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HIGHLIGHT

Predictors of prolonged ventilator weaning and mortality in critically ill patients with COVID-19

Risk factors for death in vaccinated versus unvaccinated COVID-2019 inpatients

Idiopathic pulmonary fibrosis: current diagnosis and treatment

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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Adjunctive immunomodulation in severe community-acquired pneumonia

James Bradley[1], Shriya Khurana[1], Rodrigo Cavallazzi[1]

Community-acquired pneumonia (CAP) is common, affects economically disadvantaged people disproportionally, and is one of the leading causes of death in the world. Patients with CAP can present with a large spectrum of severity. Most patients do not require hospitalization and usually fare well. In hospitalized patients, however, this scenario is different. In Brazil, there were 392,169 admissions for pneumonia in individuals ≥ 15 years of age in hospitals monitored by the Brazilian Unified Health Care System in 2022.[1] Of these, 64,704 suffered in-hospital death, which resulted in a mortality rate of 16.5%.[1] The mortality rate numbers become even more staggering when the focus is on patients requiring ICU care, which represent approximately 20% of hospitalized patients with CAP. A study in Louisville, United States, showed that adult patients with CAP requiring ICU care have 30-day and 1-year mortality rates of 27% and 47%, respectively.[2]

Different avenues of research are being developed to combat the exceedingly high mortality of patients with severe CAP. These include new diagnostic tests, the development and testing of antimicrobials, novel medications against pathogens (e.g., monoclonal antibodies), clinical pathways, and fundamental research on the pathogenesis of the disease. The recognition that many patients with CAP develop ongoing inflammation and organ failure despite being able to eradicate the causative pathogen early in the infection has sparked interest in the host response and immunomodulation.[3]

The host immune response to CAP involves a complex interplay between innate and adaptive immune responses, pattern recognition receptors, inflammasomes, airway epithelium, and alveolar macrophages.[4] This immune response can become dysregulated in some patients, resulting in organ failure, cardiovascular complications, worsening hypoxia, and death. Systemic glucocorticoids have been tried as adjunctive therapy to immunomodulate the host response and improve outcomes in patients with CAP. Interestingly, the beneficial role of systemic glucocorticoids in the treatment of specific etiologies of CAP such as severe COVID-19 and *Pneumocystis jirovecii* infection has been established.[5,6]

What if systemic glucocorticoids also showed a mortality benefit as an adjunctive therapy for patients with severe CAP of any etiology, though? This would be a breakthrough given that systemic glucocorticoids are inexpensive and CAP (and severe CAP) is common. Recently, two large randomized controlled trials attempted to address this question but on the surface since they did not provide uniform results.[7,8] In the study by Dequin et al. (CAPE COD trial),[7] which included 795 patients, the data show that early use of hydrocortisone reduced the 28-day mortality rate (6.2%; 95% CI, 3.9-8.6 in the hydrocortisone group vs. 11.9%; 95% CI, 8.7-15.1 in the placebo group; p = 0.006), reduced the need for endotracheal intubation, and reduced the number of patients requiring vasopressors with no difference in the incidence of hospital-acquired infections. Conversely, in the study by Meduri et al. (ESCAPe trial),[8] which included 584 patients, there was no difference in 60-day mortality rate in patients with severe CAP who were treated with methylprednisolone (16% in the methylprednisolone group vs. 18% in the placebo group; OR = 0.89; 95% CI, 0.58-1.38; p = 0.61).

Although both trials were multicenter, double-blinded, randomized, and contained a placebo arm, there are important differences in the inclusion and exclusion criteria that are noteworthy. In order to be eligible for the CAPE COD trial,[7] patients had to be admitted to an ICU or intermediate care unit and satisfy one of the following criteria: Pneumonia Severity Index score > 130, initiation of mechanical ventilation, or a Pao_2:Fio_2 ratio < 300 on non-rebreather mask or high-flow nasal cannula. Subsequently, patients in the hydrocortisone arm received glucocorticoids within 24 h of fulfilling one of the aforementioned severity criteria. There were several exclusion criteria (including the presence of septic shock, influenza, and aspiration pneumonia), which resulted in ~86% of the patients who were screened being excluded from the trial.[7] This may negatively have impacted the generalizability of the study. In contrast, patients in the ESCAPe trial[8] were diagnosed with severe CAP based on one major or three minor American Thoracic Society/Infectious Disease Society of America criteria for severe pneumonia and were enrolled within 72-96 h after hospital admission. These patients were predominantly male since the study was conducted within the Veteran's Health Administration.

The baseline Pao_2:Fio_2 ratio was 137-143 in patients in the CAPE COD trial[7] and 181-188 in the ESCAPe trial.[8] In both trials, the distribution of patients in each Pneumonia Severity Index class was approximately similar. A critical difference was the time from patient presentation to glucocorticoid administration. The median time from hospital admission to study treatment initiation was 40 h in the ESCAPe trial.[8] The median time from hospital admission to ICU admission was 5.5 h and from ICU admission to study treatment initiation was 15.3 h in the CAPE COD trial.[7] It is, therefore, apparent that glucocorticoids were initiated earlier in the CAPE COD trial.[7] This difference is important since earlier treatment is more likely to modulate the host inflammatory response and consequently lead to better outcomes. An extreme

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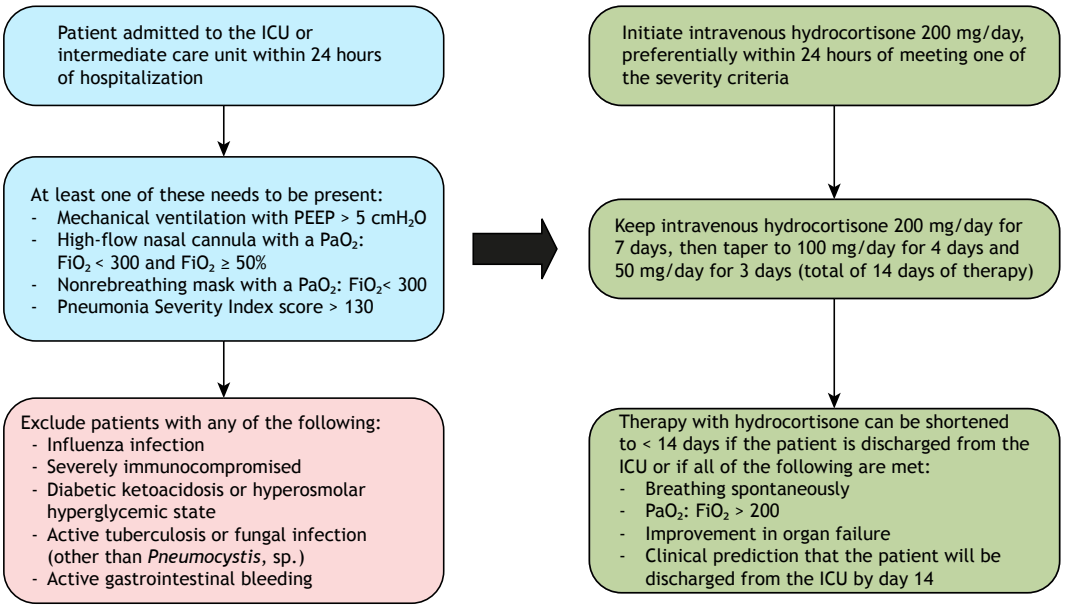

Figure 1. Strategy for initiating adjunctive immunomodulatory therapy with hydrocortisone in patients with severe CAP. Figure adapted from the trial by Dequin et al.[7]

analogy to this is the response seen with the early use of dexamethasone in bacterial meningitis, which has been shown to decrease cerebrospinal fluid levels of inflammatory cytokines and reduce cerebral edema.[9]

Overall, despite some degree of uncertainty, we believe that it is more likely that there is a benefit in the use of systemic glucocorticoids for the treatment of severe CAP (Figure 1). The mortality benefit may be more evident when systemic glucocorticoids are started earlier in the course of infection. Clinicians should be aware of clinical features, such as hypoxia, which may be an indicator of a better response to systemic glucocorticoids, and hydrocortisone should be the systemic glucocorticoid of choice in the absence of comparative data among the different glucocorticoid formulations.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

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"Post-tuberculosis financial disease"—we need to face it to eliminate tuberculosis

Ana Paula Santos[1,2], Fernanda Carvalho de Queiroz Mello[2]

In the study by Loureiro et al.,[1] published in this issue of the *Jornal Brasileiro de Pneumologia*, the authors studied the economic burden on the household during the follow-up of patients after tuberculosis diagnosis and treatment in five Brazilian capitals. They concluded that "participants incurred economic losses in the pre-diagnosis period and severe loss of income in the post-diagnosis period,", which resulted in unemployment and social sequelae caused by tuberculosis.

This topic is opportune since we face an increase in the number publications on post-tuberculosis lung disease (PTLD), which has become a more studied topic worldwide and has even been stimulating the formulation of consensus and guidelines. According to the First International Post-Tuberculosis Symposium conducted in South Africa, PTLD is defined as "evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous tuberculosis."[2]

Although the focus of studies has been directed toward physical disabilities, the "post-tuberculosis financial disease," with its economic, social, and psychological well-being consequences, has been commonly known. However, most studies regarding financial issues related to tuberculosis address costs during pre-diagnosis, diagnosis, and treatment, leaving aside post-disease losses.[3,4]

Poverty is usually considered a powerful determinant of tuberculosis, being its incidence and *per capita* gross domestic product inversely associated.[5] It is not a coincidence that reducing extreme poverty and controlling the tuberculosis epidemic are both main aims of the United Nations Sustainable Development Goals.[6]

Malnutrition status and crowded, poorly ventilated housing and working environments are often associated with poverty and constitute direct risk factors for disease transmission.[7] According to the results by Loureiro et al.,[1] the catastrophic costs induced by tuberculosis increased poverty and extreme poverty, which lead to a vicious circle that prevents us from seeing a light at the end of the tunnel.

The authors also identified an overall average cost of R$283.84 during the pre-diagnosis period and of R$4,161.86 during the post-diagnosis period, which involved not only the patients but also their households.[1] In contrast to previous studies,[4] post-tuberculosis costs were almost 15 times higher than were pre-tuberculosis costs, and that was mostly attributed to non-medical direct and indirect costs, including loss of income in 60% of cases.

The structure of tuberculosis monitoring in Brazil, including the decentralization of care to basic health care units, the strategy of active search of tuberculosis cases, and the free provision of diagnosis and treatment services by the Brazilian Unified Health Care System[8] could justify the lower costs in the pre-tuberculosis period than in the post-tuberculosis period.

Although travel expenses are cited as a contributor to the economic burden related to tuberculosis, they are afforded by the Brazilian government during treatment in order to guarantee attendance at scheduled visits and improve adherence to treatment, but the lack of information on the part of patients and health care teams that assist them, along with the delay in obtaining social benefits, can jeopardize the population and enhance the increasing catastrophic costs related to tuberculosis.[9]

To make matters worse, according to Loureiro et al.,[1] 71% of patients were unemployed after having tuberculosis, compared with 41% before the disease. These data are in accordance with Meghji et al.,[10] who also identified a decrease in paid work and in the median income one year after treatment completion when compared with the period before the onset of active tuberculosis.

The physical disability addressed by the concept of PTLD and its social consequences can feed a chain of financial vulnerability, and, besides the individual and households affected, society as a whole can suffer financial consequences. In cases of severe weakness that limits work capacity, disability-related retirement can be requested, which inflates the "pension bubble." Furthermore, long-term survival of patients treated for tuberculosis is reduced, the potential years of life lost rate being approximately four times higher than in the general population.[11]

For the ambitious targets of the End TB Strategy to be achieved, researchers suggest that, in addition to early diagnosis and treatment, PTLD should get as much attention as active tuberculosis. Moreover, to eliminate tuberculosis, structural public policies and broad actions are needed, providing PTLD patients access to health support, sanitation measures, social inclusion, education, housing, among others.

To face this national problem, the Brazilian Interministerial Committee for the Elimination of Tuberculosis and Other Socially Determined Diseases was established in April of 2023 by Decree No. 11,494. It comprises the Ministry of Health; Ministry of Science, Technology and Innovation; Ministry of Development and Social Assistance, Family, and Fight against Hunger; Ministry of Human Rights and Citizenship; Ministry of Education; Ministry of Racial Equality; Ministry of Integration and Regional Development; Ministry of Justice and Public Security; and Ministry of

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Indigenous Peoples. The Committee aims at promoting actions that contribute to the elimination of tuberculosis and other socially determined diseases by 2030.[12]

CONFLICTS OF INTEREST

None declared.

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Effect of vaccination on COVID-19 hospitalizations and mortality

Fábio Fernandes Dantas Filho[1,2,3], Karen Gomes D'Ávila[1,2], Denise Rossato Silva[1,2,4]

COVID-19, caused by SARS-CoV-2, has spread worldwide since December of 2019, causing significant morbidity and mortality. As of July 26, 2023, a total of 768,560,727 cases of COVID-19 had been confirmed worldwide, including 6,952,522 deaths. In Brazil, from January 3, 2020 to July 26, 2023, there were 37,704,598 confirmed COVID-19 cases and 704,488 COVID-19 deaths reported to the WHO.[1]

Medical conditions associated with increased COVID-19 severity and, consequently, increased likelihood of COVID-19 hospitalization include diabetes mellitus, obesity, hypertension, and heart failure. Early in the COVID-19 pandemic, it was shown that patients who were hospitalized for the disease and those who died from it were older and had more comorbidities.[2] Recent studies, published after the initiation of COVID-19 vaccination, have shown that being male, being over 60 years of age, not having been vaccinated for COVID-19, and having comorbidities are risk factors for complications resulting in hospitalization, including ICU admission.[3-5]

Vaccination has proven to be the most effective strategy to control the spread of SARS-CoV-2 infection and reduce the risk of severe COVID-19. Studies have shown that vaccination reduces COVID-19 mortality, COVID-19 severity, and the length of hospital stay.[4,6,7] Individuals with complete vaccination schedules had higher survival rates in a retrospective study evaluating 854 patients with COVID-19.[6] In addition, full vaccination reduced the need for ICU admission by 49.7% and mortality by 56.5%.[6] In a retrospective study evaluating 486 hospitalized COVID-19 patients,[4] not having been vaccinated or not having been fully vaccinated were factors associated with increased mortality. In individuals who require hospitalization despite COVID-19 vaccination, the length of hospital stay, the need for ICU admission, and mortality are lower than in unvaccinated individuals.[7]

Despite the recognized benefits of vaccination, the efficacy of vaccination in preventing moderate-to-severe COVID-19 decreases over time; this supports the recommendation for additional booster doses.[1] However, the role that the number of doses plays in the risk of severe disease and mortality has yet to be fully studied. In the current issue of the JBP, Costa et al.[8] report the results of a retrospective cohort study comparing vaccinated and unvaccinated hospitalized COVID-19 patients in terms of the risk factors for death and disease severity. The study included 1,921 patients, of whom 996 (50.8%) had been vaccinated. The risk of mortality in vaccinated patients was higher in those undergoing invasive mechanical ventilation, those over 80 years of age, and those requiring vasopressors. Symptoms were more common in unvaccinated patients than in vaccinated patients. In addition, in-hospital mortality was higher in unvaccinated patients than in vaccinated patients (60.8% vs. 48.7%). The authors also showed the benefits of multiple doses of vaccine even in hospitalized COVID-19 patients.[8] The 28-day survival rate was 38.2% in unvaccinated patients and 62.9% in patients who had received only one dose of vaccine. The 28-day survival rate increased to 74.6% in patients who had received two doses of vaccine and to 91.8% in those who had received three.

In conclusion, vaccination mitigates the severity of COVID-19, and efforts must be made to ensure adequate vaccination coverage and booster doses, especially in at-risk individuals such as the elderly and those with comorbidities. With regard to the Omicron variant, the efficacy of COVID-19 vaccines in preventing SARS-CoV-2 infection is low and short-lived after full primary immunization, although it can be enhanced by booster vaccination. For severe COVID-19, vaccine efficacy has been reported to be high and long-lasting, especially after booster vaccination.[9] Vaccine hesitancy deserves special attention from governments. Vaccine acceptance depends on individual sociocultural factors. Complacency, inconvenience in accessing vaccines, and lack of confidence are key reasons underlying vaccine hesitancy.[10] Strategies in the fight against COVID-19 include combating vaccine hesitancy by investing in public health campaigns.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

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Bronchiectasis with tracheobronchial dilation

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

A 27-year-old man complained of irritating cough and recurrent respiratory infection. He reported progressive dyspnea for 3 years. Chest CT showed diffuse bronchiectasis, with marked dilation of the trachea and main bronchi (Figure 1).

Bronchiectasis, by definition, is a permanent and irreversible dilation of the airways. Numerous etiologies can result in bronchiectasis. They include airway obstruction (tumors, foreign body aspiration, etc.), cystic fibrosis, immunological disorders, congenital alterations, lung infections (tuberculosis and allergic bronchopulmonary aspergillosis), among others.[1-3]

Bronchiectasis can be classified in several ways. Clinically, the current tendency is to classify them as fibrocystic or nonfibrocystic. Morphologically, they are classified as tubular (cylindrical), varicose, or cystic (saccular). The distribution of bronchiectasis can be important for diagnosis. They may, according to distribution, be divided into focal or diffuse, or may predominate in certain regions of the lungs. When they predominate in upper fields, cystic fibrosis, allergic bronchopulmonary aspergillosis, tuberculosis, and sarcoidosis must be remembered. When they predominate in anterior regions symmetrically and especially affecting the middle lobe and lingula, they suggest atypical mycobacteriosis. The predominance in lower fields is more often seen when they are secondary to aspiration or when associated with fibrosing diseases, such as usual interstitial pneumonia or nonspecific interstitial pneumonia. Some imaging findings are characteristic of certain etiologies, such as branched tubular opacities with high density, corresponding to dilated bronchi containing hyperdense mucus, as seen in allergic bronchopulmonary aspergillosis; bronchiectasis associated with *situs inversus totalis* and sinusitis, corresponding to the immotile cilia syndrome (Kartagener's syndrome); or bronchiectasis associated with marked dilation of the trachea and main bronchi, as observed in our patient, suggesting cartilage atrophy and characterizing tracheobronchomegaly, or Mounier-Kuhn syndrome.[1-3]

Mounier-Kuhn syndrome is a congenital condition characterized by the absence or marked atrophy of elastic fibers and smooth muscles of the walls of the trachea and main bronchi. Patients generally present with cough and recurrent respiratory infections, and imaging tests show a marked increase in the caliber of the large airways, in addition to bronchiectasis. These abnormalities can be seen on chest X-rays but are better identified on CT. The main alteration observed in the respiratory physiology of these patients is the total collapse of the airways during expiration. Small diverticula can be observed on the walls of the upper airways, also related to parietal fragility.[1-3]

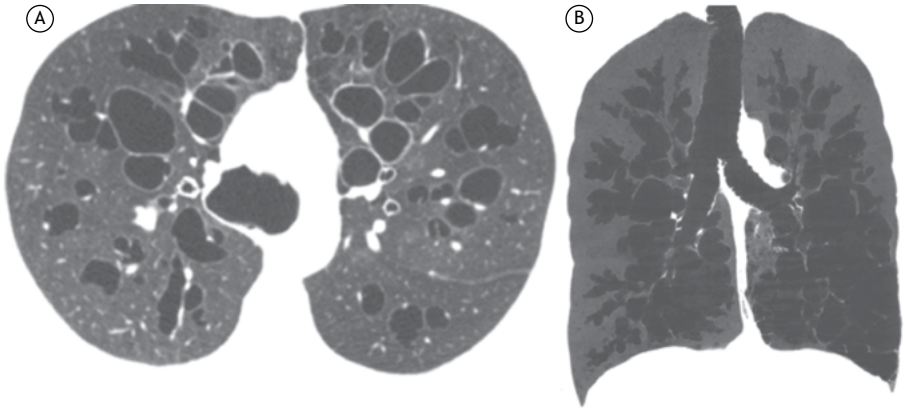

Figure 1. In A, chest CT during inspiration showing bilateral bronchiectasis, in addition to marked dilation of the main bronchi. In B, coronal reconstruction in minimal intensity projection showing, in addition to bronchiectasis, dilation of both the main bronchi and the trachea. These alterations characterized Mounier-Kuhn syndrome.

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Dealing with confounding in observational studies

Cristiane Fumo-dos-Santos[1], Juliana Carvalho Ferreira[1,2]

PRACTICAL SCENARIO

Investigators in a large academic center in São Paulo, Brazil, examined the association between the use of protective ventilation, defined as a tidal volume < 8 mL/kg of predicted body weight and plateau pressure < 30 cmH_2O, and survival in patients with severe COVID-19. They also collected data about severity of disease at ICU admission, need for renal replacement therapy, and several ventilatory parameters. They found that the use of protective ventilation was associated with improved survival, with an adjusted hazard ratio of 0.73 (95% CI, 0.57-0.94; p = 0.013).

CAUSAL INFERENCE IN OBSERVATIONAL STUDIES

In epidemiological studies, investigators do not assign interventions, but rather classify individuals as exposed or non-exposed to risk factors for developing an outcome. When a statistically significant association is found, several possible explanations need to be considered:

1. The association is real, and the predictor (protective ventilation, in our example) is truly a cause of the outcome (survival, in our example).
2. The association is real, but it is an effect-cause relationship: the outcome (survival) causes the predictor (protective ventilation). In this example it would not be plausible to consider this possibility, but there are many cases that this makes sense.
3. The association is due to chance—random error. Because we usually consider a p value < 0.05 as significant, and the p value in our example was 0.013, there is 1.3% probability that chance is the explanation for this association.
4. The association is not real, it is the result of a systematic error (bias), resulting from methodological aspects of the study, such as systematically underestimating the predicted body weight of patients.
5. The association is real, but it is confounded by the effect of other(s) variable(s) associated with both the outcome and the predictor.

WHAT IS CONFOUNDING?

Confounding derives from the Latin *confundere*, to mix. The classical definition of a confounder is any third variable that is associated with the exposure of interest, that is a cause of the outcome of interest, and that does not reside in the causal pathway between exposure and outcome (Figure 1A). For example, in our practical scenario, the investigators considered that lung compliance, among other variables, was a potential confounder, because low lung compliance is a cause of death (therefore, reducing survival), and it is also associated with the predictor—when compliance is very low, it may be more challenging to apply protective ventilation. Severity of disease at admission, on the other hand, was not treated as a confounder by the investigators, because although it is highly associated with the outcome (death), it does not have a causal relationship with the predictor of interest (protective ventilation).[1] Even though we can have confounders in experimental research, it is a more important issue to be considered in observational studies.[2]

WHY SHOULD WE CARE ABOUT IDENTIFYING CONFOUNDERS?

Confounders can lead to overestimation or underestimation of the effect of the main predictor on the outcome of interest, making the effect not reliable and interfering with our ability to draw causal inferences in observational studies.[2] Therefore, statistical strategies are recommended to control for or to adjust the analysis for confounders in order to observe the true, isolated effect of the predictor of interest on the outcome.

We should not identify a confounder based on statistical testing but on prior clinical knowledge or on the pathophysiology of the process that we are studying.[1] One of the most accepted strategies to identify a confounder is using prior knowledge about the outcome of interest to build causal models, especially graphical criteria.[2] This approach is important because the traditional way to identify the confounder, as described earlier, is often inadequate in more complex structures.[3]

HOW CAN WE DEAL WITH CONFOUNDERS?

