** Our sample comprised 700 individuals from four Brazilian regions. Prevalence of experimentation with and current use of cigarettes, water pipes, and e-cigarettes were, respectively, 39.1% and 7.9%; 42.6% and 11.4%; and 13.1% and 2.3%. Water pipe experimentation was higher among those who had a sibling (adjusted OR = 2.64; 95% CI, 1.24-5.61) or friends (adjusted OR = 2.33; 95% CI, 1.63-3.31) who smoke. The same occurred regarding e-cigarette experimentation: siblings (adjusted OR = 2.76; 95% CI, 1.17-6.50) and friends (adjusted OR = 2.47; 95% CI, 1:45-4.22). Curiosity and scent/taste were the major reasons for water pipe use and e-cigarette experimentation. Although 93% of the responders learned about health damages of smoking during medical school classes, 51.4% reported having experimented with at least one of these tobacco products. Most responders who reported feeling the presence of God/the Holy Spirit in their lives were never experimenters of water pipes (59.2%) or e-cigarettes (55.3%). **Conclusions:** There is a high prevalence of experimentation with tobacco products among medical students whose siblings or friends smoke, despite their knowledge about smoking harms.

Keywords: Education, medical; Health knowledge, attitudes, and practice; Electronic nicotine delivery systems; Smoking water pipes; Religion.

INTRODUCTION

Smoking is associated with 8 million deaths per year, being the number one cause of preventable deaths in the world.[1] Teenagers are daily enticed to try new products such as water pipes and electronic cigarettes (e-cigarettes), which are important risk factors for smoking initiation.[2,3]

In Brazil, the *Pesquisa Nacional de Saúde* (National Health Research) carried out by the *Instituto Brasileiro de Geografia e Estatística* (Brazilian Institute of Geography and Statistics) revealed a significant increase in the prevalence of water pipe smokers, from 0.6% in 2013 to 2.4% in 2019 in people between 18 and 24 years of age, and from 0.01% in 2013 to 0.1% in 2019 in those ≥ 25 years of age.[4,5]

Regarding the use of e-cigarettes with nicotine among Brazilians ≥ 15 years of age, its prevalence was 0.6% in 2019, being even more prevalent in those living in big city centers and among young people with a higher income.[5] The use of these products, which may or may not include nicotine, a potent psychoactive substance, leads to serious health issues.

A lot of young people choose to use the water pipe with non-tobacco products, but with herbal essences, full of pleasant and attractive additives such as various aromas and flavors, because they believe them to be less harmful to their health. However, it is known that except for nicotine, the concentrations of tar, carbon monoxide, polycyclic aromatic hydrocarbons, formaldehyde, acetaldehyde, and others are similar to those of the water pipe when used with tobacco.[6]

Correspondence to:
Stella Martins. Divisão de Pneumologia, Instituto do Coração, Avenida Dr. Enéas Carvalho de Aguiar, 44, Cerqueira César, CEP 05403-900, São Paulo, SP, Brasil.
Tel.: 55 11 26615191 E-mail: stellamartins@uol.com.br
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The surge in e-cigarette use is a great threat to public policies regarding tobacco control, especially among the young, because many of them are nonsmokers who experiment with the product as a trend and later develop a nicotine addiction. Approximately 40% of American high school students use the e-cigarette for ≥ 20 days a month, and almost a quarter of them use it daily.[7] It is known that the presence of propylene glycol and glycerol alone, the main substances for aerosol formation, causes damage to the health of users.[8]

Brazil has a limited amount of data regarding the use of these products, especially among medical students. This study aimed to evaluate the prevalence, beliefs, attitudes, reasons, and religiosity related to the experimentation with and use of water pipes and e-cigarettes among medical students residing in different regions in Brazil and to compare variables regarding sex, age, ethnicity, region, and income.

METHODS

This was an online survey carried out with medical students by means of a convenience sample of 11 medical schools located in the five geographic regions in Brazil. In all of the regions, two referral universities were invited to participate, except in the Southeast region, where three institutions were invited. The universities were initially contacted via an invitation letter to evaluate if they would be interested in participating in the study. Only the universities that agreed to participate were included in the study, and the research was conducted by a professor of the participating university. Students were invited to participate by the focal point during lectures and via an e-mail sent by the university secretariat. The students could access all information related to the survey, the invitation letter, the informed consent form, and the questionnaire through the link http://trabalhosmed.wix.com/pesquisacigarro.

The information collected in the questionnaire was related to demographics, socioeconomics, and experimentation with and use of smoking products, such as conventional cigarettes, water pipes, and e-cigarettes. Also, we included questions about attitudes, beliefs, and reasons for experimentation with or use of these products. These questions were administered to a pilot group before the beginning of the study and they reflected well what we wanted to investigate. There was no external validation, because our objective was to study the prevalence and profile of experimenters and users of conventional cigarettes, water pipes, and e-cigarettes.

The questionnaire was composed of questions from the Global Adult Tobacco Survey[9] and other published surveys on criteria for dependence, attitudes, beliefs, and religiosity regarding water pipes, e-cigarettes, and additional modules.[10,11]

In this study, the outcomes were experimentation with and current use of cigarettes, water pipes, and e-cigarettes. Individuals were asked about experimentation (yes or no) with each product. Individuals who reported having smoked ≥ 100 cigarettes in their lifetime and continued smoking at the time of the survey were considered cigarette smokers.[12] For water pipes and e-cigarettes, we considered any experimentation during life.

The variables studied were sex (male/female); skin color, categorized as White and non-White (black, brown, and yellow); age group (15-19, 20-24, and 25-29 years); family income (1-5, 6-10, 11-19, and ≥ 20 times the Brazilian national minimum wage at the time); region of the country where the institution is located (South, Southeast, Central-West, North, and Northeast); type of institution (public or private); current semester in medical school (semesters 1-2, 3-6, and 7-12); smokers close to the respondent (yes or no), which included friends, parents, and siblings; and two other questions: "Have you had any classes regarding smoking and its harms at your medical school?" (yes or no); and "Has any health professional ever asked you if you smoke?" (yes or no). Additionally, for those who reported having used or experimented with water pipes and e-cigarettes, we asked the reasons why (yes or no), the alternatives being scent/taste, relaxation, pleasure, curiosity, social belonging, and trend following. Regarding e-cigarettes, respondents were also asked whether their experimentation was related to reducing the consumption of conventional cigarettes or quitting smoking. The experience of religiosity was also studied in relation to whether it was associated to the consumption of tobacco products or not.

For statistical analysis, proportions of each of the outcomes were calculated for the overall population and by sample characteristics. Also, we used crude and adjusted logistic regression models to verify possible associated factors for each outcome. The adjusted model included all variables. Additionally, we described the co-occurrence of experimentation with the three tobacco products using Venn diagrams. The co-occurrence was considered as the experimentation of ≥ 2 tobacco products concomitantly. All analyses were conducted using Stata statistical software package, version 17.1 (Stata Corp LP, College Station, TX, USA).

This study was approved by the Research Ethics Committee of the *Escola de Medicina da Universidade de São Paulo* (Protocol CAAE no. 58935616.1.1001.0065).

RESULTS

The survey was available online between March of 2016 and January of 2018. The overall sample comprised 700 medical students from nine Brazilian medical schools in four of the five Brazilian regions. Despite being invited and agreeing to participate in the study, no responses were obtained from two medical schools in the Northeast region. The number of participants varied a lot among the institutions, being very low at some (Table S1).

Table 1 shows the sample characteristics as well as the prevalence of the outcomes of experimentation with and current use of conventional cigarettes, water pipes, and e-cigarettes. More than half of the sample was female, self-reported being White, were in the 20-24 year-old age group, and lived in the Southeast region. Experimentation with and use of traditional cigarettes and water pipes were lower in females than

Table 1. Sample characteristics and prevalence of experimentation with and current use of conventional cigarettes, water pipes, and electronic cigarettes (N = 700).

Variable	Sample	Experimentation (%)			Current use (%)		
	n (%)	Cigarette	Water pipe	Electronic cigarette	Cigarette	Water pipe	Electronic cigarette
Sex		p = 0.003	p = 0.055	p = 0.001	p < 0.001	p = 0.188	p = 0.960
Male	302 (43.1)	45.4	46.7	17.9	12.6	13.3	2.3
Female	398 (56.9)	34.4	39.5	9.6	4.3	10.1	2.3
Skin color		p = 0.002	p < 0.001	p = 0.001	p = 0.122	p = 0.096	p = 0.146
White	554 (79.1)	42.1	46.2	15.3	8.7	12.5	2.7
Non-White	146 (20.9)	28.1	28.8	4.8	4.8	7.5	0.7
Age group, years		p < 0.001	p = 0.005	p = 0.822	p = 0.260	p = 0.733	p = 0.003
15-19	78 (11.1)	25.6	28.2	15.4	3.9	14.1	7.7
20-24	461 (65.9)	37.3	42.3	12.8	7.9	11.1	1.7
25-29	161 (23.0)	50.9	50.3	13.0	9.9	11.2	1.2
Monthly family income, number of times the Brazilian national minimum wage		p = 0.110	p < 0.001	p = 0.068	p = 0.209	p = 0.001	p = 0.359
1-5	168 (24.0)	32.1	29.2	7.1	7.7	4.8	1.2
6-10	187 (26.7)	38.0	41.2	14.4	4.8	8.6	2.1
11-19	200 (28.6)	42.5	48.0	15.0	8.5	15.0	2.0
≥ 20	145 (20.7)	44.1	52.4	15.9	11.0	17.9	4.1
Geographic region		p = 0.006	p < 0.001	p = 0.033	p = 0.008	p = 0.033	p = 0.456
South	32 (4.6)	37.5	40.6	15.6	12.5	6.3	3.1
Southeast	375 (53.6)	44.8	50.1	14.9	10.7	12.3	2.9
Central-west	142 (20.3)	35.2	50.0	15.5	4.2	16.2	2.1
North	151 (21.6)	29.1	17.2	6.0	3.3	6.0	0.7
Type of institution		p = 0.006	p < 0.001	p < 0.001	p = 0.006	p = 0.006	p = 0.051
Public	569 (81.3)	36.7	38.5	10.9	6.5	9.8	1.8
Private	131 (18.7)	49.6	60.3	22.9	13.7	18.3	4.6
Period of the medical course, semester		p = 0.767	p = 0.028	p = 0.721	p = 0.038	p = 0.153	p = 0.683
7-12	279 (39.9)	37.6	44.1	14.0	9.7	13.3	1.8
3-6	278 (39.7)	40.7	46.0	11.9	4.7	11.9	2.9
1-2	143 (20.4)	39.2	32.9	14.0	10.5	7.0	2.1
Has a friend who smokes		p < 0.001	p < 0.001	p < 0.001	p < 0.001	p = 0.002	p = 0.027
No	322 (46.0)	30.1	30.1	7.8	2.8	7.5	0.9
Yes	378 (54.0)	46.8	53.2	17.7	12.2	14.8	3.4
Has a parent who smokes		p = 0.002	p = 0.001	p = 0.227	p = 0.076	p = 0.029	p = 0.449
No	613 (87.6)	37.0	40.1	12.6	7.2	10.4	2.5
Yes	87 (12.4)	54.0	59.8	17.2	12.6	18.4	1.2
Has a sibling who smokes		p = 0.014	p = 0.003	p = 0.022	p = 0.003	p = 0.023	p = 0.237
No	660 (94.3)	38.0	41.2	12.4	7.1	10.8	2.1
Yes	40 (5.7)	57.5	65.0	25.0	20.0	22.5	5.0
Knowledge on the harms of smoking from medical school classes		p=0.581	p = 0.733	p = 0.806	p = 0.308	p = 0.852	p = 0.267
No	49 (7.0)	42.9	44.9	14.3	4.1	12.2	0.0
Yes	651 (93.0)	38.9	42.4	13.1	8.1	11.4	2.5
Any health professional asked if you smoke		p = 0.146	p = 0.001	p = 0.041	p < 0.001	p = 0.091	p = 0.605
No	351 (50.1)	36.5	36.5	10.5	4.3	9.4	2.0
Yes	349 (49.9)	41.7	48.7	15.8	11.5	13.5	2.6
Total	700 (100)	39.1	42.6	13.1	7.9	11.4	2.3

in males, whereas experimentation with and use of e-cigarettes were similar in both sexes. More than 90% of the participants reported having learned about health damages caused by smoking during medical school classes. More than 50% of the respondents were never asked by any health care professional whether they were smokers or not (Table 1).

Regarding experimentation with tobacco products, 39.1% used conventional cigarettes, 42.6% used water pipes, and 13.1% used e-cigarettes. As for the current use of conventional cigarettes, water pipes, and e-cigarettes, prevalence was 7.9%, 11.4%, and 2.3%, respectively (Table 1).

The mean age of experimentation with cigarettes and water pipes was 16.9 years of age, whereas that of experimentation with e-cigarettes was 20.1 years. Among water pipe users, 86.9% reported sharing the mouthpiece with other users.

Figure 1 shows the co-occurrence of experimentations with cigarettes (n = 223), water pipes (n = 237), and e-cigarettes (n = 99). The majority of the respondents who experimented with water pipes also experimented with conventional cigarettes. Although the prevalence of e-cigarette use was low, the majority of the e-cigarette users also reported using water pipes and/or conventional cigarettes (Figure 1).

Factors associated with the experimentation with cigarettes, water pipes, and e-cigarettes are presented in Table 2. In the adjusted model, being female or non-White was related to lower experimentation with all tobacco products (Table 2).

Cigarette experimentation was higher among those in the 25-29 year-old age group (adjusted OR = 3.22; 95% CI, 1.72-6.02) and those whose siblings (adjusted OR = 2.18; 95% CI, 1.07-4.43), parents (adjusted OR = 2.08; 95% CI, 1.27-3.41), or friends (adjusted OR = 2.00; 95% CI, 1.41-2.82) were smokers (Table 2).

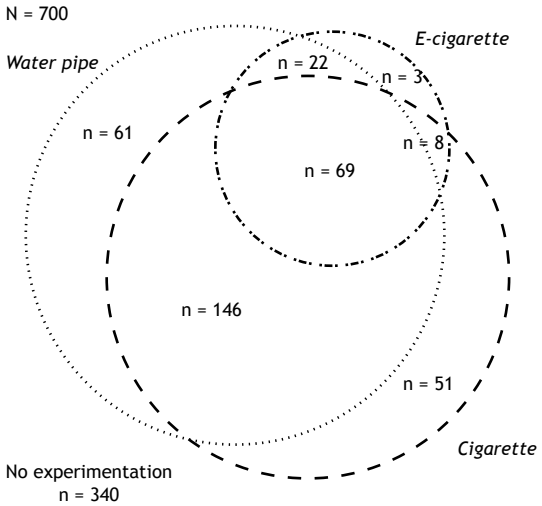

Figure 1. Co-occurrence of cigarette, water pipe, and electronic cigarette experimentation.

Table 2 shows that water pipe experimentation was more than two times higher for those having siblings (adjusted OR = 2.64; 95% CI, 1.24-5.61), friends (adjusted OR = 2.33; 95% CI, 1.63-3.31), or parents (adjusted OR = 2.25; 95% CI, 1.37; 3.77) who smoked.

E-cigarette experimentation was more than two times higher for those having siblings (adjusted OR = 2.76; 95% CI, 1.17-6.50) or friends (adjusted OR = 2.47; 95% CI, 1.45-4.22) who smoked (Table 2). E-cigarette experimentation was also associated with private institutions (adjusted OR = 3.83; 95% CI, 2.00-7.36).

The current use of cigarettes and water pipes regarding sex and having friends, parents, or siblings who smoked (Table S2) shows a similar pattern to the one seen regarding experimentation with these two products (Table 2). The two main reasons for water pipe use and e-cigarette experimentation were curiosity and scent/taste (Figure 2). Additionally, 13.0% and 26.1% of e-cigarette experimenters reported using the product as an attempt to reduce cigarette smoking and to quit smoking, respectively (Figure 2). However, those who reported using e-cigarettes to quit smoking conventional cigarettes were unable to do it, since none of them quit either.

Water pipe experimenters reported that this product causes more damages to health (42.6%) but is less addictive (69.1%) than are conventional cigarettes (Table 3). In addition, those who had never experimented and those who had experimented with e-cigarettes (55.9% and 72.8%, respectively) reported believing that e-cigarettes are less addictive than are conventional cigarettes (Table 3).

Religiosity aspects of water pipe and e-cigarette experimenters and never experimenters can be found in Table 4. There was a statistically significant difference in all study variables related to the influence of religiosity between water pipe never experimenters and experimenters. However, this relationship was not found between e-cigarette never experimenters and experimenters, except for the topic "my religious belief guides my way of living" (p = 0.016).

Feeling the presence of God/the Holy Spirit in their lives was more often reported among water piper and e-cigarette never experimenters than among experimenters (Table 4). In addition, "my religious belief guides my way of living" was more commonly reported among water pipe never experimenters (Table 4).

DISCUSSION

As far as we know, this is the first Brazilian multicentric study involving medical students with respect to tobacco products that have a great appeal among young people, such as water pipes and e-cigarettes.

One of the main findings of this study was how siblings, friends, or parents who smoked influenced

Table 2. Experimentation with conventional cigarettes, water pipes, and electronic cigarettes.

Variable	Experimentation					
	Cigarette		Water pipe		Electronic cigarette	
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex	p = 0.003	p < 0.001	p = 0.055	p = 0.001	p = 0.001	p < 0.001
Male	1.00	1.00	1.00	1.00	1.00	1.00
Female	0.63 (0.47-0.86)	0.53 (0.38-0.74)	0.74 (0.55-1.01)	0.55 (0.39-0.79)	0.48 (0.31-0.76)	0.32 (0.19-0.53)
Skin color	p = 0.002	p = 0.024	p < 0.001	p = 0.057	p = 0.002	p = 0.008
White	1.00	1.00	1.00	1.00	1.00	1.00
Non-white	0.54 (0.36-0.80)	0.59 (0.38-0.93)	0.47 (0.32-0.70)	0.63 (0.40-1.01)	0.28 (0.13-0.61)	0.31 (0.13-0.74)
Age group, years	p < 0.001	p < 0.001	p = 0.004	p = 0.012	p = 0.831	p = 0.157
15-19	1.00	1.00	1.00	1.00	1.00	1.00
20-24	1.73 (1.00-2.97)	1.67 (0.94-2.96)	1.87 (1.10-3.16)	1.53 (0.86-2.75)	0.81 (0.41-1.58)	0.55 (0.26-1.14)
25-29	3.01 (1.66-5.46)	3.22 (1.72-6.02)	2.58 (1.44-4.61)	2.75 (1.43-5.27)	0.83 (0.38-1.78)	0.57 (0.25-1.32)
Monthly family income, number of times the Brazilian national minimum wage	p = 0.099	p = 0.391	p < 0.001	p = 0.036	p = 0.026	p = 0.325
1-5	1.00	1.00	1.00	1.00	1.00	1.00
6-10	1.29 (0.83-2.00)	1.18 (0.73-1.90)	1.70 (1.09-2.65)	1.34 (0.82-2.21)	2.19 (1.07-4.84)	1.88 (0.87-4.05)
11-19	1.56 (1.02-2.39)	1.53 (0.96-2.43)	2.24 (1.45-3.46)	1.96 (1.20-3.19)	2.29 (1.13-4.64)	1.82 (0.86-3.87)
≥ 20	1.66 (1.05-2.64)	1.26 (0.76-2.09)	2.67 (1.68-4.26)	1.74 (1.03-2.93)	2.45 (1.17-5.12)	1.50 (0.68-3.30)
Geographic region	p = 0.701	p = 0.891	p = 0.049	p = 0.092	p = 0.134	p = 0.319
South	1.00	1.00	1.00	1.00	1.00	1.00
Southeast	1.35 (0.64-2.85)	1.11 (0.50-2.47)	1.47 (0.71-3.06)	1.07 (0.48-2.39)	0.95 (0.35-2.57)	0.44 (0.15-1.35)
Central-west	0.91 (0.41-2.00)	0.94 (0.41-2.17)	1.46 (0.67-3.18)	1.59 (0.69-3.68)	0.99 (0.34-2.85)	1.03 (0.33-3.24)
North	0.69 (0.31-1.52)	0.91 (0.39-2.13)	0.30 (0.13-0.69)	0.42 (0.17-1.02)	0.34 (0.11-1.10)	0.47 (0.13-1.65)
Type of institution	p = 0.007	p = 0.068	p < 0.001	p = 0.001	p < 0.001	p < 0.001
Public	1.00	1.00	1.00	1.00	1.00	1.00
Private	1.69 (1.16-2.49)	1.55 (0.97-2.47)	2.43 (1.65-3.58)	2.22 (1.37-3.58)	2.43 (1.49-3.95)	3.83 (2.00-7.36)
Period of the medical course, semester	p = 0.758	p = 0.683	p = 0.047	p = 0.118	p = 0.783	p = 0.683
7-12	1.00	1.00	1.00	1.00	1.00	1.00
3-6	1.13 (0.81-1.60)	1.17 (0.81-1.68)	1.08 (0.76-1.51)	1.15 (0.79-1.66)	0.83 (0.50-1.36)	0.85 (0.50-1.44)
1-2	1.07 (0.71-1.61)	1.13 (0.72-1.77)	0.62 (0.41-0.95)	0.66 (0.41-1.05)	1.00 (0.56-1.79)	1.10 (0.59-2.10)
Has a friend who smokes	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p = 0.001
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	2.04 (1.49-2.79)	2.00 (1.41-2.82)	2.63 (1.93-3.60)	2.33 (1.63-3.31)	2.56 (1.57-4.16)	2.47 (1.45-4.22)
Has a parent who smokes	p = 0.003	p = 0.004	p = 0.001	p = 0.002	p = 0.229	p = 0.127

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Table 2. Experimentation with conventional cigarettes, water pipes, and electronic cigarettes.

Variable	Experimentation							
	Cigarette		Water pipe		Electronic cigarette			
	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.99 (1.27-3.14)	2.08 (1.27-3.41)	2.22 (1.40-3.50)	2.25 (1.37-3.77)	1.45 (0.79-2.66)	1.69 (0.86-3.33)
Has a sibling who smokes	p = 0.017	p = 0.032	p = 0.004	p = 0.011	p = 0.026	p = 0.021
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	2.20 (1.16-4.21)	2.18 (1.07-4.43)	2.65 (1.36-5.17)	2.64 (1.24-5.61)	2.35 (1.11-4.98)	2.76 (1.17-6.50)
Knowledge on the harm of smoking from medical school classes	p = 0.434	p = 0.291	p = 0.733	p = 0.382	p = 0.806	p = 0.923
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	0.85 (0.47-1.52)	0.71 (0.37-1.35)	0.90 (0.50-1.62)	0.74 (0.38-1.44)	0.90 (0.39-2.07)	1.05 (0.42-2.58)
Any health professional asked if you smoke	p = 0.157	p = 0.950	p = 0.002	p = 0.428	p = 0.042	p = 0.560
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.25 (0.92-1.70)	0.99 (0.71-1.39)	1.65 (1.22-2.24)	1.15 (0.81-1.63)	1.59 (1.02-2.48)	1.16 (0.71-1.89)

our sample of medical students on experimenting with cigarettes, water pipes, or e-cigarettes. The adjusted ORs for experimentation with cigarettes were significantly higher in those medical students whose siblings, parents, or friends were smokers. These results corroborate studies carried out in Saudi Arabia[13] and Iran.[14] The same was true regarding water pipe users, corroborating a study regarding parental smokers in Iran[14] and an American study regarding the use of the water pipes among friends.[15] Regarding e-cigarette experimentation, the adjusted ORs were higher for those who reported having siblings or friends who smoked. In regard to the use of the three products, there was a correlation between having some kind of relationship with users of these products and the smoking behavior of the respondents.[16]

Another important result regards the knowledge and beliefs of the medical students who experimented with tobacco products. More than 42% of water pipe experimenters recognized that water pipe smoking would be more harmful than would conventional cigarette smoking. A study involving medical students revealed similar data, proving that they have knowledge about the harms of water pipe use.[17] It has been shown that a water pipe smoking session provides nicotine and carbon monoxide levels, respectively, up to 1.7 and 9.0 times higher than those provided by smoking one cigarette and that the inhaled smoke volume in a one-hour water pipe session can be equivalent to inhaling the volume of smoke of 100-200 cigarettes.[18] Regarding e-cigarettes, our study showed that 72.8% of experimenters believed that e-cigarettes are less addictive than are conventional cigarettes. The presence of nicotine salt in e-cigarettes provides the same or higher levels of nicotine than those found in conventional cigarettes, possibly leading to nicotine addiction.[19,20] Nicotine salt arises from the addition of benzoic acid to free-base nicotine. It is usually found in the fourth generation of e-cigarettes and is more addictive than free-base nicotine used in conventional cigarettes. The lower pH of the nicotine salt reduces the harshness and the unpleasant tobacco flavor, making experimentation easier for teenagers. This way, users of e-cigarettes can take deeper puffs that deliver nicotine faster and directly to the structures of the respiratory system, such as bronchi and alveoli, resulting in increased absorption.[21,22] Nicotine impacts the brain in a faster and powerful way leading teenagers and young adults to nicotine addiction in a shorter space of time.[23] At this age, the brain areas that start to suffer neuroadaptations in the presence of nicotine are yet to be fully formed.[24] The spread of the use of nicotine salt is one of the greatest dangers that public health has to face nowadays to prevent teens and young adults from becoming addicted to nicotine.