The best way to deal with confounders is to plan in advance. A randomized controlled trial randomly assigns individuals to the intervention and control arms of the study, dispersing the known and unknown confounders into each arm. However, this design is not suitable to answer many important research questions.[1]

Selecting individuals with the same characteristic is also a strategy: to study reduced lung function in asthma, researchers may exclude people with obesity. The problem with this strategy is that the results do not apply to all individuals with asthma, but only for non-obese asthma patients. Another way to deal with confounding

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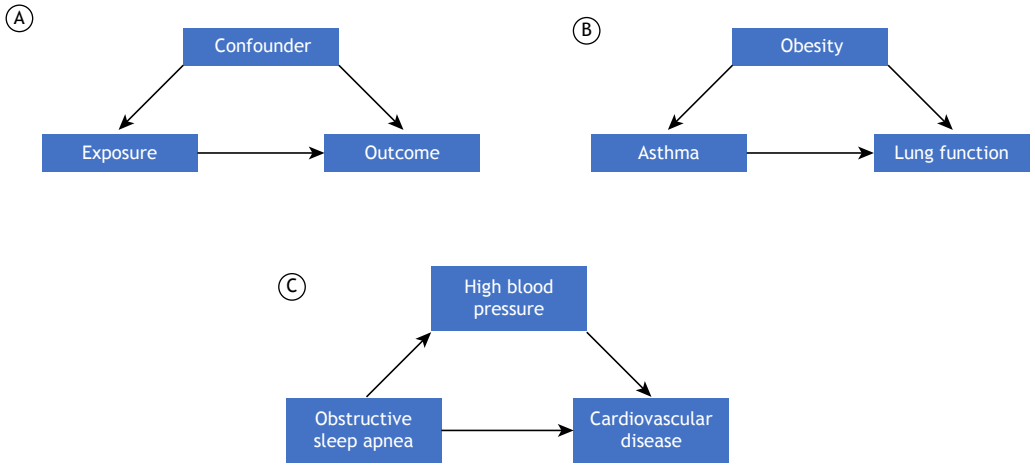

Figure 1. In A, representation of the confounding pattern: the variable is related to exposure, it is a cause of the outcome, and it is not in the causal pathway between the main exposure and the outcome of interest. In B, obesity is a confounder in the relation between asthma and lung function since obesity may worsen asthma and may cause a reduction in lung function. Adjusting for obesity is advised in this scenario. In C, the model represents a mediation effect —obstructive sleep apnea may lead to cardiovascular disease (direct effect), but obstructive sleep apnea may also lead to high blood pressure, which causes cardiovascular disease (indirect effect). In this case, adjusting for high blood pressure is not appropriate.

is matching individuals: the researcher selects the same number of participants with and without obesity both in the exposed and in the non-exposed group.[1] Again, however, the manipulation results in reduced generalizability of the results.

The most commonly used strategy to deal with confounders is controlling (or adjusting) for confounders during the statistical analysis since regression models can address several predictors at the same time.[3] In this case, it is really important to build a causal model and adjust only for confounders, instead of adjusting for all variables based on p values, for example.

The main message is that confounders can interfere with causal inference in observational studies, and we need to plan ahead to identify, measure, minimize, and adjust for confounders in order to use the results of observational studies to guide future research and clinical decision making.

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

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

BACKGROUND

Asthma is a heterogeneous, chronic airway inflammatory disease in which pulmonary function tests (PFTs) might provide valuable information for diagnosis, assessment of clinical control, and estimation of future risk.

OVERVIEW

A 57-year-old never-smoking woman reported a 10-year history of recurrent dyspnea and occasional wheezing that worsened after COVID-19 two years earlier. Dyspnea progression was associated with weight gain (BMI = 33 kg/m^2) in a background of type 2 diabetes and hypertension. She did report asthma in childhood, and her symptoms were typically precipitated by changes in the weather. Spirometry revealed mild and similar decreases in FEV_1 and FVC, with normal FEV_1/FVC ratio. Inhaled bronchodilator (BD) was associated with proportional increases in FEV_1 (↑ 0.37 L and 22%) and FVC (↑ 0.39 L and 18%), with normalization of spirometry. DL_{CO} was preserved. On the basis of her clinical history and functional data, she was diagnosed with asthma, with marked clinical improvement after a few weeks of treatment with medium-dose inhaled corticosteroids.

Reduced FVC and/or FEV_1 with normal FEV_1/FVC is a nonspecific finding that might signal restriction and/or obstruction. A commensurate improvement in FEV_1 and FVC with the use of an inhaled BD indicates lung volume recruitment, revealing underlying airway disease. If these changes are large enough to normalize the results of spirometry, asthma is the most likely diagnosis. It should be noted, however, that "fixed" airflow obstruction with variable degrees of hyperinflation and gas trapping can be seen in patients with remodeled airways and severe asthma. Variable airflow obstruction over time is commonly seen in patients with asthma, usually improving either spontaneously or secondary to treatment. In equivocal cases, airway hyperresponsiveness can be revealed by bronchial challenge testing.[1] Once treatment is initiated, between-visit variability in FEV_1 and BD responsiveness might provide ancillary information to gauge disease stability. Although it is not mandatory that maintenance or as-needed medications are withheld before testing, repeating PFTs under similar therapeutic conditions allows more meaningful interpretation. Low post-BD FEV_1 (particularly < 60% predicted)[2,3] and higher BD responsiveness[3] are independent predictors of increased risk of exacerbation, even in patients with relatively modest symptom burden (Chart 1). Indirect airway hyperresponsiveness testing with the use of hypertonic saline to determine the dose of inhaled corticosteroids has been reported to decrease the number of asthma exacerbations in children when compared with treatment based only on symptoms.[4]

CLINICAL MESSAGE

PFTs are central to the diagnosis and follow-up of patients with asthma. For instance, undiagnosed obstruction in asthma patients is more common among those who have never undergone spirometry or who have never been referred to a pulmonologist.[5] However, PFT results should not be used in isolation. The best management approach involves a longitudinal assessment of clinical endpoints (symptom control and exacerbation frequency) and laboratory data (eosinophil count, total IgE, and specific IgE) under the modulating influence of key comorbidities (obesity, rhinosinusitis, nasal polyposis, and gastroesophageal reflux disease). There is renewed interest in using lung function parameters to improve asthma phenotyping, which may shed novel light into more complex biological mechanisms (endotypes) relevant to disease pathophysiology and, ultimately, treatment choices.[6]

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

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Chart 1. Key information provided by pulmonary function testing and relevant to asthma management in individual patients.

Clinical scenario	Recommendations
Diagnosis	• In the right clinical context (e.g., recurrent wheezing, breathlessness, chest tightness, and/or cough brought on by characteristic triggers and relieved by BD therapy), variable airflow obstruction documented by BD testing or other tests is indicative of asthma.
	1) FEV_1/FVC below the lower limit of normal indicates obstruction, although elderly patients with asthma can present with FEV_1/FVC that is above the lower limit of normal but of < 0.7. Care should be taken to avoid overdiagnosis of obstruction in those with supranormal FVC caused by dysanapsis, i.e., a mismatch of airway tree caliber to lung size, particularly in children and adolescents.
	2) Excessive variability in lung function can be revealed by at least one of the following: 2.1) A "significant" response to inhaled BD from a baseline of obstruction: an increase in FEV_1 ≥ 10% predicted. Expressing FEV_1 changes relative to predicted rather than relative to baseline is recommended because ≥ 12% from baseline is easier to be reached the lower the FEV_1, the opposite being true for ≥ 200 mL.
	2.2) A "significant" response to inhaled BD from a baseline of apparent normality might be seen in patients with increased bronchomotor tone: the clinical significance of this finding requires careful clinical correlation.
	2.3) Excessive variability in twice-daily PEF measurements over 2 weeks (> 10% in adults and > 13% in children). Daily diurnal PEF variability is calculated as the highest value minus the lowest value divided by the mean of the highest and lowest values averaged over the period using the same flow meter.
	2.4) Improvement in lung function after 4 weeks of ICS-containing treatment: an increase in FEV_1 > 12% and > 200 mL (or a > 20% increase in PEF)
	2.5) Excessive variation in lung function between visits: variation in FEV_1 > 12% and > 200 mL in adults; variation in FEV_1 > 12% or variation in PEF > 15% in children
	2.6) The limitations of the % change from baseline approach (item 2.1) also apply to the effects of ICS and the between-test variability; thus, care should be taken to interpret changes in patients with markedly low or high baseline values.
	2.7) A positive exercise challenge: Decreases in FEV_1 of 10-25%, 26-50%, and > 50% indicate mild, moderate, and severe exercise-induced bronchoconstriction, respectively.
	2.8) A positive bronchial challenge test: A decrease in FEV_1 ≥ 20% with standard doses of methacholine (direct stimulation of airway smooth muscle receptors) or ≥ 15% with standardized indirect airway challenges (eucapnic voluntary hyperventilation, hypertonic saline, or dry powder mannitol) releasing endogenous mediators to cause airway smooth muscle contraction. Direct inhalation challenges are considered more sensitive but less specific; thus, indirect challenges can be used in order to confirm asthma after a positive methacholine test.
	2.9) A positive methacholine challenge test is not diagnostic of asthma without a suggestive clinical history, and, despite a high negative predictive value, it does not always rule out asthma in patients who have no symptoms at the time of testing. The severity of airway hyperresponsiveness can be used with clinical data to estimate the post-test likelihood of asthma.
	• A large volume response to inhaled BD (FVC) in a patient with COPD might be associated with a similar improvement in FEV_1: the latter finding should not be strictly interpreted as asthma. This common mistake has contributed to an increase in the prevalence of asthma-COPD overlap.
	• Increased longitudinal variability in FEV_1 in a patient with COPD, particularly when FVC varies only modestly, can be suggestive of asthma in the right clinical context, prompting a more liberal use of ICS.
	• Although not specific for asthma, subtle abnormalities such as low maximal mid- and end-expiratory flows, exaggerated flow-volume loop expiratory concavity, and increased specific airway resistance might help in diagnosing mild obstruction in suspected patients.
	• Analysis of the flow-volume loop morphology might occasionally suggest upper/central airflow obstruction, which can mimic asthma. Care should be taken to ensure that these abnormal patterns are reproducible and not related to poor technique.
	• Impulse oscillometry may be helpful in diagnosing asthma via bronchodilation or bronchoprovocation in patients with preserved spirometry. Thresholds to define airway hyperresponsiveness during bronchial challenges are also available.
	• Although a low DL_{CO} is rarely seen in asthma patients (unless there is another cause for impaired gas exchange), a normal DL_{CO} is not necessarily suggestive of asthma in the presence of obstruction, because it may occur in a patient with COPD in whom chronic bronchitis predominates over emphysema.
	• Obesity frequently creates challenges to asthma diagnosis, leading to a false-positive diagnosis (e.g., central airway compression and increased small airway collapse on forced expiration) or a false-negative diagnosis (FVC underestimation leading to "preserved" FEV_1/FVC ratio). Clinical history and laboratory data might provide important ancillary information for diagnostic clarification.

Continue...▶

Chart 1. Key information provided by pulmonary function testing and relevant to asthma management in individual patients. (Continued...)

Clinical scenario	Recommendations
Response to treatment	• Spirometry is usually recommended 3-6 months after treatment initiation, in order to record the patient's personal best lung function, and periodically thereafter (at least once every 1 or 2 years or more frequently in at-risk patients and in patients with severe asthma).
	• If the patient has persistent symptoms (e.g., dyspnea, exercise intolerance, excessive use of relievers) or airflow obstruction, more frequent testing may be warranted (e.g., at intervals of 3-6-months). Test results can be used in order to determine whether symptoms reflect poor asthma control or an alternative diagnosis/complication.
	• If symptoms are well controlled and prior spirometry is normal, follow-up spirometry can be obtained less frequently (every 1-3 years).
	• A volume response (e.g., Δinspiratory capacity > 200 mL and ΔFVC or vital capacity > 15%) might be more relevant to symptom improvement than a flow response (i.e., a significant increase in FEV_1 but not in FVC).
Disease severity/risk estimation	• Individuals with FEV_1 between 60-80% predicted have 2.5-fold-increased risk for future acute episodes, and those with FEV_1 < 60% predicted have > 4-fold-increased risk for future acute episodes when compared with those with FEV_1 > 80% predicted.
	• A 20% greater exacerbation risk is observed for every 10% increase in BD responsiveness.
	• Although the diagnosis of asthma is based on spirometry, a higher dyspnea burden can be explained by greater air trapping (increased RV) and/or lower inspiratory capacity at a given FEV_1.
	• Decreases ≥ 20% in PEF from predicted or from the patient's personal best signal an exacerbation of asthma: the exacerbation is considered "moderate" if the PEF is between 51-70% and "severe" if the PEF is of ≤ 50% of predicted.
	• PEF readings might prove useful in detecting unsuspected severe airflow obstruction in those who are "poor perceivers" of asthma symptoms.
	• Marked hypoxemia (a PaO_2 of < 60 mmHg and an SpO_2 of < 90%) is rare during uncomplicated asthma attacks, suggesting life-threatening exacerbation and possible complications (e.g., pneumonia, atelectasis caused by mucus plugging, and spontaneous pneumothorax).
	• The respiratory drive is usually increased in patients with acute asthma, resulting in hyperventilation and low $PaCO_2$. Therefore, a normal $PaCO_2$ during an asthma exacerbation might signal a severe episode. Hypercapnia and respiratory failure can develop rapidly with any further airway obstruction or with respiratory muscle fatigue. Progressive hypercapnia during an exacerbation of asthma is generally an indication for mechanical ventilation.

BD: bronchodilator; and ICS: inhaled corticosteroid(s).

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ORIGINAL ARTICLE

Predictive factors for improved diagnostic accuracy with the use of radial-probe EBUS

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Study carried out in the Serviço de Endoscopia Respiratória, Departamento de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To assess predictive factors for improved diagnostic accuracy with the use of radial-probe EBUS (RP-EBUS). **Methods:** This was a retrospective review of consecutive patients undergoing RP-EBUS between February of 2012 and January of 2020. Parameters including the presence of a bronchus sign on CT scans, the position of the radial EBUS probe, lesion size, lesion location, and lesion type were analyzed in relation to two defined outcomes (final diagnosis or no diagnosis). Univariate analysis was used in order to explore the individual effects of each parameter on diagnostic accuracy. Multivariate logistic regression was performed to identify significant predictors of diagnostic accuracy. **Results:** RP-EBUS was used for diagnostic purposes in 101 patients. The lesion was < 3 cm in size in 59 patients (58.4%) and predominantly solid in 60.3%. There was a positive correlation between radial EBUS probe position and diagnostic accuracy (p = 0.036), with 80.9% of the patients showing a bronchus sign on CT scans. Furthermore, 89% of the patients showed a bronchus sign on CT scans and a correlation with diagnostic accuracy (p = 0.030), with 65.8% of the lesions being located in the left/right upper lobe (p = 0.046). When the radial EBUS probe was within the target lesion, the diagnostic yield was = 80.8%. When the probe was adjacent to the lesion, the diagnostic yield was = 19.2%. A bronchus sign on CT scans was the only parameter that independently influenced diagnostic accuracy (adjusted OR, 3.20; 95% CI, 1.081-9.770; p = 0.036). **Conclusions:** A bronchus sign on CT scans is a powerful predictor of successful diagnosis by RP-EBUS.

Keywords: Diagnostic techniques, respiratory system; Ultrasonography; Bronchoscopy.

INTRODUCTION

EBUS was initially described by Hürter & Hanrath in 1992.[1] Since then, it has become a valuable tool for bronchoscopists to visualize the airway wall, lung, and mediastinum.[1] With the advances in EBUS, a growing number of chest diseases can now be detected by bronchoscopy.

A flexible, rotating transducer is employed in the radial EBUS probe, which can be inserted with or without a guide sheath through the working channel of a bronchoscope. This device creates a 360° (radial) image of the surrounding structures outside the airway wall, enabling the detection of peripheral lung lesions. As a result, radial-probe EBUS (RP-EBUS) has the potential to improve the diagnostic yield of conventional bronchoscopy.

RP-EBUS has gained widespread recognition as an effective procedure for enhancing the sensitivity and accuracy of diagnosing peripheral lung lesions. In fact, RP-EBUS can precisely identify the location of pulmonary nodules or masses by leveraging the distinct echogenic properties of different lung tissues. This not only aids in pinpointing the location of the lesion but can also provide valuable insights into its underlying cause.

During transbronchial lung biopsy with a flexible bronchoscope, certain anatomical factors, such as the significant branching angles of subsegmental bronchi from their parent bronchi and variations in branching angles during breathing, can present challenges.[2] As a result, identifying the correct bronchus to approach with a flexible bronchoscope can prove difficult. However, using RP-EBUS as an adjunct can provide additional information on the path leading to the lesion, thus improving success rates in biopsy procedures.

Because of its favorable risk profile when compared with transthoracic needle aspiration (with pneumothorax rates of 0.8% and 25%, respectively),[3-5] RP-EBUS has become a critical tool for diagnosing peripheral lung lesions worldwide. In this study, we sought to assess predictive factors for improved diagnostic accuracy with the use of RP-EBUS.

METHODS

Patients

Medical records of patients undergoing bronchoscopy between February of 2012 and January of 2020 at the

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University of São Paulo School of Medicine *Hospital das Clínicas* Heart Institute, located in the city of São Paulo, Brazil, were retrospectively reviewed. The present study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine *Hospital das Clínicas* (Protocol no. 4.535.270). All participating patients gave written informed consent before undergoing bronchoscopy.

Patients > 18 years of age who had a lung lesion that was visible on RP-EBUS and who had adequate clinical follow-up until confirmation of the diagnosis were included. Patients whose lesion was not visible on RP-EBUS, those who were lost to follow-up, and those diagnosed by endobronchial biopsies visible on conventional bronchoscopy were excluded.

CT analysis

All participating patients underwent CT scans of the chest. The scans were performed with patients lying in a supine position, in the craniocaudal direction, at the end of inhalation. The CT images were analyzed for various parameters, including the presence of a bronchus sign, lesion size, lesion type, and lesion location. The target bronchus for each case was identified through group discussion, and the results were confirmed accordingly. The CT scans were examined for the bronchus sign, which was defined as the presence of a bronchus leading directly to the target lesion.

RP-EBUS

After administration of topical anesthesia, all patients were lightly sedated with individually calculated doses of intravenous fentanyl, midazolam, and/or propofol.

A flexible bronchoscope with an outer diameter of 5.5 mm and a working channel of 2.2 mm and a 20-MHz flexible radial ultrasound probe (UM-S20-20R; Olympus Medical Systems Corp., Tokyo, Japan) were used. After placement of the bronchoscope near the affected bronchial segment (chosen after analysis of the chest CT images), the ultrasound probe was directed to the target area to locate the lesion. The probe was then removed from the working channel, allowing the introduction of the sampling instrument (biopsy forceps, a cytology brush, or an aspiration needle).

Study definitions

Lesions were stratified on the basis of size (≤ 3 cm or > 3 cm) and type (solid lesion, solid cavitated lesion, cavitary lesion, ground-glass opacity, or infiltrate). Lesion location was stratified into right upper lobe, right middle lobe, right lower lobe, left upper lobe, or left lower lobe. The CT bronchus sign was stratified into present or absent. The radial EBUS probe was classified as being within the lesion (when it was in the center of the lesion or surrounded by it) or adjacent to the lesion (when it was adjacent to the lesion and not completely in contact with it). The lesions were classified as being either malignant or benign on the basis of the findings of RP-EBUS biopsy.

Statistical analysis

The characteristics of the study population were described by means and interquartile ranges (for continuous variables) or absolute frequencies (for categorical variables). The Kolmogorov-Smirnov test was performed in order to test the normality of the distribution. Given that none of the variables showed a normal distribution ($p > 0.05$), nonparametric tests were performed. Spearman's correlation coefficient was used in the bivariate analysis. In the multivariate analysis, forward stepwise logistic regression was performed in order to investigate factors affecting diagnostic accuracy, which was evaluated as a dichotomous variable (accurate or inaccurate diagnosis), being considered the dependent variable. The independent variables were sex (male/female), age, lung disease, lesion size, lesion type, lesion location, CT bronchus sign, and position of the radial EBUS probe. The choice of the reference group for categorical variables (dichotomous or not) was based on the lowest absolute frequency of the category (for the variable sex) or on the first category of the variable under study (for the remaining variables). The Hosmer-Lemeshow test was used in order to fit the model with the independent variables. For model validation, its discriminatory ability, sensitivity, and specificity were analyzed by means of the AUC. All OR values were presented with their respective 95% CIs. The level of significance was set at $p = 0.05$. All statistical analyses were performed with the IBM SPSS Statistics software package for Windows, version 23.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Of the 101 patients who underwent biopsy by means of RP-EBUS, 56 (55.4%) were men and 45 (44.6%) were women. Most (56.4%) of the patients were < 65 years of age. The lesion was < 3 cm in 59 (58.4%) of the patients and predominantly solid in 60.3%. The most common lesion location was the right upper lobe (in 27.3%), followed by the left upper lobe (in 22.3%). Most of the patients (n = 85; 84.2%) had a bronchus sign on CT scans, and the probe was located within the lesion in 76 (75.2%). During the procedure, 89 patients (81.1%) had no complications. The baseline characteristics of the patients included in the study are summarized in Table 1.

Figure 1 shows the correlation between the final diagnosis obtained by RP-EBUS biopsy and the clinical characteristics of the patients. There was a positive correlation between the position of the radial EBUS probe and diagnostic accuracy ($p = 0.036$), with

Table 1. Baseline characteristics of the study population.

Characteristic	(N = 101)
Age, years	
Mean [IQR]	62 [55-71]
Minimum-maximum	19-88
Sex, n (%)	
Male	56 (55.4)
Female	45 (44.6)
Lung disease, n (%)	
Malignant	60 (59.4)
Benign	41 (40.6)
Lesion size, n (%)	
≤ 3 cm	59 (58.4)
> 3 cm	42 (41.6)
Lesion location, n (%)	
Right upper lobe	33 (32.7)
Left upper lobe	27 (26.7)
Left lower lobe	19 (18.8)
Right lower lobe	16 (15.9)
Right middle lobe	6 (5.9)
Lesion type, n (%)	
Solid lesion	73 (72.3)
Ground-glass opacity	11 (10.9)
Solid cavitated lesion	8 (7.9)
Cavitary lesion	6 (6.0)
Infiltrate	3 (2.9)
Bronchus sign on CT scan, n (%)	
Yes	85 (84.2)
No	16 (15.8)
EBUS probe position, n (%)	
Within the lesion	76 (75.2)
Adjacent to the lesion	25 (24.8)

80.9% of the patients showing the CT bronchus sign. In addition, 89% showed the CT bronchus sign and a correlation with diagnostic accuracy ($p = 0.030$), with 65.8% of the lesions being located in the left/right upper lobe ($p = 0.046$).

Table 2 shows the results of the logistic regression analysis with diagnostic accuracy as the dependent variable. The model showed a value of $p < 0.001$. The Hosmer-Lemeshow test revealed a value of $p = 0.834$, and the AUC was = 0.918, indicating that the model had excellent sensitivity and specificity (Figure 2).

DISCUSSION

The main objective of our study was to explore factors associated with improved diagnostic accuracy with the use of RP-EBUS. Thus, univariate analysis was used in order to consider the individual effects of each parameter on diagnostic accuracy. We found that the position of the probe (within the lesion), the presence of a bronchus sign on CT scans, and the location of the lesion (in the left/right upper lobe) were positively correlated with diagnostic accuracy.

The second major objective of the present study was to identify significant predictors of diagnostic accuracy. After adjusting the variables for the demographic characteristics of the study population, multivariate logistic regression clearly demonstrated that the bronchus sign is a stronger predictor than are the other parameters evaluated and is the only parameter that independently influences diagnostic accuracy.

The findings of this study differ from those of previous studies on the relationship between RP-EBUS and the bronchus sign. For instance, Yamada et al. conducted a retrospective analysis of 158 lesions and found that only RP-EBUS–based lesion identification was a significant predictor of biopsy success based on multivariate analysis.[6] However, only 58 patients were eligible for CT evaluation of the bronchus sign, and several adjuvants were used in the study, which might have reduced the significance of the bronchus sign.

Multiple studies have shown that the size of the lesion has a considerable impact on the diagnostic accuracy of RP-EBUS.[7-11] In our study, the diagnostic yield of lesions > 3 cm was higher than that of lesions < 3 cm (54.8% vs. 45.2%), but the difference was not statistically significant ($p = 0.233$).

Several factors have been consistently linked to increased diagnostic accuracy of RP-EBUS. First, using RP-EBUS to identify the target lesion has been shown to improve accuracy.[12] Second, placing the radial probe in the center of the lesion (rather than adjacent to it) has also been found to improve accuracy.[13,14] However, these factors are only identifiable during the procedure and cannot be used in order to select patients beforehand. Therefore, careful examination of the CT scan before the procedure, particularly in order to assess the presence of the bronchus sign, is crucial to enhance the diagnostic outcome.