Experimentation with harmful and addictive products highlights the cognitive distortion observed by the inconsistent relationship between cognition and attitudes, leading to risk exposure because of

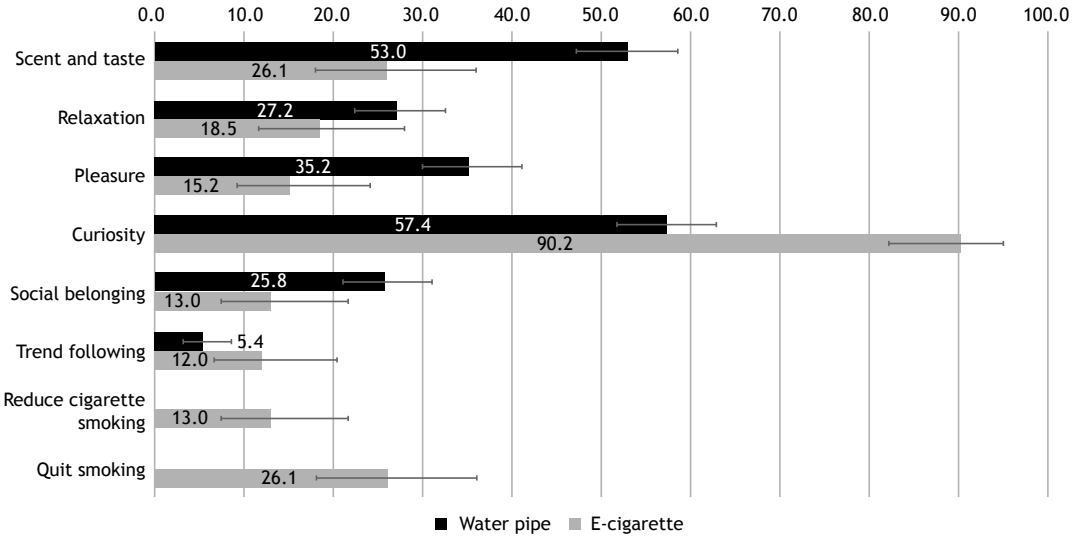

Figure 2. Prevalence (95% CI) of the reasons for water pipe use and electronic cigarette experimentation.

a false perception of personal immunity.[25-27] This is also observed regarding the high prevalence of the unsanitary sharing of the mouthpiece among water pipe users, which equally represents a health risk.[28]

Our study showed that 26.1% of the students reported e-cigarette use as an attempt to quit smoking, which is similar to the results of another study involving medical students that showed that 23.3% of the respondents believed that e-cigarette use is an option for smoking cessation.[29] However, our study observed that, none of those 26.1% managed to treat nicotine addiction because they were unable to stop using conventional cigarettes and/or e-cigarettes.

The use of e-cigarettes as a form of treatment for smoking cessation can lead to the maintenance of nicotine addiction.[30] Even if smokers reduce their cigarette consumption while using e-cigarettes, it is unlikely that there will be any cardiovascular benefit due to the highly nonlinear dose-response relationship between exposure to fine particles and risk of cardiovascular disease.[31-33]

It is worth remembering that the American Thoracic Society recommends using medications, such as varenicline and others, instead of e-cigarettes, for the treatment of smoking cessation.[34] Furthermore, the position of the US Preventive Services Task Force is that there are no conclusive data on the benefits and harms of e-cigarettes in the treatment of smoking cessation.[35] The Brazilian Medical Association, together with the Brazilian Thoracic Society, the Brazilian Pediatrics Society, and other entities, does not recommend the use of e-cigarettes either.[36] Thus, e-cigarettes are not currently seen as a safe and effective alternative for treatment for nicotine addiction, although this belief is present in a significant portion of e-cigarette users. There is an urgent need for public prevention policies and greater discussion on the subject among medical students.

The high proportion of knowledge about the health damages caused by smoking is noteworthy, which contrasts with the relevant prevalence of experimentation with conventional cigarettes, water pipes, and e-cigarettes, especially among men. However, because of our study design and sample size, we could not associate knowledge of the addictive power of water pipe and e-cigarette use as a factor for reducing the experimentation of these products.

As for religiosity, we observed that almost 80% of those who reported that they totally believed that they feel the presence of God/the Holy Spirit in their lives had never experimented with water pipes (40.8%) or e-cigarettes (36.5%). Studies confirm that young people who experience their religiosity are more protected from tobacco use.[37] Religious involvement may lead individuals to assume healthier behaviors. Explanations for this phenomenon can be due to the promotion of self-esteem, self-control, and a sense of mastery.[38]

Other major reasons for water pipe use and e-cigarette experimentation were curiosity, scent/taste, pursuit of pleasure, relaxation, and group belonging. Pleasure and relaxation were also reported to be the most common reasons for the use of water pipes in a systematic review.[39] Curiosity and scent/taste delivered by the attractive additives present in e-cigarettes were also the two major reasons reported in another study that investigated the reasons for e-cigarette experimentation.[40] The World Health Organization has long warned about the appealing flavors in tobacco products that impart attractive taste and scent as a risk factor for smoking initiation.[41]

Our study has some limitations. We intended to make a census of all the medical students of the selected medical schools; thus a sample size calculation was not performed. We used a virtual platform for the feasibility of the study, and the invitation to participate in the research was sent to the students through

Table 3. Beliefs regarding harms to health and addiction caused by water pipes and electronic cigarettes among never experimenters versus experimenters.[a]

Belief	Water pipe/electronic cigarette use	Water pipe			Electronic cigarette		
		Never experimenter (n = 402)	Experimenter (n = 298)	p*	Never experimenter (n = 608)	Experimenter (n = 92)	p*
Harm to health	Not harmful	2 (0.5)	3 (1.0)	0.001	24 (4.0)	4 (4.3)	0.282
	Less harmful than cigarettes	32 (8.0))	50 (16.8)		332 (54.6)	59 (64.1)	
	As harmful as cigarettes	157 (39.1)	118 (39.6)		222 (36.5)	27 (29.4)	
	More harmful than cigarettes	211 (52.5)	127 (42.6)		30 (4.9)	2 (2.2)	
Addiction	Less addictive than cigarettes	169 (42.0)	206 (69.1)	< 0.001	340 (55.9)	67 (72.8)	0.001
	As addictive as cigarettes	179 (44.6)	75 (25.2)		251 (41.3)	20 (21.7)	
	More addictive than cigarettes	54 (13.4)	17 (5.7)		17 (2.8)	5 (5.4)	

[a]Values expressed as n (%). *Chi-square test

Table 4. Influence of religiosity among water pipe and electronic cigarette never experimenters versus experimenters.

Religiosity	Response	Water pipe			Electronic cigarette		
		Never experimenter (n = 402)	Experimenter (n = 298)	p*	Never experimenter (n = 608)	Experimenter (n = 92)	p*
Frequency of going to a church, temple, or religious meetings	Once a week or more	31 (7.7)	7 (2.4)	< 0.001	35 (5.7)	3 (3.3)	0.146
	Once a week	64 (15.9)	16 (5.4)		73 (12.0)	7 (7.6)	
	2-3 times a month	32 (8.0)	17 (5.7)		45 (7.4)	4 (4.4)	
	A few times a year	103 (25.6)	98 (32.9)		167 (27.5)	34 (37.0)	
	Once a year or less	65 (16.2)	52 (17.5)		106 (17.4)	11 (12.0)	
	Never	107 (26.6)	108 (36.2)		182 (29.9)	33 (35.9)	
Frequency of individual religious activities (prayer, meditation, religious text reading)	More than once a day	17 (4.2)	7 (2.4)	0.033	23 (3.8)	1 (1.1)	0.362
	Once a day	100 (24.9)	53 (17.8)		137 (22.5)	16 (17.4)	
	2-3 times a week	54 (13.4)	32 (10.7)		76 (12.5)	10 (10.9)	
	Once a week	25 (6.2)	15 (5.0)		36 (5.9)	4 (4.4)	
	A few times a month	47 (11.7)	45 (15.1)		80 (13.2)	12 (13.0)	
	Rarely or never	159 (39.6)	146 (49.0)		256 (42.1)	49 (53.3)	
I feel the presence of God/the Holy Spirit in my life	Totally true	164 (40.8)	78 (26.2)	0.002	222 (36.5)	20 (21.7)	0.068
	Usually true	74 (18.4)	64 (21.5)		114 (18.8)	24 (26.1)	
	Not sure	49 (12.2)	43 (14.4)		77 (12.7)	15 (16.3)	
	Usually not true	22 (5.5)	25 (84.4)		39 (6.4)	8 (8.7)	
	Not true	93 (23.1)	88 (29.5)		156 (25.7)	25 (27.2)	

Continue...▶

Table 4. Influence of religiosity among water pipe and electronic cigarette never experimenters versus experimenters. (Continued...)

Religiosity	Response	Water pipe			Electronic cigarette		
		Never experimenter (n = 402)	Experimenter (n = 298)	p*	Never experimenter (n = 608)	Experimenter (n = 92)	p*
My religious belief guides my way of living	Totally true	71 (17.7)	20 (6.7)	< 0.001	87 (14.3)	4 (4.4)	0.016
	Usually true	119 (29.6)	76 (25.5)		175 (28.8)	20 (21.7)	
	Not sure	49 (12.2)	38 (12.8)		71 (11.7)	16 (17.4)	
	Usually not true	37 (9.2)	35 (11.7)		62 (10.2)	10 (10.9)	
	Not true	126 (31.3)	129 (43.3)		213 (35.0)	42 (45.6)	
I make a lot of effort to live my religion in all aspects of my life	Totally true	59 (14.7)	18 (6.0)	< 0.001	72 (11.8)	5 (5.4)	0.06
	Usually true	99 (24.6)	54 (18.1)		137 (22.5)	16 (17.4)	
	Not sure	62 (15.4)	37 (12.4)		89 (14.6)	10 (10.9)	
	Usually not true	31 (7.7)	52 (17.5)		67 (11.0)	16 (17.4)	
	Not true	151 (37.6)	137 (46.0)		243 (40.0)	45 (48.9)	

[a]Values expressed as n (%). *Chi-square test.

the focal point and the university secretariat, so the sample was not randomly selected. Because students rarely access their e-mails and are in high demands to participate in research, it might have been difficult for them to adhere. Also, students who smoke or experiment with tobacco products might not have wanted to complete the questionnaire, which could have led to a selection bias. Additionally, the majority of answers were from students in the Southeast region, and no responses were collected from the Northeast region of Brazil, which could have led to a selection bias and impaired the generalization of the results. Therefore, considering all of the impairments, extrapolation should be done cautiously because our findings may not reflect other realities.

In conclusion, smoking and tobacco issues should continue to be discussed and taught in the undergraduate health professional curriculum because, although the majority of the respondents reported having learned about the health damages of tobacco products in medical school classes, more than half of those also reported having experimented with cigarettes, water pipes, and/or e-cigarettes. Also, more studies are necessary to understand the attitudes and beliefs of health professionals regarding the tobacco products available on the market and the risks to public health.

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AUTHOR CONTRIBUTIONS

SRM: study design; coordination, collection, and organization of data for statistical analysis; data analysis; interpretation of results; drafting and revision of the manuscript; and approval of the final version. AJA: study design; coordination, collection, and organization of data for statistical analysis; statistical analysis performance; and interpretation of results. FCW: organization of data for statistical analysis; statistical analysis performance; interpretation of results; revision of the manuscript; and approval of the final version. BMF: data analysis; interpretation of results; drafting and revision of the manuscript; and approval of the final version. RGB: study design; coordination and collection of data; drafting of the manuscript; and approval of the final version. ANCS: coordination and collection of data; drafting of the manuscript; and approval of the final

version. UPS: revision of the manuscript; and approval of the final version.

CONFLICTS OF INTEREST

None declared.

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Use of electronic cigarettes and hookah in Brazil: a new and emerging landscape. The Covitel study, 2022

Ana Maria Baptista Menezes[1], Fernando C Wehrmeister[1], Luciana Monteiro Vasconcelos Sardinha[2], Pedro do Carmo Baumgratz de Paula[2], Tainá de Almeida Costa[2], Pedro Augusto Crespo[1], Pedro C Hallal[1]

1. Universidade Federal de Pelotas, Pelotas (RS) Brasil.
2. Vital Strategies, São Paulo (SP) Brasil.

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Study carried out at the Universidade Federal de Pelotas, Pelotas (RS) Brasil.

ABSTRACT

Objective: To estimate the prevalence of current commercial cigarette smoking, as well as those of e-cigarette and hookah experimentation and current use among adults (≥ 18 years of age) in Brazil. **Methods:** This study was based on a countrywide cross-sectional telephone-based survey conducted in 2022. The sample was designed to be representative of the five macroregions in Brazil and included 1,800 individuals from each of the regions. Telephone numbers, using a random digit dialing procedure, were proportionally selected for each direct distance dialing code in each region and then electronically validated (i.e., 900 cell and 900 landline phone numbers per region). Information on current commercial cigarette smoking (regardless of frequency/amount), as well as lifetime history of or current e-cigarette and hookah use (regardless of amount), were collected. **Results:** The prevalence of lifetime history of e-cigarette and hookah use was identical (7.3%; 95% CI: 6.0-8.9), whereas the prevalence of current commercial cigarette smoking was 12.2% (95% CI: 10.4-14.1). Young adults (18-24 years) had the highest prevalence of e-cigarette experimentation (19.7%; 95% CI: 15.1-17.0) and hookah experimentation (17%; 95% CI: 12.2-23.2). E-cigarette and hookah use was more common in the Central-West region and among those with a high level of education, whereas current commercial cigarette smoking was more common among those with a lower level of education. Individuals who used the three forms of nicotine delivery corresponded to 1.5% of the sample (nearly 2 million individuals based on the estimated size of the Brazilian adult population). **Conclusions:** Surveillance is essential for the monitoring and prevention of these new forms of nicotine consumption.

Keywords: Electronic nicotine delivery systems; Smoking water pipes; Nicotine; Tobacco products; Adults.

INTRODUCTION

Over the past few years, the world has been facing a smoking paradox: on the one hand, there has been a decline in commercial cigarette smoking due to long-term public policies. On the other hand, there has been a rise in other forms of smoking or vaping, such as electronic cigarettes (e-cigarettes) and hookah (also known as water pipe or shisha).[1-3] While health institutions and governments have been fighting against and banning all kinds of tobacco, the industry finds other ways to profit through creative means. Vaping mainly targets young people and, most importantly, is advertised as harmless and safe.[1,4] Despite that industry message, it is known that most of the new vaping devices contain nicotine (the concentration of which is unknown in some cases) hidden by colors, flavors, and a variety of other disguises to reach new customers.[1,4-8]

Brazil has achieved one of the most significant declines in the prevalence of smoking in the world: a nearly 70% decline among adults (≥ 20 years of age) from 1990 to 2017 (35.3% to 11.3%).[2] This resulted from a series of regulatory measures and anti-tobacco policies implemented in the country.[9] However, the new nicotine delivery systems, already very common in the USA and elsewhere,[1,10] are fashionable in Brazil, not only among teenagers but also among young adults.[11-13] Today, health care providers and researchers must inquire patients not only on the use of commercial cigarettes but also on other types of smoking/vaping, the type of device, and the frequency of use (or number of sessions), since subjects can use more than one type (known as the dual use).[14,15]

According to surveys in Brazil, the most recent prevalence estimates of electronic nicotine delivery systems (ENDS) experimental use among adults varied from 1.6% in 2013[13,16] to 6.7% in 2019.[17] A previous national survey carried out in 2013 found that the prevalence of hookah use among adults who self-reported its use was 1.2%.[13,16] However, these surveys differed in the wording of the questions, the interview strategies (face-to-face or via

Correspondence to:
Ana Maria Baptista Menezes. Rua Marechal Deodoro, 1160, 3º andar, CEP 96020-220, Pelotas, RS, Brasil.
Tel./Fax: 55 53 3284-1300. E-mail: anamene.epi@gmail.com
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telephone) and the sampling strategies. A countrywide cross-sectional telephone-based survey (designated Covitel) was launched in 2022 to estimate the burden of risk factors for noncommunicable diseases in Brazil. The objective of the present study was to estimate the prevalence of commercial cigarette smoking, focusing on e-cigarette and hookah experimentation in adults (≥ 18 years of age).

METHODS

This study was based on a countrywide cross-sectional telephone-based survey carried out during the first trimester of 2022 in Brazil. The survey was designed to represent the country and its five macroregions for the population aged 18 years or older. The sample size was calculated with a 95% CI and a margin of error of prevalence estimates of up to three percentage points. This resulted in a sample of 1,800 (900 cell phones and 900 landline phones) individuals per region, totaling 9,000 people.

Telephone numbers were selected using a random digit dialing procedure proportionally for each direct distance dialing code in each region (primary sampling unit). The telephone numbers were electronically checked, and those validated in each region were randomly selected for interview. In the case of cell phones, the person who answered the call was interviewed if he/she met the inclusion criterion (≥ 18 years of age); as for landline phones, a list of all household members aged 18 years or older was made before a random selection of one individual living in the household.

Participants were presented with an informed consent form, and those who accepted it gave verbal consent. All interviews were recorded and securely stored. The Research Ethics Committee of the *Escola Superior de Educação Física* of the *Universidade Federal de Pelotas* approved the research project (CAAE no. 53255321.9.0000.5313; approval protocol no. 5125635).

A brief questionnaire was administered to those who agreed to participate. The three outcome variables were based on the following questions: (1) "Currently, do you smoke (commercial cigarettes)?"; (2) "Have you ever used electronic cigarettes to smoke or vape?"; (3) "Have you ever used hookah to smoke or vape?" For e-cigarettes and hookahs, we additionally asked about the frequency of use. We considered as current users those who answered "yes, daily" or "yes, but not daily."

Other variables collected for the analyses were sex (male/female); self-reported skin color (white, black, brown, and other); age, in completed years (18- to 24-year, 25- to 34-year, 35- to 59-year, and ≥ 60 year age groups); level of education, in completed years of schooling (0-8, 9-11, and ≥ 12 years); and country macroregion (Central-West, Northeast, North, Southeast, and South).

In the statistical analysis, we first described the prevalence of the three outcomes according to the characteristics of the sample, presenting the point estimate and the corresponding 95% CI. For specific analysis, we calculated the prevalence of each outcome by sex and region. Finally, we made a Venn diagram to understand the co-occurrence of the three outcomes. All analyses were carried out using the sample weight calculated to represent the Brazilian population, considering the regions of residence, sex, years of schooling, and age brackets; the software Stata, version 14.0 (Stata Corp LP, College Station, TX, USA) was used for the statistical analyses.

RESULTS

We evaluated 9,004 individuals, corresponding to an extrapolated 134 million Brazilians aged 18 years or older. Table 1 describes the characteristics of the sample regarding tobacco/nicotine consumption. The prevalence of current commercial cigarette smoking, lifetime history of e-cigarette use, and lifetime history of hookah use was, respectively, 12.2%, 7.3%, and 7.3%. The prevalence of all three was higher in men than in women.

Current commercial cigarette smoking was more prevalent among those in the 25-to 34-year age bracket, whereas a lifetime history of e-cigarette and hookah use was more common in younger adults (18-24 years). A history of e-cigarette and hookah use was lower among those with a lower level of education (0-8 years of schooling), whereas the prevalence of current commercial cigarette smoking was lower among those with a higher level of education.

Figure 1 displays current commercial cigarette smoking and lifetime history of e-cigarette and hookah use in men and women in Brazil and in the five macroregions of the country. Nearly 20% of males in the Central-West, Southeast, and South regions, as well as 14% of females in the South region, reported being current cigarette smokers. In both men and women, a history of e-cigarette (14.6% vs. 7.9%) and hookah use (17.4% vs. 10.2%) was highest in the Central-West region.

The categorized frequencies of e-cigarette and hookah use by macroregion and sex are shown in Figure 2. Regarding e-cigarettes, 1.4% of women in the Central-West region reported using them daily, as did 0.9% and 1.0% of men in the Central-West and North regions, respectively. Among men in the South region, 5.7% reported using e-cigarettes sporadically. In the Southeast region, 1.1% of men reported smoking hookah daily, whereas, in the South, 5.5% of men and 3.0% of women reported using it sporadically.

Figure 3 displays a Venn diagram of commercial cigarette, e-cigarette, and hookah use co-occurrence. One in every five individuals was a current smoker or had a lifetime history of e-cigarette or hookah use, accounting for more than 25 million adults in Brazil. Individuals who used all three products corresponded to 1.5% of the sample (nearly 2 million individuals). Among the almost 20 million individuals who had a

Table 1. Sample[a] characteristics and prevalence of commercial cigarette smoking and lifetime history of electronic cigarette and hookah use in the first trimester of 2022. The Covitel study, 2022.

Characteristic	Total (estimate)		Commercial cigarette		Electronic cigarette		Hookah	
	n	%	%	95% CI	%	95% CI	%	95% CI
Sex								
Male	64,896,014	48.2	14.5	12.2-17.2	10.1	8.1-12.4	9.8	7.7-12.3
Female	69,726,066	51.8	9.9	8.1-12.2	4.8	3.6-6.3	5.0	3.8-6.6
Skin color								
White	52,096,874	38.7	10.8	9.0-13.1	7.4	5.8-9.4	7.0	5.8-8.4
Black	17,800,606	13.2	16.4	12.2-21.6	9.3	5.5-15-1	9.3	5.5-15.2
Brown	55,389,447	41.1	11.1	8.8-14.0	7.2	5.5-9.3	7.1	5.1-10.0
Other	9,335,153	6.9	17.7	11.8-25.7	4.0	2.2-7.1	6.8	2.8-15.7
Age in completed years								
18-24	21,117,143	15.7	12.1	8.4-17.1	19.7	15.1-25.2	17.0	12.2-23.2
25-34	35,765,977	26.6	14.5	9.9-20.9	10.3	7.7-13.8	11.9	9.0-15.4
35-59	52,159,635	38.7	12.0	9.9-14.4	3.0	2.4-3.8	3.3	2.6-4.1
60 or more	25,579,326	19.0	9.2	7.1-11.9	1.6	1.0-2.6	1.3	0.8-2.1
Level of education in completed years of formal education								
0-8	67,991,097	50.5	14.7	12.4-17.3	5.0	3.3-7.6	4.9	3.4-6.9
9-11	39,731,189	29.5	11.6	9.0-14.7	10.5	8.4-13.1	10.4	8.0-13.4
12 or more	26,899,807	20.0	6.5	5.4-7.8	8.4	7.1-9.9	9.0	7.5-10.9
Country region								
Central-West	9,858,685	7.3	12.6	10.3-15.2	11.2	8.5-14.7	13.7	9.8-19.0
Northeast	35,890,341	26.7	7.9	5.8-10.7	6.1	4.1-8.9	2.9	1.7-4.8
North	9,926,494	7.4	8.0	6.1-10.4	6.4	4.9-8.3	4.8	3.9-6.0
Southeast	58,951,426	43.8	14.3	12.0-16.8	6.6	4.6-9.3	8.0	6.1-10.3
South	19,995,121	14.9	15.5	11.9-19.9	10.2	7.4-14.0	11.5	8.3-15.8
Total	134,622,080		12.2	10.4-14.1	7.3	6.0-8.9	7.3	6.0-8.9

[a]≥ 18 years of age.

lifetime history of e-cigarette or hookah use, only one third exclusively used these products.

DISCUSSION

The Covitel findings reinforce our concern about a possible increase in e-cigarette and hookah experimentation and daily use as a new path toward nicotine addiction. The literature has documented that these new forms of vaping/smoking have been used by teenagers mainly, since the industry created special devices targeting this age group (e-cigarettes look very fashionable, and hookah also has an appealing design and can be shared with friends). As per the Covitel results, we should also be concerned about young adults (18-24 years), who had the highest prevalence of e-cigarette/hookah experimentation among all adults. Nicotine is present in most of these devices, and approximately 2.5% of the participants stated being current, albeit not daily, users of e-cigarettes or hookah. It is possible that these young adults will gradually become addicted to nicotine and will increasingly need to consume it. In a study involving 14-year-old adolescents, those who had experimented with e-cigarettes had a two-fold greater likelihood of having heavy smoking patterns at a six-month follow-up.[18] In addition, the uncertainty around nicotine concentrations among the different types of e-cigarettes is concerning, because they vary significantly and can even be higher than those in manufactured cigarettes.[19]

There have been few nationalwide studies examining the use of e-cigarettes, hookah, or ENDS in adults in Brazil. The first representative survey to investigate the use of e-cigarettes and hookah (as well as commercial cigarette smoking) was the third Brazilian Household Survey on Substance Use (BHSU-3), which was conducted in 2015 and involved people between 12 and 65 years of age.[12,13] Prevalence was calculated by means of the question "have you used e-cigarettes within the last 12 months?"; the same wording was applied to hookah (narghile) and commercial cigarettes. The prevalence of e-cigarette, hookah, and commercial cigarette use was 0.4%, 1.7%, and 15.4%, respectively. Other nationally representative surveys involving adults were the *Pesquisa Nacional de Saúde* (PNS, National Health Survey), carried out in 2013 and 2019,[13,16] and the *Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico* (VIGITEL, Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases), carried out between 2006 and 2021.[17] ENDS were not investigated in the 2013 PNS (but hookah use was); in the 2019 PNS and throughout VIGITEL surveys, the outcome was ENDS, and prevalence was derived from the following question: "Have you used electronic devices with

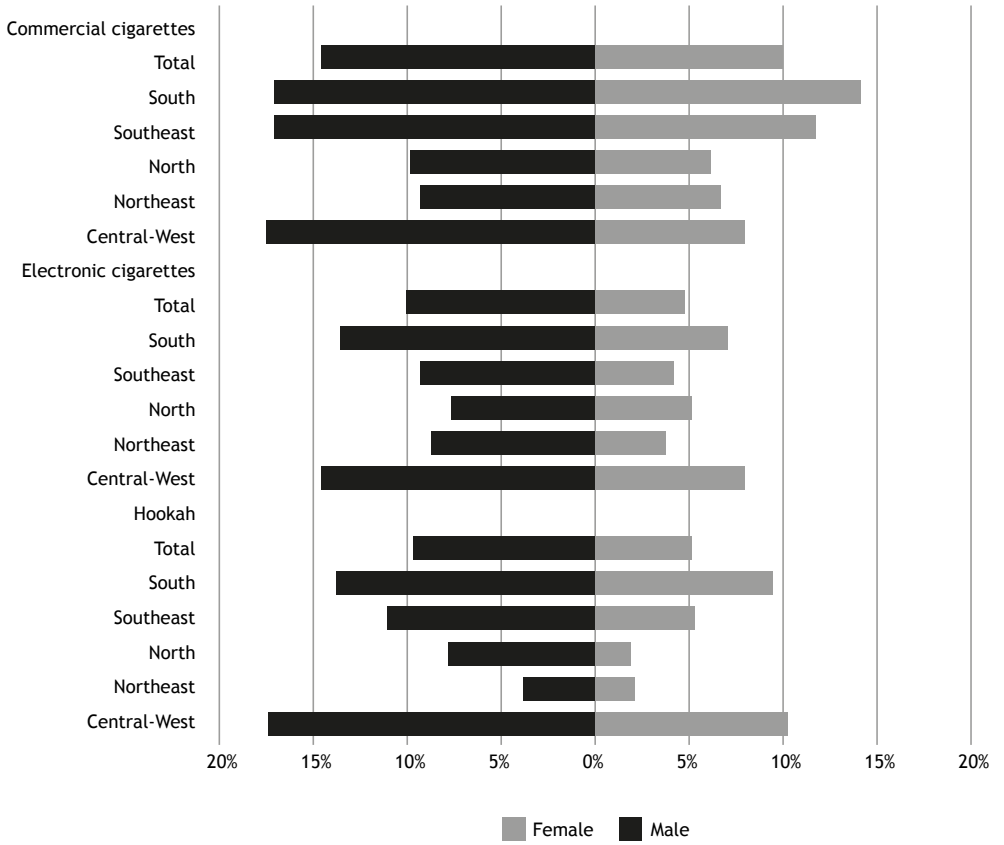


Figure 1. Prevalence of current commercial cigarette smoking and lifetime history of electronic cigarette and hookah use by sex, country macroregion, and whole country. The Covitel study, 2022.

liquid nicotine or chopped tobacco leaves (electronic cigarettes, electronic water pipes, heated cigarettes, or other electronic smoking devices) to smoke or vape?"; it should be highlighted that in the 2019 PNS and in the VIGITEL surveys "ENDS" encompassed both electronic and heat-not-burn tobacco devices, and respondents might have misunderstood that definition. Therefore, comparisons between the surveys should be cautious. The prevalence of a lifetime history of ENDS use was 1.6% in the population ≥ 15 years of age in the 2019 PNS, whereas it was 6.7% in the 2019 VIGITEL (≥ 18 years of age)[13,17]; regarding current hookah use, the 2019 PNS asked about the number of sessions at any frequency (daily, weekly, or monthly), and the prevalence was 0.47%.[13]

Although both BHSU-3 and Covitel used yes/no questions regarding the use of e-cigarettes and hookah, the former included a time frame (within the last 12 months), and the latter asked about a lifetime history of their use, making it challenging to compare their point prevalence. Regarding how the questionnaires were administered, a face-to-face approach was used in the BHSU-3 and the PNS, whereas a telephone interview method was used in the VIGITEL and the Covitel. Another characteristic of the Covitel was that the questions were simple, which might have avoided misunderstanding, especially in the elderly population, who could find it difficult to understand long questions. Also, the questionnaire had been piloted, and the respondents encountered no difficulties to answer the questions.

Another point worth highlighting is the representativeness of Covitel: the sample was designed to represent each of the five Brazilian macroregions and the entire country. Sampling procedures considered the number of registered landline and cell phones in each country region, and the telephone numbers were proportionally selected including all direct distance dialing codes in the respective region. In this sense, it is possible that a selection bias was introduced because most of the landline and cell phone numbers come from large cities and capitals. Although most of the regional populations are concentrated in these locations, a person having more than one cell phone line is common. Therefore, the prevalence of the outcome "experimenting with e-cigarettes and hookah" tends to be overestimated. However, to minimize this bias, we recalculated the sample weights using the projections for the Brazilian population based on the 2010 Brazilian demographic census, considering the expected proportions of sexes, levels of education, and ages. Although this procedure aimed to correct the point estimate of e-cigarette and hookah use at some time in life, we cannot completely rule out some degree of selection bias.

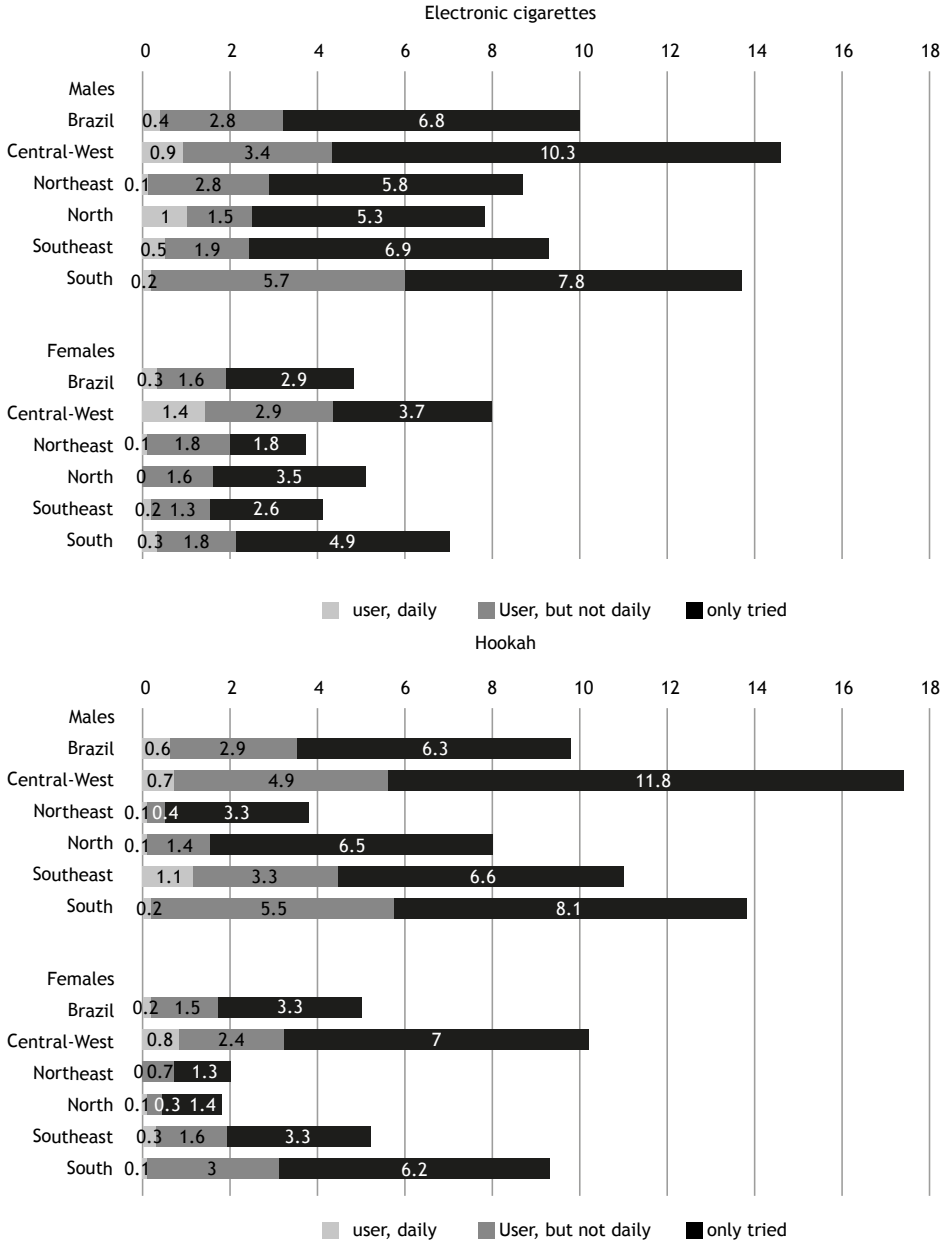
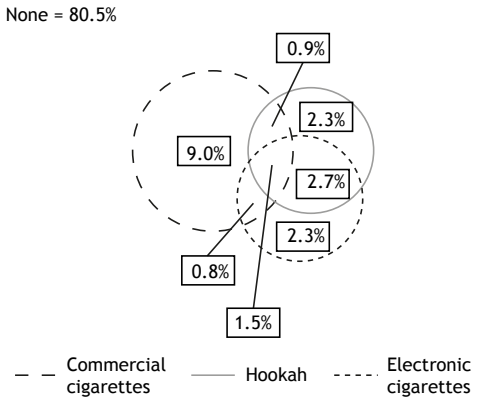


Figure 2. Frequency of electronic cigarette and hookah use by sex, country macroregion, and whole country. The Covitel study, 2022.

The abovementioned surveys and the international literature have shown that being a young adult with a high level of education or a high family income is associated with the use of ENDS, e-cigarettes, and hookah.[12,13,16,17] On the other hand, cigarette smokers tend to be older and have a lower level of education or lower family income. Covitel revealed that the prevalence of e-cigarette experimentation among young adults was nearly 20%, while that was 1.6% among those aged ≥ 60 years. The same occurred regarding hookah experimentation (17% vs. 1.3%).

Concerning the five Brazilian macroregions, the use of e-cigarettes and hookah was more common in the Central-West region, followed by the South region. Similar results were found in other studies in the country: the prevalence of hookah experimentation was 3.4% in both regions according to the 2013 PNS, and that of ENDS experimentation in the Central-West region was, respectively, 2.8% and 11.59% in the 2019 PNS and in 2019 VIGITEL.[13,16] We believe that ENDS experimentation might be related to the smuggling of these devices, since it is forbidden to market, import, and advertise any of these products, in accordance with a Brazilian Health Regulatory Agency resolution issued in 2009.[20] Unfortunately, online sales do happen very easily, and these products can also be



Possible combination	Estimated population
None	108,307,774
Commercial cigarettes only	12,115,987
Electronic cigarettes only	3,096,308
Hookah only	3,096,308
Commercial and electronic cigarettes	1,076,977
Commercial cigarettes and hookah	1,211,599
Eletronic cigarrete and hookah	3,634,796
All three	2,019,331

Figure 3. Venn diagram of current commercial cigarette smoking and lifetime history of electronic cigarette and hookah use. The Covitel study, 2022.

found in several places where tobacco is sold in Brazil. However, because free Internet access is not available for everyone and these devices are rather expensive in Brazil, this might be the reason why their use is associated with higher levels of education and income. The highest frequency of daily e-cigarette use (1.4%) was found among women in the South region, which rates second in the consumption of tobacco products in the country. The overall prevalence of commercial cigarette smoking found in this study is in accordance with the decline observed in the last decade in Brazil: the prevalence is higher among males and adults (25-69 years of age), whereas other forms of smoking/vaping are more common in the younger age range.

Although comparisons among studies are difficult, it seems that experimenting with and currently using e-cigarettes and hookah are increasing in Brazil. All efforts should be made to allow for comparisons among international and, mainly, Brazilian studies, including the standardization of the wording used in the questions. According to the core questionnaire of the Global Adult Tobacco Survey,[21] questions about different categories of tobacco/nicotine products should be asked separately. For each category, there should be questions such as current use or a lifetime history of use, daily or weekly use, age at initiation and cessation, among others; however, the validity of a single-item question covering many products is unknown. Local specificities will demand adaptations; however, because of the size of the Global Adult Tobacco Survey,[21] this can be quite demanding, and only the main questions should be selected to allow us to compare the prevalence of each one of the major products. Continued surveillance in the digital environment, at borders, and at points of sale, as well as educational campaigns in the media, mainly focusing on young people and adolescents, is essential to preventing smoking/vaping initiation and contributing to regulatory measures and public policies to catalyze a reduction in the use of e-cigarettes and hookah in the future.

Long-term studies in order to monitor the prevalence curve of these products and their harm to health are also fundamental to identify possible impacts on tobacco control policies.

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AUTHOR CONTRIBUTIONS

AMBM, FCW, LMVS, PCBP, TAC, PAC, and PCH: conceptualization. LMVS, PCBP, and TAC: funding acquisition. AMBM, FCW, PAC, and PCH: formal analysis. AMBM, FCW, LMVS, PCBP, TAC, PAC, and PCH: methodology. LMVS, PCBP, and TAC: project administration. AMBM, FCW, and PCH: supervision. AMBM, FCW, PAC, and PCH: visualization. AMBM, FCW, PAC, and PCH: drafting the manuscript. AMBM, FCW, LMVS, PCBP, TAC, PAC, and PCH: reviewing and editing of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Prevalence, outcomes, and predictors of multidrug-resistant nosocomial lower respiratory tract infections among patients in an ICU

Ana Beatriz Souza de Oliveira[1], Guilherme Hirassawa Sacillotto[2], Manuela Francisco Balthazar Neves[2], Andressa Hellen Nora da Silva[2], Tamiris Adriane Moimaz[3], Joelma Villafanha Gandolfi[3], Mara Correa Lelles Nogueira[3], Suzana Margareth Lobo[3]

1. Faculdade de Medicina de São José do Rio Preto – FAMERP – São José do Rio Preto (SP), Brasil.
2. Residência em Medicina Intensiva, Hospital de Base, Faculdade de Medicina de São José do Rio Preto – FAMERP – São José do Rio Preto (SP), Brasil.
3. Serviço de Medicina Intensiva, Hospital de Base, Faculdade de Medicina de São José do Rio Preto – FAMERP – São José do Rio Preto (SP), Brasil.

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Study carried out in the Serviço de Medicina Intensiva, Hospital de Base, Faculdade de Medicina de São José do Rio Preto – FAMERP – São José do Rio Preto (SP) Brasil.

ABSTRACT

Objective: To determine the prevalence, outcomes, and predictors of multidrug-resistant nosocomial lower respiratory tract infections (LRTI) in patients in an ICU. **Methods:** This was an observational cohort study involving patients with nosocomial LRTI (health care-associated pneumonia, hospital-acquired pneumonia, or ventilator-associated pneumonia). Data were prospectively collected between 2015 and 2019. The multidrug-resistant pathogens (MDRPs) identified in the isolates studied included resistant to extended-spectrum cephalosporin-resistant and carbapenem-resistant *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus* at microbiological diagnosis. **Results:** During the study period, 267 patients in the ICU were diagnosed with LRTI, microbiological confirmation of LRTI having been obtained in 237. Of these, 146 (62%) had at least one MDRP isolate. Patients infected with MDRP were found to have poorer outcomes than patients infected with susceptible strains, such as prolonged mechanical ventilation (18.0 days vs. 12.0 days; $p < 0.001$), prolonged ICU length of stay (23.0 days vs.16.0 days; $p < 0.001$), and higher mortality (73% vs. 53%; $p < 0.001$) when compared with patients infected with susceptible strains. Hospital length of stay ≥ 5 days (OR = 3.20; 95% CI: 1.39-7.39; $p = 0.005$) and prolonged use vasoactive drugs (OR = 3.15; 95% CI: 1.42-7.01; $p = 0.004$) were independent predictors of LRTI caused by MDRPs (LRTI-MDRP). The presence of LRTI-MDRP was found to be an independent predictor of death (OR = 2.311; 95% CI: 1.091-4.894; $p = 0.028$). **Conclusions:** Prolonged use of vasoactive drugs and prolonged hospital length of stay were independent predictors of LRTI-MDRP in this population of critically ill patients with very poor outcomes.

Keywords: Drug resistance, multiple; Healthcare-associated pneumonia; Pneumonia, ventilator-associated; Cross infection; Intensive care units.

INTRODUCTION

The increased prevalence of pathogens that express resistance to β-lactams due to the production of extended-spectrum β-lactamases, AmpC β-lactamases, and carbapenemases, in addition to the alteration of the cell wall promoting methicillin resistance, has compromised the therapeutic effectiveness of current treatments. Hospitalized patients with infections caused by multidrug-resistant pathogens (MDRPs) are at a higher risk of receiving inappropriate therapy and, consequently, of treatment failure, increasing the burden of disease in ICUs.[1]

Pneumonia in critically ill patients at a higher risk of MDRP infection may be healthcare-associated pneumonia (HCAP), hospital-acquired pneumonia (HAP), or ventilator-associated pneumonia (VAP), which are usually associated with extrapulmonary complications and high mortality.[2] Patient characteristics, infection with specific pathogens, and severity of illness influence the selection of antibiotics. Antibiotic resistance is a major concern in lower respiratory tract infection (LRTI) globally, especially because of its association with prolonged hospital length of stay and high mortality.[2] Appropriate antibiotic therapies are fundamental to better outcomes in critically ill patients suffering from infections. It is therefore important to identify those patients who are at a higher risk of MDRP infections. Understanding epidemiological features and risk factors for pulmonary infections due to MDRPs is important to inform earlier and more appropriate treatment options.

Correspondence to:
Suzana Margareth Lobo. Hospital de Base, Faculdade de Medicina de São José do Rio Preto, Avenida Brigadeiro Faria Lima, 5544, Vila São José, CEP 15090-000, São José do Rio Preto, SP, Brasil.
Tel.: 55 17 3231-5054. E-mail: suzanaalobo@gmail.com
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There are known risk factors for MDRP such as sociodemographic factors, severity of disease, comorbidities, and previous use of antibiotics, among many others that can vary according to the population and type of health care setting.[2-6] We hypothesized that patients with LRTI caused by MDRPs (LRTI-MDRP) have worse outcomes and possibly different patterns of inflammatory response, as well as different features, in comparison with those with infections secondary to susceptible organisms. We aimed to evaluate the outcomes and to identify early predictors of LRTI-MDRP.

METHODS

Study design, setting, and participants

This observational cohort study was a retrospective analysis of a prospective collection of data from subjects with LRTI who were admitted to a 40-bed, mixed ICU at the *Hospital de Base*, a tertiary care university hospital, located in the city of São José do Rio Preto, Brazil. Data were collected between August 1, 2015 and August 1, 2019. The sample size was determined by a convenience sample of patients with microbiologically confirmed LRTI who were included in our registry database during the study period. The study was approved by the local institutional review board (Protocol no. 12569319.1.0000.5415) and followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[7]

Inclusion criteria were being ≥ 18 years of age and diagnosed with an LRTI (HCAP, HAP, or VAP). Hospital and ICU lengths of stay prior to the diagnosis of LRTI were recorded for each subject (days from admission to diagnosis). Antibiotic treatment was prescribed in accordance with local guidelines. HCAP was defined in accordance with the 2007 Infectious Diseases Society of America/American Thoracic Society criteria.[8] HAP was defined as the presence of clinical signs and symptoms of pneumonia with a new or progressive infiltrate on chest radiography occurring after hospitalization for > 48 h or within 7 days after hospital discharge or at least 48 h for non-intubated patients. Clinical signs and symptoms were cough, tachypnea (RR > 25 breaths/min), purulent sputum, hypoxemia, need for mechanical ventilation, and acute changes in the ventilator support system to increase oxygenation, as well as at least one of the following signs: fever (body temperature ≥ 38°C) and total number of peripheral leukocytes ≥ 10,000 or ≤ 4,500 cells/mm^3.[9] VAP was defined as the presence of a new or progressive infiltrate and signs of infection in a patient receiving mechanical ventilation via an endotracheal tube for at least 48 h. ARDS was diagnosed on the basis of the 2012 Berlin definitions.[10]

Data collection

Data on clinical characteristics, laboratory tests, and types of organ support needed were collected. The SOFA score, the Simplified Acute Physiology Score III (SAPS III), and the Clinical Pulmonary Infection Score (CPIS) were calculated.[11-13] Qualitative and quantitative cultures from endotracheal aspirates (n = 210) or sputum (n = 27) were performed as per standard methods. Data on C-reactive protein (CRP) levels measured within the first 48 h after admission, corticosteroid use, and duration of mechanical ventilation and of vasopressor use were collected. The lowest serum albumin level obtained within the first 48 h from admission was recorded. Radiological assessment included chest radiography and CT (or chest CT angiography).

Patients were divided into two groups: MDRP− and MDRP+. The MDRP− group included LTRI-related non-multidrug resistant strains in the isolates studied, whereas the MDRP+ group included at least one of the following multidrug-resistant strains: *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* strains with a multidrug resistant phenotype, that is, resistance to more than one antimicrobial agent in three or more different antimicrobial categories, including extended-spectrum cephalosporins (ceftriaxone, ceftazidime, and cefepime) and/or carbapenems (imipenem and meropenem).[14] Carbapenem-resistant Enterobacteriaceae and methicillin-resistant *Staphylococcus aureus* were also included in that group. All isolates were revised and classified by a microbiologist. The outcomes evaluated were death, bacteremia, ARDS, and hospital and ICU lengths of stay.

Statistical analysis

For statistical analysis, we used descriptive statistics and comparison of proportions. In the case of a non-Gaussian distribution, continuous variables were analyzed using the Kruskal-Wallis test. Categorical variables were analyzed using either the Pearson's chi-square test or the Fisher's exact test. Univariate and multivariate (forward stepwise technique) logistic regression analyses were performed to determine the independent predictors of the presence of MDRPs. Median values were used as breakpoints to determine binary categories for continuous variables. Dependent variables were LRTI-MDRP and death. The independent variables with a value < 0.25 in the univariate analysis were selected for the binary logistic regression analysis. The variables tested for LRTI-MDRP in the multivariate analysis were sex, SOFA score, SAPS III, COPD (reference: no COPD), CRP-to-albumin ratio, use of corticosteroids (reference: no use), use of vasoactive drugs, hospital and ICU lengths of stay prior to LRTI diagnosis, and reason for hospital admission (reference: surgery). The variables tested for death in the multivariate analysis were age, SOFA score, SAPS III, COPD (reference: no COPD), CRP-to-albumin ratio, and reason for hospital admission (reference: surgery). Variance inflation factors were calculated to test for multicollinearity; for all of the covariates, a factor < 5 was suggestive of no multicollinearity. Adjusted odds ratios and 95% confidence intervals were calculated

for the predictors. A p value < 0.05 was considered statistically significant.

RESULTS

Overall, 267 patients with LRTI were screened. Of these, 237 patients were included after microbiological confirmation, and 146 (62%) of whom were infected with at least one MDRP (Table 1). The mean age was 57.2 ± 17.1 years, and the mean SAPS III, SOFA score, and CPIS were 64.7 ± 16.6; 8.7 ± 3.9; and 6.1 ± 1.9, respectively. The incidence and mortality rates according to the type of LRTI are shown in Figure 1.

The clinical characteristics and outcomes in the MDRP+ and MDRP− groups are shown in Table 1. COPD was significantly more common in the MDRP+ group than in the MDRP− group (10.2% vs. 5.5%; p = 0.029; Table 1). Hospital and ICU lengths of stay prior to the diagnosis of LRTI were significantly longer in the MDRP+ group than in the MDRP− group. The patients in the MDRP+ group, when compared with those in the MDRP− group, used vasopressors (median: 11 [6-18] days vs. 6 [4-12] days; p < 0.001) and were on mechanical ventilation (median: 18.0 [11.5-26.0] days vs. 12.0 [6.0-22.0] days; p < 0.001) for a longer time. In addition, those in the MDRP+ group had longer ICU length of stay (median: 23 [15-33] days vs. 16 [10-24] days; p < 0.001), longer hospital length of stay (median: 31.0 [21.0-50.5] days vs. 26.0 [15.0-41.0] days; p = 0.004), and higher mortality (73% vs. 53%; p = 0.001; Table 1).

In the binary logistic regression analysis, a hospital length of stay ≥ 5 days (OR = 3.20; 95% CI: 1.39-7.39; p = 0.005) and prolonged duration of treatment (≥ 9 days) with vasoactive drugs (OR = 3.15, 95% CI: 1.42-7.01; p = 0.004) were independent predictors of LRTI-MDRP in this population of critically ill patients (Table 2). The presence of LRTI-MDRP was found to be the only independent predictor of death (OR = 2.31; 95% CI: 1.091-4.894; p = 0.028).

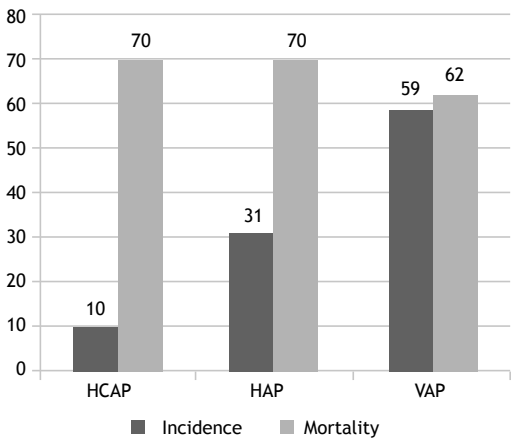

Figure 1. Incidence of lower respiratory tract infections according to diagnosis and respective mortality rates (in %). Observation: rounded numbers. HCAP: health care-associated pneumonia; HAP: hospital-acquired pneumonia; and VAP: ventilator-associated pneumonia.