In order to improve the pretest probability of a successful RP-EBUS procedure, several steps can be taken. First, it is important to have a solid understanding of bronchial segmentation. Second, a CT scan should be performed no later than 3-4 months before the RP-EBUS procedure. Third, the path from the major bronchus to the lesion subsegment should be traced. Fourth, the location of the lesion in the subsegmental bronchus should be identified by means of the radial EBUS probe. Finally, RP-EBUS screening should not be delayed, because of the possibility of atelectasis resulting from anesthesia or sedation.

It is important to acknowledge the limitations of our study. First, the fact that this was a single-center retrospective nonrandomized study might have introduced a selection bias. Second, the bronchoscopy procedures were not performed by the same bronchoscopist, and we did not measure the impact of differences in skill levels on diagnostic accuracy. Third,

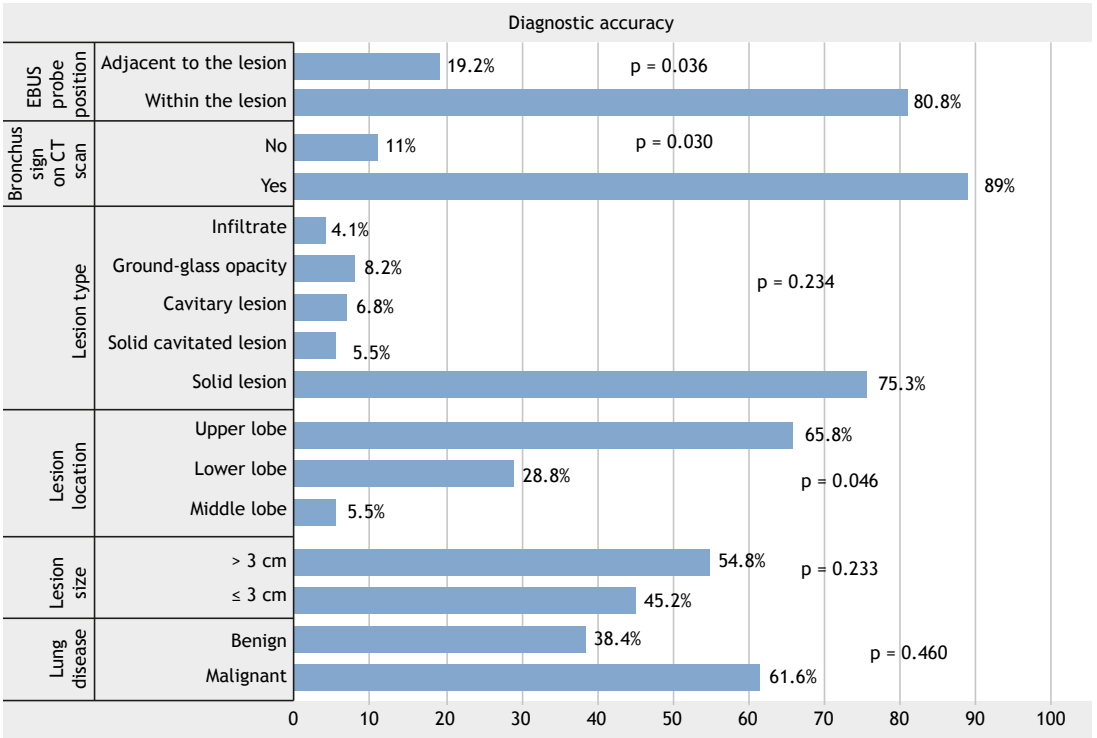

Figure 1. Diagnostic accuracy of radial-probe EBUS, on the basis of clinical characteristics. In the multivariate analysis, the presence of a bronchus sign on CT scans remained as the only independent predictor of diagnostic accuracy (adjusted OR, 3.20; 95% CI, 1.081-9.770; p = 0.036).

Table 2. Multivariate logistic regression for factors affecting the accuracy of diagnosis.[a]

Multivariate analysis		
Independent variable	Adjusted OR (95% CI)	p
Bronchus sign on CT scan		
No (reference group)	1	
Yes	3.250 (1.081-9.770)	0.036

[a]Variables included in the model: sex, age, lung disease, lesion size, lesion location, lesion type, bronchus sign on CT scan, EBUS probe position, and complications.

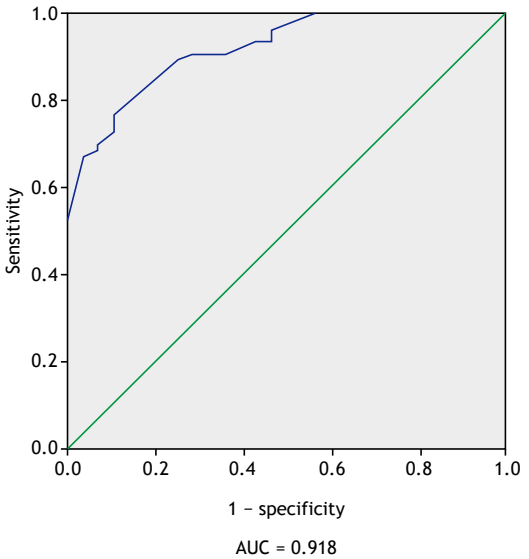

Figure 2. ROC curve for factors affecting the accuracy of diagnosis.

the choice of bronchoscope and sampling devices varied independently for each case. Fourth, we did not have access to rapid on-site evaluation during the procedure. Prospective randomized studies are needed for further evaluation of the diagnostic accuracy of RP-EBUS and to identify potential areas for improvement.

In conclusion, this study found that the presence of a bronchus sign on CT scans was a significant predictor of improved diagnostic accuracy with the use of RP-EBUS, regardless of lesion size, location, or type. This suggests that patients with a bronchus sign on CT scans may be good candidates for RP-EBUS because they have a higher probability of diagnostic success with this procedure.

AUTHOR CONTRIBUTIONS

AB: study conception and design; interpretation of the data; and drafting of the manuscript. MCC: analysis and interpretation of the data. FL, AP, SED,

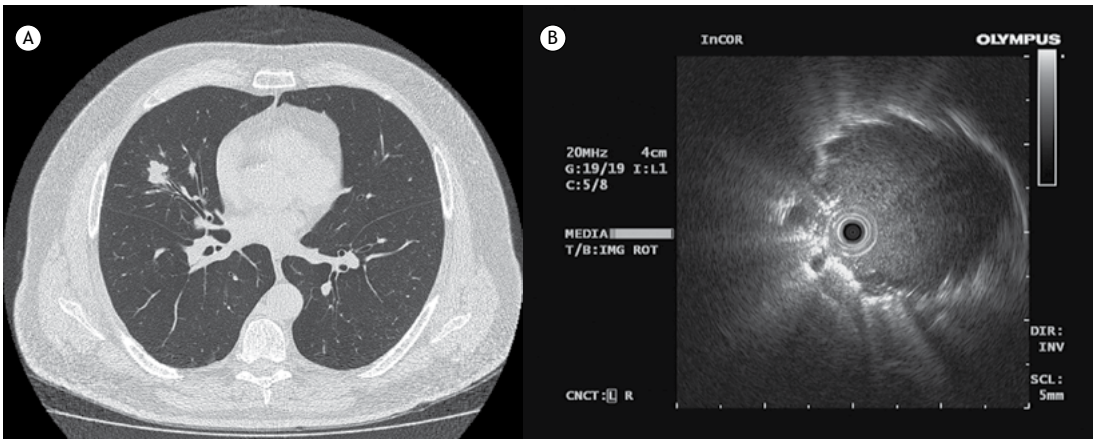

Figure 3. Comparison between CT (n A) and radial-probe EBUS with the probe positioned within the lesion (in B).

VRF, and MJ: critical revision of the manuscript for important intellectual content and final approval of the version to be published.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Risk factors for death and illness severity in vaccinated versus unvaccinated COVID-2019 inpatients: a retrospective cohort study

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ABSTRACT

Objective: To determine the clinical profile of COVID-19 inpatients who were vaccinated prior to hospitalization and to compare the risk factors for death and the 28-day survival rate of between those inpatients vaccinated with one, two, or three doses and unvaccinated COVID-19 inpatients. **Methods:** This was a retrospective observational cohort study involving COVID-19 patients admitted to a referral hospital in the city of Recife, Brazil, between July of 2020 and June of 2022. **Results:** The sample comprised 1,921 inpatients, 996 of whom (50.8%) were vaccinated prior to hospitalization. After adjusting the mortality risk for vaccinated patients, those undergoing invasive mechanical ventilation (IMV) had the highest mortality risk (adjusted OR [aOR] = 7.4; 95% CI, 3.8-14.1; $p < 0.001$), followed by patients > 80 years of age (aOR = 7.3; 95% CI, 3.4-15.4; $p < 0.001$), and those needing vasopressors (aOR = 5.6; 95% CI, 2.9-10.9; $p < 0.001$). After adjusting the mortality risk for all patients, having received three vaccine doses (aOR = 0.06; 95% CI, 0.03-0.11; $p < 0.001$) was the most important protective factor against death. There were progressive benefits of vaccination, reducing the frequency of ICU admissions, use for IMV, and death (respectively, from 44.9%, 39.0% and 39.9% after the first dose to 16.7%, 6.2% and 4.4% after the third dose), as well as significant improvements in survival after each subsequent dose ($p < 0.001$). **Conclusions:** Vaccines were effective in reducing illness severity and death in this cohort of COVID-19 inpatients, and the administration of additional doses conferred them with accumulative vaccine protection.

Keywords: COVID-19; Risk factors; Hospital mortality; Vaccination.

INTRODUCTION

Globally, until November 30, 2022, there were more than 640 million confirmed cases of COVID-19 and 6.6 million deaths; in addition, a total of 13 billion vaccine doses were administered, according to the WHO.[1] In Brazil, during the same period, there were more than 35 million cases and approximately 690,000 deaths due to COVID-19, and almost 493 million vaccine doses were administered.[1] In addition, hospitalized COVID-19 patients were the most costly for the health care system and had a high mortality rate, especially those being admitted to critical care units.[2-4]

Vaccination programs have reduced COVID-19-related hospitalizations, ICU admissions, and mortality rates.[5,6] An important observational, population-based study in Israel showed that the vaccination program against COVID-19 significantly reduced the number of asymptomatic and symptomatic cases of SARS-CoV-2 infections, hospitalizations, cases of severe disease, and deaths, even in older adults.[5] An international, randomized, double-blind, placebo-controlled phase 3 trial showed that efficacy of a single-dose vaccine for severe/critical COVID-19 cases with onset at least 14 days and at least ≥ 28 days after administration was, respectively, 76.7% and 85.4%, with decreasing numbers of hospitalizations and deaths.[7] Another study showed that fully vaccinated COVID-19 inpatients had a mortality rate of less than 50% and that the need for invasive mechanical ventilation (IMV) was less frequent in those patients than in unvaccinated patients. However, these studies did not assess the individual benefits of administering multiple doses of vaccines, even when patients were hospitalized for COVID-19.

In Brazil, the COVID-19 vaccination program started on January 17, 2021, prioritizing health professionals, the elderly population, and patients with chronic comorbidities. New outbreaks of COVID-19 may still happen in the future,[8] and it is imperative to identify the risk factors for death in vaccinated patients who are hospitalized for

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COVID-19, so that proper public health policies can be implemented. Thus, the aim of this study was to determine the clinical profile of COVID-19 inpatients who were vaccinated prior to hospitalization and to compare the risk factors for death and the 28-day survival rate between those inpatients vaccinated with one, two, or three doses and unvaccinated COVID-19 inpatients.

METHODS

Study design

In this retrospective, observational cohort study, we analyzed data from the medical records of patients admitted to at a referral hospital with 100 ICU beds and 200 ward beds for diagnosing and treating suspected or confirmed COVID-19 cases in the city of Recife, Brazil, between July 1, 2020, and June 30, 2022. Patients were enrolled in the cohort if they were 18 years of age or older, had a confirmed positive result for COVID-19 by RT-PCR SARS-CoV-2 testing, and were admitted to the hospital. Patients were grouped as vaccinated (those who were vaccinated against COVID-19 before hospitalization) or as nonvaccinated (those who did not receive any vaccine dose against COVID-19 before hospitalization).

Patients were excluded from the study if they were vaccinated after hospitalization or if vaccination data could not be identified. Patients were followed up until hospital discharge or death. The Research Ethics Committee of the *Instituto de Medicina Integral Prof. Fernando Figueira* reviewed and approved this research (CAAE no. 35243120.7.0000.5205). The Strengthening the Reporting of Observational Studies in Epidemiology guideline recommendations were used as a reference.[9]

The primary outcome was in-hospital mortality. The secondary outcomes were frequency of admission to the ICU and need for IMV. The following demographic, epidemiological, and clinical variables were evaluated: age (years), age group (< 50, 50–59, 60–69, 70–79 and > 80 years), gender (male or female), ethnicity (White or others), marital status (single [divorced, unmarried, widowed] or married [married, living with a partner]), area of residence (Recife, metropolitan area of Recife, or other), symptoms (fever, cough, dyspnea, diarrhea, and vomiting; each symptom was dichotomized as yes or no), vital signs (Spo_2, RR, and HR); comorbidities (systemic arterial hypertension, diabetes mellitus, obesity, chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, chronic hematologic disease, chronic neurologic disease, chronic liver disease, cancer, and immunodeficiency; each comorbidity was dichotomized as yes or no); virus variant (Gamma, Delta and Omicron; inference based on viral circulation at the period of study in Brazil), ICU admission (dichotomized as yes or no), chest CT pattern (typical or atypical for the disease), respiratory support (IMV, noninvasive mechanical ventilation, oxygen therapy, and/or none); use of vasopressors (dichotomized as yes or no), renal replacement therapy (dichotomized as yes or no); time spent on IMV (days); length of hospital stay (days); length of ICU stay (days); and in-hospital mortality rate.

Statistical analysis

Data were analyzed using the IBM SPSS Statistics software package, version 28.0 (IBM Corporation, Armonk, NY, USA). Analyses were performed using only valid data. A descriptive analysis of the study population was performed using mean and standard deviation measures for continuous variables and absolute and relative frequency distributions for categorical variables. To compare continuous and categorical variables, respectively, the t-test and the chi-square test were used. We used logistic regression analyses to explore associations among the variables, with an emphasis on the vaccination status of each patient and the risk of death. Variables that showed an association with the outcomes in the univariate analyses ($p < 0.15$) were sequentially tested in a multivariate model, starting with the variable most strongly associated with the risk of death and continuing until no other variable reached significance. Variables with a p-value < 0.05 were considered statistically significant in the multivariate model.[10] We used the Kaplan-Meier method to evaluate survival within 28 days in inpatients vaccinated with one, two, or three vaccine doses versus unvaccinated inpatients, using the log-rank test to evaluate differences between the curves. Differences were considered significant at $p < 0.05$.

RESULTS

During the period of this study, 3,930 hospitalized patients were selected from those who had confirmed COVID-19 by RT-PCR SARS-CoV-2 testing. Of these patients, 1,044 were excluded because no vaccination data could be identified, and 996 were excluded because they were vaccinated after hospitalization. Therefore, 1,921 patients were included in this study: 996 vaccinated patients (50.8%) and 925 unvaccinated patients (49.2%). Most of the patients were older (mean age = 62.2 ± 15.9 years), male (53.9%), living alone or without a partner (80.3%), non-White (71.2%), and residing in the metropolitan area of Recife (41.7%). Vaccinated patients were older than were unvaccinated patients: 66.5 ± 15.5 years vs. 57.6 ± 15.1 years ($p < 0.001$). There were no significant differences in gender, ethnicity, marital status, or area of residence between vaccinated and unvaccinated patients (Table 1).

With regard to the symptoms related to COVID-19, the most frequent ones were dyspnea (in 73.1%), cough (in 55.6%), and fever (in 42.7%). Unvaccinated COVID-19 patients showed a higher frequency of most of the symptoms ($p < 0.001$). Most of the patients had hypertension (53.5%) and diabetes (31.8%). Except for obesity and chronic pulmonary disease,

comorbidities were more often reported in vaccinated patients than in unvaccinated patients ($p < 0.001$). In our sample, of the 989 patients who underwent chest CT, 756 (76.4%) had a typical pattern for COVID-19. In addition, of the 1,921 patients, 1,022 (53.2%) were admitted to the ICU, 867 (45.1%) needed IMV, 763 (39.7%) used vasopressors, and 125 (6.5%) received hemodialysis. The overall in-hospital mortality rate was 48.7%, and this was higher among unvaccinated patients (60.8% vs. 37.4%; $p < 0.001$). Unvaccinated COVID-19 patients, in comparison with vaccinated patients, more frequently had a typical COVID-19 pattern on chest CT (84.1% vs. 70.6%; $p < 0.001$), were more frequently admitted to the ICU (60.9% vs. 46.1%; $p < 0.001$), and more frequently needed IMV (57.2% vs. 33.9%; $p < 0.001$) and vasopressors (50.1% vs. 30.1%; $p < 0.001$; Table 2).

In general, COVID-19 nonsurvivors, when compared with survivors, were older, had more comorbidities, required more ICU admissions, had more severe disease, and more often used IMV, vasopressors, and hemodialysis, in both vaccinated and unvaccinated groups (Table 3). Vaccinated COVID-19 survivors, when compared with vaccinated nonsurvivors, were younger (64.0 ± 16.3 years vs. 70.6 ± 13.2 years; $p < 0.001$), less often had dyspnea (66.3% vs. 75.3%; $p = 0.003$), had a higher mean Spo_2 at hospital admission (96 ± 3% vs. 94 ± 6%; $p < 0.001$), were less often admitted to the ICU (29.7% vs. 73.5%; $p < 0.001$), and less often needed IMV (8% vs. 77%; $p < 0.001$), vasopressors (5.8% vs. 70.8%; $p < 0.001$), or hemodialysis (4.2% vs. 12.1%; $p < 0.001$; Table 3).

The frequency of death, use of IMV, and ICU admission was, respectively, 60.8%, 57.2% and 60.9% for unvaccinated patients ($p < 0.001$); 39.9%, 39.0% and 44.9% for one-dose vaccinated patients ($p < 0.001$); 25.5%, 25.2% and 34.8% for two-dose vaccinated patients ($p < 0.001$); and 4.4%, 6.2%, and 16.7% for three-dose vaccinated patients (Figure 1A). As for COVID-19 variants, patients infected with the Gamma variant had a higher frequency of death, use of IMV, and ICU admission (Figure 1B).

The frequency of death, use of IMV, and ICU admission was, respectively, 38.4%, 33.0% and 46.0%, for those whose first dose was the AstraZeneca vaccine, and 37.4%, 35.1%, and 46.7% for those whose first dose was the CoronaVac vaccine ($p > 0.05$). The frequency of death, use of IMV, and ICU admission was 23.4%, 20.7%, and 38.3% ($p < 0.001$), respectively, for those whose second dose was the AstraZeneca vaccine, and 31.4%, 31.4% and 45.9% for those whose second dose was the CoronaVac vaccine ($p < 0.001$; Figure 1C). The CoronaVac, the AstraZeneca, and the Pfizer vaccines were administered as the first dose, respectively, in 45.7%, 45.0%, and 6.6% of the patients; whereas they were administered as the second dose, respectively, in 51.0%, 39.5%, and 8.8%; and, as the third dose, in 1.3%, 6.6%, and 86.1% (Figure 1D).

Table 1. Demographic characteristics of COVID-19 inpatients (N = 1,921) by vaccination status, 2020-2022.[a]

Characteristic	Group			p*
	Overall sample	Vaccinated n = 996 (50.8)	Unvaccinated n = 925 (49.2)	
Age, years				
Mean ± SD	62.2 ± 15.9	66.5 ± 15.5	57.6 ± 15.1	< 0.001
Median	63	68	57	
Age group, years				
< 50	446 (23.2)	158 (15.9)	288 (31.1)	< 0.001
50-59	357 (18.6)	125 (12.6)	232 (25.1)	
60-69	448 (23.3)	257 (25.8)	191 (20.6)	
70-79	379 (19.7)	242 (24.3)	137 (14.8)	
≥ 80	291 (15.1)	214 (21.5)	77 (8.3)	
Sex				
Male	1,035 (53.9)	540 (54.2)	495 (53.5)	0.757
Female	886 (46.1)	456 (45.8)	430 (46.5)	
Ethnicity/skin color[b]				
White	305 (28.8)	143 (28.1)	162 (29.5)	0.625
Other	754 (71.2)	366 (71.9)	388 (70.5)	
Marital status[c]				
Single	1,536 (80.3)	819 (82.4)	717 (78.0)	0.016
Married	377 (19.7)	175 (17.6)	202 (22.0)	
Area of residence[d]				
Recife	680 (35.8)	358 (35.9)	322 (35.6)	0.952
Metropolitan area of Recife	793 (41.7)	417 (41.9)	376 (41.6)	
Other	427 (22.5)	221 (22.2)	206 (22.8)	

[a]Values expressed as n (%), except where otherwise indicated. [b]n = 1,059. [c]n = 1,913. [d]n = 1,900. *Chi-square test.

Table 2. Clinical characteristics among COVID-19 inpatients (N = 1,921) by vaccination status, 2020-2022.[a]

Characteristic	Overall sample	Group		p*
		Vaccinated n = 996 (50.8)	Unvaccinated n = 925 (49.2)	
Symptoms/vital signs				
Fever	820 (42.7)	393 (39.5)	427 (46.2)	0.003
Cough	1,068 (55.6)	517 (51.9)	551 (59.6)	< 0.001
Dyspnea	1,404(73.1)	694 (69.7)	710 (76.8)	< 0.001
Diarrhea	118 (6.1)	61 (6.1)	57 (6.2)	0.973
Vomit/nausea	56 (2.9)	32 (3.2)	24 (2.6)	0.421
Spo_2	94.0 ± 5.7	95.0 ± 4.4	93.0 ± 6.7	< 0.001
RR, breaths/min	22. ± 6.4	20.9 ± 5.4	23.4 ± 7.1	< 0.001
HR, bpm[b]	88.5 ± 18.9	88.3 ± 18.8	88.7 ± 19.1	0.612
Comorbidities				
Hypertension	1,028 (53.5)	580 (58.2)	448 (48.4)	< 0.001
Diabetes	610 (31.8)	358 (35.9)	252 (27.2)	< 0.001
Obesity	536 (27.9)	252 (25.3)	284 (30.7)	< 0.001
Chronic cardiac disease	191 (9.9)	128 (12.9)	63 (6.8)	< 0.001
Chronic kidney disease	176 (9.2)	104 (10.4)	72 (7.8)	0.044
Chronic neurologic disease	217 (11.3)	147 (14.8)	70 (7.6)	< 0.001
Chronic pulmonary disease	138 (7.2)	70 (7.0)	68 (7.4)	0.784
Chronic hematologic disease	24 (1.2)	17 (1.7)	7 (0.8)	0.061
Chronic liver disease	29 (1.5)	18 (1.8)	11 (1.2)	0.267
Cancer	62 (3.2)	38 (3.8)	24 (2.6)	0.130
Immunodeficiency	63 (3.3)	42 (4.2)	21 (2.3)	0.017
Typical CT pattern[c]	756 (76.4)	397 (70.6)	359 (84.1)	< 0.001
ICU admission	1,022 (53.2)	459 (46.1)	563 (60.9)	< 0.001
Respiratory support				
IMV	867 (45.1)	338 (33.9)	529 (57.2)	
Noninvasive ventilation	292 (15.2)	144 (14.5)	148 (16.0)	< 0.001
Oxygen therapy	426 (22.2)	270 (27.1)	156 (16.9)	
None	333 (17.5)	244 (24.5)	92 (9.9)	
Vasopressor	763 (39.7)	300 (30.1)	463 (50.1)	< 0.001
Hemodialysis	125 (6.5)	71 (7.1)	54 (5.8)	0.252
Length of hospital stay, days	12.1 ± 11.9	11.8 ± 12.1	12.2 ± 11.8	0.480
Duration of IMV, days	8.5 ± 14.4	7.2 ± 20.3	9.4 ± 8.7	0.031
In-hospital mortality rate	935 (48.7)	373 (37.4)	562 (60.8)	< 0.001

IMV: invasive mechanical ventilation. [a]Values expressed as n (%) or mean ± SD. [b]n = 1,919. [c]n = 989. *Chi-square test.