The main demographic and clinical characteristics of the patients infected with either multidrug-resistant gram-negative or gram-positive strains are shown in Table 3. Figure 2 shows the distribution of MDRPs in number of patients and of isolates.

DISCUSSION

The main findings in our study are as follows: MDRPs were the cause of LRTI in almost two-thirds of the ICU patients; the mortality rate was remarkably high in this heterogeneous population of critically ill patients; prolonged ICU length of stay (≥ 5 days) and prolonged treatment with vasopressors (≥ 9 days) were found to be predictors of LRTI-MDRP; and the presence of LRTI-MDRP was identified as the only independent risk factor for death.

A large proportion of our ICU population with LRTI was infected with MDRPs (62%). At ICU admission, SAPS III and the SOFA score were not significantly different when we compared the LRTI patients with susceptible and resistant strains; nevertheless, those in the MDRP+ group had higher mortality rates and higher resource utilization as shown by the longer use of mechanical ventilation and vasopressors, as well as longer ICU and hospital lengths of stay in comparison with those in the MDRP− group. The mortality rate was 73% in the MDRP+ group.

Other authors have reported similar results (higher mortality rates) when they compared hospitalized adults infected with carbapenem-resistant *K. pneumoniae* with matching controls infected with susceptible *K. pneumoniae* strains.[15,16] The mortality of patients infected with multidrug-resistant bacteria was significantly higher than that of those infected with non-multidrug-resistant bacteria [51.85% vs. 30.56%] in patients with VAP in a county hospital in China.[17] In a study conducted in Brazil, the mortality rate for VAP caused by MDRPs was 61.3%, whereas that for VAP not caused by MDRPs was 25.0%.[18] Differences in the severity of disease, as shown by high SOFA scores and SAPS III, can explain the even higher mortality observed in our study. Our data suggest that multidrug resistance is the cause of high mortality since isolation of an MDRP was found to be the only independent predictor of death, even when variables such as age, SAPS III, and SOFA score entered the logistic regression model. One fundamental reason for higher mortality might be a delay in providing appropriate antibiotic therapy.[19] In addition, *A. baumannii* and *K. pneumoniae* had the highest prevalence in our patients with LRTI, both of which are related to worse prognosis.

We found that a hospital length of stay ≥ 5 days and being on vasopressors for ≥ 9 days more than tripled the likelihood of having LRTI-MDRP. Other studies have reported many other risk factors associated with MDRPs in hospitalized patients such as mechanical ventilation, previous use of antibiotics, and indwelling catheters.[4] In a review including a total of 92 studies, the risk factors most frequently reported as significantly associated

Table 1. Demographic and clinical characteristics of the sample as a whole and of the two study groups.[a]

Characteristic	Total	Group		p
		MDRP−	MDRP+	
	(N = 237)	(n = 91)	(n = 146)	
Age, years	57.2 ± 17.1	57.3 ± 16.6	57.2 ± 17.5	0.800
Male sex	160 (67.5)	66 (72.5)	94 (64.4)	0.193
Severity scores				
SAPS III	64.7 ± 16.6	62.5 ± 17.7	66.0 ±15.7	0.193
SOFA at admission	8.7 ± 3.9	9.3 ± 4.0	8. 3 ± 3.8	0.098
CPIS	6.1 ± 1.9	6.0 ± 1.8	6.1 ± 1.9	0.680
CRP (day 1)	19.3 ± 14.1	19.4 ±16.0	19.1 ± 12.8	0.647
CRP-to-albumin ratio	7.6 ± 6.9	5.9 ± 5.0	8.4 ± 7.6	0.083
Type of admission				
Medical	135 (57.0)	52 (57.2)	83 (56.8)	0.965
Surgical	102 (43.0)	39 (42.9)	63 (43.2)	0.965
Trauma	52 (21.9)	23 (25.27)	29 (19.86)	0.330
Comorbidities				
COPD	20 (8.4)	5 (5.5)	15 (10.23)	0.029
Diabetes mellitus	23 (9.7)	10 (11.1)	13 (8.9)	0.689
Smoking	21 (8.9)	9 (9.8)	12 (8.21)	0.554
Cardiovascular disease	52 (21.9)	21 (23.1)	31 (21.2)	0.739
Respiratory disease	51 (21.5)	16 (17.6)	35 (23.9)	0.240
Corticosteroid use	31 (13.1)	8 (8.8)	23 (15.8)	0.109
LRTI				
HCAP	23 (9.7)	12 (13.2)	11 (7.5)	0.150
HAP	73 (30.8)	29 (31.9)	44 (30.1)	0.779
VAP	139 (58.6)	51 (56.0)	88 (60.3)	0.585
ICU LOS prior to LRTI diagnosis	3 [0-6]	2 [0-4]	4 [1-9]	< 0.001
Hospital LOS prior to LRTI diagnosis	5.5 [2-13]	4 [1-7]	7 [4-15]	< 0.001
Supportive therapies				
Vasoactive drugs	224 (94.9)	84 (92.3)	140 (95.9)	0.155
Vasoactive drugs, days	9 [5-16]	6 [4-12]	11 [6-18]	< 0.001
Mechanical ventilation	210 (88.6)	85 (93.40)	125 (86.20)	0.076
Mechanical ventilation, days	16 [9-24]	12 [6-22]	18 [12-26]	< 0.001
Outcomes				
ARDS	36 (15.2)	13 (13.9)	23 (22.1)	0.742
Bacteremia	70 (32.6)	23 (25.1)	47 (44.9)	0.528
ICU LOS, days	20 [13-30]	16 [10-24]	23 [15-33]	< 0.001
Hospital LOS, days	30 [18-45]	26 [15-41]	31 [21-51]	0.004
In-hospital mortality	154 (65.2)	48 (53.0)	106 (73.0)	< 0.001

MDRP: multidrug-resistant pathogens; SAPS III: Simplified Acute Physiology Score III; CPIS: Clinical Pulmonary Infection Score; CRP: C-reactive protein; LRTI: lower respiratory tract infection; HCAP: healthcare-associated pneumonia; HAP: hospital-acquired pneumonia; VAP: ventilator-associated pneumonia; and LOS, length of stay. [a]Values expressed as n (%), mean ± SD, or median [IQR].

with gram-negative carbapenem-resistant infections were previous antibiotic use, previous colonization, mechanical ventilation, dialysis, hospital length of stay, comorbidities, APACHE II score, and intubation.[3] The population included in our study was homogeneous in terms of severity of the disease; almost all of the patients were intubated or in septic shock, which poses difficulties for comparing our population with those from other studies, because these variables could not be tested in the regression analysis.

In our study only COPD was associated with MDRPs. Prolonged use of vasoactive drugs and prolonged hospital length of stay were associated with LRTI-MDRP. Increased mortality has been reported in patients infected with carbapenem-resistant *K. pneumoniae* who had other comorbidities.[20] In a prospective parallel matched cohort study in Europe, an excess hospital length of stay of 5 days could be attributed to resistance to third-generation cephalosporins in *Escherichia coli* bloodstream infections.[21] The reason for the association of duration of treatment with vasoactive drugs with MDRP infections is yet to be known. We can speculate that it may be a surrogate marker for difficult-to-treat infections, inappropriate initial antibiotic therapies, or

Table 2. Multivariate logistic regression with independent predictors of multidrug-resistant pathogen infection and death in patients with lower tract respiratory infection.[a]

	OR	95% CI	p
MDRP			
Vasoactive drugs, days	3.159	1.423-7.013	0.004
Hospital LOS prior to LRTI diagnosis	3.205	1.390-7.390	0.005
COPD	9.770	1.062-89.870	0.014
Death			
MDRP	2,311	1.091-4.894	0.028

MDRP: multidrug-resistant pathogens; LOS, length of stay; LRTI: lower respiratory tract infection; ref: reference; and CRP: C-reactive protein. [a]Variables entering logistic regression: sex; SOFA; SAPS III; COPD (ref: no COPD); CRP-to-albumin ratio; corticosteroids (ref: no use); vasoactive drugs, days; hospital LOS prior to LRTI diagnosis; and type of admission (ref. surgical). Cutoff points: SOFA (≤ 9), SAPS III (≤ 65.5), CRP-albumin rate (≤ 6), vasoactive drugs; days (≤ 9), and hospital LOS prior to LRTI diagnosis (≤ 5).

Table 3. Demographic and clinical characteristics of the patients infected with multidrug-resistant Gram-negative or multidrug-resistant Gram-positive strains.[a]

Variable	Group		p
	MDR Gram-negative (n = 114)	MDR Gram-positive (n = 32)	
Age, years	57.7 ± 17.4	55.4 ± 18.1	0.714
Male sex	75 (65.8)	19 (59.4)	0.506
CRP-to-albumin ratio	8.7 ± 7.8	6.8 ± 6.6	0.400
Severity scores			
SAPS III	67.1 ± 16.2	62.4 ± 13.4	0.220
SOFA at admission	8.6 ± 3.9	7.3 ± 3.1	0.072
CPIS	6.1 ± 2.0	6.2 ± 1.5	0.264
Type of admission			
Medical	66 (58.0)	17 (53.1)	0.631
Surgical	48 (42.0)	15 (46.9)	0.631
Coexisting diseases			
COPD	11 (9.6)	4 (12.5)	0.639
Corticosteroid use	16 (14.0)	3 (9.4)	0.489
Hospital LOS prior to LRTI diagnosis	5.0 [2.0-11.7]	9.0 [4.0-23.2]	0.013
Vasoactive drugs, days	14.5 ± 13.3	12.5 ± 10.2	0.464
In-hospital mortality rates	81 (71.7)	25 (78.1)	0.468

MDR: multidrug resistant; ; CRP: C-reactive protein; SAPS III: Simplified Acute Physiology Score III; CPIS: Clinical Pulmonary Infection Score; LOS: length of stay; and LRTI: lower respiratory tract infection. [a]Values expressed as n (%), mean ± SD, or median [IQR].

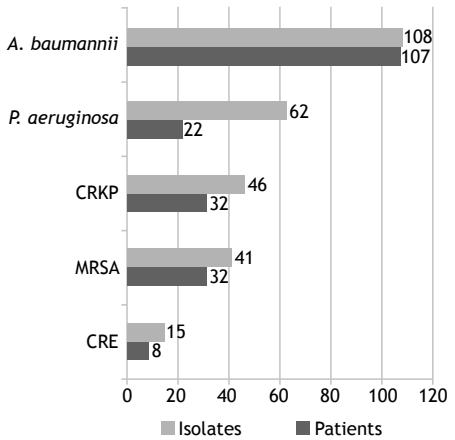

Figure 2. Distribution of multidrug-resistant pathogens and number of isolates in the sample. A.: *Acinetobacter*; P.: *Pseudomonas*; CRKP: carbapenem-resistant *Klebsiella pneumoniae*; MRSA, methicillin-resistant *Staphylococcus aureus*; and CRE: carbapenem-resistant Enterobacteriaceae.

more severe disease; consequently, sepsis reversal would take a longer time.

Infections caused by resistant pathogens are associated with increased costs.[22] Effective antimicrobial stewardship and infection prevention programs are needed to prevent these infections. Difficulties in weaning patients from vasoactive drugs should be a warning signal for MDRP infections, and this hypothesis should be tested in prospective studies. It is therefore of utmost importance to be aware of the risk factors for MDRPs and to develop strategies to identify patients at a higher risk in order to seek appropriate and adequate antibiotic therapies, along with antibiotic stewardship policies.

This study has various weaknesses. First, the single-center and university setting nature of this study might preclude the generalization of the findings to other hospitals or populations of hospitalized patients. Second, this population of critically ill patients is unique;

because almost all patients were admitted to the ICU on antibiotic therapy, used indwelling catheters, were intubated, and developed sepsis, it was impossible to identify any of these variables as predictors of LRTI-MDRP; therefore, attention to other risk factors must be part of our daily patient care. Nonetheless, we hope that our results will increase awareness for clinicians working in ICUs. The main strength of our study was the careful and prospective collection of data that were revised by a microbiologist.

In conclusion, in ICU patients with LRTI infections, prolonged hospital length of stay and prolonged use of vasopressors were predictive of infections caused by MDRPs and were associated with poor outcomes.

AUTHOR CONTRIBUTIONS

SML: study design; study proposal; data analysis; and drafting and revision of the manuscript. ABSO: study design; data acquisition and interpretation; data analysis; drafting of the manuscript; and approval of the final version. GHS, MFBN, TAM, and AHNS: data acquisition; revision of the manuscript; and approval of the final version. JVG and MCLN: data interpretation and analysis; drafting of the manuscript; and approval of the final version.

CONFLICTS OF INTEREST

None declared.

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Tomographic pleuropulmonary manifestations in rheumatoid arthritis: a pictorial essay

Guilherme das Posses Bridi[1], Márcio Valente Yamada Sawamura[2], Mark Wanderley[1], Luciana Volpon Soares Souza[3], Ronaldo Adib Kairalla[1,4], Letícia Kawano-Dourado[1,5,6], Bruno Guedes Baldi[1,7]

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Instituto de Radiologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Ultra X, São José do Rio Preto (SP) Brasil.
4. Núcleo de Tórax, Hospital Sírio-Libanês, São Paulo, Brasil.
5. Hcor Research Institute, Hospital do Coração, São Paulo (SP) Brasil.
6. MAGIC Evidence Ecosystem Foundation, Oslo, Norway.
7. Hospital do Coração, São Paulo (SP) Brasil.

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune inflammatory and heterogeneous disease that affects several systems, especially the joints. Among the extra-articular manifestations of RA, pleuropulmonary involvement occurs frequently, with different presentations, potentially in all anatomic thoracic compartments, and may determine high morbidity and mortality. The most common pleuropulmonary manifestations in patients with RA include interstitial lung disease (ILD), pleural disease, pulmonary arterial hypertension, rheumatoid lung nodules, airway disease (bronchiectasis and bronchiolitis), and lymphadenopathy. Pulmonary hypertension and ILD are the manifestations with the greatest negative impact in prognosis. HRCT of the chest is essential in the evaluation of patients with RA with respiratory symptoms, especially those with higher risk factors for ILD, such as male gender, smoking, older age, high levels of rheumatoid factor, or positive anti-cyclic citrullinated peptide antibody results. Additionally, other etiologies that may determine tomographic pleuropulmonary manifestations in patients with RA are infections, neoplasms, and drug-induced lung disease. In these scenarios, clinical presentation is heterogeneous, varying from being asymptomatic to having progressive respiratory failure. Knowledge on the potential etiologies causing tomographic pleuropulmonary manifestations in patients with RA coupled with proper clinical reasoning is crucial to diagnose and treat these patients.

Keywords: Lung diseases, interstitial; Lung diseases; Pleural diseases; Pulmonary arterial hypertension; Arthritis, rheumatoid; Tomography.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune rheumatic disease that most commonly affects the joints. Pleuropulmonary manifestations are common and significantly contribute to increase morbidity and mortality in RA, affecting up to 60% of the patients during the disease course. All anatomic thoracic compartments can be involved in RA, including the pleura and pulmonary parenchyma, as well as small and large airways.[1-3] Clinical presentation is heterogeneous, varying from being asymptomatic to having progressive respiratory failure, and may have acute or insidious onset.[1,4] Pulmonary involvement in RA usually occurs within five years after the diagnosis of RA, but it is important to reinforce that it may precede the articular involvement.[2,3]

To evaluate the different pleuropulmonary manifestations of RA, CT is essential because it allows not only the detailing of the lesions, but also their precise location. Additionally, CT is important to assess other etiologies that may determine pulmonary lesions in patients with RA, such as infections, drug-induced lung disease (DILD), neoplasms, and response to treatment.[5]

Although there is no formal recommendation to screen patients with RA for the presence of pleuropulmonary involvement, screening may be recommended in those with respiratory symptoms and/or changes in pulmonary examinations, CT scans, or pulmonary function tests. Additionally, patients with a higher risk of pulmonary involvement due to factors such as male gender, older age, smoking, positive results for anti-cyclic citrullinated peptide antibodies, or high titers of rheumatoid factor should undergo CT and pulmonary function evaluation.

The main pleuropulmonary manifestations that may occur in patients with RA include interstitial lung disease (ILD), pleural disease, pulmonary arterial hypertension (PAH), rheumatoid lung nodules, airway disease (bronchiectasis and bronchiolitis), lymphadenopathy, and DILD.

The objective of this pictorial essay was to present the main tomographic pleuropulmonary manifestations that may be identified in patients with RA (Chart 1).

ILD

ILD is one of the most common pulmonary manifestations of RA and the second leading cause of mortality, primarily

Correspondence to:
Bruno Guedes Baldi. Avenida Dr. Enéas de Carvalho Aguiar, 44, 8º andar, Bloco II, Cerqueira César, CEP 05403-900, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5695. Fax: 55 11 2661-5695. E-mail: bruno.baldi@hc.fm.usp.br
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Chart 1. Summary of the main pleuropulmonary manifestations of rheumatoid arthritis.

Disease pattern	Radiological manifestations	Other features
Usual interstitial pneumonia	Basilar and peripheral traction bronchiectasis, with or without honeycombing Exuberant honeycombing, straight edge sign, and anterior upper lobe involvement	Most common ILD pattern (60%) Worst prognosis among all ILD patterns
Nonspecific interstitial pneumonia	Basilar and peripheral ground-glass opacities and fine reticulation; traction bronchiectasis Usually symmetric Subpleural sparing may occur	Association with longer duration of joint disease, lower risk of disease progression, and greater treatment response
Organizing pneumonia	Peripheral and peribronchovascular consolidation; ground-glass opacities Nodules and reversed halo sign may occur less frequently	Abnormalities are often fleeting or migratory Usually has good prognosis
Lymphocytic interstitial pneumonia	Lower lobe-predominant and peribronchovascular thin-walled cysts Ground-glass opacities and septal thickening	More commonly associated with Sjögren's syndrome
Desquamative interstitial pneumonia	Ground-glass opacities and mild reticulation Cysts may be found Basal and peripheral predominance	Rare and may precede the onset of RA by years
Inflammatory pleural effusion	Usually unilateral with small pleural enhancement	Most patients are asymptomatic Usually exudative with low glucose levels, low pH levels, high LDH levels, high rheumatoid factor titers, low total complement activity, and low C3 and C4 levels
Pulmonary arterial hypertension	Enlarged pulmonary arteries, dilatation of right-sided cardiac chambers, and right ventricular hypertrophy Mosaic attenuation in the lungs as an indirect sign	Rare and usually seen in older patients with long-standing RA-ILD
Rheumatoid lung nodules	Round opacities with variable size, usually multiple and cavitated Usually in the subpleural region	Usually asymptomatic and associated with subcutaneous nodules
Bronchiectasis	Cylindrical, varicose, and cystic bronchiectasis may occur	Chronic suppurative infections, treatment with disease-modifying antirheumatic drugs, and genetic predisposition may be related to bronchiectasis
Constrictive bronchiolitis	Bronchial wall thickening, bronchiectasis, and mosaic attenuation pattern	More common in females and in those with long-standing untreated disease Airflow obstruction and air trapping in pulmonary function tests
Follicular bronchiolitis	Small centrilobular nodules with branching structures (tree-in-bud sign) Air trapping and peribronchovascular and septal thickening may also occur	Associated with RA or Sjögren's syndrome

Continue...▶

Chart 1. Summary of the main pleuropulmonary manifestations of rheumatoid arthritis. (Continued...)

Disease pattern	Radiological manifestations	Other features
Caplan Syndrome (rheumatoid pneumoconiosis)	Multiple peripheral lung nodules with cavitations or calcifications in some cases	Associated with exposure to coal, asbestos, or silica May precede the onset of RA by more than 10 years Most patients are asymptomatic
Lymphadenopathy	Mediastinal or axillary	Approximately 70% of patients with RA Patients may show signs of inflammatory activity
Drug-induced lung disease	Patterns suggestive of hypersensitivity pneumonitis, eosinophilic pneumonia, pulmonary edema, organizing pneumonia, and diffuse alveolar damage	Secondary to immune-mediated reaction or direct toxicity Diagnosis usually based on symptoms, tomographic pattern, and time between treatment initiation and drug discontinuation Symptoms usually improve with drug discontinuation

ILD: interstitial lung disease; and RA: rheumatoid arthritis.

owing to respiratory failure, superimposed infection, and lung cancer.[6,7] ILD is responsible for 10-20% of RA-related mortality, and approximately 10% of patients have clinically significant disease. RA-ILD may determine a variable spectrum of presentations, from acute to chronic ones, including diffuse alveolar damage (DAD), organizing pneumonia (OP), and fibrotic disorders.[8]

Risk factors for RA-ILD include smoking, male sex, older age, duration/activity of RA, and seropositivity for rheumatoid factor or anti-cyclic citrullinated peptide antibodies.[2,9] Patients with RA rarely need to undergo lung biopsy to confirm the diagnosis of ILD, which is most of the time based on tomographic patterns.

Usual interstitial pneumonia associated with RA

Usual interstitial pneumonia (UIP) is the most common ILD pattern in RA, with a prevalence of about 60%. UIP carries the worst prognosis among all patients with ILD secondary to RA, the surviving rates being quite similar to those of patients with idiopathic pulmonary fibrosis (IPF).[10] The main CT features are basilar and peripheral traction bronchiectasis and/or bronchiolectasis, with or without honeycombing, and minimal or absent ground-glass opacities.[2,11] The imaging presentation of RA-UIP and IPF may be identical. Chung et al.[12] have described three features favoring the presence of autoimmune rheumatic diseases as the etiology of UIP over IPF: exuberant honeycombing; straight edge sign, characterized as the isolation of fibrosis in the lower zones with sharp demarcation between fibrotic and normal lung in the craniocaudal plane and without substantial extension of fibrosis along the lateral margins at coronal imaging; and anterior upper lobe involvement (Figure 1).

Nonspecific interstitial pneumonia and other ILD patterns

Nonspecific interstitial pneumonia (NSIP) is the second most common ILD pattern in RA, occurring in around one-third of cases.[10] NSIP is associated with longer duration of joint disease, lower risk of disease progression, greater treatment response, and better outcomes when compared with UIP.[13] There is no difference in prognosis when comparing idiopathic NSIP with autoimmune rheumatic disease-associated NSIP.[7] CT findings in NSIP include basilar- and peripheral-predominant ground-glass opacities and reticulation, with or without immediate subpleural sparing, and traction bronchiectasis (Figure 2). The tomographic presentation of NSIP is typically homogeneous and symmetric, and traction bronchiectasis is often relatively central in comparison with UIP.[2,10,11]

The third most common ILD pattern in RA is OP, which tends to be more aggressive and to determine more symptoms than does cryptogenic OP.[7,14] Tomographic features of OP vary and commonly include peripheral and peribronchovascular consolidations, ground-glass opacities, and, less frequently, nodules (Figure 3). A reversed halo sign, characterized by a central ground-glass area surrounded by a complete or incomplete ring of peripheral consolidation, and perilobular opacities may also be identified. These abnormalities are often fleeting or migratory.[10,11]

Lymphocytic interstitial pneumonia (LIP) is a benign lymphoproliferative ILD that may occur in patients with RA, but more commonly occurs in association with Sjögren's syndrome (SS). Because secondary SS is the most common extra-articular manifestation in RA, affecting approximately 35% of patients, cases of LIP in RA may be associated with SS.[15] LIP is part of a continuum of reactive

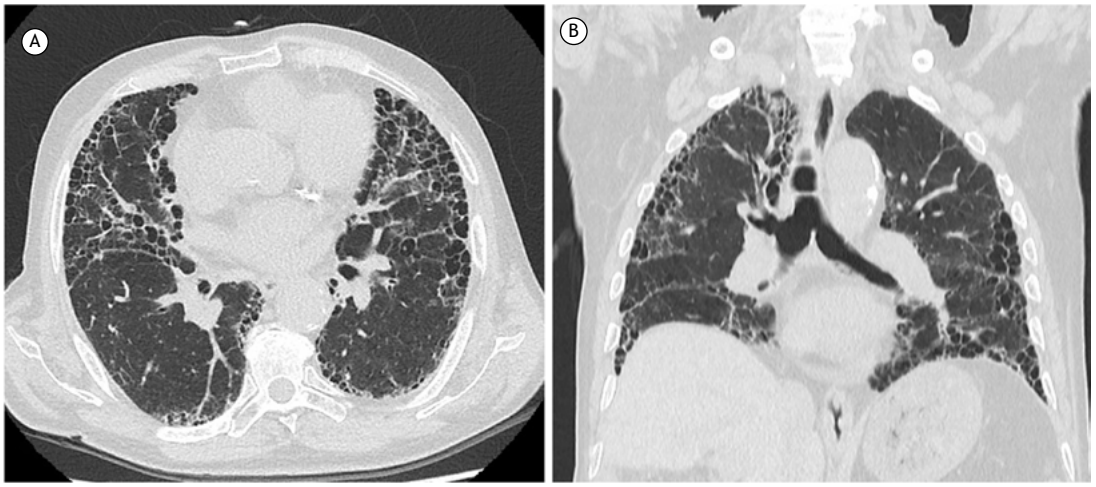

Figure 1. CT scans of an 87-year-old male patient with rheumatoid arthritis, usual interstitial pneumonia, and exuberant honeycombing. In A, axial reconstruction: large and predominantly peripheral cysts, and some areas with traction bronchiolectasis. In B, coronal reconstruction: lesions in the apicobasal axis.