When analyzing the adjusted risk of mortality (measured using the adjusted odds ratio [aOR]) for all patients, those undergoing IMV had the highest risk of death (aOR = 14.6; 95% CI, 8.1-26.2; p < 0.001), followed by patients > 80 years of age (aOR = 7.0; 95% CI, 3.5-13.9; p < 0.001), those admitted to the ICU (aOR = 4.6; 95% CI, 2.7-7.8; p < 0.001), those needing vasopressors (aOR = 2.8; 95% CI, 1.6-5.1; p < 0.001) and patients in the 70-79 year-old group (aOR = 4.6; 95% CI, 2.2-9.6; p < 0.001). Having received three doses of vaccine was the best protective factor against death (aOR = 0.076; 95% CI, 0.04-0.146; p < 0.001; Figure 2A).

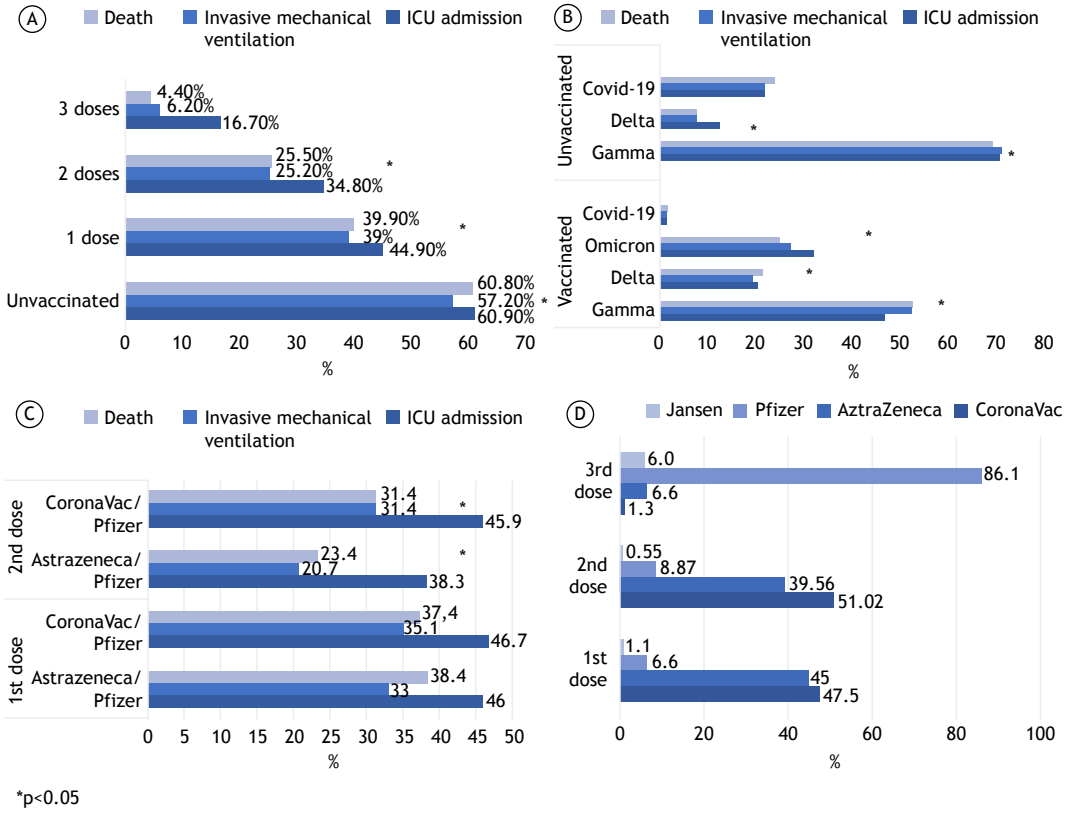
When analyzing the adjusted risk of mortality for vaccinated patients (Figure 2B), those undergoing IMV had the highest risk of death (aOR = 7.4; 95% CI, 3.8-14.1; p < 0.001), followed by patients > 80 years of age (aOR = 7.3; 95% CI, 3.4-15.4; p < 0.001), those needing vasopressors (aOR = 5.6; 95% CI, 2.9-10.9; p < 0.001), patients in the 70-79-year-old group (aOR = 4.6; 95% CI = 2.2–9.6; *p* < 0.001), those admitted to the ICU (aOR = 3.7; 95% CI, 2.2-6.1; p < 0.001), those needing hemodialysis (aOR = 3.0; 95% CI, 1.4-6.7; p < 0.001), and those in the 60-69-year-old group (aOR = 3.1; 95% CI, 1.5-6.4; p < 0.001). The presence of fever at hospital admission (aOR = 0.63; 95% CI, 0.42-0.96; p < 0.001) was a protective factor against death.

When analyzing the adjusted risk of mortality for unvaccinated patients (Figure 2C), those who underwent IMV had the highest risk (aOR = 11.2; 95% CI, 6.3-20.2; p < 0.001), followed by those needing vasopressors (aOR = 2.9; 95% CI, 1.6-5.4;

Table 3. Demographic and clinical characteristics among hospitalized COVID-19 survivors and nonsurvivors by vaccination status, 2020-2022.[a]

Characteristic	Group					
	Vaccinated n = 996 (50.8)		p	Unvaccinated n = 925 (49.2)		p
	Survivor	Nonsurvivor		Survivor	Nonsurvivor	
Age, years	64.0 ± 16.3	70.6 ± 13.2	< 0.001	55.3 ± 15.1	59.1 ± 14.9	< 0.001
Median	66	72		55	58	
Age group, years						
< 50	130 (20.9)	28 (7.5)		135 (37.2)	153 (27.2)	
50-59	88 (14.1)	37 (9.9)		92 (25.3)	140 (24.9)	
60-69	153 (24.6)	104 (27.9)	< 0.001	72 (19.8)	119 (21.2)	0.004
70-79	136 (21.8)	106 (28.4)		40 (11)	97 (17.3)	
≥ 80	116 (18.6)	98 (26.3)		24 (6.6)	53 (9.4)	
Sex						
Male	341 (54.7)	199 (53.4)	0.671	195 (53.7)	300 (53.4)	0.920
Female	282 (45.3)	174 (46.6)		168 (46.3)	262 (46.6)	
Ethnicity/skin color						
White	83 (26.1)	60 (31.4)	0.197	69 (33.3)	93 (27.1)	0.121
Other	234 (73.9)	131 (68.6)		138 (66.7)	250 (72.9)	
Marital status						
Single	509 (82)	310 (83.1)	0.646	280 (77.3)	437 (78.5)	0.692
Married	112 (18)	63 (16.9)		82 (22.7)	120 (21.5)	
Area of residence						
Recife	228 (36.6)	130 (34.9)	0.431	145 (41.3)	177 (32)	0.004
Metropolitan area of Recife	265 (42.5)	152 (40.8)		143 (40.7)	233 (42.1)	
Other	130 (20.9)	91 (24.4)		63 (17.9)	143 (25.9)	
Symptoms at admission						
Fever	264 (42.4)	129 (34.6)	0.015	178 (49)	249 (44.3)	0.159
Cough	349 (56)	168 (45)	< 0.001	222 (61.2)	329 (58.5)	0.429
Dyspnea	413 (66.3)	281 (75.3)	0.003	280 (77.1)	430 (76.5)	0.827
Diarrhea	41 (6.6)	20 (5.4)	0.437	25 (6.9)	32 (5.7)	0.461
Vomiting	21 (3.4)	11 (2.9)	0.715	12 (3.3)	12 (2.1)	0.274
Vital signs at admission						
Spo_2	96 + 3	94 + 6	< 0.001	95 + 3	92 + 7	< 0.001
RR, breaths/min	20 + 5	22 + 6	< 0.001	21.6 + 6	24.6 + 7	< 0.001
HR, bpm	86 + 16	92 + 22	< 0.001	85 + 16	90 + 20	< 0.001
Comorbidities						
Hypertension	360 (57.8)	220 (59)	0.648	161 (44.4)	287 (51.1)	0.046
Diabetes	213 (34.2)	145 (38.9)	0.136	84 (23.1)	168 (29.9)	0.024
Obesity	162 (27.9)	90 (27.4)	0.737	113 (40.6)	171 (41.8)	0.472
Chronic cardiac disease	72 (11.6)	56 (15)	0.115	29 (8)	34 (6)	0.253
Chronic kidney disease	64 (10.3)	40 (10.7)	0.822	25 (6.9)	47 (8.4)	0.413
Chronic neurologic disease	79 (12.7)	68 (18.2)	0.017	27 (7.4)	43 (7.7)	0.905
Chronic pulmonary disease	46 (7.4)	24 (6.4)	0.571	30 (8.3)	38 (6.8)	0.392
Chronic hematologic disease	13 (2.1)	4 (1.1)	0.232	4 (1.1)	3 (0.5)	0.330
Chronic liver disease	9 (1.4)	9 (2.4)	0.267	5 (1.4)	6 (1.1)	0.671
Cancer	19 (3)	19 (5.1)	0.103	11 (3)	13 (2.3)	0.503
Immunodeficiency	26 (4.2)	16 (4.3)	0.930	11 (3.3)	10 (1.8)	0.212
ICU admission	185 (29.7)	274 (73.5)	< 0.001	131 (36.1)	432 (76.9)	< 0.001
Invasive mechanical ventilation	50 (8)	288 (77)	< 0.001	44 (12.1)	485 (86.3)	< 0.001
Vasopressor	36 (5.8)	264 (70.8)	< 0.001	36 (9.9)	427 (76)	< 0.001
Hemodialysis	26 (4.2)	45 (12.1)	< 0.001	14 (3.9)	40 (7.1)	0.039
CT pattern						
Typical	302 (69.9)	95 (73.1)	0.585	270 (74.4)	195 (34.7)	< 0.001
Atypical	108 (25)	31 (23.8)		93 (25.6)	367 (65.3)	
Variant						
Delta	159 (25.5)	79 (21.3)	0.280	48 (13.2)	43 (7.7)	0.018
Gamma	303 (48.6)	195 (52.3)		240 (66.1)	386 (68.7)	
Omicron	156 (25)	93 (24.9)		-	-	
Length of hospital stay, days	11.4 ± 11.4	12.6 ± 13.1	0.134	12.24 ± 10.7	12.24 ± 13.3	0.998

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



*p<0.05

Figure 1. Mortality rates, use of invasive mechanical ventilation, and ICU admission by number of vaccine doses administered (in A); SARS-CoV-2 variant (in B); vaccination schedule (in C); and type of vaccine per dose (in D).

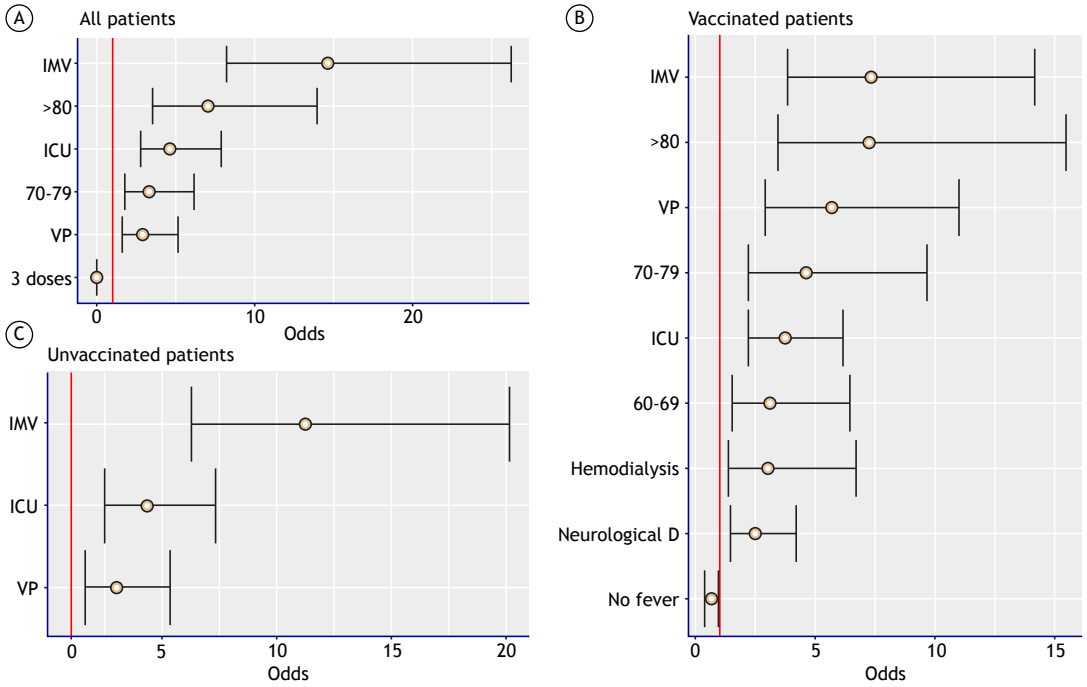


Figure 2. Risk factors for death among COVID-19 inpatients: all patients (in A); vaccinated patients (in B); and unvaccinated patients (in C). IMV: invasive mechanical ventilation; >80: age > 80 years; ICU: admitted to the ICU; 70-79: 70-79 age bracket; VP: vasopressor; ;60-69: 60-69 age bracket; and D: disease.

p < 0.001), and those admitted to the ICU (aOR = 4.3; 95% CI, 2.5-7.4; p < 0.001).

According to the Kaplan-Meier curves (Figure 3A), the 28-day survival rates were 38.2% and 62.9%,

respectively, in unvaccinated patients and in one-dose vaccinated patients ($p < 0.001$). The 28-day survival rates were, respectively, 74.6% and 91.8% in two-dose and three-dose vaccinated patients ($p < 0.001$ for both; Figures 3B and 3C).

DISCUSSION

In this study, data from COVID-19 patients who were hospitalized after the initiation of the vaccination program in Brazil showed greater protection against ICU admissions, use of IMV, and death with each additional dose of vaccine, even for those who were older and had more comorbidities when compared with unvaccinated patients. Furthermore, this study also demonstrated the clinical profile of vaccinated nonsurvivors (older patients with more severe illness who were often admitted to the ICU and made greater use of IMV, vasopressors, and hemodialysis when compared with vaccinated survivors).

Older age, comorbidities, and dysfunctional organs are the most prevalent risk factors for death among hospitalized COVID-19 patients.[2-4,11,12] Vaccines against SARS-CoV-2 have been effective in reducing the number of new COVID-19 cases, hospitalizations, ICU admissions, and deaths.[5,6,13] Our study showed that, after multivariate regression analysis, the risk factors for death, even in vaccinated patients after the multivariate regression analysis, were critical illness and need for IMV, vasopressors, or hemodialysis, even though obesity and fever at admission were protective factors against death. However, the frequency of ICU admissions, the need for IMV, and the number of deaths were significantly higher in unvaccinated patients than in vaccinated patients. Thus, we can infer that the vaccination program against COVID-19 has been the most important measure for saving lives, controlling the transmission of SARS-CoV-2 and reducing health care costs, regardless of age, comorbidities, and severity of illness.

The COVID-19 vaccines have even been effective at protecting hospitalized patients.[14] Among these patients, vaccination has been effective in reducing in-hospital death,[14] risk of developing severe/critical disease,[15] emergency hospitalizations,[16] and length of hospital stay,[17] even in patients on IMV[14] and with different COVID-19 variants,[16] when compared with unvaccinated COVID-19 inpatients. Furthermore, the cumulative benefits of a higher number of vaccine doses[18] and prior infection-acquired immunity[19] have been shown to protect against severe cases,[20] the need for IMV,[21] or death,[21,22] even in older patients.[6] Our study also confirmed the progressive benefits of the vaccines because improvements were found in the overall survival rate as the number of doses administered increased, having the effect of reducing the frequency of ICU admissions, use of IMV, and death (respectively, from 44.9%, 39.0%, and 39.9% after the first dose to 16.7%, 6.2%, and 4.4% after the third dose). We would expect the vaccination program against SARS-CoV-2 to be expanded to include children and adolescents and vaccine doses to be administered twice a year in order to control possible recurrent outbreaks with new variants in the future, given that vaccine protection waned considerably after six months.[19]

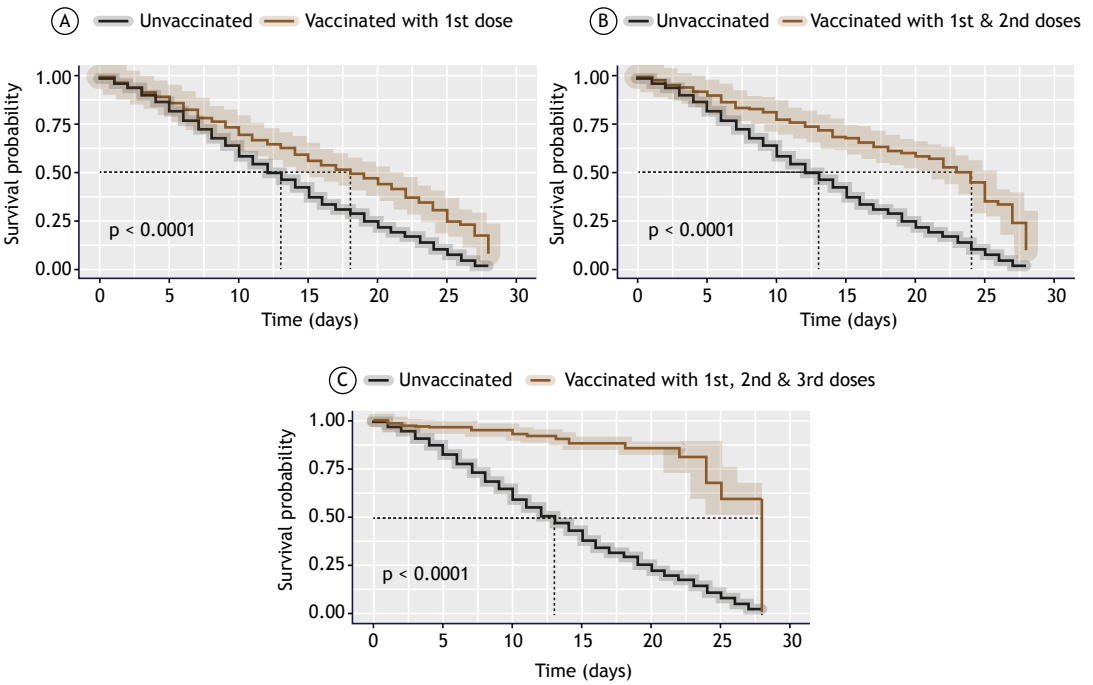


Figure 3. 28-day survival rates of COVID-19 inpatients by number of vaccine doses administered. In A, unvaccinated patients vs. patients vaccinated with one dose. In B, unvaccinated patients vs. patients vaccinated with two doses. In C, unvaccinated patients vs. patients vaccinated with three doses.

There are still many people either without access to vaccines[23,24] or who are avoiding taking the vaccines worldwide.[1,24] Having a large number of unvaccinated COVID-19 patients leads not only to a higher risk of death but also to a higher risk of emerging new variants of SARS-CoV-2, and, consequently, new outbreaks in the future.[8] Unfortunately, low-income countries still face challenges in vaccinating their populations completely.[25,26] Even in Brazil, by the end of November of 2022, 12-13% of the population had never received any dose of vaccine, and almost 20% had an incomplete vaccination schedule.[1] However, although systemic and local side effects from all vaccines against COVID-19 have been reported in almost one-third of vaccinated patients, the symptoms were self-limited and for a short time,[27] and therefore they do not justify avoidance or delay in taking additional vaccine doses yearly.

This study has some limitations. First, it had a retrospective observational design with data obtained from a single center, and the authors did not have full access to data regarding vaccination or history of previous COVID-19 infection for all of the COVID-19 inpatients in the study; thus, confounding factors may exist. However, the *Hospital Alfa* was created to provide specialized health assistance in COVID-19 cases and has acquired a high level of expertise by treating almost 7,000 patients with suspected or confirmed COVID-19. Second, the RT-PCR test results that confirmed the COVID-19 cases could not be reviewed, which created some bias about the patients included, albeit all patients admitted to the *Hospital Alfa* underwent the same COVID-19 diagnostic protocol. Third, the authors had no full access to information about adverse effects of the vaccines, especially after multiple doses. Finally, virus sequencing was not carried out, making it impossible to define which variant caused the hospitalization. However, our analysis might be very important for improving knowledge about the vaccines under different clinical conditions (i.e., frequency and risk of death), especially in COVID-19 inpatients because they were evaluated over a long period of time and had different levels of severity.

This important Brazilian study evaluated the clinical profile, illness severity, and risk factors for death in vaccinated versus unvaccinated COVID-19 inpatients, and it determined the overall survival rate of vaccinated patients who had received one, two, or three vaccine doses. This information might provide important support for better decision-making by governments, institutions, and/or health professionals in order to stimulate their patients to follow the vaccination program, regardless of age, gender, or clinical performance.

In conclusion, this Brazilian study showed that the vaccines against SARS-CoV-2 were effective in reducing illness severity and death even in COVID-19 inpatients, who usually have more severe disease, causing more expenses for the health care system, and have higher mortality rates. Furthermore, the use of multiple vaccine doses conferred cumulative vaccine protection to these patients.

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AUTHOR CONTRIBUTIONS

GJC, JRSJ, CCAS, TPFL, JICJ, and MJTS: study design, conception, and planning; interpretation of evidence; and drafting and revision of the manuscript. CCAS, TPFL, MMC, MHOS, and GCSC: study conception and planning; data collection; interpretation of evidence; and data acquisition. GJC, JRSJ, CCAS, TPFL, MMC, MHOS, GCSC, JICJ, and MJTS: approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Predictors of prolonged ventilator weaning and mortality in critically ill patients with COVID-19

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ABSTRACT

Objective: To identify factors associated with prolonged weaning and mortality in critically ill COVID-19 patients admitted to ICUs and under invasive mechanical ventilation. **Methods:** Between March of 2020 and July of 2021, we retrospectively recorded clinical and ventilatory characteristics of critically ill COVID-19 patients from the day of intubation to the outcome. We classified the patients regarding the weaning period in accordance with established criteria. A logistic regression analysis was performed to identify variables associated with prolonged weaning and mortality. **Results:** The study involved 303 patients, 100 of whom (33.0%) had a prolonged weaning period. Most of the patients were male (69.6%), 136 (44.8%) had more than 50% of pulmonary involvement on chest CT, and 93 (30.6%) had severe ARDS. Within the prolonged weaning group, 62% died within 60 days. Multivariate analysis revealed that lung involvement greater than 50% on CT and delay from intubation to the first separation attempt from mechanical ventilation were significantly associated with prolonged weaning, whereas age and prolonged weaning were significantly associated with mortality. **Conclusions:** Prolonged weaning can be used as a milestone in predicting mortality in critically ill COVID-19 patients. Lung involvement greater than 50% on CT and delay from intubation to the first separation attempt from mechanical ventilation were identified as significant predictors of prolonged weaning. These results might provide valuable information for healthcare professionals when making clinical decisions regarding the management of critically ill COVID-19 patients who are on mechanical ventilation.

Keywords: COVID-19; Pneumonia, viral; Respiratory distress syndrome; Respiration, artificial; Ventilator weaning; Cohort studies; Hospital mortality; Patient outcome assessment.

INTRODUCTION

A SARS-CoV-2 infection can present with mild symptoms or progress to severe complications, including shock, multiple organ failure, arrhythmia, coagulopathy, cardiac injury, and ARDS.[1,2] According to cohorts in Italy and China, approximately 70% of patients with COVID-19 admitted to ICUs required ventilatory support, and most of them were mechanically ventilated for extended periods.[3,4] The severity of acute respiratory failure, the incidence of complications, and hospital structural limitations (such as shortages of ICU beds and of mechanical ventilators) have been cited as factors that could contribute to the longer duration of invasive mechanical ventilation (IMV) in COVID-19 patients.[5] It is worth noting that the longer the duration of mechanical ventilation is, the higher the morbidity and mortality rates in medical and surgical patients are.[6]

In addition to the aforementioned difficulties, challenges are added during the weaning phase, that is, the entire process of discontinuing IMV from the first effort to reduce ventilatory support to the removal of the endotracheal tube. This process is estimated to encompass about 40% of the total IMV time[7] and is therefore an important phase during the patient's stay in the ICU. The discontinuation of the mechanical ventilator depends on numerous factors and should be individualized and evaluated daily by a multidisciplinary team.[7-9]

Since mechanical ventilation is a critical phase during a patient's stay in the ICU, identifying factors that prolong weaning can allow for individualized approaches, such as transferring patients to facilities for extended weaning or recommending tracheostomy. Therefore, the objective of this study was to determine the factors associated with prolonged ventilator weaning and mortality in patients who were intubated due to acute respiratory failure caused by COVID-19.