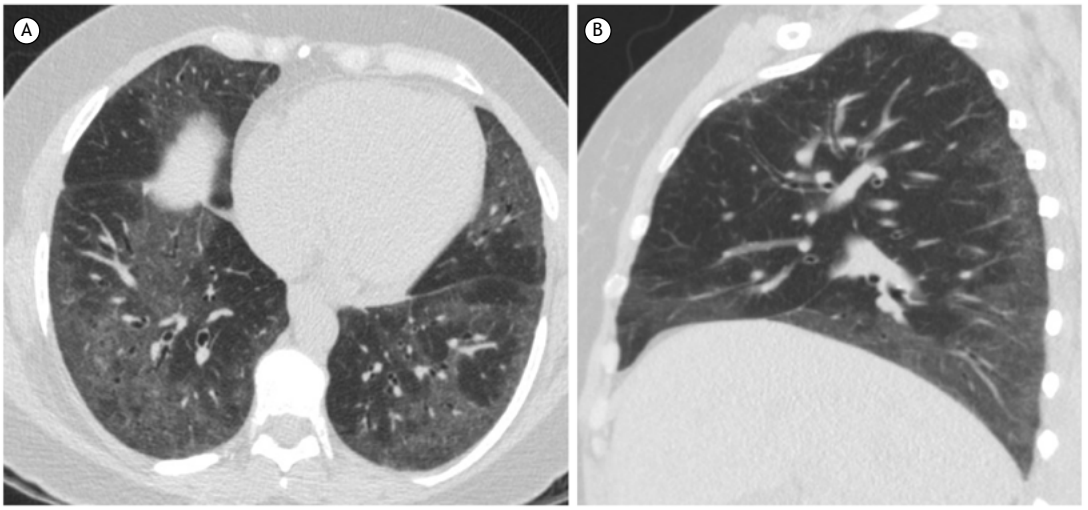

Figure 2. CT scans of a 37-year-old female patient with rheumatoid arthritis and nonspecific interstitial pneumonia. In A, axial reconstruction: diffuse ground-glass opacities and fine reticulation, predominantly in the lower lobes. In B, sagittal reconstruction showing subpleural sparing.

lymphoproliferation with follicular bronchiolitis. CT findings of LIP include lower lobe-predominant thin-walled cysts adjacent to vessels (perivascular distribution), with or without septal thickening and ground-glass opacities (Figure 4).[11,16]

Interstitial lung abnormalities (ILAs) and ILD are seen in up to 60% of individuals with RA, and some patients with such lesions may have disease progression with a significant impact on morbidity and mortality rates.[17,18] Estimates of the rate of imaging progression of ILAs range from 20% to 48% over five years. Additionally, the increase in the rate of mortality was most strongly associated with the imaging progression of ILAs, and specific imaging patterns indicative of pulmonary fibrosis were associated with earlier mortality.[19] Kawano-Dourado et al.,[17] in a retrospective study with patients with RA, quantified the initial CT pattern as compared to a second CT four years after the initial imaging. Of the 56 individuals with ILA/ILD, 21 (38%) had imaging evidence of disease progression. Subpleural distribution and higher baseline ILA/ILD extent were predictors of a higher risk of imaging progression. However, prospective longitudinal studies with patients with RA-ILA are necessary to better the understanding of the impact and the risk of progression of ILA.

Desquamative interstitial pneumonia (DIP) is a rare subtype of ILD. Although DIP is usually associated with exposure to tobacco smoke, some cases have been associated with autoimmune rheumatic diseases such as RA. Tomographic features of DIP[20] include ground-glass opacities with mild reticulation, basal and peripheral predominance, and, less frequently, cystic lesions (Figure 5).

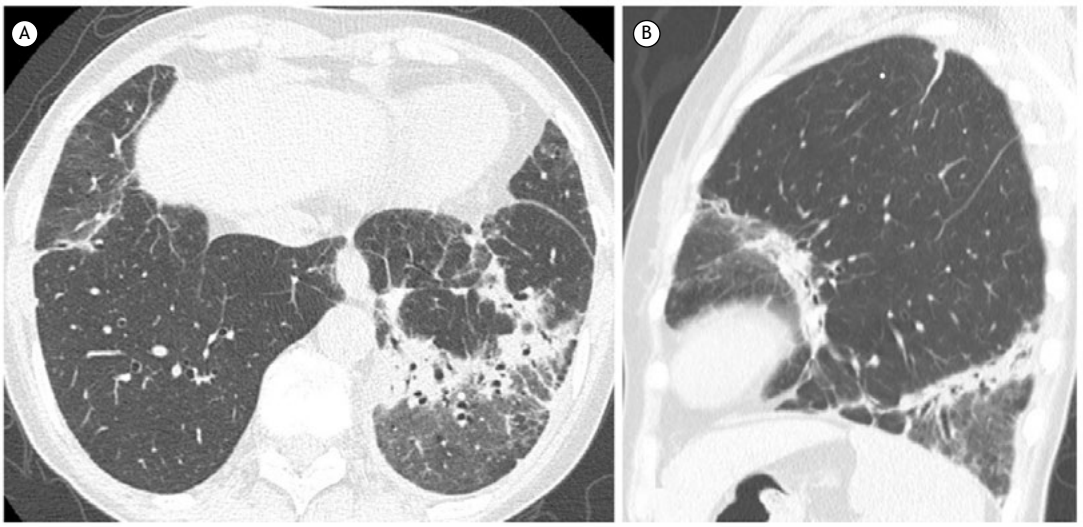

Figure 3. CT scans in axial (in A) and sagittal (in B) reconstructions of a male patient with rheumatoid arthritis. The scans demonstrate peripheral and peribronchovascular consolidations, which is compatible with organizing pneumonia.

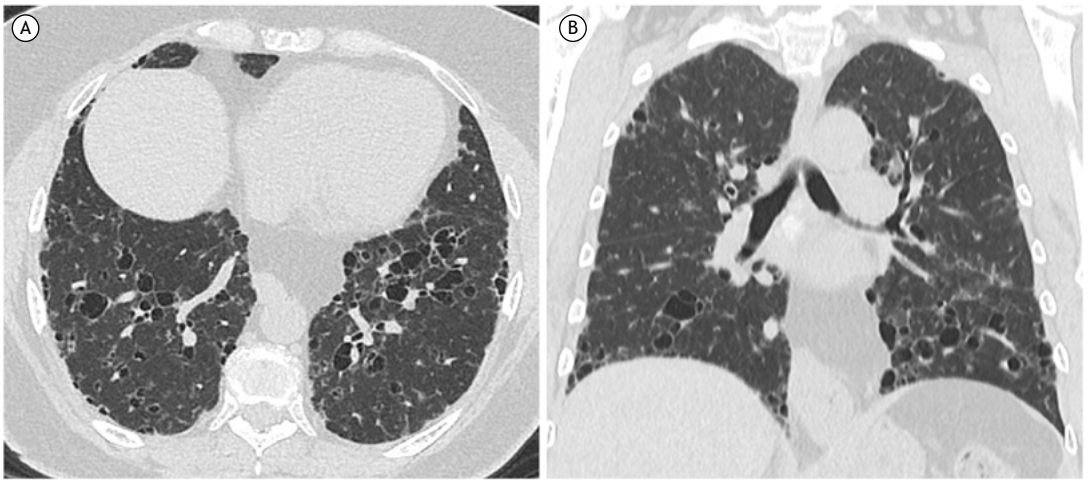

Figure 4. CT scans of a 60-year-old female patient with rheumatoid arthritis and lymphocytic interstitial pneumonia. Axial (in A) and coronal (in B) reconstructions show thin-walled cysts with variable sizes and discrete ground-glass opacities, predominating in the lower lobes and along the peribronchovascular bundle.

PLEURAL MANIFESTATIONS

Pleural disease is considered the most common thoracic manifestation in patients with RA and was identified in 73% of patients in a postmortem study.[21] However, most patients are asymptomatic, and few present with chest pain or dyspnea.[1,21] The most common pleural manifestations are effusions and pleurisy, with a prevalence of approximately 3% and 20%, respectively.[4]

Pleural effusion can occur due to pleural inflammation (Figure 6), infections, or RA-associated cardiac disease in patients with RA. Pleural effusions secondary to cardiac failure are usually bilateral, which is different from those secondary to pleural inflammation or infections, which are usually unilateral and present with small volume. Pleural effusion associated with inflammation is usually exudative with low glucose levels (≤ 25 mg/dL), low pH levels (< 7.3), high LDH levels (> 700 IU/L), high rheumatoid factor titers, and low total complement activity levels, as well as low C3 and C4 levels. Chronic pleural inflammation may result in pleural involvement with thickening of both parietal and visceral pleurae, which is quite similar to empyema. Pleural involvement can also be nodular, mimicking neoplasms.[4]

Pleural effusion may be transient, persistent, or relapsing, and when untreated or recurrent, pleuritis can lead to pleural fibrosis, trapped lung, and lung restriction.[1] Bronchopleural fistulae and pneumothorax are other less common findings that are usually associated with the rupture of rheumatoid lung nodules. Bronchopleural fistulae, immunosuppression, and chronic pleural disease fistulae increase the risk of empyema.[1,4]

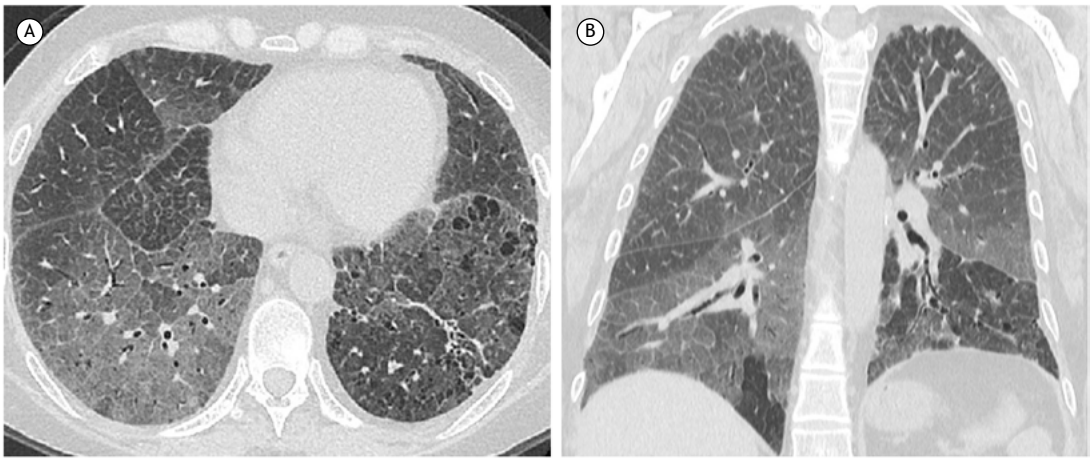

Figure 5. CT scans of a 45-year-old female patient with rheumatoid arthritis and desquamative interstitial pneumonia. Axial (in A) and coronal (in B) reconstructions demonstrate diffuse ground-glass opacities, interlobular septal thickening, and cysts, predominating in the lower lobes.

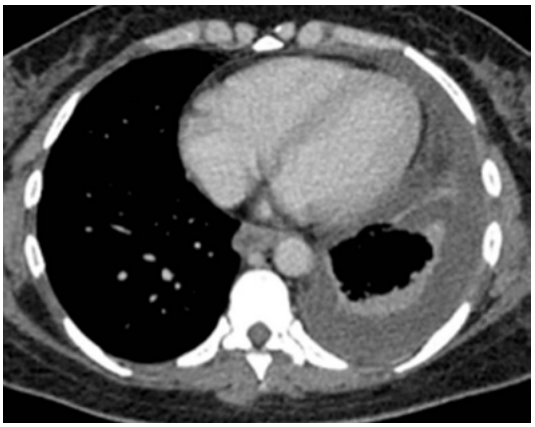

Figure 6. Axial reconstruction of a CT scan of a female patient with a left pleural effusion secondary to rheumatoid arthritis.

PAH

In patients with RA, PAH may be seen in isolation or in association with ILD. It is rare as an isolated finding in RA and is more common in older patients with long-standing ILD. PAH can lead to chronic respiratory failure and right heart failure, and it rarely occurs secondary to RA vasculitis.[1,4,22]

Direct CT findings of PAH are enlarged pulmonary arteries, main pulmonary artery diameter to ascending aorta diameter ratio > 1, dilatation of right-sided cardiac chambers, and right ventricular hypertrophy. Indirect signs in the lungs may be identified, such as mosaic attenuation, indicating regional differences in pulmonary perfusion.[1,4]

RHEUMATOID LUNG NODULES

Rheumatoid lung nodules or necrobiotic lung nodules are described in up to 20% of RA patients and are usually associated with subcutaneous nodules. Patients are frequently asymptomatic but may develop symptoms if nodules cavitate to the pleural space. Rheumatoid lung nodules are characterized on CT scans as round opacities, from few millimeters to several centimeters in size, typically located in the subpleural region, and are usually multiple and cavitated (Figure 7A).[23,24]

Because rheumatoid lung nodules have radiological characteristics quite similar to those of granulomatous and neoplastic diseases, they may represent a diagnostic challenge. Imaging features more commonly associated with rheumatoid lung nodules as compared to malignancy include multiplicity, smooth border, cavitation, satellite nodules, and pleural contact.[4,23] Histologically, rheumatoid nodules are composed of central fibrinoid necrosis surrounded by palisading epithelioid histiocytes and peripheral, chronic inflammatory cells.

The risk of malignancy in RA, such as primary lung cancer and lymphoproliferative disorders, particularly diffuse B-cell lymphoma, is overall 10% higher in comparison with that observed in the general population. Higher rates of malignancy may be explained by RA host factors, such as immune-mediated mechanisms, inflammation, viruses, and genetic predispositions, and non-RA risk factors, such as smoking, chronic lung inflammation, and pulmonary fibrosis.[4] Adenocarcinoma is the most common histopathological pattern of lung cancer in patients with RA,[23] followed by squamous cell carcinoma and small cell carcinoma (Figures 7B and 7C).

Caplan syndrome

Caplan syndrome (rheumatoid pneumoconiosis) was first described in a large cohort of coal miners with RA in 1953,[24] and it can be associated with exposure to coal, asbestos, or silica. The prevalence is less than 1% in the USA in autopsy series[25] and is more common in patients with silicosis. The disease is

characterized by the presence of multiple peripheral rheumatoid lung nodules and may precede the onset of arthritis by more than ten years. Radiographically, nodules tend to form rapidly and persist over years, approximately 10% of which developing cavitations or calcifications.[7] The nodules vary from 0.5 to 5 cm and may coalesce (Figure 7D).[4]

Most patients with Caplan syndrome are asymptomatic, and there is no impact on their pulmonary function test results.[3] Although a causal link between RA and dust exposure has not been completely established, it has been hypothesized that exposure to foreign particles leads to chronic immune activity that might facilitate the formation of autoantibodies, promoting the occurrence of RA. Indeed, pneumoconiosis may be associated with increased formation of immune complexes and increased rheumatoid factor levels, even without a definitive autoimmune diagnosis. The question of individual susceptibility remains unanswered.[2,26]

AIRWAY DISEASE

Bronchiectasis

Previous studies described bronchiectasis in 30-40% of RA patients.[4,27] Since bronchiectasis may be clinically silent, the real prevalence may be even greater (Figure 8). Chronic suppurative infections, treatment with disease modifying anti-rheumatic drugs, and genetic predisposition are some of the hypotheses associated with the development of bronchiectasis. Of note, a higher mortality rate was described in patients with RA and bronchiectasis than in those with either condition alone.[27]

Bronchiolitis

Constrictive and follicular bronchiolitis may occur in patients with RA. Constrictive bronchiolitis, also known as obliterative bronchiolitis, is characterized by bronchiolar inflammation with submucosal peribronchial fibrosis associated with luminal stenosis and occlusion. Although uncommon, it is a severe and

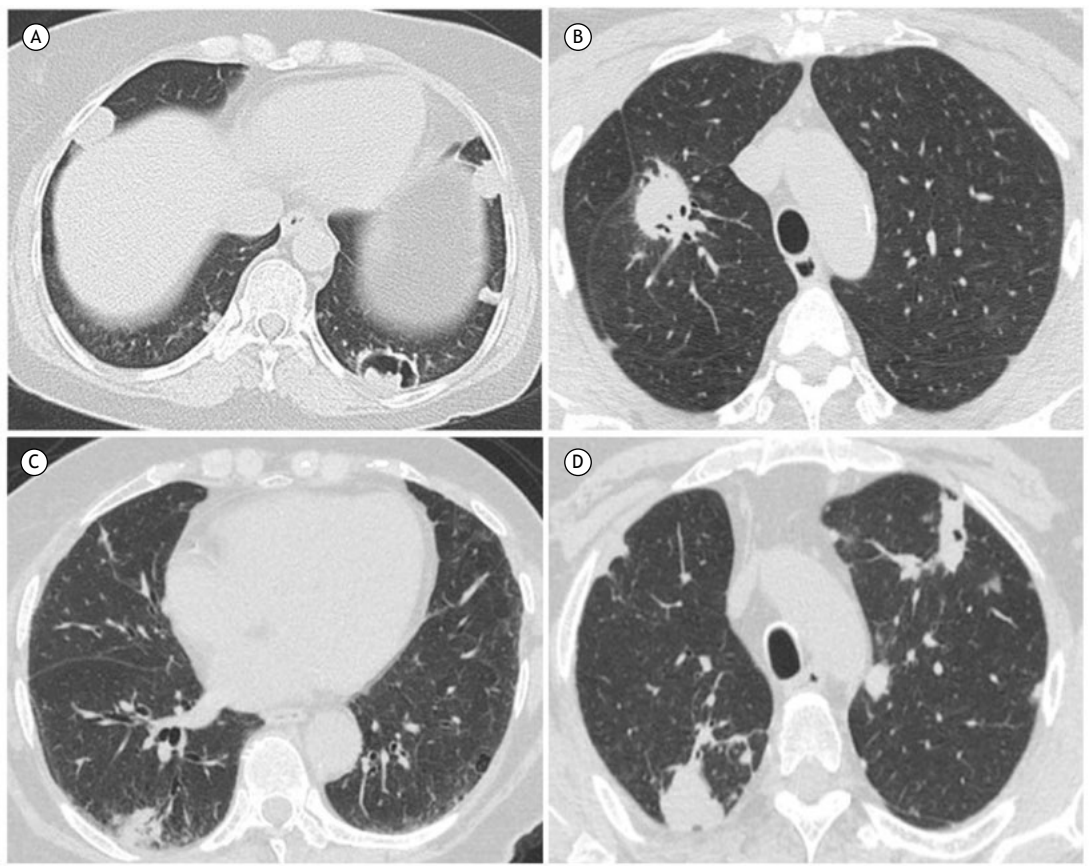

Figure 7. In A, a CT scan in axial reconstruction of a 50-year-old female patient with rheumatoid arthritis shows multiple bilateral subpleural nodules, the largest one being cavitated in the left lower lobe, which is compatible with rheumatoid nodules. In B, a CT scan in axial reconstruction of a patient with rheumatoid arthritis demonstrates a pulmonary nodule in the upper right lobe. Histopathological analysis was compatible with lung adenocarcinoma. In C, a CT scan in axial reconstruction of a patient with rheumatoid arthritis shows a pulmonary nodule in the lower right lobe. Histopathological analysis was compatible with lung adenocarcinoma. In D, a CT scan in axial reconstruction of a 68-year-old male patient with rheumatoid arthritis and Caplan syndrome demonstrates subpleural nodules predominantly in the upper lobes, one with central cavitation.

potentially fatal condition. Constrictive bronchiolitis in RA is more common in females and in those with positive rheumatoid factor results and long-standing untreated disease, but it may also occur secondary to use of medications, including sulfasalazine.[2,27] Patients usually develop progressive dyspnea, cough, and bronchorrhea, and it may occur in the absence of other systemic symptoms.[27] Pulmonary function tests usually show airflow obstruction and air trapping. Tomographic findings include bronchial wall thickening, bronchiectasis, and a mosaic attenuation pattern, with areas of decreased lung attenuation representing air trapping (Figure 9A). Additional expiratory CT images are helpful in this setting to confirm the presence of air trapping.[4]

Follicular bronchiolitis is characterized by reactive hyperplasia of bronchus-associated lymphoid tissue. It is usually secondary to autoimmune rheumatic diseases, mainly RA and SS, and has good prognosis. Tomographic features of follicular bronchiolitis include small centrilobular nodules with branching structures (tree-in-bud sign), corresponding to bronchial dilation, wall thickening, and mucoid impaction (Figure 9B). Air trapping and peribronchovascular and septal thickening may also be seen and correspond to proliferative lymphatic tissue.[4,27]

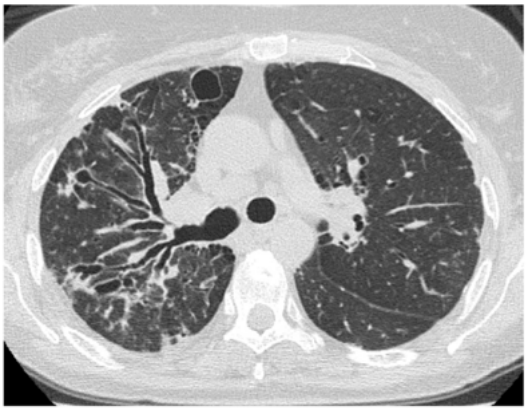

Figure 8. A CT scan in axial reconstruction of a 54-year-old female patient with rheumatoid arthritis demonstrates cylindrical, varicose, and cystic bronchiectasis in the right lung.

Lymphadenopathy

Axillary and mediastinal lymph node enlargement may occur in 20-70% of patients with RA, especially in those with RA-ILD.[4,28] The biology underpinning this enlargement remains unclear. However, migration of immune cells from the peripheral circulation through mediastinal lymph nodes to the lungs has been suggested to contribute to pulmonary fibrosis.[29] Furthermore, patients with either mediastinal or axillary lymphadenopathy showed significantly higher simple disease activity index than did those with no lymphadenopathy, which is a valid and sensitive tool to assess disease activity in patients with RA. Therefore, lymphadenopathy may be associated with signs of inflammatory activity in RA and is usually mild (Figure 10). Although lymphadenopathy in RA patients is mostly part of an inflammatory process, it is essential to exclude the presence of a malignant process or sarcoid reaction in those using TNF-α inhibitors.[4,30]

DILD

DILD in patients with RA can occur by immune-mediated reactions related to the mechanism of action of the drug or due to its direct toxicity and is usually associated with use of disease-modifying antirheumatic drugs and nonsteroidal anti-inflammatory agents.[1,4] The onset of DILD can be within days or years after treatment initiation with the suspected drug, but symptoms are nonspecific. The most common radiologic patterns of drug toxicity are: hypersensitivity reaction, resembling hypersensitivity pneumonitis,

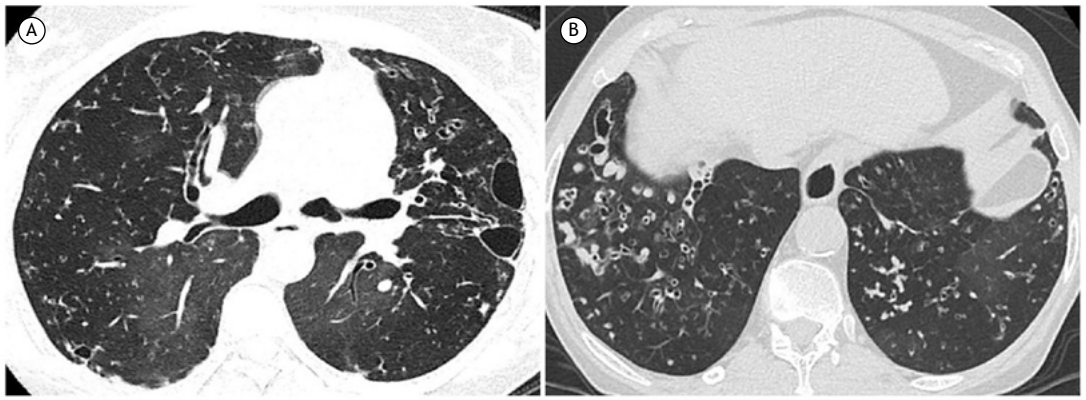

Figure 9. In A, a CT scan in axial reconstruction of a 60-year-old female patient with rheumatoid arthritis and constrictive bronchiolitis demonstrates bronchial wall thickening, bilateral centrilobular opacities, bronchiectasis, and mosaic attenuation pattern, compatible with air trapping. In B, a CT scan in axial reconstruction of a 50-year-old female patient with rheumatoid arthritis and follicular bronchiolitis shows diffuse small centrilobular nodules, tree-in-bud opacities, some bronchiolectasis, and bronchiolar wall thickening, predominating in the lower lung zones.

eosinophilic pneumonia, pulmonary edema, OP, and DAD. The diagnosis is based on clinical and imaging findings, as well as the time between treatment initiation and drug discontinuation and, less frequently, on histopathological findings. The main differential diagnoses include RA-ILD progression or exacerbation, infection, and cardiogenic pulmonary edema.[4]

Methotrexate-induced lung disease is the archetype of drug-induced pulmonary toxicity in patients with RA, usually occurring early with the beginning of therapy. The most common CT and histologic findings of methotrexate-induced lung disease are similar to those of hypersensitivity pneumonitis (Figures 11A and 11B). Other patterns include OP and DAD. Symptoms usually improve with drug discontinuation.[4] In a case-control study[31] with discovery and international replication samples, the association of methotrexate exposure with ILD was evaluated in 410 patients with chronic fibrotic ILD associated with RA (RA-ILD), and 673 patients with RA without ILD. The results suggested that methotrexate use was not associated with an increased risk of RA-ILD in patients with RA and that ILD was often detected later in methotrexate-treated patients.[31]

The use of TNF-α inhibitors is frequently associated with infectious and noninfectious granulomatous lung disease, DAD, and, less often, pulmonary fibrosis. Sarcoidosis-like disease in patients with RA is more common in those that received etanercept. Tomographic features are similar to the typical findings of sarcoidosis, including micronodules and lymphadenopathy (Figures 11C and 11D). Another pattern that can occur is OP, associated with DAD or as a distinct DILD. Rituximab is used in patients with an inadequate TNF-α inhibitor response and can also lead to DAD and OP.[4]

Leflunomide can lead to ILD exacerbation, accelerated formation of pulmonary rheumatoid nodules, and diffuse alveolar hemorrhage. Nonsteroidal anti-inflammatory drugs, including ibuprofen, aspirin, and acetaminophen, have been reported as potential etiologies for DILD and may present as allergic-type reactions, such as eosinophilic pneumonia and pulmonary edema.[1,4]

FINAL CONSIDERATIONS

It is essential to evaluate the presence of respiratory symptoms and objective pleuropulmonary involvement regularly in patients with RA due to the high prevalence of pleuropulmonary manifestations and their potential to increase morbidity and mortality. ILD is associated with worse prognosis, mainly the UIP pattern.