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METHODS

This retrospective cohort study was conducted in two ICUs dedicated to the care of subjects with COVID-19 in a large-size public teaching hospital in the city of São Paulo, Brazil, with a total of 75 ICU beds. The study was approved by the *Universidade Federal de São Paulo* Research Ethics Committee (Process no. CAAE 46961021.10000.5505). Since this is an observational study, informed consent was waived. Between March of 2020 and July of 2021, we included all subjects aged 18 years or older admitted to the participating ICUs who were mechanically ventilated due to confirmed COVID-19 pneumonia (clinical and tomographic findings suggestive of viral pneumonia and a positive RT-PCR test for SARS-CoV-2).

Because this is a retrospective study, the authors had no influence on either the choice of the optimal weaning moment or the way the process was conducted. The weaning process was performed based on literature criteria, clinical stability, and staff decision. A separation attempt (SA) from mechanical ventilation was considered a spontaneous breathing trial with pressure support less than or equal to 7 cmH_2O, followed by extubation or not, or an extubation performed without a previous spontaneous breathing trial. Successful weaning was defined as extubation without reintubation or death within the following 48 h,[9] regardless of the need for noninvasive ventilation (NIV) after extubation. For tracheostomized subjects, successful weaning was defined as spontaneous ventilation without any IMV support for 7 consecutive days.

Data were collected from the hospital's electronic medical record system by one of the researchers and kept confidential. The following variables were recorded on admission: age, sex, BMI, Simplified Acute Physiology Score 3 (SAPS 3),[10] Charlson Comorbidity Index (CCI),[11] endotracheal intubation (EI), severity of ARDS based on the Berlin definition,[12] and proportion of lung parenchyma affected by COVID-19 on chest CT as determined by a radiologist or the attending physician.

During the first 7 days of mechanical ventilation (or until extubation or death, whichever occurred first), we recorded the following ventilatory parameters: V_T, RR, F_{IO_2}, PEEP, plateau pressure (Pplat), driving pressure (ΔP, calculated as Pplat minus total PEEP), respiratory system compliance (C_{rs}, calculated as V_T divided by ΔP), and arterial blood gas analysis (including pH, Pao_2, $Paco_2$, and Pao_2/F_{IO_2}). Additionally, we collected information on the use of high-flow nasal cannula (HFNC) and NIV prior to EI.

The main outcome was to classify the subjects into four groups based on the weaning classification (known as the WIND study) by Béduneau et al.[9] These groups were as follows: "no weaning" group, consisting of subjects who had not undergone any SA from IMV; "short weaning" group, comprising subjects whose first SA resulted in either successful weaning or death within 1 day; "difficult weaning" group, consisting of subjects whose weaning was completed (either successfully or resulting in death) more than 1 day but less than one week after the first SA; and "prolonged weaning" group, comprising subjects in whom weaning was still not terminated 7 days after the first SA. For patients who failed and required reintubation in less than 48 h, the ventilatory period count was continuous.

The study also examined several secondary outcomes, including ventilator-associated pneumonia (VAP), pulmonary embolism (PE), reintubation rate, tracheostomy rate, number of ventilator-free days at day 28, ICU mortality, and 60-day mortality. Ventilator-free days were defined as the number of days during which the subjects were able to breathe spontaneously without any ventilatory assistance for 24 consecutive hours. If a subject died before day 28, they were considered to have had no ventilator-free days.

Statistical analysis

Data are presented as mean ± SD, median [IQR], or absolute and relative frequencies, as appropriate. For continuous variables with normal distribution, the groups were compared using one-way ANOVA; for categorical variables, groups were compared using the chi-square test. A multivariate logistic regression model was constructed to assess variables independently associated with prolonged weaning. The following variables were selected for initial assessment according to clinical relevance: age, sex, BMI, SAPS 3 at admission, CCI, pulmonary involvement on CT, previous HFNC or NIV use, arterial blood gas after EI (pH and Pao_2/F_{IO_2} ratio), ventilatory parameters after EI (ΔP; C_{rs}), and delay from EI to first SA. Variables with a $p < 0.20$ in the univariate logistic regression model were included in the multivariate model. Results were reported as OR (95% CI). A second multivariate logistic model was performed to assess if prolonged weaning was independently associated with ICU mortality. We built a directed acyclic graph (DAG) to choose the confounders and to avoid overfitting of the model.[13] Briefly, a DAG is a graphical tool that enables the visualization of the relationships between the exposure of interest, the outcome being studied, and all other variables that are associated in some way with at least two other variables in the diagram (supplementary figure).[14-16] The following confounders were selected for the DAG: age, SAPS 3, CCI, BMI, previous HFNC or NIV use, PE, VAP, worsening of ventilatory parameters (lower C_{rs}; higher ΔP) and of Pao_2/F_{IO_2} ratio within the first 7 days of IMV.

RESULTS

During the period studied, 817 subjects were admitted to the ICU, 303 of whom (37%) required IMV and were included in the study. After applying the WIND classification,[9] it was found that 102 subjects (33.7%) were classified in the "no weaning" group; 53 (17.5%), in the "short weaning" group; 48 (15.8%), in the "difficult weaning" group; and 100 (33.0%), in the

"prolonged weaning" group (Figure 1). Additional data on ventilatory and blood gas analysis variables at EI and the first SA day are presented in the supplementary material (supplementary table).

NIV or HFNC were used in 181 (59.7%) of the subjects before EI. At ICU admission, 136 (44.8%) of the subjects had more than 50% pulmonary involvement on chest CT, and 243 (80.1%) had a Pao_2/Fio_2 ratio < 150 mmHg on the first blood gas analysis after EI. Baseline characteristics of the subjects in each group are shown in Table 1. Almost half of the subjects (47.8%) had more than four comorbidities, the most prevalent ones being high blood pressure (in 64.1%), overweight (in 53.1%), diabetes mellitus (in 40.7%), and chronic kidney disease (in 33.5%). Significant differences were observed among the weaning groups for the following variables: age (p = 0.02); CCI (p = 0.04); severe ARDS (Pao_2/Fio_2 ratio < 150 mmHg; p < 0.01); pulmonary involvement over 50% on chest CT (p = 0.03); and previous use of NIV (p = 0.04). Tracheostomy was performed in 57 (18.8%) of the subjects, 47 (82%) of whom being in the prolonged weaning group, with a delay of 28 ± 10 days from EI.

Table 2 displays the outcomes of the study participants. The "prolonged weaning group had significantly higher VAP and tracheostomy rates than did the other groups (p < 0.01). Additionally, the 60-day mortality rate was significantly higher in this group (p < 0.01). Table 3 shows the variables that were independently associated with prolonged weaning. The proportion of lung involvement on chest CT (p = 0.04) and the delay from EI to first SA (p < 0.01) were found to be significant predictors of prolonged weaning. The study also found that the optimal cutoff point between EI and SA to indicate a risk for prolonged weaning was 9 days, with an AUC of 0.798 (95% CI, 0.734-0.862), a sensitivity of 72%, and a specificity of 79%. Table 4 displays the multivariate analyses that identified prolonged weaning and advanced age as independent risk factors for 60-day mortality (p < 0.01 for both).

DISCUSSION

In our study, we discovered two critical findings that shed light on the prolonged weaning process in critically ill patients with COVID-19. Firstly, we found that delaying the initiation of SA for more than 9 days after EI significantly increases the risk of prolonged weaning. Furthermore, our study uncovered an important association between prolonged weaning and mortality, emphasizing the need for close monitoring and timely interventions during the weaning process.

Our study revealed a noteworthy trend of patients dying before undergoing a weaning process, which aligns with the weaning profile identified in another study[17] that categorized the weaning of critically ill COVID-19 patients using the WIND study.[9] This finding is concerning and requires careful interpretation and investigation. There are several potential explanations for this trend. Firstly, the severity of the disease may contribute to a higher mortality rate before the opportunity for weaning arises.[18] Secondly, delayed recognition of weaning potential is another possibility, which could be attributed to various factors such as a focus on immediate life-saving interventions, the presence of comorbidities, or a lack of clear guidelines for identifying suitable weaning candidates.[19,20] Additionally, barriers to weaning, including unresolved underlying medical conditions, complications related to mechanical ventilation, or insufficient resources and expertise to effectively support the weaning process, may also play a role.[21] Identifying and addressing these

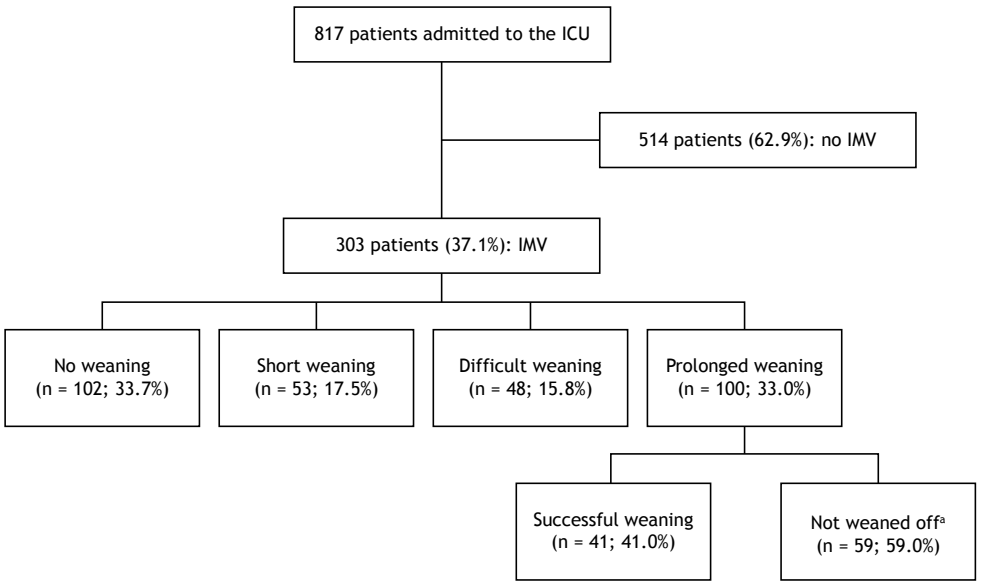

Figure 1. Flow chart of patient selection process and classification of selected patients in accordance with the classification system by Béduneau et al.[9] between March of 2020 and July of 2021. IMV: invasive mechanical ventilation. [a]After 60 days of follow-up.

Table 1. Demographic and clinical characteristics of critically ill COVID-19 patients on mechanical ventilation.[a]

Characteristic	All patients	Group				p*
		No weaning	Short weaning	Difficult weaning	Prolonged weaning	
	N = 303	n = 102 (33.7%)	n = 53 (17.5%)	n = 48 (15.8%)	n = 100 (33.0%)	
Age, years	61 ± 14	63 ± 14	55 ± 16	60 ± 14	61 ± 12	0.02
Gender, male	211 (69.6)	74 (72.5)	42 (79.2)	38 (79.1)	57 (57.0)	0.86
SAPS-3	58 ± 14	60 ± 15	55 ± 13	55 ± 15	58 ± 13	0.49
BMI, kg/m^2	28 ± 10	28 ± 6	27 ± 4	28 ± 4	28 ± 5	0.49
CCI > 4	145 (47.8)	49 (45.5)	6 (28.8)	16 (41.3)	74 (50.5)	0.04
Pao_2/Fio_2 < 150	243 (80.1)	87 (85.2)	35 (66.0)	33 (68.7)	88 (88.0)	< 0.01
CT lung involvement > 50%	136 (44.8)	47 (46.5)	7 (35.0)	12 (30.5)	70 (47.6)	0.03
EI before ICU admission	120 (39.6)	43 (42.1)	11 (20.7)	13 (27.0)	53 (53.0)	0.23
NIV before EI	134 (44.2)	37 (36.2)	9 (16.9)	21(43.7)	67 (67.0)	0.04
HFNC before EI	47(16.1)	11(10.8)	2 (3.7)	6 (12.5)	28 (28.0)	0.08
Delay from EI to first SA, days	6 [5-64]	-	6 [3-27]	17 [5-24]	23 [9-64]	< 0.01
Mechanical ventilation free days	3 [0-28]	-	19 [2-28]	10 [0-18]	2 [0-4]	0.06
Time on IMV, days	12 ± 9	11 ± 18	2 ± 1	6 ± 1	25 ± 15	< 0.01
Prone positioning	138 (45)	51 (50)	-	18 (37)	69 (69)	0.51
Neuromuscular blockade	224 (73)	79 (77)	3 (5)	32 (66)	100 (100)	0.67
Length of ICU stay, days	19 [11-173]	10 [5-172]	13 [10-56]	20 [14-79]	37 [26-128]	< 0.01
Survivors, length of ICU stay, days	19 [12-106]	-	13 [10-47]	22 [14-58]	53 [29-128]	< 0.01

SAPS-3: Simplified Acute Physiology Score 3; CCI: Charlson Comorbidity Index; EI: endotracheal intubation; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; SA: separation attempt; IMV: invasive mechanical ventilation. [a]Values are expressed as n (%), mean ± SD, or median [IQR]. *p-value states an overall comparison between the groups.

Table 2. Outcomes of critically ill COVID-19 patients on mechanical ventilation.[a]

Outcome	Group				p*
	No weaning	Short weaning	Difficult weaning	Prolonged weaning	
	n = 102 (33.7%)	n = 53 (17.5%)	n = 48 (15.8%)	n = 100 (33.0%)	
Reintubation	-	5 (9.4)	9 (18.7)	26 (26.0)	0.05
Tracheostomy	6 (5.8)	0 (0)	4 (8.3)	47 (47.0)	< 0.01
Pulmonary embolism	15 (14.8)	3 (5.6)	8 (16.6)	25 (25.0)	0.47
VAP	29 (28.7)	6 (11.3)	14 (29.1)	69 (69.0)	< 0.01
60-day mortality	102 (100)	3(5.6)	9 (18.7)	62 (62.0)	< 0.01

VAP: ventilator-associated pneumonia. [a]Values are expressed as n (%). *p-value states an overall comparison between the groups.

barriers is crucial for enhancing patient management and optimizing outcomes.

We observed that approximately one-third of the patients in our study experienced a prolonged weaning process. In our cohort, the mean duration of IMV was 12 days, slightly longer than the median duration of 8 days reported in an international COVID-19 cohort study.[21] This extended duration of IMV may contribute to the heightened risk of prolonged weaning observed in our study. However, a critical finding emerged from our analysis, revealing a significant association between delayed SA and extended duration of weaning. This association suggests that early initiation of SA plays a crucial role in facilitating a smoother and more efficient weaning process. When SA is delayed, patients may remain in a deeper sedation state[19] for a prolonged period, resulting in muscle weakness,[22] deconditioning, and increased challenges in liberating these patients from IMV. The implications of our findings align with the results of a meta-analysis on liberation from IMV, emphasizing the substantial challenges encountered in this process.[23] That meta-analysis indicated that only 50% of patients who required IMV for more than 17 days were successfully liberated, highlighting the complexity of prolonged weaning in critically ill patients, including those with COVID-19. Indeed, a study[24] that compared the weaning process between patients with COVID-19-associated ARDS and those with non-COVID-19 ARDS revealed that COVID-19 patients had a longer duration of IMV and encountered more challenges during the weaning transition, primarily due to weaning unreadiness. The presence of uncontrolled immune responses in COVID-19 patients may hinder lung recovery and complicate the assessment of readiness for ventilatory weaning.[20,25]

The association between pulmonary involvement on chest CT and prolonged weaning also raises significant concerns. Chest CT has been widely used during the

Table 3. Binary univariate logistic regression analysis of factors associated with prolonged weaning in critically ill COVID-19 patients on mechanical ventilation.

Variable	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.104 (0.993-1.035)	0.17	1.027 (0.994-1.061)	0.13
Gender, male	1.145 (0.625-2.099)	0.66		
BMI, kg/m^2	1.027 (0.996-1.093)	0.39		
CCI	1.418 (0.987-2.036)	0.59		
SAPS-3	1.029 (0.994-1.065)	0.11	0.988 (0.990-1.006)	0.37
CT lung involvement > 50%	2.007 (1.347-2.990)	<0.01	1.765 (1.015-3.070)	0.04
NIV or HFNC before EI	0.886 (0.505-1.555)	0.67		
pH[a]	0.999 (0.992-1.006)	0.27		
Pao_2/Fio_2[a]	0.989 (0.984-0.995)	< 0.01	1.020 (0.710-1.465)	0.91
C_{rs}[a]	0.973 (0.935-1.014)	0.19	0.978 (0.936-1.022)	0.32
ΔP[a]	0.956 (0.835-1.003)	0.50		
Delay from EI to first SA	1.195 (1.125-1.269)	< 0.01	1.249 (1.131-1.380)	< 0.01

CCI: Charlson Comorbidity Index; SAPS-3: Simplified Acute Physiologic Score 3; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; EI: endotracheal intubation; C_{rs}: respiratory system compliance; ΔP: driving pressure; and SA: separation attempt. [a]First values after EI.

Table 4. Binary logistic regression analysis of factors associated with mortality in critically ill COVID-19 patients on mechanical ventilation.[a]

Variable	Multivariate analysis	
	OR (95% CI)	p
Age	1.077 (1.039-1.116)	< 0.01
BMI	0.972 (0.913-1.035)	0.37
CCI	0.712 (0.434-1.167)	0.17
SAPS 3	1.006 (0.975-1.039)	0.64
CT lung involvement (>50%)	1.211 (0.842-1.744)	0.30
NIV or HFNC before EI	0.983 (0.460-2.098)	0.96
Pulmonary embolism	1.534 (0.696-3.384)	0.28
VAP	1.118 (0.527-2.369)	0.77
Pao_2/Fio_2[b]	1.003(0.994-1.012)	0.52
C_{rs}[b]	1.011(0.948-1.078)	0.74
ΔP[b]	0.966 (0.879-1.061)	0.46
Prolonged weaning	6.579 (2.649-11.441)	< 0.01

CCI: Charlson Comorbidity Index; SAPS-3: Simplified Acute Physiologic Score 3; NIV: noninvasive ventilation; HFNC: high-flow nasal cannula; EI: endotracheal intubation; VAP: ventilator-associated pneumonia; C_{rs}: respiratory system compliance; and ΔP: driving pressure. [a]The entire sample is included except for the no weaning group. [b]It represents the worst value within the first 7 days on invasive mechanical ventilation.

pandemic to assess the severity of COVID-19, identify complications, and predict disease progression in severe cases.[26] Greater pulmonary involvement, as observed on chest CT, directly impacts on pulmonary function and dyspnea scores.[27] Consistently with our cohort, Maes et al.[27] found that patients with more severe involvement on chest CT images tended to be older and had a higher incidence of comorbidities. Understanding this association has important clinical implications. It highlights the importance of considering the extent of lung involvement identified on chest CT when evaluating patients' readiness for weaning and planning appropriate management strategies. Future research should focus on investigating the specific characteristics of lung involvement on chest CT that are associated with prolonged weaning. This might help refine risk stratification and guide decisions regarding the timing and intensity of interventions during the weaning process.

Finally, our study revealed that prolonged weaning patients have a higher incidence of complications, mainly VAP. Although the association between VAP and mortality in COVID-19 is well known,[27,28] our study did not directly indicate a significant impact of VAP on mortality outcomes. However, it is important to acknowledge that VAP can lead to complications and prolong recovery, potentially contributing to delayed weaning.[28]

In contrast, our findings identified prolonged weaning as an independent factor associated with poor prognosis, influenced by a complex interplay of multiple factors affecting patient outcomes. Firstly, underlying disease severity can compromise lung function and reduce physiological reserves, making the weaning process more challenging and increasing the risk of adverse outcomes, including mortality.[29] Secondly, prolonged mechanical ventilation and immobility during critical

illness can result in muscle wasting and weakness, which can impact outcomes.[23,24] Additionally, inflammatory responses, especially in severe cases of COVID-19, can cause lung damage and hinder lung function recovery.[20,30] Persistent inflammation and unresolved pulmonary complications may delay the weaning process and contribute to an increased risk of mortality.[30]

These factors highlight the complexity of the relationship between prolonged weaning and mortality. The duration of weaning alone does not fully explain the observed outcomes. It is crucial to consider underlying disease severity, muscle weakness, and inflammation as intertwined factors that influence the impact of prolonged weaning on mortality. By understanding and addressing these factors, healthcare professionals can develop targeted interventions and optimize the management of patients undergoing the weaning process, ultimately improving patient outcomes.

Our study has several methodological limitations that should be acknowledged. Firstly, it is retrospective in nature, which may introduce biases in data collection and analysis. Secondly, the study was conducted in a single-center public service with challenges related to limited supplies and staff, potentially affecting the generalizability of the findings. Additionally, important data on the use of sedatives and incidence of delirium were not collected, which could provide further insights into the factors influencing the outcomes. Moreover, the absence of a comparison group of non-COVID-19 patients with respiratory failure limits our ability to make direct comparisons and draw conclusive interpretations. Despite all these limitations, it is important to consider that our research was carried out during the early waves of the COVID-19 pandemic in Brazil, when vaccination coverage was low and there was a presence of highly virulent SARS-CoV-2 variants. Therefore, caution should be exercised when generalizing these findings to the current context, because the dynamics of the pandemic and the availability of preventive measures and treatments may have evolved.

In conclusion, prolonged weaning is a valuable indicator for predicting mortality in critically ill COVID-19 patients. Our study identified two significant factors associated with prolonged weaning: lung involvement greater than 50% on chest CT and delay in performing the first SA after EI. Addressing the prolonged duration of mechanical ventilation and optimizing the timing of SA are crucial steps towards improving the weaning process and ultimately enhancing patient outcomes. Future research should focus on developing strategies that promote early awakening, minimize sedation duration, and streamline the weaning process for critically ill patients with COVID-19.

AUTHOR CONTRIBUTIONS

MMM, BVP, and OSB: study design. MMM and FF: data collection. MMM, BVP, and RPR: statistical analysis. MMM, RPR, LDC, and DSAP: drafting of the manuscript. RPR, JSOA, and FRM: critical review of the manuscript. All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Cultural adaptation and validation of the Brazilian Portuguese version of the PROactive Physical Activity in COPD–clinical visit instrument for individuals with COPD

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ABSTRACT

Objective: To adapt the PROactive Physical Activity in COPD–clinical visit (C-PPAC) instrument to the cultural setting in Brazil and to determine the criterion validity, test-retest reliability agreement, and internal consistency of this version. **Methods:** A protocol for cultural adaptation and validation was provided by the authors of the original instrument and, together with another guideline, was applied in a Portuguese-language version developed by a partner research group from Portugal. The adapted Brazilian Portuguese version was then cross-sectionally administered twice within a seven-day interval to 30 individuals with COPD (57% were men; mean age was 69 ± 6 years; and mean FEV_1 was 53 ± 18% of predicted) to evaluate internal consistency and test-retest reliability. Participants also completed the International Physical Activity Questionnaire (IPAQ), the modified Medical Research Council scale, the COPD Assessment Test, and Saint George's Respiratory Questionnaire to evaluate criterion validity. **Results:** The C-PPAC instrument showed good internal consistency and excellent test-retest reliability: "amount" domain = 0.87 (95% CI, 0.73-0.94) and "difficulty" domain = 0.90 (95% CI, 0.76-0.96). Bland & Altman plots, together with high Lin's concordance correlation coefficients, reinforced that agreement. Criterion validity showed moderate-to-strong correlations of the C-PPAC with all of the other instruments evaluated, especially with the IPAQ (rho = −0.63). **Conclusions:** The Brazilian Portuguese version of the C-PPAC is a reliable and valid instrument for evaluating the experience of Brazilian individuals with COPD with their physical activity in daily life.

Keywords: Pulmonary disease, chronic obstructive; Validation study; Activities of daily living; Psychometrics.

INTRODUCTION

Individuals with COPD have lower levels of physical activities (PAs) in daily life as compared to healthy older people,[1-4] and this reduction is associated with a higher risk of exacerbations and mortality.[5-7] In order to be able to evaluate and tackle reduced levels of PA in individuals, the use of validated instruments to quantify such levels is vital. In general, for the objective assessment of the amount of PA performed on a daily basis, PA monitors are considered more accurate than are questionnaire-based self-reported PA.[8-10] Yet, PA monitors do not capture other important PA dimensions, such as the difficulties experienced when being active and how individuals with COPD adapt or modify their activities. This concerns the particular and self-reported view of the patient (usually through standardized questionnaires) about his/her difficulty in performing PAs. This is a relevant aspect, because the adequate representation of how the patient perceives the practice of PAs should cover different dimensions that influence that performance. Therefore, quantity and difficulty are two different but

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complementary approaches for the evaluation of PA because they respectively capture the objective aspect of the amount of PA performed and the subjective difficulty in performing these activities.[11,12]

The PROactive Physical Activity in COPD (PPAC) is an innovative hybrid instrument that integrates the dimensions of PA that people with COPD consider important in two domains: amount and difficulty.[12,13] The "amount" domain integrates information obtained from an activity monitor (objective amount and intensity) and self-reported items, whereas the "difficulty" domain relies on self-report only. Two applications have been developed for the PPAC instrument, that is, one to be used during clinical visits (C-PPAC), with a seven-day recall period, and one to be completed on a daily basis (D-PPAC). The C-PPAC instrument in particular is more applicable for use in routine clinical practice. The PPAC instruments were originally published in English and were carefully planned and developed based on a modern conceptual model, using qualitative input from several European COPD populations.[11,12] These instruments were subsequently translated into several languages using a culturally-sensitive translation methodology, including be4ing translated into Portuguese by a research group from Portugal, which is a partner of the present group. However, the PPAC has yet to have a validated Brazilian Portuguese version. For its reliable use, the instrument needs adaptation and adequate investigation of its metric properties. Therefore, with the permission of the original instrument development team and the research group from Portugal, this study aimed to adapt the self-reported items of the C-PPAC to the cultural setting in Brazil and to determine the test-retest reliability, agreement, internal consistency, and criterion validity of the Brazilian Portuguese version of the instrument. We decided to focus on the clinic visit version of the PPAC only since we were not planning to use the D-PPAC as part of our routine COPD care.

METHODS

Study design and ethics

This was a cross-sectional study involving the cultural adaptation and validation of the Brazilian Portuguese version of the C-PPAC instrument, following the protocol indicated by the original authors of the instrument in English. The guidelines by Beaton et al.[14] were also considered in the cross-cultural adaptation process. The study was approved by the Research Ethics Committee of the State University of Londrina (Protocol no. 36966920.7.0000.5231). Of note, the original authors fully agreed to the cultural adaptation of the C-PPAC with no similar process regarding the D-PPAC at that moment and to the cultural adaptation not from the original instrument in English but from the adapted Portuguese-language version developed in Portugal. An informed consent form, explaining the ethical and legal aspects of the research, was signed by all participants before starting data collection.

The PPAC instrument

The PPAC[12] is an instrument for the hybrid evaluation of PA experience in daily life (i.e., subjective assessment plus objective quantification). Its clinical-visit version (C-PPAC) consists of two items derived from a validated activity monitor (steps and vector magnitude units converted into an item score) and 12 questions addressing the experienced amount of PA within the last seven days, as well as the difficulties in performing PAs. All of the questions are scored from zero to four, except for the first question, whose score ranges from zero to three. The first 2 questions compose the "amount of PA" domain, together with two separate self-reported items (at the end of the instrument) which complement the items extracted from the PA assessment using PA monitors worn during the week preceding the instrument application, which runs in parallel with the recall period for the questions. In the original study, the use of one of two PA monitors was recommended: ActiGraph wGT3X (ActiGraph, Pensacola, FL, USA) or DynaPort Activity Monitor (McRoberts, the Hague, the Netherlands).[12] The former was used in the present study by all subjects for one week (additional information on the C-PPAC and its scoring characteristics are provided in the methods section in the supplementary material). Despite the fact that the PA monitors were worn for one week by all subjects, the present study focused primarily on the validation of the questions of the instrument (i.e., the 10 questions about "experienced difficulty" and the 2 questions about "experienced amount"), although the validity of the total score and each specific domain (amount and difficulty) were also studied based on the assessment with the full instrument. In general, it is encouraged that these scores be summed up to compose the total score for the full administration of the instrument.

Cultural adaptation for the Brazilian Portuguese version

Initially, the version developed by the research group from Portugal (already translated into Portuguese and in the process of validation in that country) was adapted for Brazilian Portuguese by a panel of five Brazilian experts (further details in the methods section in the supplementary material). The Portuguese translation of the items and instructions was discussed and modified to better fit with the Portuguese language used in Brazil until consensus was reached among the experts. Next, the Brazilian Portuguese version was presented to a group of five individuals with COPD, who were asked to indicate any words that were unclear or not reflecting lay language understood by the majority of the Brazilian population. Based on their feedback, the adaptation of the C-PPAC questionnaire was further modified by the expert panel and the final version was defined (Chart S1). Then, the Brazilian Portuguese translation of the instrument was back-translated into English by a qualified professional, fluent in both English and Brazilian Portuguese, and the version generated in English was sent to the original developers of the

instrument for review. Upon minor clarifications and approval by the original authors, that version was considered adequate to be integrated in the validation study (Figure S1).

No reduction of items or significant adaptations of the instrument was necessary for the process of cross-cultural adaptation and linguistic validation from the Portuguese from Portugal version to the Brazilian Portuguese version. Furthermore, there were no items with floor or ceiling effect. Only minor adaptations were made both in the patient and the evaluator guidelines and in the "thank you" text, in addition to minimal changes in the items of the instrument that were unusual in Brazilian Portuguese (Chart S2).

The Brazilian Portuguese version of the C-PPAC is available in Chart S1. For clinical use, the tool can be used by clinicians without restrictions and with no need of authorization from the original team or from the authors of the present study. For clinical studies (i.e., scientific investigations), the original authors should be contacted and approve the use of the tool. Authorization should be asked to Professor Dr. Thierry Troosters at the following e-mail: thierry.troosters@kuleuven.be.

Establishing the psychometric properties of the C-PPAC instrument—Brazilian Portuguese version

Sample and setting

Sample size calculation was performed using G*Power, version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany), and the minimum sample size was defined as 15 individuals (methods section in the supplementary material). However, aiming at reducing bias, a larger sample was included.

A convenience sample was formed by individuals followed up in projects developed in the Laboratory of Research in Respiratory Physiotherapy, linked to the State University of Londrina, in the city of Londrina, Brazil. A randomized list of eligible individuals was contacted by telephone using the number that appeared in their follow-up records in the abovementioned research laboratory, and, upon interest in participating in the study, the individuals were screened in accordance with the inclusion criteria. Inclusion criteria were as follows: diagnosis of COPD established according to the GOLD guidelines[15]; fluency in Brazilian Portuguese; clinical stability, that is, no acute exacerbation for at least one month prior to inclusion; no concomitant diagnosis of severe and/or unstable heart disease; and no neuromusculoskeletal dysfunction that could limit the performance of PA in daily life. Exclusion criteria were the occurrence of any clinical condition that could interfere with the level of daily PA (e.g., surgeries, orthopedic disorders, or neurological disorders) or the impossibility of readministering the instrument for any reason (e.g., refusal to continue participating in the study).

The individuals included received two home visits, one week apart. In each visit they completed the Brazilian Portuguese version of the C-PPAC in interview mode for test-retest purposes. In addition, only in the first visit, they completed self-reported instruments for assessment: the short-form International Physical Activity Questionnaire (IPAQ) for assessing the level of PA[16]; the modified Medical Research Council scale (mMRC) for the assessment of dyspnea[17]; the modified version of the Saint George's Respiratory Questionnaire (mSGRQ) for the assessment of health-related quality of life[18]; and the COPD Assessment Test (CAT) for assessing the health status of the participants.[19] All of these instruments have been validated for use in Brazil and were administered in an interview. The C-PPAC was administered twice to all individuals by the same evaluator. In addition to the instruments, the individuals wore the PA monitor ActiGraph wGT3X-BT (ActiGraph) for 8 h/day (agreed time) for seven consecutive days between the first and second evaluations (for more details, see the methods section in the supplementary material).

Statistical analysis

Statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). According to the Shapiro-Wilk normality test, continuous variables were expressed as mean ± standard deviation or median [interquartile range]. Categorical variables were expressed as absolute and/or relative frequency.

Cronbach's alpha coefficients were calculated for the two domains, (amount and difficulty) using the first and second assessments for the evaluation of internal consistency, and values above 0.70 were considered adequate. Likewise, the intraobserver test-retest reliability of the C-PPAC was calculated by the two-way mixed effects intraclass correlation coefficient (ICC) for test and retest, an ideal value being equal to or greater than 0.8. The test-retest agreement for the questions of the C-PPAC was studied using Bland & Altman plots and their 95% limits of agreement, as well as the Lin's concordance correlation coefficient.[20,21] Finally, the criterion validity of the C-PPAC (second visit) complete data, that is, including data from the one-week PA monitor assessment plus the self-reported items (encompassing the total score and the two domains) was evaluated by using the Spearman's correlation coefficient with the IPAQ, mMRC, CAT, and mSGRQ instruments. The interpretation of the correlations was as follows: weak: $0 < \text{rho} \leq 0.30$; moderate: $0.30 < \text{rho} \leq 0.60$; strong: $0.60 < \text{rho} \leq 0.90$; and very strong: $0.90 < \text{rho} \leq 1$.[22]

RESULTS

The convenience sample consisted of 30 individuals with COPD, 17 of whom (57%) were male, and the age range was between 57 and 88 years. The median C-PPAC score was 67 [58-78], and most participants presented with moderate-to-very-severe disease (mean FEV_1 = 53 ± 18% of the predicted values).

The general characteristics of the participants are described in Table 1.

Regarding the psychometric properties of the C-PPAC, there was excellent internal consistency (Cronbach's alpha for the "amount" and "difficulty" domains were 0.87 and 0.91, respectively) and excellent test-retest reliability, with an ICC(2,1) of 0.87 (95% CI, 0.73-0.94) and of 0.90 (95% CI, 0.76-0.96), respectively. Furthermore, good agreement between the data obtained in the first and second administration of the instrument was demonstrated by the Bland & Altman plots, with a test-retest difference of nearly zero and relatively narrow confidence intervals, with no signs of systematic errors for either domain (Figure 1). The excellent agreement between the two administrations of the C-PPAC was strengthened by the Lin's concordance correlation coefficient (Rc of 0.77 and of 0.81 for the "amount" and "difficulty" domains, respectively), with a test-retest difference of nearly zero (Figure 2). Criterion validity of the C-PPAC total score (i.e., including PA monitor data) was demonstrated by its moderate correlations with the IPAQ, CAT, and mSGRQ instruments ($p < 0.05$ for all), as well as with the mMRC scale ($p = 0.067$; Figure 3). Figures 4 and 5, respectively, show the correlations of the "amount" and "difficulty" domains of the C-PPAC instrument separated by the two domains with the other self-reported measures. The "amount" domain was moderately correlated with the IPAQ (Figure 4), whereas the "difficulty" domain was moderately to strongly correlated with the IPAQ, CAT, mMRC scale, and mSGRQ ($p < 0.05$ for all; Figure 5).

Table 1. Characteristics of the participants (N = 30).[a]

Variable	Result
Male sex	57%
Age, years	69 ± 6
BMI, kg/m^2	30 ± 14
FEV_1, L	1.47 ± 0.56
FEV_1, % predicted	53 ± 18
FEV_1/FVC, %	55 ± 14
Steps/day	4,355 ± 2,841
Time spent/day in MVPA, min/day	11 ± 14
C-PPAC	
Total score	67 [58-78]
Amount domain score	63 [45-77]
Difficulty domain score	78 [61-84]
IPAQ (1-4)	3 [2-3]
CAT (0-40)	13 [8-22]
mMRC scale (1-5)	3 [2-4]
mSGRQ (0-100)	37 [28-50]

MVPA: moderate-to-vigorous physical activity; C-PPAC: PROactive Physical Activity in COPD-clinical visit; IPAQ: International Physical Activity Questionnaire; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; mSGRQ: modified version of Saint George's Respiratory Questionnaire. [a]Values expressed as n (%), mean ± SD, or median [IQR], except where otherwise indicated.

DISCUSSION

This study provides a novel validated C-PPAC version for use in Brazil. This C-PPAC version (self-reported portion) had high Cronbach's alpha coefficients for both domains (amount and difficulty), yielding excellent internal consistency of the instrument. There was also excellent test-retest reliability and good agreement between the two administrations of the instrument, which were revealed by Bland & Altman plots and the Lin's concordance correlation coefficients. Finally, there was a moderate correlation between C-PPAC (total score) and IPAQ, defined as a validation criterion, as well as moderate correlations with CAT, mSGRQ and mMRC scale. Scores of the two specific domains were also moderately to strongly correlated with these outcome measures. These results show that, overall, the Brazilian Portuguese version of the instrument was valid and reproducible to evaluate the experience of Brazilian individuals with COPD regarding their PA in daily life.

Instruments that assess different aspects of PA in daily life have widely been used in studies involving several populations, including individuals with

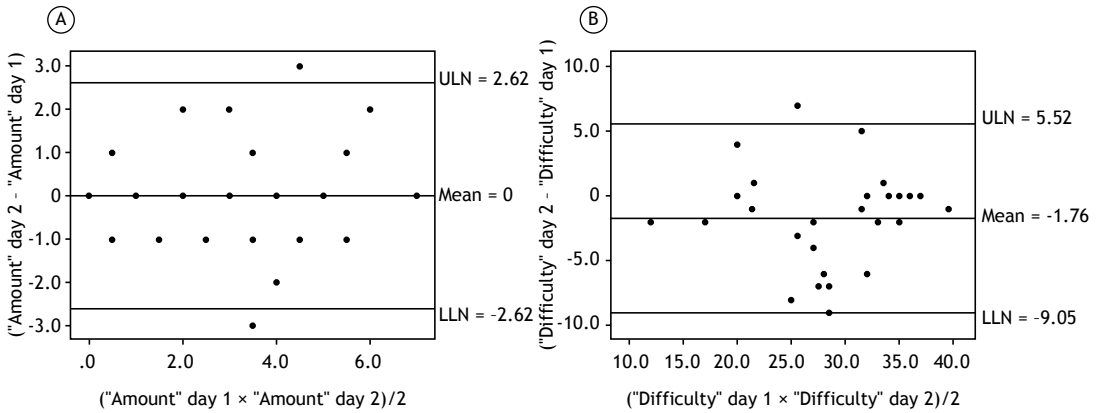

Figure 1. Bland & Altman plots comparing the first and second administration of the PROactive Physical Activity in COPD–clinical visit for the "Amount" domain (in A) and the "Difficulty" domain (in B). ULN: upper limit of normal; mean: mean difference; and LLN: lower limit of normal.

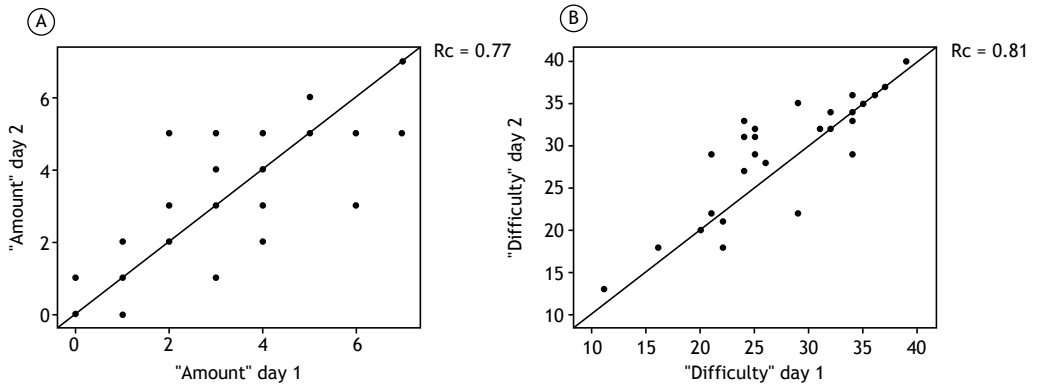

Figure 2. Plots of Lin's concordance correlation coefficient graphic dispositions between the first and second administration of the PROactive Physical Activity in COPD–clinical visit for the "Amount" domain (in A) and the "Difficulty" domain (in B).

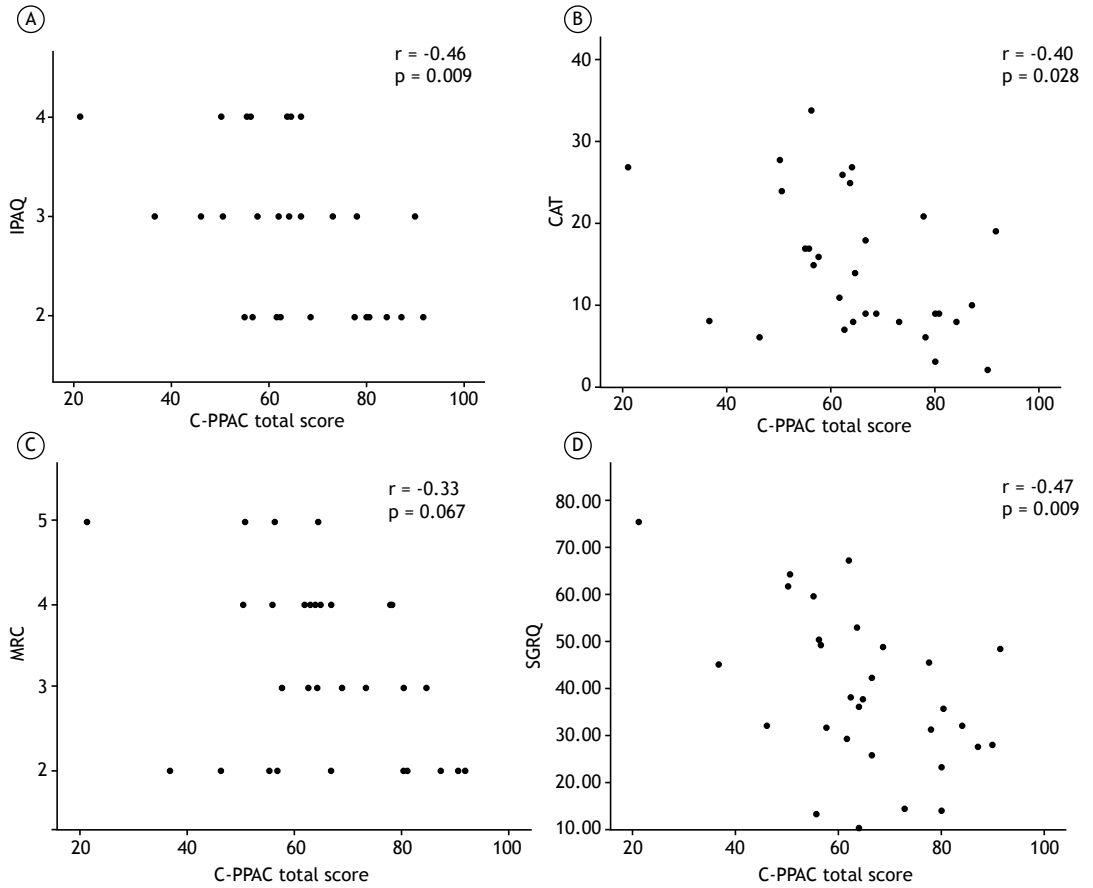

Figure 3. Correlations of the PROactive Physical Activity in COPD–clinical visit (C-PPAC) total score (i.e., including physical activity monitor data) with: A, the International Physical Activity Questionnaire (IPAQ); B, the COPD Assessment Test (CAT); C, the modified Medical Research Council (mMRC) scale; and D, the modified version of the Saint George's Respiratory Questionnaire (SGRQm).

COPD.[23,24] One of the most commonly used and cited questionnaires in the literature is the IPAQ, which provides a classification in terms of the level of PA based on international recommendations.[16] Despite the frequent use of IPAQ and other questionnaires, it is known that self-report measures are biased and not the most accurate method to quantify PA because the subjectivity of the answers makes the quantification of PA less realistic.[25] In this sense, PA monitors are more accurate and, therefore, more recommended to quantify the level of PA in daily life from a quantitative point of view. On the other hand, only quantifying PA may not fully reflect the experience that an individual has when performing such PA. PA experienced by patients includes the experienced amount as well as the experienced difficulties and adaptations needed. In

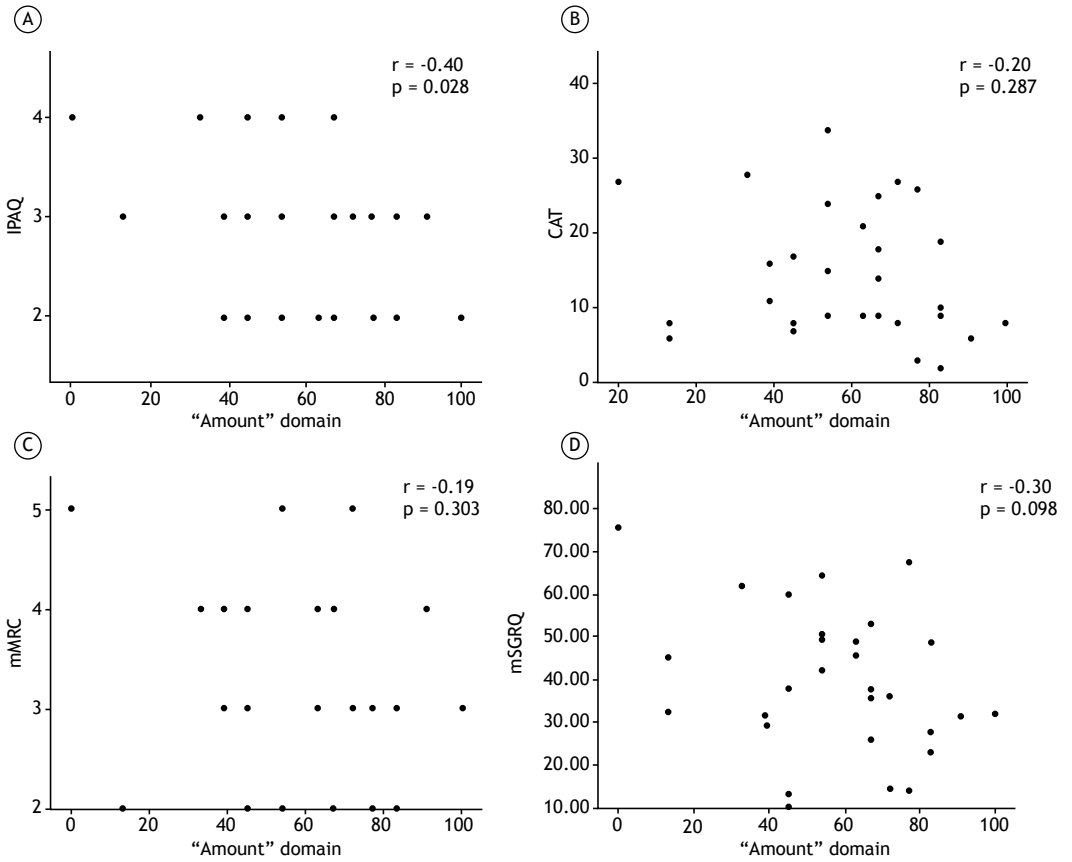

Figure 4. Correlations of the PROactive Physical Activity in COPD–clinical visit (C-PPAC) "Amount" domain (second visit) with: A, the International Physical Activity Questionnaire (IPAQ); B, the COPD Assessment Test (CAT); C, with the modified Medical Research Council (mMRC) scale; and D, the modified version of the Saint George's Respiratory Questionnaire (SGRQm).

this regard, the C-PPAC has shown to be an innovative instrument.[12] The instrument includes the use of the monitor to quantify PA in daily life broadly, as well as including items that capture the perception of patients regarding their PA. The present study did not aim to cover the validity of PA monitors in COPD since this has already been done.[8] Another advantage of the use of this instrument in individuals with COPD is that it was developed specifically for this population, in contrast to other instruments which were developed for other populations and simply validated for individuals with COPD. The items are therefore specifically tailored to individuals with COPD. Also, in the target population of the present study, individual answers spanned the complete range of answer options, showing the relevance of the questions to Brazilian patients with different COPD severity levels.