CT is an indispensable tool to evaluate the several potential pleuropulmonary manifestations that may occur in patients with RA and often allows the establishment of a diagnosis without the need of histopathological analysis. The widespread use of CT increased the identification of such manifestations, although the differential diagnoses are variable and often challenging, including infections, DILD, and neoplasms.

AUTHOR CONTRIBUTIONS

GPB and MVYS: study design; data collection; data analysis; and drafting and review of the manuscript. MW: data collection; data analysis; and drafting and review of the manuscript. LVSS: data collection; and drafting and review of the manuscript. RAK and LKD: data analysis; and drafting and review of the manuscript. BGB: guarantor of the study; study design; data collection; data analysis; and drafting and review of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

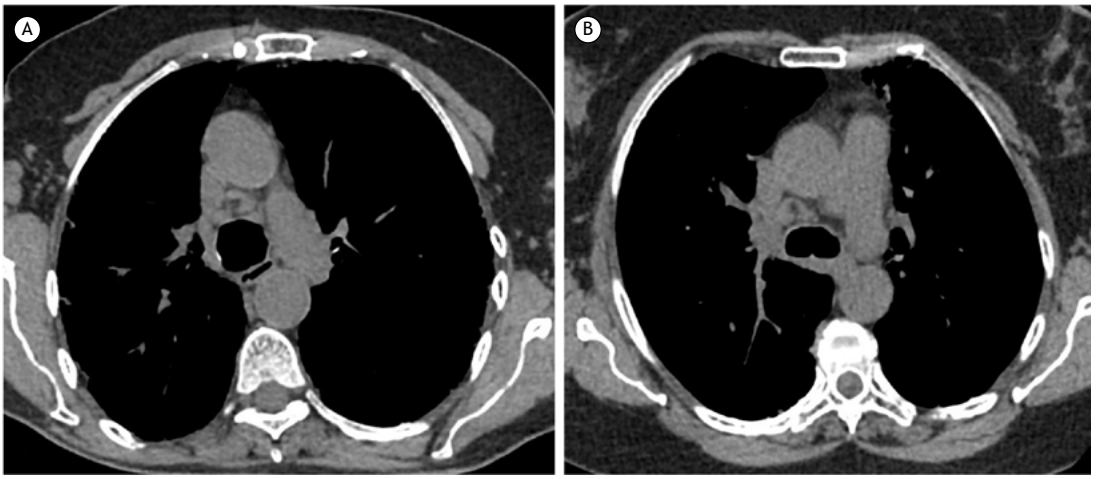

Figure 10. CT scans in axial reconstructions of a 64-year-old female patient with rheumatoid arthritis show mediastinal lymph node enlargement.

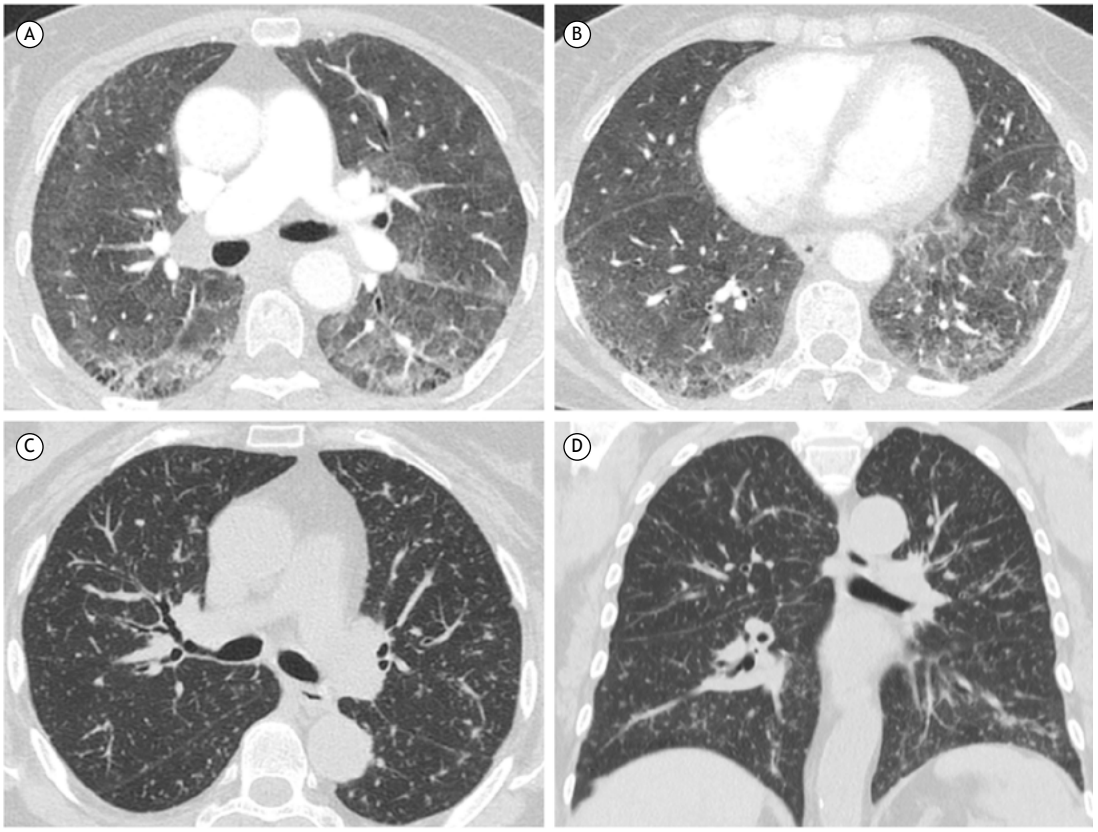

Figure 11. Drug-induced lung disease. In A and B, CT scans in axial reconstructions of a patient with rheumatoid arthritis and lung toxicity associated with the use of methotrexate demonstrate diffuse ground-glass opacities, compatible with hypersensitivity reaction. In C and D, CT scans in axial reconstructions of a patient with rheumatoid arthritis and sarcoid-like reaction associated with the use of TNF-α inhibitor demonstrate diffuse, predominantly perilymphatic, micronodules.

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Correlation between the Brody score and lung function using an ultra-low-dose CT protocol without anesthesia in children with cystic fibrosis

Suélen Camargo[1], Frederico Friedrich[2], Marina Puerari Pieta[2], Luíza C. S. Martins[2], Leonardo A. Pinto[1,2]

TO THE EDITOR,

Cystic Fibrosis (CF) is a multisystemic disease; however, the extent of pulmonary impairment is decisive for the course of the disease and survival.[1,2] Lung function tests are crucial to assess the progression and severity of lung disease.[2,3] Studies have shown that the forced expiratory volume in the first second (FEV_1) is also a relevant index in the early detection of pulmonary exacerbations, improving the survival of patients with CF.[4]

The progression of CF lung disease is associated with a decline in FEV_1.[2] Although the lung parenchyma remains largely intact for much of the course of the disease, Brody et al. (2005) demonstrated that patients with normal FEV_1 already had structural changes upon chest computed tomography (CT).[5-7]

Early methods of predicting lung involvement in CF patients are essential to target treatment and prevent loss of lung function and respiratory failure. Chest CTs show findings that can assist in predicting the progression of lung disease, such as the presence of bronchiectasis and obstructive changes in the lung parenchyma.[8] In addition, chest CT scans in children currently adopt low doses of radiation, often without the need for anesthesia, which implies greater ease in acquiring images and less exposure to radiation and possible complications resulting from anesthesia.

In order to track pulmonary changes before clinical symptoms become apparent, the evaluation of new strategies is essential. Spirometry is used for monitoring, but FEV_1 often remains normal in advanced stages of lung disease. Thus, the aim of this study was to determine the correlation between the Brody score and lung function in subjects with CF.

This retrospective, cross-sectional study included all CF patients aged over five years old, with available chest CT scans, who were assisted in the outpatient CF Clinic of the São Lucas Hospital (HSL) Pulmonology Service between July and November 2020. Subjects in which the period between pulmonary function testing and chest CT was longer than three months were excluded.

The diagnosis of patients with CF was confirmed according to the CF Foundation Consensus Report.[1] Demographic and clinical data and information on genetic mutations (mild - classes III to VI, and severe - classes I and II) and lung function (% predicted FEV_1) were collected from physical and electronic medical records. The spirometry test was performed according to the recommendations of the American Thoracic Society and European Respiratory Society.

The Brody score was evaluated by chest CT scans using an ultra-low radiation dose, without anesthesia. CT scans were obtained in all patients in supine position, in both the expiratory and inspiratory phases, from the lung apex to below the costophrenic angles. Chest CT was performed using a CT 16 multislice scanner (LightSpeed VCT; GE Healthcare, Milwaukee, WI, USA) according to the following protocol: collimation of 1.25 mm, Gantry rotation of 0.5 s, 80 kV, and 30 mAs; without anesthesia.[9] The Brody score is calculated based on four parameters: diameter and extent of bronchiectasis, thickening of the peribronchial wall, air trapping, and the extent of lung parenchyma impairment.[10]

All statistical analyses were performed using the Statistical Package for the Social Sciences software, version 20.0, for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were described as absolute and relative, while continuous variables as median and interquartile range. The categorical variables were analyzed through the Chi-square test. Spearman's correlation coefficient was calculated to evaluate the association of lung impairment by the Brody score and FEV_1. P-values below 0.05 were considered significant. This study was approved by the Research Ethics Committee of the Pontifícia Universidade Católica do Rio Grande do Sul, Brazil (CAAE No. 49692115.7.0000.5336).

A total of 25 subjects were included, with a median age of 7 years [interquartile range: 5.1 – 15.1]; there was a predominance of males (n = 15; 60%). Ten (40%) subjects were homozygous for F508del, 10 (40%) were heterozygous for F508del, and five (20%) carried other CFTR mutations. The median % predicted FEV_1 was 81 [54.5 - 105.0], and 19 (76%) subjects had bronchiectasis upon chest CT.

A moderate positive correlation was observed between the Brody score and age ($r = 0.42$, $p = 0.034$), while a negative correlation was observed between FEV_1 and age ($r = -0.57$, $p = 0.006$), indicating that the severity of the Brody score is associated with the progression of lung disease over the years.

Figure 1 shows the correlation between the Brody score and FEV_1, adjusted by age ($r = -0.582$, $p = 0.006$). Five (31.2%) subjects aged 12 years or less presented Brody

1. Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS), Brasil.
2. Faculdade de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS), Brasil.

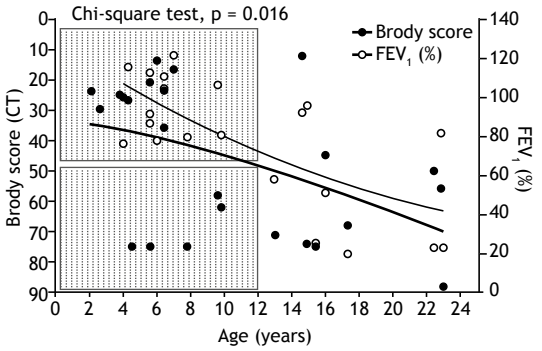

Figure 1. Brody score and FEV_1 by age in patients attended at the CF Reference Center at HSL-PUC. CT = Computed tomography; FEV_1 = Forced expiratory volume in the first second.

scores above 50, showing early and relevant pulmonary alterations by chest CT. In contrast, none of the patients aged 12 years or less showed a significant change in % predicted FEV_1 (Brody score vs. FEV_1, p = 0.016).

Our findings revealed high Brody scores in young patients who did not yet exhibit reduced lung function, highlighting the importance of early interventions to reduce future damage. In addition, the sample showed a high prevalence of bronchiectasis in childhood and adolescence. A significant correlation between the Brody score and FEV_1, adjusted by age, was found in this study. Furthermore, five patients with preserved lung function already presented lung impairment when evaluated by the Brody score, performed by chest CT. These findings are important, particularly at the preschool age, when the child is unable to perform spirometry.

Relevant findings of lung disease on chest CT were present in CF patients with mild to moderate disease, according to FEV_1 parameters. Although bronchiectasis was present in most CT scans, in only half of the cases (20%) was the Brody score above 50, a sign of advancing lung disease.

This study had some limitations. First, it is a retrospective, cross-sectional study. Second, it was performed on a small sample size; and third, it was carried out in a single center. However, only some studies have explored the use of the Brody score in ultra-low-dose chest CT without anesthesia for the early assessment of pulmonary involvement in children with cystic fibrosis. The Brody score measured by chest CT provided advantages, such as the early detection of pulmonary impairment. This scoring system is a simple method that can be performed without anesthesia, using an ultra-low CT radiation dose, which is safer and more effective.

In conclusion, the present study showed a positive correlation between the Brody score and lung function in CF subjects. Moreover, these results indicate that chest CT could assess and detect early structural changes related to lung disease progression. However, more studies with larger sample sizes are needed to elucidate the potential of chest CT as an early detector of lung disease.

AUTHOR CONTRIBUTIONS

SC: study conception, methodology, visualization, writing of the original draft, and review and editing. FF and LAP: study conception, methodology, visualization, and review and editing. MPP and LCSM: study methodology, visualization, and review and editing. All authors approved the final version of the manuscript for publication.

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Temporal trend of Tuberculosis incidence in northeastern Brazilian municipalities according to Social Vulnerability Index parameters: An ecological study

João P. S. Paiva[1], Alyne B. Brito[1], Márcio Bezerra-Santos[2], Rodrigo F. Carmo[3,4], Carlos D. F. Souza[5]

TO THE EDITOR,

Tuberculosis (TB) is an infectious and contagious disease of chronic evolution caused by the intracellular bacillus *Mycobacterium tuberculosis*, which is transmitted primarily through the airways by the dispersion of aerosols expelled by individuals with active disease.[1,2] It is estimated that one-third of the world's population is infected with this bacillus and that nearly 10 million new cases are registered every year. In addition, TB is currently the second leading infectious disease in the world in terms of mortality, with approximately 1.3 million deaths annually.[1-3]

Aside from the biological component, the occurrence of TB is associated with precarious living conditions, such as poverty, poor nutrition, and the existence of crowded households. These living circumstances to which people are exposed are known as social determinants of health.[4,5] These determinants, although dynamic, can be measured using indicators that express the degree of human development and pragmatic social vulnerability of the population.[6]

Considering the need to monitor the temporal evolution of the disease and provide knowledge on the TB elimination process in the country, the aim of the present study was to analyze the temporal trend of TB incidence in northeastern Brazilian municipalities, according to Social Vulnerability Index (SVI) parameters, from 2001 to 2017.

This ecological study was carried out in the Brazilian Northeast, a region which comprises nine states and 1,793 municipalities. Here, we analyzed the following epidemiological indicators: annual and average TB incidence rate per 100,000 inhabitants from 2001 to 2017. Data regarding new cases of TB were obtained from the National System of Notifiable Diseases (SINAN).

The SVI was created to indicate the access to or insufficiency of social assets, whose possession or deprivation determines the welfare conditions of the populations in areas of the Brazilian territory.[6] It comprises 16 variables grouped into the following three dimensions: i) urban infrastructure, ii) human capital, and iii) income and work. The SVI varies from 0 to 1, where 0 corresponds to the ideal (desirable) social situation and 1, the worst. Municipalities are classified as follows: very low social vulnerability (0 to 0.200), low (0.200 to 0.300), medium (0.300 to 0.400), high (0.400 to 0.500), and very high (greater than 0.500).[10] The social vulnerability indicators were obtained from the Atlas of Social Vulnerability of the Institute for Applied Economic Research (IPEA - http://ivs.ipea.gov.br).

Trend analysis was carried out with the use of a joinpoint regression model. This model evaluates whether a line with multiple segments is statistically better to describe the temporal evolution of a dataset than a straight line or a line with fewer segments. The annual percent change (APC) was calculated, considering a confidence interval of 95% and 5% significance.[7] Trend analysis was performed using the Joinpoint Regression software, version 4.5.0.1 (National Cancer Institute, Bethesda, MD, USA). The study did not require ethics committee approval since it used secondary data from the public domain.

Regarding the SVI-human capital, municipalities with low (n = 6; 0.3%; 40.69/100,000) and medium SVI (n = 67; 3.7%; 38.28/100,000) had higher TB incidence rates than those with high (n = 443; 24.7%; 25.50/100,000) and very high SVI (n = 1277; 71.2%; 23.86/100,000). Three strata showed decreasing trends (low, medium, and high), with the largest annual percentage decline observed in the high SVI stratum (AAPC: -2.7; 95% CI: -4.0 to -1.5) (Table 1).

Regarding the SVI-income and work, municipalities with low SVI (n = 8; 0.4%; 41.95/100,000) showed a higher TB incidence rate when compared to municipalities with very high SVI (n = 1320; 73.6%; 23.72/100,000). Only the medium, high, and very high strata showed decreasing trends over the studied period (2001 - 2017) (Table 1).

The SVI-urban infrastructure dimension showed an inverse behavior compared to the others. Municipalities with high (n = 221; 12.3%; 28.79/100,000) and very high SVI (n = 208; 11.6%; 25.14/100,000) showed the highest TB incidence rates. Three strata showed decreasing trends (high, low, and very low). However, the trends were stationary in the medium (AAPC = -1.9; 95% CI: -4.0 to 0.2) and very high (AAPC: -2.1; 95% CI: -4.3 to 0.1) strata, with a greater percentage reduction in the very low stratum (AAPC: -3.1; 95% CI: -5.9 to -0.2) (Table 1).

Notably, the relationship between TB and living conditions is not static. This is because, in endemic areas, better

1. Departamento de Medicina, Universidade Federal de Alagoas, Arapiraca (AL), Brasil.
2. Universidade Federal de Sergipe, Aracaju (SE), Brasil.
3. Programa de Pós-Graduação em Ciências da Saúde e Biológicas, Universidade Federal do Vale do São Francisco, Petrolina (PE), Brasil.
4. Programa de Pós-Graduação em Biociências, Universidade Federal do Vale do São Francisco, Petrolina (PE), Brasil.
5. Programa de Pós-Graduação em Saúde da Família, Departamento de Medicina, Universidade Federal de Alagoas, Arapiraca (AL), Brasil.

Table 1. Trends in TB incidence rates in northeastern municipalities according to the dimensions of the Social Vulnerability Index (SVI), Brazil, 2001-2017.

SVI Overall	Number of Municipalities	Incidence/ 100,000	Period	APC/ AAPC	(95% CI)	Trend
Very low	0	-				
Low	32	30.19	2001-2017	-3.5	-3.9; -3.0	Decreasing
Medium	315	26.66	2001-2017	-3.6	-4.1; -3.0	Decreasing
High	859	24.70	2001-2005	2.2	-1.2; 5.7	Increasing
			2005-2012	-3.5	-5.1; -1.8	Stationary
			2012-2015	-7.4	-18.3; 5.0	Decreasing
			2015-2017	4.0	-8.5; 18.1	Stationary
			2001-2017	-1.9	-4.3; 0.5	Stationary
Very high	587	23.84	2001-2006	2.6	0.5; 4.8	Increasing
			2006-2015	-5.7	-6.6; -4.9	Decreasing
			2015-2017	1.4	-14.2; 19.9	Stationary
			2001-2017	-2.3	-4.2; -0.4	Decreasing
SVI Urban Infrastructure	**Number of Municipalities**	**Incidence/ 100,000**	**Period**	**APC/ AAPC**	**(95% CI)**	**Trend**
Very low	435	24.57	2001-2006	0.5	-2.4; 3.5	Stationary
			2006-2012	-5.0	-7.7; -2.2	Decreasing
			2012-2015	-9.3	-21.8; 5.3	Stationary
			2015-2017	3.9	-10.6; 20.7	Stationary
			2001-2017	-3.1	-5.9; -0.2	Decreasing
Low	504	24.34	2001-2004	0.8	-4.7; 6.5	Stationary
			2004-2012	-3.4	-4.8; -2.1	Decreasing
			2012-2015	-6.7	-17.0; 5.0	Stationary
			2015-2017	4.0	-7.6; 17.1	Stationary
			2001-2017	-2.4	-4.6; -0.1	Decreasing
Medium	425	23.60	2001-2006	2.7	0.8; 4.6	Increasing
			2006-2012	-4.4	-6.1; -2.6	Decreasing
			2012-2015	-7.4	-17.0; 3.3	Stationary
			2015-2017	3.1	-8.0; 15.5	Stationary
			2001-2017	-1.9	-4.0; 0.2	Stationary
High	221	28.79	2001-2017	-1.5	-1.9; -1.1	Decreasing
Very high	208	25.14	2001-2005	7.0	3.0; 11.2	Increasing
			2005-2015	-6.7	-7.6; -5.8	Decreasing
			2015-2017	3.8	-13.6; 24.7	Stationary
			2001-2017	-2.1	-4.3; 0.1	Stationary
SVI Human Capital	**Number of Municipalities**	**Incidence/ 100,000**	**Period**	**APC/ AAPC**	**(95% CI)**	**Trend**
Very low	0	-				
Low	6	40.69	2001-2009	-4.4	-6.1; -2.6	Decreasing
			2009-2017	-0.6	-2.4; 1.2	Stationary
			2001-2017	-2.5	-3.6; -1.4	Decreasing
Medium	67	38.28	2001-2004	4.0	-6.1; 15.1	Stationary
			2004-2017	-3.9	-4.7; -3.1	Decreasing
			2001-2017	-2.5	-4.2; -0.7	Decreasing
High	443	25.50	2001-2005	1.8	-3.3; 7.2	Stationary
			2005-2017	-4.2	-5.1; -3.4	Decreasing
			2001-2017	-2.7	-4.0; -1.5	Decreasing
Very high	1277	23.86	2001-2005	2.2	-0.6; 5.1	Stationary
			2005-2012	-3.8	-5.1; -2.5	Decreasing
			2012-2015	-7.7	-17.6; 3.5	Stationary
			2015-2017	3.8	-8.0; 17.1	Stationary
			2001-2017	-2.2	-4.3; 0.1	Stationary
SVI Income and Work	**Number of Municipalities**	**Incidence/ 100,000**	**Period**	**APC/ AAPC**	**(95% CI)**	**Trend**
Very low	0	-				
Low	8	41.95	2001-2003	25.4	-2.7; 61.6	Stationary
			2003-2017	-4.0	-4.8; -3.2	Decreasing
			2001-2017	-0.8	-3.6; 2.2	Stationary

Continue...▶

Table 1. Trends in TB incidence rates in northeastern municipalities according to the dimensions of the Social Vulnerability Index (SVI), Brazil, 2001-2017. (Continued...)

SVI Income and Work	Number of Municipalities	Incidence/ 100,000	Period	APC/ AAPC	(95% CI)	Trend
Medium	71	33.89	2001-2017	-2.2	-2.5; -1.8	Decreasing
High	394	26.70	2001-2003	7.7	-6.3; 23.9	Stationary
			2003-2017	-3.1	-3.5; -2.7	Decreasing
			2001-2017	-1.8	-3.4; -0.2	Decreasing
Very high	1320	23.72	2001-2006	2.0	-0.8; 4.8	Stationary
			2006-2015	-5.7	-6.8; -4.5	Decreasing
			2015-2017	1.2	-13.8; 18.7	Stationary
			2001-2017	-2.5	-4.4; -0.5	Decreasing

APC: Annual Percent Change; AAPC: Average Annual Percent Change. 95% CI: 95% Confidence Interval; SVI: Social Vulnerability Index.

living conditions may result in greater diagnoses and, consequently, higher incidence rates, at least in a first moment. On the other hand, vulnerability, while contributing to the maintenance of the disease, leaves sick subjects invisible to the health system, while good living conditions have the opposite effect.[8]

Low education and exposure to poverty, for example, are factors that hamper access to services for the diagnosis and treatment of the disease. If, on the one hand, exposure to social vulnerability keeps the chain of transmission active in the community, on the other hand, it can prevent sick individuals from being diagnosed, as many are disregarded by the health system, thus fostering the underreporting of disease data.[9,10]

Another important issue concerns the lower capacity to reduce the incidence in municipalities with very high SVI (Human Capital and Urban Infrastructure). However, it is already known that in order to eliminate this disease, it is necessary to have treatment coverage of at least 90% of the latent form, with contact testing and the use of rapid tests in the same proportion.[2,5] This condition can only be achieved by improving these social indicators, which reflect the population's living situation.

Therefore, the results obtained in this study indicate the urgent need to strengthen local actions against TB, especially in more vulnerable areas.