In the original C-PPAC validation studies,[12,13] strong internal consistency of the instrument was found (Cronbach's alpha coefficient > 0.9), as well as excellent test-retest reliability (ICC > 0.8), which was corroborated by the present results. Vaidya et al.[26] performed the cultural adaptation and translation of the C-PPAC into French and also showed good results (Cronbach's alpha coefficient > 0.90 and ICC ≥ 0.8). Although Brazilian individuals with COPD are known to be more active than are individuals with COPD from some other countries,[27,28] this difference did not seem to influence the performance of the C-PPAC. Of note, the present study used the same validation strategy as did the French study,[26] focusing mainly on the validation of the self-report items of the instrument.

In this study, the correlations of the C-PPAC with other criterion instruments were moderate to strong. In the study by Gimeno-Santos et al.,[12] correlation analyses were performed for each domain separately ("experienced amount" and "experienced difficulty"). For the "experienced amount" domain, there were weak to moderate correlations with the instruments used for validation, whereas for the "experienced difficulty" domain, as evaluated in the present study, there were also moderate-to-strong correlations.

It is worth remembering that the C-PPAC is a hybrid instrument,[12] in which the two dimensions complement each other. By means of the criterion validity analyses shown in Figures 3-5, we could demonstrate the ability of the C-PPAC to measure the constructs that it proposes to measure PA as a hybrid instrument. Moderate to strong correlations were observed both

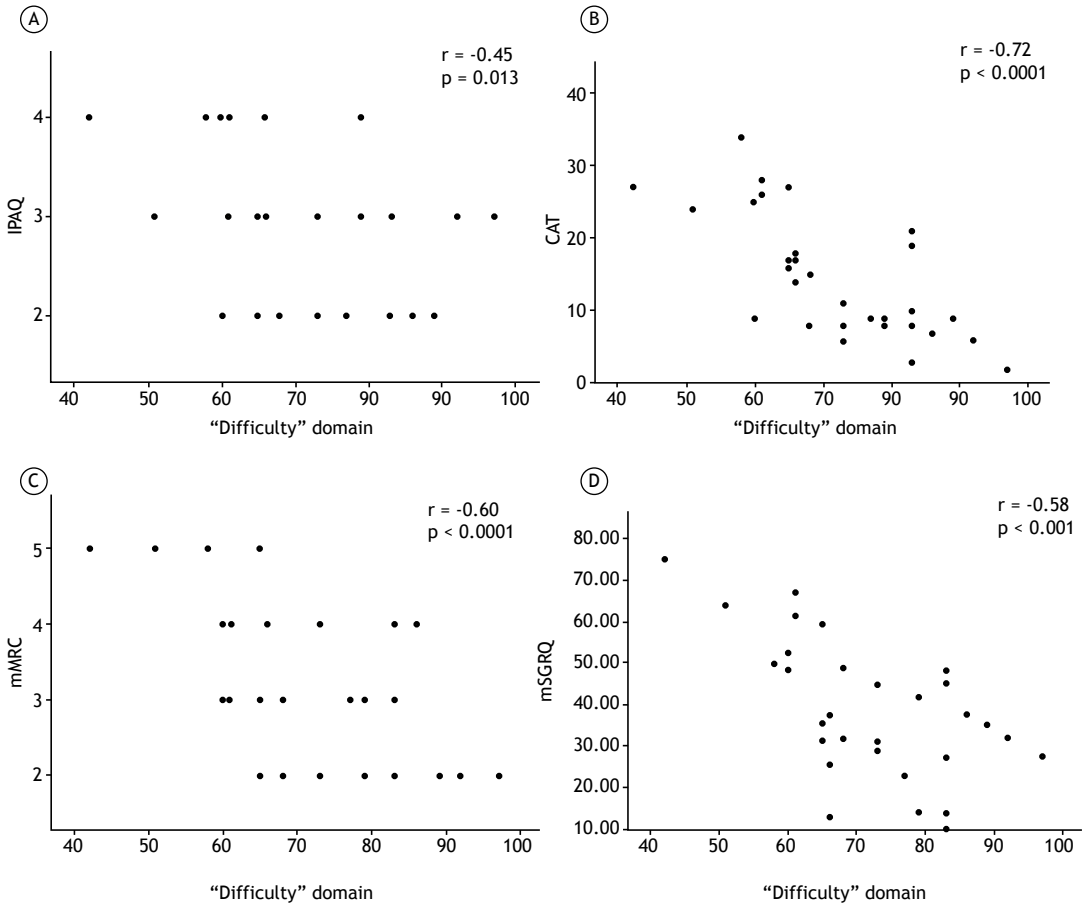

Figure 5. Correlations of the PROactive Physical Activity in COPD–clinical visit (C-PPAC) "Difficulty" domain (second visit) with: A, the International Physical Activity Questionnaire (IPAQ); B, the COPD Assessment Test (CAT); C, with the modified Medical Research Council (mMRC) scale; and D, the modified version of the Saint George's Respiratory Questionnaire (mSGRQ).

in the total score (Figure 3) and in the two domains separately (Figures 4 and 5).

The present study has some limitations: the selection of a convenience sample from a single center makes it uncertain that the sample was representative of the profile of the entire population of Brazilian individuals with COPD. However, to mitigate the selection bias, all registered individuals in the research laboratory were randomized, creating a sequence for the recruitment of participants, which was carried out consecutively. Due to the relatively small sample, it was not feasible to investigate the metric properties of the instrument in separate subgroups stratified by disease severity, although this is not necessarily a standard procedure. In this sense, future studies with larger samples may add relevant information. Additionally, further studies are needed to verify the responsiveness of the C-PPAC to interventions in individuals with COPD, in addition to confirming whether the six-point value for minimal important difference applies to the Brazilian population.[13] Furthermore, the present study focused on the C-PPAC, the most widely used of the two PROactive instruments, although future validation of the D-PPAC would be useful to provide additional insights on PA assessment in this population. Finally, the present study focused on the validation of self-reported difficulty related to PA, since the validity of the proposed PA monitors was already carefully studied and confirmed in COPD.[8] The use of PA monitors is not dependent on language adaptation; therefore, the present study enables the use of the full PROactive tool (i.e., amount [hybrid] + difficulty [self-report]) to assess Brazilian individuals with COPD by adding up the original "amount" assessment with PA monitors to this newly validated version of the self-reported "difficulty" domain.

In conclusion, according to the results of the present study, the Brazilian Portuguese version of the C-PPAC has proven to be reproducible and valid for evaluating the experience of Brazilian individuals with COPD regarding their PA in daily life.

AUTHOR CONTRIBUTIONS

AVS and ADF: study planning and design; data collection; data analysis and interpretation; and drafting of the manuscript. RCA, LCM, CAC, and KCF: data collection; and data analysis and interpretation. FR, JC, AM, CJ, HD, FD, JGA, and TT: study planning

and design; interpretation of data; and revision and approval of the final version of the manuscript. NAH: study planning and design; data collection; data analysis and interpretation; and review and approval of the final version of the manuscript. FP: study planning and design; data collection; data analysis and interpretation; drafting of the manuscript; and revision and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Factors associated with pulmonary infection in kidney and kidney-pancreas transplant recipients: a case-control study

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Study carried out at the Hospital Felício Rocho, Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: To evaluate the etiology of and factors associated with pulmonary infection in kidney and kidney-pancreas transplant recipients. **Methods:** This was a single-center case-control study conducted between December of 2017 and March of 2020 at a referral center for kidney transplantation in the city of Belo Horizonte, Brazil. The case:control ratio was 1:1.8. Cases included kidney or kidney-pancreas transplant recipients hospitalized with pulmonary infection. Controls included kidney or kidney-pancreas transplant recipients without pulmonary infection and matched to cases for sex, age group, and donor type (living or deceased). **Results:** A total of 197 patients were included in the study. Of those, 70 were cases and 127 were controls. The mean age was 55 years (for cases) and 53 years (for controls), with a predominance of males. Corticosteroid use, bronchiectasis, and being overweight were associated with pulmonary infection risk in the multivariate logistic regression model. The most common etiologic agent of infection was cytomegalovirus (in 14.3% of the cases), followed by *Mycobacterium tuberculosis* (in 10%), *Histoplasma capsulatum* (in 7.1%), and *Pseudomonas aeruginosa* (in 7.1%). **Conclusions:** Corticosteroid use, bronchiectasis, and being overweight appear to be risk factors for pulmonary infection in kidney/kidney-pancreas transplant recipients, endemic mycoses being prevalent in this population. Appropriate planning and follow-up play an important role in identifying kidney and kidney-pancreas transplant recipients at risk of pulmonary infection.

Keywords: Kidney transplantation; Immunosuppression therapy; Pneumonia.

INTRODUCTION

Over the past few years there has been an increase in the development of public health policies for solid organ transplantation in Brazil, especially kidney and kidney-pancreas transplantation. The Brazilian National Transplant System acts by coordinating and regulating the transplantation program in the country.[1] In patients with stage 5 chronic kidney disease, kidney transplantation improves quality of life and reduces mortality when compared with renal replacement therapy.[2,3] However, health complications, particularly respiratory complications, are common because of continuous immunosuppression (triple therapy with steroids, calcineurin inhibitors, and antiproliferative agents in most cases) to avoid immune rejection. Patients undergoing deceased-donor kidney transplantation have a higher risk of developing pulmonary infectious complications in the post-transplant period.[4,5]

Brazil has distinct characteristics regarding the prevalence of infections in kidney transplant recipients. This is possibly due to environmental exposure and the population profile, which is different from the population profiles in North America and Europe. Studies conducted in Brazil and investigating invasive fungal diseases have shown an increased prevalence of cryptococcosis and histoplasmosis in the country. There is currently a lack of data regarding pulmonary infectious complications in kidney transplant recipients in Brazil; the epidemiological features of pulmonary infectious complications in this population; and the relationship between infectious events and the intrinsic characteristics of this population.[4-7]

The objective of the present study was to evaluate the etiology of and factors associated with pulmonary infection in patients undergoing kidney or kidney-pancreas transplantation at a referral center for kidney transplantation in the state of Minas Gerais, Brazil.

METHODS

This was a single-center case-control study conducted between December of 2017 and March of 2020 at *Hospital Felício Rocho*, a general hospital that is a referral center for kidney transplantation in the city of Belo Horizonte, Brazil. The hospital specializes in minimally invasive and highly complex procedures such as robotic, neurological, cardiac, and transplant surgeries, and provides care to patients in the public and private health care systems.

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Cases and controls were matched for sex, age group (18-24 years, 25-34 years, 35-44 years, 45-54 years, and 55-64 years), and donor type (living or deceased). The case:control ratio was 1:1.8. Cases included kidney or kidney-pancreas transplant recipients ≥ 18 years of age hospitalized with suspected pulmonary parenchymal infection, characterized by one or more of the following: fever (body temperature > 38.0°C) or hypothermia (body temperature of < 36.0°C), acute cough, purulent sputum, chest discomfort, or dyspnea in association with pulmonary opacities of infectious etiology on chest HRCT scans or identification of infectious agents by serological methods; direct identification of infectious agents in pulmonary or lung biopsy specimens (transbronchial biopsy or surgical lung biopsy specimens); or identification of infectious agents by indirect methods, such as assays for cell-surface or cell-wall antigens and molecular biology tests. All cases were considered incident cases (i.e., new cases). Controls included kidney or kidney-pancreas transplant recipients without respiratory symptoms or pulmonary opacities of infectious etiology, having undergone transplantation within three months after the cases and being recruited in an outpatient follow-up setting.

For cases and controls, the exclusion criteria were withdrawal of participation in the study and incomplete medical records. Because of the population profile, the study sample was a convenience sample, with no sample size calculation being performed.

The following patient data were collected: age; sex; occupation; transplant type; place of residence; donor type (living or deceased); transplant date; BMI; pre-transplant dialysis duration; post-transplant antimicrobial prophylaxis; previous pulmonary infections; pre-transplant tuberculin skin test results; diagnosis of diabetes mellitus; smoking status; diagnosis of lung disease prior to transplantation; etiology of kidney disease; cardiovascular disease; current or previous neoplastic disease; recurrent urinary tract infections; immunosuppressive regimen (calcineurin inhibitors, mammalian target of rapamycin inhibitors, antiproliferative agents, and corticosteroids); cytomegalovirus infection status (in case patients); pulse therapy with methylprednisolone and/or use of antilymphocyte antibodies in the post-transplant period; and prior diagnosis of humoral or cellular rejection. In addition to the aforementioned patient data, the following chest HRCT findings were collected: ground-glass opacities, consolidation, pleural effusion, nodules/micronodules, and cavitation.

BAL and transbronchial biopsy were performed by fiberoptic bronchoscopy. BAL fluid and transbronchial biopsy samples underwent the following: Gram staining; total and differential cell counts; cytometry; bacterial culture; antimicrobial susceptibility testing; microscopy for *Pneumocystis jirovecii*; and sputum smear microscopy for AFB, fungi, and parasites. Cultures for mycobacteria and fungi were also performed, as were detection of galactomannan in BAL fluid and PCR for cytomegalovirus. All transbronchial biopsy samples underwent pathological examination for identification of etiologic agents.

Surgical lung biopsy by video-assisted thoracoscopy under general anesthesia was considered in cases in which the etiologic agent could not be identified. All decisions regarding the diagnostic workup and treatment of the patients included in the present study were made by the team of attending physicians.

Ethical aspects

All of the study participants gave written informed consent. The study project was approved by the Research Ethics Committees of the *Hospital Felício Rocho* Health Sciences Center and the Federal University of Minas Gerais (CAAE no. 88306218.5.0000.5125). All patients were treated in accordance with current guidelines for the management of infectious diseases.

Statistical analysis

Data were presented as absolute and relative frequencies, and as mean ± standard deviation or median (interquartile range) for quantitative variables, which were tested for normality by means of the Kolmogorov-Smirnov test. Variables with a non-normal distribution were compared by means of the Mann-Whitney test, and variables with normal distribution were compared by means of the Student's t-test. In order to compare independent categorical variables and to assess associations between qualitative variables, the nonparametric chi-square test was used. Fisher's exact test was used for variables with a value of less than five. All of the variables showing $p < 0.20$ in the univariate analysis were included in the stepwise multivariate logistic regression model. For all tests, the level of significance was set at a two-sided value of $p \leq 0.05$. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 197 patients were included in the present study. Of those, 70 were included as cases and 127 were included as controls. Table 1 shows the main characteristics of the study population.

Cases and controls were similar in terms of the proportions of respiratory comorbidities, cardiovascular comorbidities, neoplasms, and recurrent urinary tract infections. The BMI was significantly lower in cases than in controls ($p = 0.013$). As can be seen in Table 1, bronchiectasis was the only comorbidity that was significantly more prevalent in cases than in controls (12.9% vs. 2.4%; OR = 6.1; 95% CI, 1.6-23.2; $p = 0.003$). With regard to the use of immunosuppressants, there were no significant differences between cases and controls, the exception being corticosteroid use, which was significantly more common in cases than in controls (95.7% vs. 83.7%; OR = 4.4; 95% CI, 1.3-15.4; $p = 0.012$). As can be seen in Table 2, there was no significant difference between the two groups

of patients regarding the use of other drugs for organ rejection prevention.

The variables age, BMI, smoking, calcineurin inhibitors, corticosteroids, methylprednisolone, use of antilymphocyte antibodies, and bronchiectasis were included in the multivariate logistic regression model (Table 3). In the final model, the variables BMI, use of corticosteroids, and bronchiectasis had a joint effect with the outcome of respiratory infection. An overweight individual was found to be 2.21 times more likely to have a respiratory infection than an individual with a normal BMI. An individual who used corticosteroids was found to be 4.22 times more likely to have a respiratory infection than an individual who did not. An individual with bronchiectasis was found to be 7.01 times more likely to have a respiratory infection than an individual without it.

As can be seen in Table 4, the most common etiologic agent of infection was cytomegalovirus (in 14.3% of the cases), followed by *Mycobacterium tuberculosis* (in 10%), *Histoplasma capsulatum* (in 7.1%), and *Pseudomonas aeruginosa* (in 7.1%). The etiologic agent remained unidentified in one third of the cases. As can be seen in Table 5, the most common chest HRCT findings were ground-glass opacities (in 50% of the cases), followed by consolidation (in 48.6%) and nodules (in 45.7%).

DISCUSSION

This was a single-center case-control study including 70 cases and 127 controls and conducted between December of 2017 and March of 2020. Cases and controls were matched for demographic variables related to the post-transplant period. All comparisons were homogeneous and included age and mean dialysis duration in the pre-transplant period. With regard to general characteristics, males predominated in both groups, a finding that is consistent with those of a meta-analysis conducted in Brazil and investigating patients with stage 5 chronic kidney disease.[8] When the etiology cannot be determined by accurate methods, diagnosis is commonly delayed.[9,10]

The variables age, BMI, smoking, calcineurin inhibitors, corticosteroids, methylprednisolone, use

Table 1. General characteristics of cases and controls, as well as comorbidities found in both groups.[a]

Variable	Group			OR	95% CI	p
	Case (n = 70)	Control (n = 127)	Total (N = 197)			
Age, years	55 (44-63)	53 (43-59)				0.139*
Pre-transplant dialysis duration, months	60 (19.5-84)	44.5 (32-72)				0.846*
Sex						
Female	28 (40%)	46 (36.2%)	74 (37.6%)			0.600**
Male	42 (60%)	81 (63.8%)	123 (62.4%)			
BMI						
Underweight	10 (14.3%)	5 (3.9%)	15 (7.6%)	0.52	0.27-0.98	0.013**
Normal	40 (57.1%)	62 (48.8%)	102 (51.8%)			
Overweight	14 (20%)	41 (32.3%)	55 (27.9%)			
Obese	6 (8.6%)	19 (15%)	25 (12.7%)			
Transplant type						
Kidney	63	113	176			
Kidney-pancreas	7	14	21			
Donor type						
Deceased	56 (80%)	107 (84.3%)	163 (82.7%)			0.575**
Living	14 (20%)	20 (15.8%)	34 (17.3%)			
Smoking	21 (30%)	24 (18.9%)	45 (22.8%)			0.076**
Comorbidities						
COPD	2 (2.9%)	1 (0.8%)	3 (1.5%)			0.256**
Bronchiectasis	9 (12.9%)	3 (2.4%)	12 (6.1%)	6.1	1.6-23.2	0.003**
Pulmonary arterial hypertension	2 (2.9%)	3 (2.4%)	5 (2.5%)			1.000**
Asthma	3 (4.3%)	4 (3.1%)	7 (3.6%)			0.701**
Diabetes mellitus	25 (35.7%)	55 (43.3%)	80 (40.6%)			0.299*
Hypertension	55 (78.6%)	106 (83.5%)	161 (81.7%)			0.395*
Coronary artery disease	7 (10%)	12 (9.4%)	19 (9.6%)			0.900*
Heart failure	11 (15.7%)	19 (15%)	30 (15.2%)			0.888*
Dyslipidemia	20 (28.6%)	43 (33.9%)	63 (32%)			0.466
Cancer	5 (7.1%)	9 (7.1%)	14 (7.1%)			1.000*
Recurrent urinary tract infection	11 (15.7%)	17 (13.4%)	28 (14.2%)			0.654**

[a]Data presented as n, n (%), or median (IQR). *Chi-square test. **Fisher's exact test.

Table 2. Immunosuppressants and pulse therapy used in cases and controls.[a]

Variable	Group		Total	OR	95% CI	p*
	Case (n = 70)	Control (n = 127)	(N = 197)			
Calcineurin inhibitors						
No	16 (22.9%)	18 (14.2%)	34 (17.3%)			
Yes	54 (77.1%)	109 (85.8%)	163 (82.7%)			0.123
Antiproliferative agents						
No	10 (14.3%)	21 (16.5%)	31 (15.7%)			
Yes	60 (85.7%)	106 (83.5%)	166 (84.3%)			0.678
Corticosteroids						
No	3 (4.3%)	21 (16.5%)	24 (12.2%)			
Yes	67 (95.7%)	106 (83.5%)	173 (87.8%)	4.4	1.3-15.4	0.012
Inhibitors of mTOR						
No	52 (74.3%)	94 (74%)	146 (74.1%)			
Yes	18 (25.7%)	33 (26%)	51 (25.9%)			0.967
Pulse therapy with methylprednisolone						
No	59 (84.3%)	116 (91.3%)	175 (88.8%)			
Yes	11 (15.7%)	11 (8.7%)	22 (11.2%)			0.158
Use of antilymphocyte antibodies						
No	63 (90%)	123 (96.9%)	186 (94.4%)			
Yes	7 (10%)	4 (3.1%)	11 (5.6%)			0.056

mTOR: mammalian target of rapamycin. [a]Data presented as n (%). *Chi-square test.

Table 3. Final multivariate logistic regression model for the respiratory infection outcome.*

Variable	β	SE	Wald	df	p	OR	95% CI	
							Lower	Higher
Corticosteroids	1.439	0.667	4.652	1	0.031	4.22	1.14	15.60
Bronchiectasis	1.947	0.717	7.380	1	0.007	7.01	1.72	28.56
BMI								
Normal			9.253	2	0.010			
Underweight	−0.884	0.600	2.170	1	0.141	0.41	0.13	1.34
Overweight	0.791	0.347	5.199	1	0.023	2.21	1.12	4.35

of antilymphocyte antibodies, and bronchiectasis showed $p < 0.20$ in the univariate analysis and were therefore included in the multivariate logistic regression model, which showed that BMI, corticosteroid use for immunosuppression, bronchiectasis, and being overweight were risk factors for pulmonary infection in kidney/kidney-pancreas transplant recipients, having a joint effect with the outcome of respiratory infection.

With regard to nutritional status (as assessed by the BMI), an overweight individual was found to be 2.21 times more likely to have a respiratory infection than an individual with a normal BMI. Studies examining the negative impact of poor nutrition on the risk of infection have shown that immune disorders such as leukopenia and decreased CD4+ lymphocyte count and antibodies directed to opsonization of encapsulated bacteria can increase the risk of infections.[11,12]

With regard to donor type, there was no significant difference between cases and controls, deceased donors having predominated. In a previously published meta-analysis, receiving a transplant from a deceased donor was found to be an independent risk factor for pulmonary infection in cases of prolonged organ ischemia.[12] In the present study, corticosteroid use was associated with pulmonary infection occurrence. Our multivariate logistic regression model showed that individuals using corticosteroids were 4.22 times more likely to have a respiratory infection. No positive association was found between the use of antilymphocyte antibodies and pulmonary infections ($p = 0.056$). This is probably due to the size of the study sample. In any case, the use of polyclonal antibodies against human lymphoid tissue in pulse therapy regimens for acute rejection must be highlighted, because of lymphopenia in the spleen and thymus.[13-16]

Corticosteroids have numerous therapeutic effects, part of them not yet understood, which involve blocking the expression of genes responsible for cytokine synthesis (IL-1, IL-2, IL-3, IL-6, and TNF-α).[14-16] In general terms, the use of corticosteroids in kidney transplant recipients may be associated with a higher risk of complications of an infectious nature. Nonetheless, it is of note that ours is a peculiar study population and this was a single-center study, the number of cases therefore being limited. In addition, we were unable to determine the mean dose of corticosteroids used

Table 4. Etiologic agents of infection in case patients (n = 70).

Etiologic agent	n (%)
Aspergillus fumigatus	2 (2.9)
Gram-negative bacilli	2 (2.9)
Cytomegalovirus	10 (14.3)
Gram-positive cocci in pairs	1 (1.4)
Cryptococcus neoformans	3 (4.3)
Eikenella corrodens	1 (1.4)
Enterobacter cloacae	1 (1.4)
Escherichia coli	1 (1.4)
Histoplasma capsulatum	5 (7.1)
Influenza virus	1 (1.4)
Klebsiella pneumoniae	1 (1.4)
Klebsiella pneumoniae/*Moraxella catarrhalis*	1 (1.4)
Leishmania braziliensis	1 (1.4)
Mycobacterium tuberculosis	7 (10)
Unidentified	21 (30)
Paracoccidioides brasiliensis	3 (4.3)
Pneumocystis jirovecii	2 (2.9)
Pseudomonas aeruginosa	5 (7.1)
Streptococcus agalactiae/*Pseudomonas aeruginosa*	1 (1.4)
Streptococcus pneumoniae	1 (1.4)
Total	70 (100)

Table 5. Chest HRCT findings in case patients (n = 70).