AUTHOR CONTRIBUTIONS

JPSP, ABB, MB, RFC, and CDFS: study conception and design. JPSP: data collection and writing of the Introduction section. JPSP, MB, and CDFS: data collection, writing of the Methods and Results sections, and statistical analysis. JPSP, ABB, RFC, and CDFS: writing of the Discussion section. All authors contributed to the initial draft and reviewed and approved the final version of the manuscript.

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COVID-19 and pulmonary alveolar proteinosis: an unusual combination

Philippe de Figueiredo Braga Colares[1], Natalia Fernandes da Silva[1], Ronaldo Adib Kairalla[1], Bruno Guedes Baldi[1]

TO THE EDITOR:

Pulmonary alveolar proteinosis (PAP) is a rare entity characterized by the alveolar accumulation of lipoproteins, secondary to macrophage dysfunction, which leads to impaired surfactant clearance. According to the pathogenetic mechanism and responsible etiology, the disease may be classified into three distinct groups: primary (autoimmune or hereditary), secondary, and congenital.[1,2] Additionally, all etiologies are associated with the deregulation of activation and differentiation of lung defense cells, mainly alveolar macrophages, resulting in a greater predisposition to the development of opportunistic lung infections. In recent years, COVID-19 has become the leading cause of respiratory failure worldwide, with a potential to determine worse outcomes in patients with previous lung disease.[3]

An international multicenter study[4] showed that patients with interstitial lung disease are at an increased risk of death from COVID-19, when compared with patients with no interstitial lung disease or other chronic lung disease (overall mortality was 49% and 35%, respectively; p = 0.013), particularly those with poor lung function (FVC < 80% of predicted) and obesity. However, there are few data regarding COVID-19 and rare lung diseases. Recent series[5,6] in patients with lymphangioleiomyomatosis and PAP showed increased rates of hospitalization in these populations (approximately one-third of these patients in both studies).

Although we were unable to quantify anti-GM-CSF antibodies, given the absence of an underlying disorder causing secondary PAP (hematologic diseases, immune defects, or inhalational exposures), we report herein the cases of two patients with presumable autoimmune PAP and COVID-19. The first patient was a 46-year-old woman with stable PAP, diagnosed nine years before, who underwent whole lung lavage (WLL) four years before. After WLL, basal SpO_2 remained stable at 95% on room air. She was admitted to the emergency unit with a complaint of dyspnea for one week, fever (38°C), tachycardia, and SpO_2 = 80% on room air. Chest CT scans, when compared with those taken five months before, showed an increase in the extent of bilateral diffuse ground-glass opacities with inter- and intralobular septal thickening that were compatible with the crazy-paving pattern (Figures 1A and 1B). Nasopharyngeal PCR for SARS-CoV-2 was positive. The patient was initially treated with methylprednisolone (1 mg/kg per day), ceftriaxone plus azithromycin, and supplemental oxygen via nasal cannula. After one week, she had partial clinical improvement, but persisted with SpO_2 = 83-85% on room air. Then, a WLL was initially performed on the left lung with the infusion of 30 liters of 0.9% saline at 37°C, and the patient was subsequently referred to the ICU. Two weeks later, the same procedure was performed on the right lung. After one week, she presented progressive clinical improvement, and SpO_2 was 92% on room air. She was discharged after 49 days of hospitalization. Chest CT scans at discharge demonstrated a significant reduction in the extent of pulmonary opacities (Figure 1C).

The second patient was a 48-year-old man, diagnosed with PAP five years before, who underwent one WLL three years before. He was admitted to the emergency unit complaining of odynophagia and fever for 5 days, subsequently evolving to dyspnea and dry cough. SpO_2 was 88% on room air and PCR for SARS-CoV-2 was positive. Six months before, he was stable, and SpO_2 was 95% on room air. CT scans, when compared with those taken nine months before, demonstrated an increase in the extent of bilateral diffuse ground-glass opacities with thickening of the inter- and intralobular septa, confirming the identification of the crazy-paving pattern (Figures 1D and 1E). He was initially treated with supplemental oxygen via nasal cannula and methylprednisolone (1 mg/kg per day). The patient presented with significant clinical improvement and was discharged 10 days after hospitalization (SpO_2 = 93% on room air). However, he needed supplemental oxygen to perform his daily activities and has been under follow-up in the outpatient clinic, repeating the chest CT two months after discharge (Figure 1F).

Few studies described the combination of PAP and COVID-19, and none, to the best of our knowledge, described the performance of WLL in patients with both diseases. A recent European multicenter study[6] described the incidence and outcomes of patients with PAP coinfected with COVID-19. Despite having similar COVID-19 rates when compared with the general population (about 15%), patients with PAP had a higher risk of hospitalization and death (35% required hospitalization, almost 50% of those in the ICU, and, of these, 27% died or underwent lung transplantation). Treatment with inhaled GM-CSF was discontinued in all patients, and no patient underwent WLL during hospitalization.[6]

Some studies have evaluated the relationship between COVID-19 and the role of GM-CSF.[7] In the early stages of infection, the role of GM-CSF may be protective as it would help limit virus-related lesions. However, in the later stages of COVID-19, inadequate release of several cytokines (cytokine storm), including IL-6 and GM-CSF, predisposes to inflammatory lung injury, and, finally, to ARDS.[7]

1. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP), Brasil.

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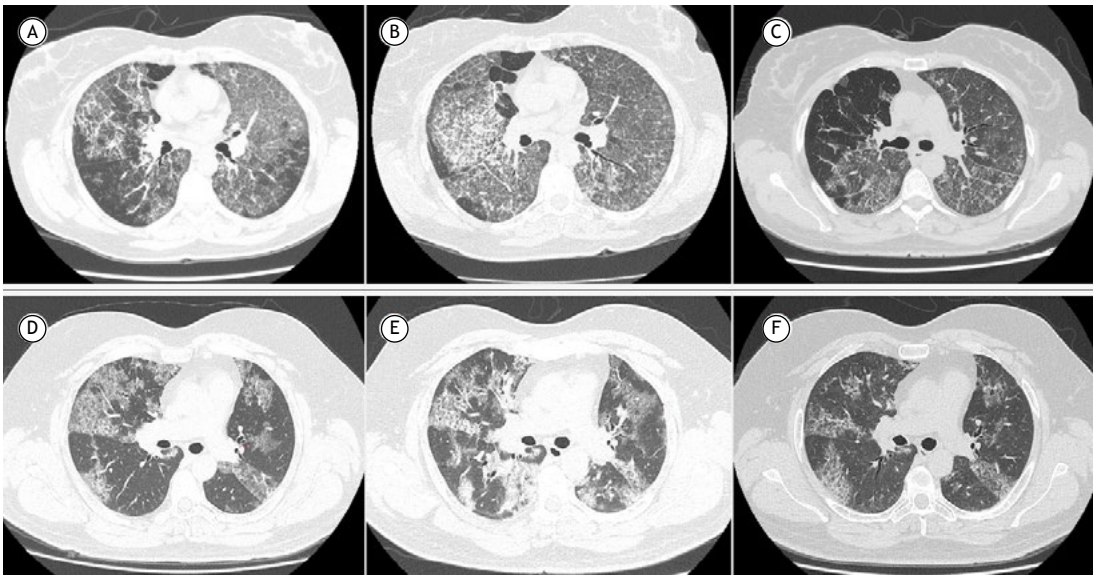

Figure 1. Chest CT scans showing bilateral and diffuse ground-glass opacities with inter- and intralobular septal thickening (crazy-paving pattern). Chest CT scans of a 46-year-old female patient taken five months before the COVID-19 infection (in A); during the COVID-19 infection (in B), showing an increase in the extent of lesions; and after whole lung lavage (in C). Chest CT scans of a 48-year-old male patient taken nine months before the COVID-19 infection (in D); during the COVID-19 infection (in E), showing an increase in opacities and appearance of new lesions; and two months after discharge (in F).

Management of PAP depends on its etiology and severity, and aims to relieve symptoms, improve oxygenation, and improve the quality of life of patients. Asymptomatic patients or those with mild symptoms do not require immediate treatment and can be followed with periodic reassessment. However, in patients with moderate to severe disease and progressive respiratory failure, the gold standard treatment is WLL.[1,2] In patients with autoimmune PAP, an association with experimental therapies, such as (subcutaneous or inhaled) recombinant GM-CSF, rituximab, or plasmapheresis may be performed. In selected, refractory cases, lung transplantation may be an option.[8]

It is also noteworthy that the two cases reported here had stable disease for years and were hospitalized with significant worsening of respiratory symptoms, hypoxemia, and an increase in the extent of tomographic opacities, probably secondary to COVID-19. Furthermore, the imaging findings were insufficient to differentiate between worsening of PAP and COVID-19. Neither received GM-CSF therapy, since this is unavailable in our center; however, one patient underwent WLL, which was indicated by the presence of persistent hypoxemia.

In conclusion, it is yet to be known whether the clinical and tomographic worsening observed in these two patients was related to COVID-19 itself or whether there was an activation of PAP triggered by the infection. The course of PAP is variable, and the prognosis is unpredictable. Additionally, COVID-19 may determine exacerbation of symptoms and CT worsening in patients with PAP, and WLL may be an option in this scenario, especially in centers with low availability of GM-CSF therapy.

AUTHOR CONTRIBUTIONS

PFBC: study design; data collection; drafting and revision of the manuscript; and approval of the final version of the manuscript. NFS: data collection; drafting of the manuscript; and approval of the final version of the manuscript. RAK: study design; revision of the manuscript; and approval of the final version of the manuscript. BGB: study design; drafting and revision of the manuscript; and approval of the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

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Constrictive bronchiolitis secondary to exposure to flavoring agents: a little known occupational hazard

Gustavo Corrêa de Almeida[1], Rafael Futoshi Mizutani[1], Mario Terra-Filho[1], Ubiratan de Paula Santos[1]

TO THE EDITOR:

Bronchiolitis is a generic term applied to a heterogeneous group of diseases that affect the small airways (internal diameter ≤ 2 mm), resulting in inflammation and/or fibrosis.[1] This diversified entity has several presentations with varied etiologies and evolutionary prognoses. The classification is usually based on the underlying histopathological pattern, which generally correlates with the clinical and radiological presentations.[2] The most common patterns are respiratory bronchiolitis, acute bronchiolitis, follicular bronchiolitis, diffuse aspiration bronchiolitis, diffuse panbronchiolitis, and constrictive bronchiolitis.[2] Constrictive bronchiolitis, also called obliterative bronchiolitis, has been proposed to have a pathogenic mechanism of an aberrant response resulting from injury and inflammation of epithelial cells and subepithelial structures of the small airway, leading to excessive fibroproliferation and reduction of its lumen.[3] Among the causes are autoimmune diseases, post-infectious viral sequelae, graft-versus-host disease after hematopoietic stem cell transplantation, bronchiolitis obliterans syndrome after lung transplantation, drug toxicity, inflammatory bowel diseases, paraneoplastic pemphigus, and exposure to and inhalation of volatile chemicals.[2,3] Exposures to chemical agents include those of occupational origin, and among them, we highlight exposure to diacetyl (2,3-butanedione) and 2-3-pentadione. The association of diacetyl, used in the food industry as a flavoring agent because its flavor and aroma are similar to butter, with constrictive bronchiolitis was initially described in 2002 in the microwave popcorn industry.[4] Since then, several other cases have been diagnosed, not only in this activity but also in flavoring manufacturing, snack food production, pet food production, coffee roasting, and packaging facilities.[5] Animal studies indicate that the respiratory epithelium suffers directly from diacetyl and 2-3-pentadione toxicity after inhalation. Persistent tissue damage can lead to aberrant airway epithelium repair causing intraluminal fibrosis resulting in constrictive bronchiolitis.[6]

Two men aged 21 and 36 years (patients A and B, respectively) with no known comorbidities and no history of smoking were referred to our hospital for evaluation. Both worked in a factory that produced flavors for food and cosmetics in the metropolitan region of São Paulo and developed progressive dyspnea on exertion, coughing, and wheezing after the start of exposure. Patient A presented symptoms 1 year after starting the job, being removed from exposure 1 year after the onset of symptoms, and patient B developed symptoms after 2 years of exposure and was removed 6 months later.

The work involved mixing concentrated flavoring agents with powdered products as diluents. Mixing was performed manually, followed by grinding and sieving, and then the product was packed in a 20-m^2 room. The room contained a mill, a mixer, a sieve, and a balance, with four to five workers being present simultaneously. During the work period, they used N95 particulate filtering facepiece respirators with daily changes. During a visit to the workplace, poor natural ventilation and lack of exhaust ventilation were found in the processes. The clothes of the workers worn while working had strong odors of the flavoring agents used and were dirty with dust. It was verified that in areas adjacent to the room where they worked, hundreds of flavoring agents were stored with the most diverse aromas and flavors, including that of butter.

The chest HRCT of both patients showed signs of thickening of the airway walls, bronchiectasis, mosaic attenuation, and lung hyperinflation (Figure 1). Functional assessment with pulmonary function testing by plethysmography and measurement of DL_{CO} revealed the presence of marked fixed obstructive ventilatory disorder with evidence of air trapping and small airway disease shown by high specific airway resistance, elevation of RV and of the RV/TLC ratio in both patients. Patient A had a marked reduction in DL_{CO}, whereas that was within normal limits in patient B.

Investigation of autoimmune diseases and viral serology for HIV, hepatitis B, and hepatitis C yielded negative results. Patient B had undergone a bronchoscopy with transbronchial biopsy in an external service; however, there was a complication (pneumothorax). Anatomopathological findings were inconclusive because of scarcity of material.

The diagnosis of constrictive bronchiolitis secondary to diacetyl exposure was established based on clinical history, functional assessment, imaging findings, and occupational anamnesis. Both patients were not further exposed. Patient A was initially started on treatment with corticosteroids (prednisone, 1 mg/kg per day) for 15 days and subsequent reduction over three months as he showed no improvement in clinical or functional parameters. Treatment with long-acting bronchodilators and azithromycin three times a week was instituted for both patients, with slight clinical improvement, but with no improvements in pulmonary function test results. Both patients were referred for evaluation for

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clinicas Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

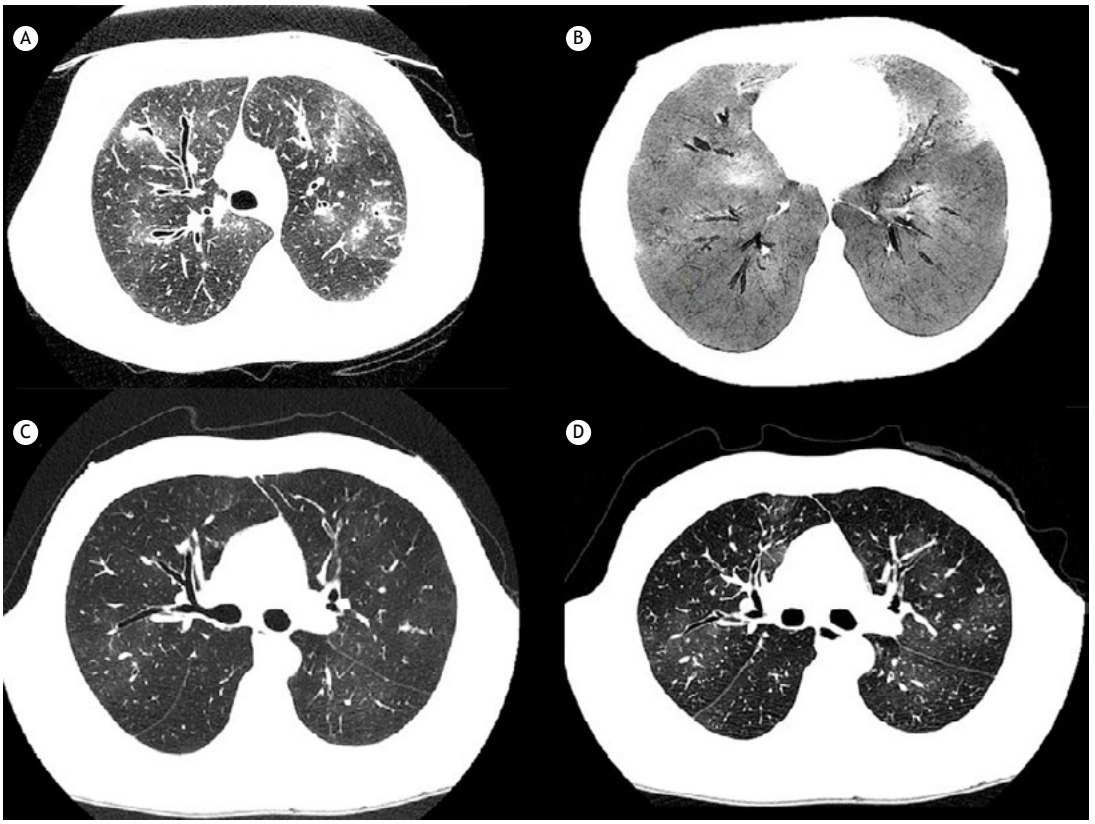

Figure 1. Axial chest HRCT scans (in A and C) of patients A and B, respectively, demonstrating diffuse bronchial wall thickening and mosaic attenuation pattern. There are areas of decreased lung attenuation associated with vessels of reduced caliber representing air trapping and regional oligemia. Minimum intensity projection reformation (in B) better depicts those areas in patient A. Expiratory acquisition (in D) confirms air trapping in patient B.

lung transplantation. At the moment of this writing, patient A is on the waiting list, while patient B is still being evaluated.

The attempt to investigate the existence of other workers affected by that type of exposure in the same factory was faced with resistance from those responsible for it; they provided some data such as spirometry tests, but those data were insufficient for an adequate analysis due to the poor quality of the tests.

Constrictive bronchiolitis secondary to exposure to flavoring agents is a potentially serious but preventable disease. The first Brazilian case series on exposed workers in a cookie factory was published in 2012,[7] but there has been a lack of national literature since then. In the northern hemisphere, several epidemiological surveillance studies in companies related to the use of flavoring agents have diagnosed multiple cases.[5]

The most commonly reported symptoms are dyspnea on exertion and dry cough that can manifest months or years after exposure onset.[5] The most common functional change in spirometry is obstructive respiratory disorder, but results can be normal or reveal restrictive or mixed disorders.[5,8] Chest HRCT demonstrates mosaic attenuation, which is consistent with air trapping.[5,8] In the majority of cases, diagnosis can be established by analyzing the history of exposure, presence of symptoms, and pulmonary function test results. Early withdrawal from exposure can halt disease progression.[5]

The motivation of this letter is to highlight that during evaluation of patients with bronchiolitis, attention should be paid to occupational causes, and the identification of a sentinel case should be seen as a signal for the investigation of other workers at risk, indicating the need for the adoption of exposure control measures such as local exhaust ventilation. Finally, the presence of diacetyl and other flavors in e-cigarettes and vaping solutions has recently been identified.[9] This fact should be viewed with concern, given the possibility of development of a similar pattern of bronchiolitis obliterans among individuals with chronic exposure to e-cigarette aerosols of solutions containing flavoring agents.[10,11]

AUTHOR CONTRIBUTIONS

GCA: study conception; data collection; and drafting of the manuscript. RFM: manuscript revision. All of the authors approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

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Post-thoracotomy lung hernia

Paula Duarte D'Ambrosio[1], Higor Felipe Silva[1], Alessandro Wasum Mariani[1], Aurelino Fernandes Schmidt Junior[1], Paulo Manuel Pêgo-Fernandes[1]

TO THE EDITOR:

A 66-year-old male, active smoker (45 pack-years), and a history of COPD, bronchial amyloidosis, and steroid dependence was referred to thoracic surgery due to chronic chest pain and chest wall deformity for the last 2 years. Six years before, he underwent a middle lobectomy at another hospital due to lung hamartoma.

Marked protrusion of the lung through a single intercostal space was identified at physical examination, revealing gross instability of the right lower lateral chest wall and costal margin, with reducible swelling and an overlying cough impulse. Chest CT confirmed lung herniation through the lateral portion of the fifth intercostal space (Figures 1A and 1B).

The patient underwent a right thoracotomy under general anesthesia with one-lung ventilation. The hernia sac was adherent to the edges of the thoracotomy. It was dissected from the surrounding tissue, and the lung was easily accessed. The herniated lung was viable, and the hernia was manually reduced. A prolene mesh patch was attached to the costal margins with nonabsorbable suture at the parietal pleural level, covering the defect (Figure 1C). The patient presented with bronchospasm during the postoperative period and required use of oral steroid therapy. Apart from that, the postoperative course was uneventful, and the patient was discharged on the ninth postoperative day. On follow-up, three months after surgery, there was no sign of recurrence.

Here, we reported the case of a patient with lung hernia at the lateral chest wall through the fifth intercostal space and not associated with costal fracture. The patient had undergone thoracotomy 6 years prior. Pain presented as the main symptom. Incarceration or ischemia of the tissue was not present.

Intercostal lung hernias are rare conditions characterized by the protrusion of lung parenchyma outside the thoracic cage.[1] The most common cause of acquired lung herniation is trauma, and injuries such as pneumothorax or rupture of great vessels can be associated.[2] It may also occur after thoracotomy, intercostal tube placement, thoracoscopy, and violent coughing episodes.[3,4] There may be late presentation.

Postsurgical lung hernias have also been reported after less extensive surgical procedures, such as minimally invasive cardiac surgery[5] or robotic thymectomy for thymomas.[6] In theory, robotic instruments have a remote center and are designed for being placed into the chest wall. This center offers a fixed point of rotation around which the instrument arm pivots, minimizing any tissue trauma. However, if the remote center has not been placed exactly into the intercostal space, a pulmonary hernia may occur at the site of the minithoracotomy working port site.[5]

Acquired lung hernias most commonly occur on the right side in the fifth intercostal space, containing lung tissue.[3] However, it may also contain abdominal contents if there is a transdiaphragmatic or thoracoabdominal component.[3] Current data suggests that, in the setting of disrupted intercostal musculature from previous thoracotomy, predisposing factors for chest wall herniation include hyperinflation caused by COPD, poor tissue quality and healing capacity resulting from diabetes, obesity, and oral steroid use.[3]

The presentation of a chest wall hernia can be variable, ranging from asymptomatic reducible bulge to severe pain, persistent cough, shortness of breath, and hemoptysis.[7] Consistent with this case, pain is the most common symptom associated with this condition.[3] The diagnosis can be made clinically. However, imaging studies play an important role in the diagnosis of thoracic herniation. Although chest X-rays may help diagnosis, CT scanning is considered the gold standard to evaluate this condition, because it clearly demonstrates the defect protruding out of the thoracic wall.[4] In the setting of acute traumatic chest wall injuries, in which the patient is too unstable for being transported to the chest CT room, the use of ultrasonography has been recently reported.[8]

There is a significant controversy as to the ideal management of these patients. Indications for acquired chest wall hernia repair include symptoms and incarceration.[3] In cases of asymptomatic hernias, conservative management has also been described; however, surgical repair is generally recommended to avoid the risk of strangulation of the hernia contents.[9,10] Thus, serial clinical and radiographic follow-up is mandatory.

Repair techniques may vary, ranging from primary closure to implantation of prosthetic or autologous material. In our case the intercostal hernia was repaired using a prolene mesh patch. To date, few studies have compared primary and prosthetic repair for differences in postoperative complications.[3] In a retrospective review, 27 patients underwent chest wall herniorrhaphy. Mesh repair and primary repair were performed in 9 and 18 patients, respectively, and the complication rates were 22% and 42%. Prosthetic herniorrhaphy was not associated with an increased risk of postoperative complications in comparison with primary repair.[3]

This letter describes a post-thoracotomy chest wall lung hernia in a patient with COPD and steroid dependence. Surgical repair with prosthetic material was uneventful and, after three months, there was no sign of recurrence.

1. Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

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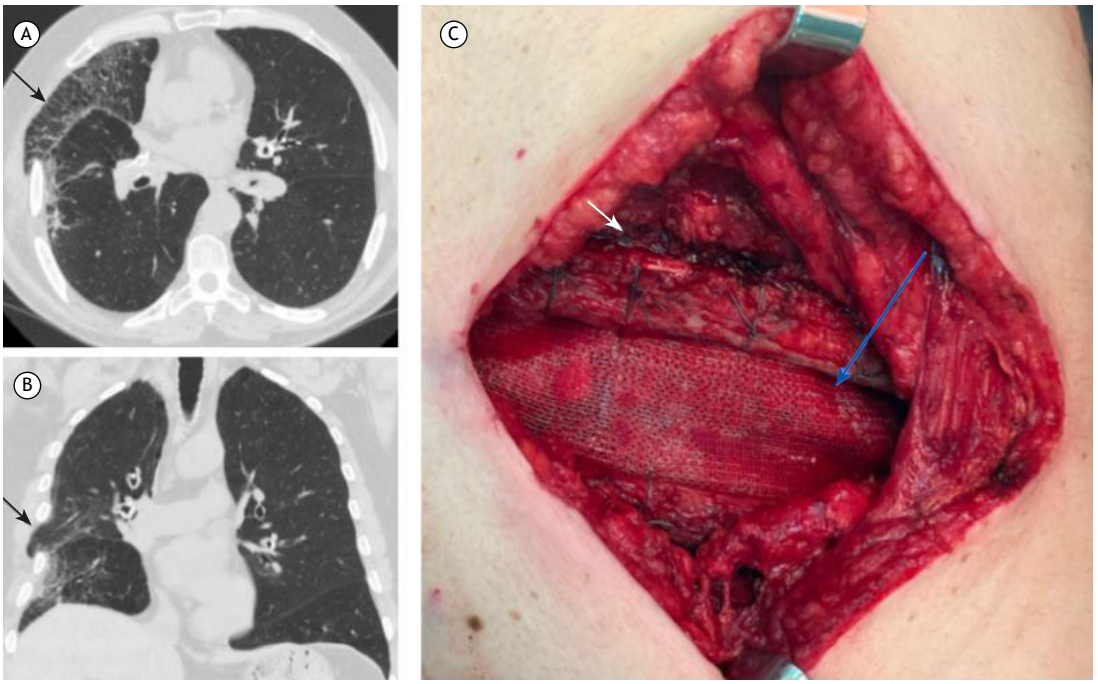

Figure 1. Axial and coronal CT scans of the chest during a Valsava maneuver (in A and B, respectively). In C, a photography showing a prolene mesh patch attached to the costal margins with nonabsorbable suture at the parietal pleural level covering the defect.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

None declared.

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Hypoxemia and hypertension in obstructive sleep apnea: the forgotten variable

Eduardo Borsini[1], Carlos Nigro[2]

TO THE EDITOR:

The apnea-hypopnea index (AHI), expressed as events/h, is used in order to define normality and to classify the severity of obstructive sleep apnea (OSA).[1] AHI measures the frequency of respiratory events throughout the night and the degree of sleep fragmentation, since apnea/hypopnea events are frequently followed by an electroencephalographic reaction. In addition, AHI gives us indirect information about hypoxemia, because respiratory events are often accompanied by a variable decrease in SpO_2.[2] The proportion of time spent in $SpO_2 \leq 90\%$ (T90) is an accurate parameter to assess nighttime hypoxemia, since a 90% SpO_2 at sea level equals a PaO_2 of approximately 60 mmHg according to the oxygen-hemoglobin dissociation curve.[2] The correlation between AHI and T90 is moderate (r = 0.6-0.7), because not all respiratory events are followed by a drop in $SpO_2 \leq 90\%$.

OSA has been identified as a risk factor for hypertension in population-based studies.[3,4] Underlying mechanisms would be related to sympathetic activity secondary to hypoxia/hypercapnia cycles, increased intrathoracic pressure, and microarousals that follow apneas/hypopneas, which favor an increase in blood pressure.[4] Both animal and human studies have shown that intermittent hypoxemia can trigger hypertension.[4] Similarly to the hypothesis of other authors, ours was that T90 might be associated to hypertension in OSA patients.

In a preliminary and retrospective study based on the systematic collection database from the *Hospital Británico* of Buenos Aires sleep unit between 2011 and 2019, we included consecutive adult patients who underwent home-based respiratory polygraphy due to suspicion of OSA according to the results in the Berlin questionnaire (high risk), the Epworth Sleepiness Scale (ESS; > 10 points), or the STOP-Bang questionnaire (> 3 components). The study was approved by the institutional research ethics committee and the *Plataforma de Registro Informatizado de Investigaciones en Salud de Buenos Aires* in accordance with the standards of the Declaration of Helsinki, as amended (protocol #1242).

The diagnosis of hypertension was considered when it was self-referred, whether it was documented in the medical records, or whether the patient was on antihypertensive medication. These diagnostic strategies for hypertension have been validated and showed a good performance.[5] Automatic signal analysis was performed by trained physicians and was followed by manual corrections based on international criteria.[6] We calculated the T90 in % and the number of oxygen desaturations ≥ 3% (ODI, oxygen desaturation index) over valid recording time, after sequential manual revision. Multiple logistic regression analysis was used in order to establish the relationship between hypertension (dependent variable) and age, sex, BMI, AHI, and T90 (independent variables). For this purpose, study physicians performed a ROC analysis to establish the best cutoffs to differentiate between patients with and without hypertension. Predictive models also relied on traditional cutoffs, such as AHI (≥ 10 and ≥15 events/h).

We included 3.854 patients (median age = 55 years) who were mostly male (61.5% vs. 38.5%; p < 0.001). Prevalence of obesity and hypertension was 57.0% and 52.3%, respectively. In the study sample, 48% was classified as having moderate-to-severe OSA, and 29% of patients reported excessive daytime sleepiness (ESS > 10 points).

The best area under the ROC curve (AUC-ROC) to differentiate between patients with and without hypertension included the following cutoffs: age ≥ 52 years; BMI ≥ 30 kg/m^2; AHI ≥ 14 events/h; and T90 ≥ 3%. Table 1 presents multiple logistic regression models including AHI and T90: age (OR = 3.27-3.29; 95% CI: 2.83-3.80; p < 0.0001); male sex (OR = 1.34-1.35; 95% CI: 1.16-1.56; p < 0.001); BMI (OR = 1.82-1.83; 95% CI: 1.58-2.11; p < 0.0001); AHI (OR = 1.21-1.24; 95% CI: 1.03-1.45; p < 0.01); and T90 (OR = 1.54- – 1.57; 95% CI: 0.31-1.84; p < 0.0001).

Our main finding was that nighttime hypoxemia defined as T90 ≥ 3% was independently associated to the development of hypertension in OSA patients. This highlights the importance of nighttime hypoxemia as an independent risk factor for hypertension in patients with OSA, who represent the population of patients treated in a sleep unit. This observation was consistent after adjusting for other covariates (age, sex, BMI, and AHI), which is in line with experimental models that have established the role of hypoxemia as a mechanism of hypertension in OSA.[7,8] Two large studies reported that AHI ≥ 30 events/h and T90 ≥ 12%,[9] or quartiles 3 and 4 of ODI ≥ 4% (ODI4)[10] were independently associated with hypertension—T90 ≥ 12% (OR = 1.46; 95% CI: 1.12-1.88) and ODI4 (OR = 2.01; 95% CI: 1.6-2.5). In a study involving patients with moderate-to-severe OSA in use of CPAP,[8] CPAP was withdrawn for two weeks, and the patients were randomized to receive supplemental oxygen or air (sham) during sleep. Those who received supplemental oxygen had the rise in morning blood pressure virtually abolished.[8] Dean et al.[9] demonstrated that every standard deviation of increment

1. Unidad de Sueño y Ventilación, Hospital Británico, Buenos Aires, Argentina.
2. Servicio de Neumología, Hospital Alemán, Buenos Aires, Argentina.

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Table 1. Multiple logistic regression predictive models for hypertension.

Variable	Coefficient	OR	95% CI	p
Model 1				
Age ≥ 52 years	1.19	3.3	2.86-3.80	< 0.0001
Male sex	0.34	1.4	1.2-1.6	< 0.0001
BMI ≥ 30 kg/m^2	0.63	1.9	1.6-2.2	< 0.0001
AHI ≥ 5 events/h	0.06	1.06	0.87-1.29	0.58
T90 ≥ 3%	0.52	1.7	1.45-1.96	< 0.0001
Model 2				
Age ≥ 52 years	1.18	3.27	2.83-3.77	< 0.0001
Male sex	0.30	1.35	1.17-1.56	< 0.0001
BMI ≥ 30 kg/m^2	0.60	1.83	1.59-2.11	< 0.0001
AHI ≥ 10 events/h	0.19	1.21	1.03-1.42	0.0205
T90 ≥ 3%	0.45	1.57	1.33-1.84	< 0.0001
Model 3				
Age ≥ 52 years	1.19	3.28	2.84-3.79	< 0.0001
Male sex	0.30	1.34	1.16-1.55	0.0001
BMI ≥ 30 kg/m^2	0.60	1.82	1.58-2.10	< 0.0001
AHI ≥ 14 events/h	0.22	1.24	1.07-1.45	0.0058
T90 ≥ 3%	0.43	1.54	1.31-1.81	< 0.0001
Model 4				
Age ≥ 52 years	1.19	3.29	2.85-3.80	< 0.0001
Male sex	0.30	1.35	1.17-1.56	0.0001
BMI ≥ 30 kg/m^2	0.60	1.83	1.59-2.11	< 0.0001
AHI ≥ 15 events/h	0.20	1.22	1.05-1.43	0.0112
T90 ≥ 3%	0.44	1.56	1.32-1.83	< 0.0001

AHI: apnea-hypopnea index; T90: proportion of total recording time with SpO_2 ≤ 90%.

in log-transformed hypoxic burden was associated with a 1.1% increase in systolic blood pressure and a 1.9% increase in diastolic blood pressure among those patients not using antihypertensive medications. Using a large cohort of moderate-to-severe OSA patients in South America, Labarca et al.[10] developed predictive models of cardiometabolic risk from indicators of hypoxemia (T90, minimum SpO_2 and ODI) and showed that a T90 > 10% was a predictor of arterial hypertension.

The limitation of the present study was that the diagnosis of hypertension was based on self-reporting, medical history records, or the history of antihypertensive drug use. However, despite this limitation, our observations are in line with the important body of experimental evidence in animals and humans that links intermittent hypoxemia with the development of hypertension.

In conclusion, nighttime hypoxemia defined as T90 ≥ 3% was an independent risk factor for hypertension in a clinical population of patients with suspected sleep apnea. This preliminary finding must be confirmed in prospective longitudinal studies.

Author contributions

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

CONFLICT OF INTEREST

None declared.

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Is there any kind of relationship between alpha-1 antitrypsin levels and lung function parameters?

José María Hernández-Pérez[1], Claudia Viviana López-Charry[1]

TO THE EDITOR:

Alpha-1 antitrypsin (AAT) deficiency is a genetic condition that predisposes those who have it to develop lung involvement in the form of emphysema and/or liver involvement in the form of cirrhosis or fibrosis.[1] AAT levels in routine clinical practice are requested as a starting point within the AAT deficiency diagnostic algorithm, without providing any type of information except for the quantitative point of view to define only the existence of that deficiency. To date, few studies have tried to relate AAT levels with possible alterations in pulmonary function parameters. Therefore, our objective was to study whether there was any type of association between AAT levels and functional parameters measured by spirometry.

We carried out a prospective study involving 1,510 consecutive subjects who sought the outpatient pulmonology clinic of our hospital for any reason and underwent blood workup and spirometry at the same visit. Patients were recruited during 54 consecutive months (between January of 2011 and June of 2015). Spirometric parameters were obtained with the use of a spirometer (Datospir 600; Sibelmed®, Barcelona, Spain). Pre- and post-bronchodilator spirometry was performed to obtain at least three acceptable and reproducible maneuvers according to standard quality criteria.[2] Four variables were used to define lung function impairment: FVC < 80% of the predicted value, FEV_1 < 80% of the predicted value, FEV_1/FVC ratio < 70%, and/or $FEF_{25-75\%}$ < 60%.

Inclusion criteria were giving written informed consent, being able to perform spirometry successfully (three acceptable and reproducible maneuvers), and undergoing spirometry and determination of AAT levels in blood by nephelometry at the same visit. The final sample comprised 1,334 subjects, because 176 individuals did not meet the inclusion criteria. The study was approved by the research ethics committee of the institution (Protocol HGLaPalma_2010_7).

In the sample as a whole, 770 subjects were male (57.7%), the mean age was 56.4 ± 18.5 years, and the mean weight was 81.4 ± 18.6 kg. As for smoking status, 263 (19.7%) and 494 (37.0%) of the subjects were active and former smokers, respectively. The mean AAT level was 125.1 ± 31.9 mg/dL, and to 362 (27.1%) of the subjects presented with an obstructive pattern in spirometry (FEV_1/FVC < 70%).

A statistical analysis of the relationship between AAT levels and lung function parameters showed a statistically significant association between the lung function parameters that are indicative of airflow obstruction and an AAT level < 40 mg/dL ($\chi^2 = 22.61$; $p < 0.0001$; OR = 5.46; 95% CI, 1.36-21.96; $p < 0.05$; Figure 1).

These results seem to show that patients with low AAT levels (0-40 mg/dL) are associated with altered lung function parameters in the form of airflow obstruction, and this interval would correspond to the most deficient genotypes (*Pi*ZZ* and some rare variants), a fact that is consistent with those collected in previous studies,[3] although, in the study by Tanash et al.,[4] the sample comprised children who had been exposed to tobacco smoke, a factor that is well known to be associated with significant deterioration of lung function.[5] However, considering AAT levels in the range of 41-65 mg/dL, the obstructive pattern was present in of 17.3% of the sample, which would mostly correspond to the *Pi*SZ* and *Pi*MZ* genotypes or some rare variants, showing how important it is to monitor these genotypes, especially when they are associated with smoking.[6] Other authors[7] found no relationship between AAT levels and lung function parameters measured by spirometry, although the cohort studied involved patients diagnosed with COPD, and genotyping in search of AAT deficiency alleles was not performed; therefore, it is impossible to rule out AAT deficiency in either of the studies.

In conclusion, this study shows that we must take into account AAT levels since, in addition determining whether a patient has AAT deficiency or not, they can guide us as to the probability of a patient developing lung function impairment.

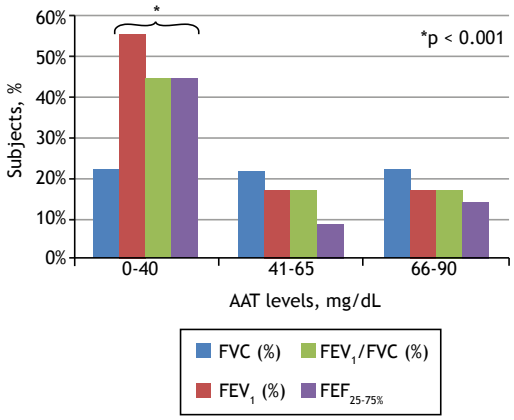

Figure 1. Association between alpha-1 antitrypsin (AAT) levels and lung function parameters that indicate lung function impairment, namely: FVC < 80% of the predicted value; FEV_1 < 80% of the predicted value; FEV_1/FVC ratio < 70%; and $FEF_{25-75\%}$ < 60%. *Chi-square test.

1. Departamento de Neumología. Hospital Universitario Nuestra Señora de Candelaria, 38010, Santa Cruz de Tenerife, España.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICTS OF INTEREST

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Pathophysiology of reduced forced vital capacity with airflow obstruction on spirometry: performance of two mathematical models in clinical practice

Bruno de Moraes Santos Wong[1], Andria Machado da Silva[2], Rosemeri Maurici[3], José Tavares de Melo Júnior[1]

TO THE EDITOR:

Spirometry has limitations when it comes to airflow obstruction (AO) associated with reduced FVC, a common situation in which the cause of this reduction needs to be clarified. FVC can be reduced due to associated ventilatory restriction, characterizing a mixed pattern (MP), or as a result of air trapping with increased RV, characterizing pure AO (PAO).[1]

In this context, it is recommended that pulmonary volumes (TLC and RV) be measured by available methods.[1-3] The problem with these methods is that they are costly and difficult to access through the public health care system. In order to gauge the cause of the FVC reduction in the presence of AO solely on the basis of spirometry data, several mathematical models have been created,[4-7] with the first ones being that by Pereira et al.[4] in 1991 and that by Lefante et al.[5] in 1996, which are herein referred to as Pereira's model and Lefante's model.

Pereira et al.[4] suggested that, in the presence of AO with a reduced FVC, the difference between percent predicted FVC (FVC%) and percent predicted FEV_1 (FEV_1%), that is, ▲%, should be calculated in the pre-bronchodilator phase (pre-BD). If ▲% is equal to or greater than 25%, the cause of the FVC reduction is hyperinflation, and it is a case of PAO. If ▲% is equal to or smaller than 12%, MP can be inferred. When ▲% is between 12% and 25%, the only option available is TLC measurement.[2,4]

Lefante et al.[5] proposed another solution: in the presence of AO with FEV_1/FVC equal to or less than 0.7, FVC% can be adjusted on the basis of the degree of obstruction (FEV_1/FVC) observed, by using the following formula: adjusted FVC% = observed FVC% + 76 − (105 × FEV_1/FVC). If the adjusted FVC% is equal to or above the lower limit of normal (LLN), it is a case of PAO. If the adjusted FVC% remains below the LLN, it is probably a case of MP.

Our objective was to evaluate the performance of these two mathematical models by measuring their sensibility, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) in determining the cause of the FVC reduction in patients with AO, using plethysmographic TLC values as the gold standard.

This was a cross-sectional analytical study of spirometry and plethysmography data. All tests were performed at the Laboratory of Pulmonary Function of the *Núcleo de Pesquisa em Asma e Inflamação das Vias Aéreas* (NUPAIVA, Center for Research on Asthma and Airway Inflammation) at the *Hospital Universitário Polydoro Ernani de São Thiago da Universidade Federal de Santa Catarina* (HU-UFSC, Polydoro Ernani de São Thiago University Hospital of the Federal University of Santa Catarina) with automated testing equipment (Vmax Autobox V62J; SensorMedics, Yorba Linda, CA, USA). The study was approved by the Research Ethics Committee of the HU-UFSC (Protocol no. 4.459.996).

Data collection extended from July of 2018 to May of 2022. The inclusion criteria were as follows: spirometry and plethysmography data from each patient who underwent both tests on the same occasion at NUPAIVA Laboratory of Pulmonary Function; pre-BD FEV_1/FVC ≤ 0.7; and reduced pre-BD FVC (below the LLN).

The selected tests were classified based on Pereira's and Lefante's models, and compared with the gold standard (i.e., plethysmographic TLC values), as either MP (TLC < LLN) or PAO (TLC ≥ LLN), the former being defined as a positive test result and the latter being defined as a negative test result.

Statistical descriptive analysis was performed for the variables sex, height, and weight of the patients, as well as for their pre-BD FEV_1%, pre-BD FVC%, pre-BD FEV_1/FVC, TLC%, ▲% and adjusted FVC% (Table 1).

Continuous data were analyzed by the Shapiro-Wilk test and were expressed as mean ± SD or median ± IQR. Differences between groups were assessed using the t test for independent samples or the Wilcoxon test, depending on data distribution. The R software, version 4.1.0 (The R Project for Statistical Computing, Vienna, Austria), was used.

The outcomes ▲% and adjusted FVC% were evaluated for accuracy, sensibility, specificity, PPV, NPV, LR+ and LR− in diagnosing MP, using plethysmographic TLC values as the gold standard (Table 1).

Of 277 tests, 76 met the inclusion criteria. Of those 76 tests, 68 were classified as PAO and 8 were classified as MP.

Lefante's model was more accurate in differentiating cases of PAO from cases of MP, reaching an accuracy of

1. Programa de Pós-Graduação em Ciências Médicas, Universidade Federal de Santa Catarina, Florianópolis (SC) Brasil.
2. Hospital Universitário Polydoro Ernani de São Thiago, Universidade Federal de Santa Catarina – HU-UFSC – Florianópolis (SC) Brasil.
3. Faculdade de Medicina, Universidade Federal de Santa Catarina – UFSC – Florianópolis (SC) Brasil.

Table 1. Main characteristics of the participants as classified by spirometry and plethysmography and performance of Lefante's model vs. Pereira's model.[a,b]

	PAO	MP	p
Tests	68	8	
Male sex	37	6	
Female sex	31	2	
Age*	63.4 ± 13.9	58.1 ± 11.9	0.211
Height	160.2 ± 8.1	165.6 ± 12.7	0.100
Weight	69.3 ± 16.7	71.7 ± 17.3	0.696
Pre-BD FEV_1%	38.4 ± 12.2	48 ± 9.8	0.036
Pre-BD FVC%*	62.3 ± 10.5	63.4 ± 6.9	0.963
Pre-BD FEV_1/FVC†	0.5 ± 0.2	0.6 ± 0.1	0.012
TLC%*	116.9 ± 32.2	74 ± 9	0.000
▲%*	23.9 ± 10.3	15.4 ± 7	0.024
Adjusted FVC%†	89.5 ± 24.2	71.6 ± 11.1	0.041
Model	Lefante's	Pereira's[c]	
Performance parameters			
Sensitivity	63%	38%	
Specificity	72%	44%	
PPV	21%	23%	
NPV	94%	97%	
LR+	2.24	2.55	
LR−	0.52	0.28	
Accuracy	71%	43%	

PAO: pure airway obstruction; MP: mixed pattern; BD: bronchodilator; FEV_1%: percent predicted FEV_1; FVC%: percent predicted FVC; TLC%: percent predicted TLC; ▲%: pre-BD FVC% − pre-BD FEV_1%; adjusted FVC%: observed FVC% + 76 − (105 × FEV_1/FVC); PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, and LR−: negative likelihood ratio. [a]Values expressed as n or mean ± SD except where otherwise indicated. [b]Reference equations: Pereira et al.[8] for spirometry; Lessa et al.[9] for plethysmography. The LLN was defined as the 5th percentile of the predicted value. [c]Considering cases classified as undefined (25% > ▲% > 12%) by the model. *Variables showing parametric distribution after Box-Cox transformation. †Variables with non parametric distribution are expressed as median ± IQR.

71%, which contrasts with the accuracy of Pereira's model of only 43%. Pereira's model failed to classify 42.1% of the cases, considering 32 tests to be undefined. This high number of undefined cases is consistent with findings of the original study by Pereira et al.,[4] in which 50% of the tests were classified as undefined (30/60 cases), which has been an inherent limitation of Pereira's model since its proposal.

In our study, Pereira's model showed a PPV of only 23% in detecting MP, which contrasts with the 85% reported in the original study,[4] as well as a NPV of 97%, which is closer to the 95% reported in that study.[4] A possible explanation for the discrepancy in PPV may be the difference in the prevalence of MP between the two samples. In the study by Pereira et al.,[4] 30 patients with MP and 30 with PAO were artificially selected, that is, a MP prevalence of 50%, while in our consecutive sample we obtained a prevalence of 10.5%.

In 2019, Sadigursky et al.[10] also revisited Pereira's model, assessing its accuracy against plethysmographic measurement of lung volumes, and found that Pereira's model had a low PPV in detecting MP, which is consistent with our findings.

Considering that Pereira's model reliably classifies the cause of the FVC reduction only in patients with ▲% ≥ 25%, 45 (59.2%) of the patients in our sample (i.e., those with ▲% < 25%) would be referred for plethysmography accordingly. In contrast, if we consider that only cases classified as suspected MP by Lefante's model would have to undergo plethysmography, only 24 (31.6%) of the patients in our sample would need to undergo this test. Classifying all cases, including those classified as undefined by Pereira's model, Lefante's model maintained a high NPV of 94%, demonstrating the model's power to detect cases of PAO accurately. From these results, it is possible to envision the potential advantage of Lefante's model in terms of defining a greater number of cases regarding the pathophysiological diagnosis, saving costs and time.

This study has some limitations. First, it is a single-center study. Second, it was performed during the restrictions imposed by the COVID-19 pandemic. This limited the sample size.

We infer that Lefante's model has its greatest value in cases of negative test results, in which it has a high degree of accuracy in diagnosing PAO, identifying patients who would not require plethysmography and showing a significant gain in accuracy when compared with Pereira's model.

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AUTHOR CONTRIBUTIONS

BMSW and JTMJ: conception and planning of the study; interpretation of evidence; drafting and revision of the preliminary and final versions of the manuscript; and approval of the final version of the manuscript. AMS: planning of the study. RMS: conception and planning of the study.

CONFLICTS OF INTEREST

None declared.

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An undescribed cause of hemoptysis

Marta Carvalho Silva[1], João Filipe Cruz[1]

A 59-year-old female smoker with a history of breast cancer that was treated with surgery, chemotherapy, and hormone therapy went to the ER with a first episode of hemoptysis and productive cough. Blood analyses were normal and chest CT excluded pulmonary embolism but revealed the presence of mild bronchiectasis and a pulmonary infectious process with endobronchial dissemination. It also showed the presence of a tubular structure within the pulmonary artery, probably a central venous catheter (CVC), with one end in the branch of the posterior segment of the right upper lobe and the other end in the segmental branch of the anterior segment of the right lower lobe, adjacent to the segmental bronchus (Figures 1A and 1B). The patient confirmed that the CVC tip was accidentally left inside the heart after its removal, and this finding was considered as a probable cause for hemoptysis.[1,2] Interventional cardiology was requested; pulmonary catheterization was performed and revealed a fragment of the catheter tip with a path involving two sub-branches of the right pulmonary artery, both ends being inaccessible (Figure 1C). However, after several twisting movements, one end of the catheter was recovered to the main pulmonary artery, making it accessible and the entire fragment was recovered.

AUTHOR CONTRIBUTIONS

Both authors contributed to the writing and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

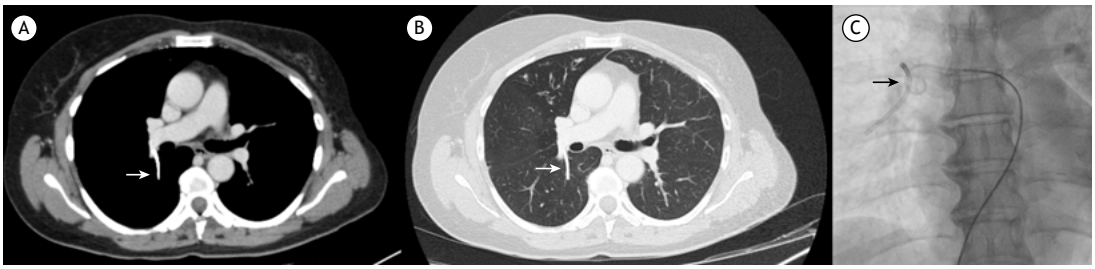

Figure 1. Axial chest CT scan for soft tissue reconstruction (in A) and with lung window settings (in B) showing a central venous catheter fragment in the pulmonary artery that was removed by pulmonary catheterization (in C).

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1. Serviço de Pneumologia, Hospital de Braga, Braga, Portugal.

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

SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.

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