Chest HRCT finding	n (%)
Ground-glass opacities	35 (50)
Nodules	32 (45.7)
Cavitation	7 (10)
Consolidation	34 (48.6)
Pleural effusion	11 (15.7)

by the patients. The use of lower doses (2.5-5 mg/day) could reduce undesirable side effects and not increase the immunological risk.[17]

Of the comorbidities evaluated in this study, only bronchiectasis was associated with the occurrence of infection. Our multivariate logistic regression model showed that an individual with bronchiectasis was 7.01 times more likely to have a respiratory infection. Bronchiectasis is a chronic respiratory disease whose clinical manifestations include cough, sputum production, and bronchial infections, and whose radiological features include abnormal and permanent dilation of the bronchi. This means that bronchiectasis is a structural lung disease in which recurrent bronchopulmonary infections constitute the main complication. This can explain the association between bronchiectasis and immunosuppression as a risk factor for respiratory infections.[18,19]

With regard to chest HRCT findings, ground-glass opacities predominated in the case patients in the present study, being found in approximately 50%. The differential diagnosis is extensive, requiring an in-depth knowledge of the patient history of diseases and patient immunosuppression status, and can be closely associated with infectious conditions.[20-22] With regard to the etiologic agents of infection, fungal agents were highly prevalent in the study population, being found in 21.4%. Cytomegalovirus was also prevalent, being found in 14.3%. These findings reinforce the need for an etiologic diagnosis for optimal clinical outcomes in this group of patients.

The present study has limitations. First, it was a single-center study, meaning that the number of case patients was limited. Second, regional differences could prevent the generalization of the results. Third, information regarding patient exposure and identified etiologic factors was obtained after the infection, being the main limiting factor of the study.

The present study is unique in the regional context, involving a population of kidney/kidney-pancreas transplant recipients with respiratory infections. The study can contribute to improving early identification of kidney and kidney-pancreas transplant recipients especially susceptible to lower respiratory tract infections.

AUTHOR CONTRIBUTIONS

LMF, VN, and RAC: study design; data analysis; and reviewing of the manuscript. LROG and CMS: data analysis and reviewing of the manuscript. ADS, DRE, and BPP: reviewing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Follow-up of patients diagnosed with and treated for tuberculosis in Brazil: financial burden on the household

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ABSTRACT

Objective: To evaluate the implications of the proportion of annual family income spent in the pre- and post-diagnosis periods in tuberculosis patients followed for after at least one year after completing tuberculosis treatment in Brazil. **Methods:** This was a cross-sectional study of tuberculosis patients followed for at least one year after completing tuberculosis treatment in five Brazilian capitals (one in each region of the country). **Results:** A total of 62 patients were included in the analysis. The overall average cost of tuberculosis was 283.84 Brazilian reals (R$) in the pre-diagnosis period and R$4,161.86 in the post-diagnosis period. After the costs of tuberculosis disease, 71% of the patients became unemployed, with an overall increase in unemployment; in addition, the number of patients living in nonpoverty decreased by 5%, the number of patients living in poverty increased by 6%, and the number of patients living in extreme poverty increased by 5%. The largest proportion of annual household income to cover the total costs of tuberculosis was for the extremely poor (i.e., 40.37% vs. 11.43% for the less poor). **Conclusions:** Policies to mitigate catastrophic costs should include interventions planned by the health care system and social protection measures for tuberculosis patients with lower incomes in order to eliminate the global tuberculosis epidemic by 2035—a WHO goal in line with the United Nations Sustainable Development Goals.

Keywords: Tuberculosis/diagnosis; Tuberculosis/therapy; Costs and cost analysis; Financial stress; Brazil.

INTRODUCTION

Tuberculosis is an infectious disease that remains a major public health problem worldwide. It is one of the ten leading causes of death in the world[1] and can represent a significant financial burden because of the costs of diagnosis[2] and treatment (direct and indirect costs), exacerbating poverty.[3-5] In 2021, the WHO estimated that approximately 10.6 million new tuberculosis cases and 1.6 million tuberculosis deaths occurred worldwide.[1] The 2022 WHO Global Tuberculosis Report[1] showed that access to health services remains a challenge and that the global goals of prevention, diagnosis, and treatment agreed upon in the historic United Nations General Assembly session in September of 2018 will only be achieved through a multisectoral approach addressing the broader determinants of the tuberculosis epidemic and its socioeconomic impact. An estimated 5.4 billion U.S. dollars (US$) were spent on tuberculosis diagnosis, treatment, and prevention in low- and middle-income countries in 2021. This was slightly less than the US$5.5 billion spent in 2020 and down 10% less than the US$6.0 billion spent in 2019. The US$5.4 billion spent in 2021 represents less than 50% of the United Nation's global target of spending at least US$13 billion annually by 2022.[1]

Brazil remains among the 30 countries with the highest burden of tuberculosis and tuberculosis/HIV coinfection,

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being considered a priority for disease control in the world by the WHO.[1] There were 68,271 new tuberculosis cases in Brazil in 2021, with an incidence rate of 32 cases per 100,000 population. In 2020, approximately 4,543 tuberculosis deaths were reported, with a mortality rate of 2.1 deaths per 100,000 population.[6] Geographic, social, cultural, and economic barriers to accessing tuberculosis treatment and poverty are major factors contributing to this situation and pose challenges to tuberculosis management.[1] In developing countries, such as Brazil, tuberculosis has increased poverty for underprivileged populations because of the costs of diagnosis and treatment, resulting in work absenteeism, unemployment, sequelae, and death.

The WHO has proposed a new strategy to eliminate tuberculosis worldwide through three high-level indicators. The strategy includes targets for major reductions in tuberculosis incidence, tuberculosis deaths, and costs faced by tuberculosis patients and their families between 2015 and 2035.[1,7]

Although the *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System) was built on the principles of universality, comprehensiveness, and equity,[8] it is the patient who bears the costs involved in the diagnosis and management of tuberculosis. This can aggravate the economic burden on patients and their families and lead to impoverishment[9] as a result of direct costs and reduced income.

A conceptual framework of the financial burden of tuberculosis for the patient/household is shown in Figure 1. The household is the preferred unit of analysis in the evaluation of costs because all treatment-related decisions are made by the family on the basis of the household budget.[10] In response to the first perceived symptoms of the disease in the pre-diagnosis period (Figure 1), decisions are made regarding the search for the first health service for diagnosis. The health care system is an out-of-home resource that will be sought by the family and will provide access to the diagnosis of the disease and quality of care in the post-diagnosis period (Figure 1). Illness costs are classified into direct and indirect, and will depend on the type and severity of the illness and on the health service characteristics that influence access and quality of care (Figure 1). The costs of illness can lead to an impact on income, and, when they exceed the monthly household income, they can trigger coping strategies such as loans and asset sales (Figure 1). The cost burden corresponds to

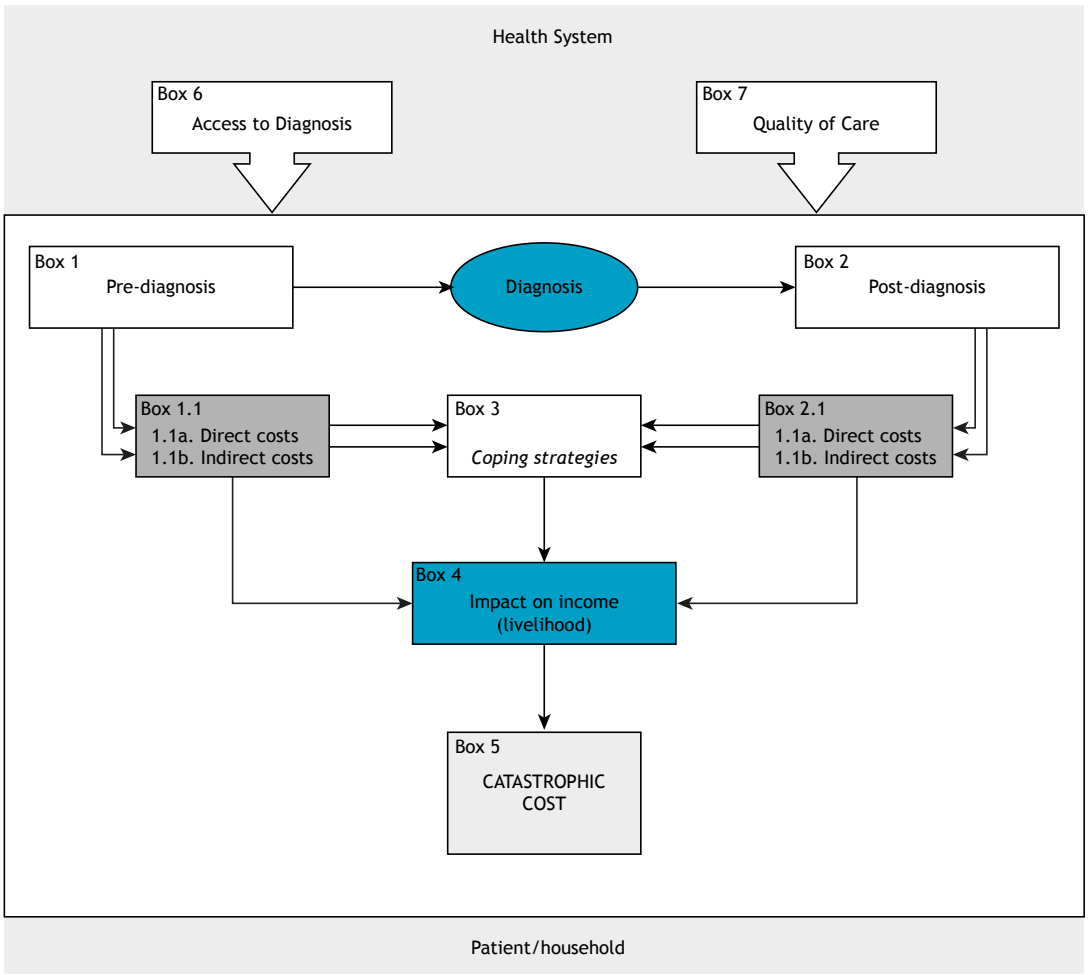

Figure 1. Conceptual framework for analysis of the economic burden of tuberculosis on the patient/household.

the sum of the direct and indirect costs expressed as a percentage of the annual household income; when higher than 20%, it can result in catastrophic costs (Figure 1),[7] which will likely force family members to cuts in consumption of basic necessities, the sale of assets, high levels of debt, and impoverishment.

In this context, the objective of the present study was to evaluate the implications of the proportion of annual family income spent in the pre- and post-diagnosis periods in tuberculosis patients followed for at least one year after completing tuberculosis treatment in Brazil.

METHODS

In each of the five regions of Brazil, we selected a capital that is a priority city for tuberculosis control because of the high rates of new cases of tuberculosis: the city of Vitória, in the state of Espírito Santo, in southeastern Brazil; the city of Campo Grande, in the state of Mato Grosso do Sul, in central-western Brazil; the city of Recife, in the state of Pernambuco, in northeastern Brazil; the city of Porto Alegre, in the state of Rio Grande do Sul, in southern Brazil; and the city of Manaus, in the state of Amazonas, in northern Brazil. We selected a total of 14 health care facilities distributed among the five capitals and providing tuberculosis treatment in accordance with the Brazilian National Ministry of Health guidelines.

We performed a cross-sectional study of prospective data collected by interviewing tuberculosis patients enrolled in the *Programa Nacional de Controle da Tuberculose* (PNCT, Brazilian National Tuberculosis Control Program). The patients were interviewed at least one year after having completed the treatment of tuberculosis in one of the 14 health care facilities selected for inclusion in the study.

The study was approved by the Human Research Ethics Committee of the *Centro de Ciências da Saúde da Universidade Federal do Espírito Santo*, located in the city of Vitória, Brazil (Ruling no. 3.412.838, issued on June 25, 2019; Protocol no. 61080416.7.0000.5060).

The study population consisted of patients who had pulmonary or extrapulmonary tuberculosis and who were consecutively treated in any of the 14 selected health care facilities between June of 2016 and July of 2018. The sample size was calculated on the basis of a previous study,[11] being estimated at 362 participants. The inclusion criteria were as follows: being ≥ 18 years of age; and having completed tuberculosis treatment at least one year prior in any of the 14 selected health care facilities. Data were collected through face-to-face interviews performed between July of 2019 and July of 2021.

The Portuguese version of the WHO Tool to Estimate Patients' Costs, cross-culturally adapted to the needs of the SUS,[12] was used in order to estimate the costs of tuberculosis patients.

All costs were calculated for the period between the onset of reported symptoms and completion of 6-8 months of treatment. All costs related to the pre- and post-diagnosis periods were estimated in Brazilian reals (R$), on the basis of the mean exchange rate for 2016 (i.e., US$1.00 = R$3.4901).[13] Direct medical costs included all of the expenses incurred by the patient as a result of tuberculosis disease, including tests, medications, follow-up, and hospitalization. Direct nonmedical costs included all of the expenses incurred by the tuberculosis patient for transportation to health care facilities, food purchased during the waiting time in the health care facility, and accommodation, as well as administrative expenses and special food costs. These costs were assessed for the patients and their caregivers. Indirect costs included absenteeism from work because of visits to health care facilities or hospitalization and loss of wages because of tuberculosis-related work disability. To quantify the magnitude of the loss of income, the number of days absent from work was multiplied by the estimated daily income of the patient or caregiver. These costs were assessed for the patients and their caregivers. The total costs included all direct and indirect costs incurred in the pre- and post-diagnosis periods.

The WHO definition of catastrophic costs[9,14-16]—total costs (i.e., the sum of direct medical costs, direct nonmedical costs, and indirect costs) greater than 20% of the household's annual income (monthly family income multiplied by 12)—was used in order to estimate the proportion of the sample that experienced catastrophic costs associated with tuberculosis. The total catastrophic cost approach emphasizes the impact of lost revenue through overall indirect costs and also provides a clearer description of the severity of the financial impact.[17]

The statistical analysis was performed with the Stata statistical software package, version 14.0 (StataCorp LLC, College Station, TX, USA). The poverty level was classified in accordance with the World Bank guidelines, which establish extreme poverty for residents with a per capita income of less than 1/4 the minimum wage; poverty for residents with a per capita income of less than 1/2 the minimum wage; and nonpoverty for residents with a per capita income of more than 1/2 the minimum wage.[18]

RESULTS

Of the 362 patients who were eligible for interview, only 62 (42 men and 20 women; 17.12%) were included in the analysis. Of those, 4 were followed in the city of Vitória, 12 were followed in the city of Campo Grande, 12 were followed in the city of Recife, 16 were followed in the city of Porto Alegre, and 18 were followed in the city of Manaus. Figure 2 shows a flow chart of the study population.

Of the 62 patients included in the analysis, 27 (43.5%) were in the 46- to 65-year age bracket (mean age, 58.91 ± 7.42 years), 42 (68%) were male, 35 (56%) had had more than eight years of schooling, 44 (71%) were unemployed, 22 (35.5%) became unemployed

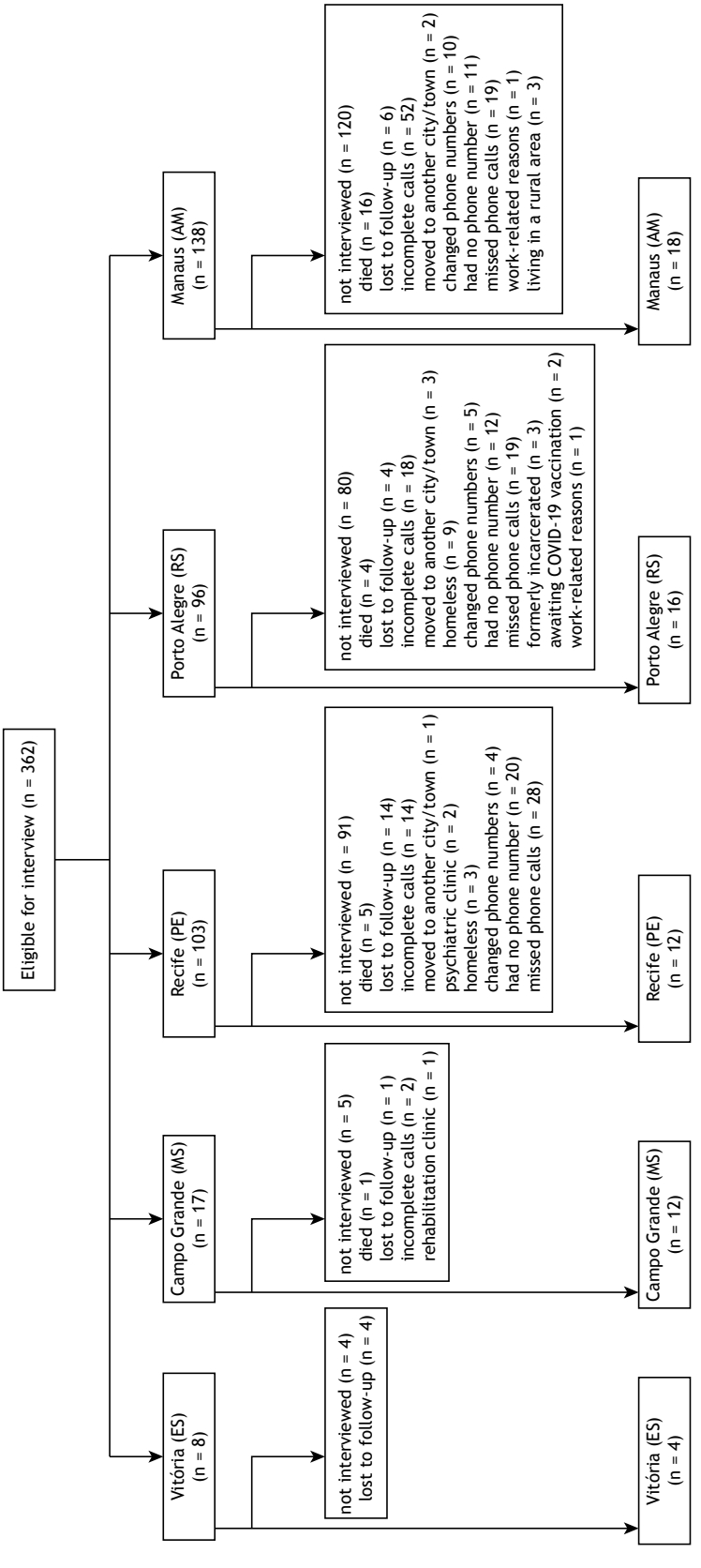

Figure 2. Flow chart of the study population. ES: Espírito Santo; MS: Mato Grosso do Sul; PE: Pernambuco; RS: Rio Grande do Sul; and AM: Amazonas.

because of tuberculosis, 10 (16%) had an annual per capita income of less than R$2,994.00, being extremely poor, and 33 (53%) had only one household member who earned an income. Overall, 15 patients (24%) had extrapulmonary tuberculosis, and 30 (48%) had comorbidities (Table 1).

With regard to costs incurred in the pre-diagnosis period, the overall average cost was R$283.84, with direct medical costs accounting for R$194.36 and direct nonmedical costs accounting for R$89.48. Regarding the costs incurred in the post-diagnosis period, the overall average cost was R$4,161.86 (per month of treatment), with direct medical costs accounting for R$15.64, direct nonmedical costs accounting for R$ 206.23, and indirect costs (loss of income) accounting for R$3,940.09. The overall average cost for the caregiver (including direct and indirect costs) was R$1,362.60 (Table 2).

Direct medical costs were higher in the pre-diagnosis period, and direct nonmedical costs were higher in the post-diagnosis period. During the pre-diagnosis period, none of the patients had indirect costs; however, the indirect costs incurred in the post-diagnosis period were higher than the direct costs incurred in both the pre- and post-diagnosis periods. During the pre-diagnosis period, almost 90% of the patients had direct costs; during the post-diagnosis period, 60% experienced indirect costs (loss of income; Table 2).

In the pre-diagnosis period, 22 patients (35%) incurred expenses pertaining to medications, 55 (89%) incurred travel expenses, and 25 (40%) incurred food expenses. In the post-diagnosis period, 11 patients (18%) incurred hospitalization costs, 55 (89%) incurred travel expenses, and 35 (56%) incurred special food costs. Indirect costs were incurred by 37 (60%) of the patients. Moreover, more than 30% had to borrow money for their treatment, and nearly 90% sought the SUS for a diagnosis: the PNCT, in 42%; a local public hospital, in 29%; and a primary health care clinic, in 18% (Table S1). A total of 40.32% of the patients included in the study experienced catastrophic costs related to tuberculosis (Table S2). Before the costs of tuberculosis disease, 42% of the study patients were unemployed; after the costs of tuberculosis disease, 71% became unemployed (Table S3).

Most (47) of the patients (76%) were nonpoor before the costs of tuberculosis disease and incurred higher mean total costs of tuberculosis (R$4,361.30 for the less poor vs. R$3,626.20 for the extremely poor); however, the largest proportion of annual household income to cover total costs was for the extremely poor (40.37% vs. 11.43%; Figure 3).

The willingness to pay to prevent tuberculosis was evaluated on the basis of the premise that patients had infinite resources. Most (74%) of the patients were willing to pay more than three times the Brazilian national minimum wage, whereas 14% were willing to pay up to one time the Brazilian national minimum wage. The main measure chosen by patients to alleviate the economic burden of tuberculosis was food, followed by a more efficient health care system (Figure 4).

DISCUSSION

This study contributes to the global monitoring of the WHO End TB Strategy targets.[9,19] A total of 40.32% of the study participants experienced catastrophic costs associated with tuberculosis, despite the provision of diagnosis and treatment free of charge in the SUS.

In the present study, the costs incurred in the pre-diagnosis period were found to be lower than those incurred in the post-diagnosis period, a finding that is in disagreement with those of other studies, in which the pre-diagnosis period was reported as being critical.[20,21] This can be attributed to improved patient perception of tuberculosis symptoms. The fact that more than 40% of the study participants first sought medical attention under the PNCT prevented them from taking a complex path in seeking care and seeking out several doctors for the diagnosis of the disease. However, the high costs of medications in the pre-diagnosis period can be attributed to a delay in seeking medical attention in the SUS and a delay in the diagnosis of tuberculosis in the SUS.[22] Active case finding for early and increased detection of cases could minimize pre-diagnosis costs for patients.[23]

The increase in post-diagnosis costs can be attributed, at least in part, to an increased number of visits to health care facilities because of improved adherence to treatment and to an increased intake of special foods. In addition, the fact that patients are required to rest implies work absenteeism, which leads to loss of income and substantially contributes to increased treatment costs. In the present study, 89% of the patients had travel expenses and 56% had expenses for special foods during tuberculosis treatment. This finding suggests that it is essential to provide treatment as close as possible to where patients live. We found that 60% of the patients included in the present study experienced loss of income, and that family members also experienced work absenteeism because of the demands of patient care. Of the sample as a whole, 58% were employed before the diagnosis of tuberculosis, 43.5% were the only income earner in the family, 83% were male patients with pulmonary tuberculosis and 43.5% had relatives who stayed at home to take care of them. After the costs of tuberculosis disease, 71% of the patients included in the present study became unemployed, and 50% remained unemployed because of the physical and social consequences of tuberculosis (physical vulnerability and stigma); in addition, 53% of the households had only one income earner in the family. Risk factors for catastrophic costs include barriers to accessing the health care system, such as long travel times to reach health care facilities, and sociodemographic factors such as unemployment, older age, and fewer family members.[24] Studies have shown that tuberculosis remains associated with

Table 1. Demographic, socioeconomic, and clinical characteristics of the study population.[a]

Characteristic	Vitória (ES) Participants			Campo Grande (MS) Participants			Recife (PE) Participants			Porto Alegre (RS) Participants			Manaus (AM) Participants			Brazil Participants		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
Demographic and socioeconomic	1 (25)	3 (75)	4 (100)	4 (33)	8 (67)	12(100)	2 (17)	10 (83)	12(100)	8 (50)	8 (50)	16 (100)	5 (28)	13 (72)	18 (100)	20 (32)	42 (68)	62 (100)
Age, years																		
18-45	1 (100)	1 (33.3)	2 (50)	2 (50)	3 (37.5)	5 (41.7)	-	5 (50)	5 (42)	5 (62.5)	3 (37.5)	8 (50)	1 (20)	6 (46)	7 (39)	9 (45)	18 (43)	27 (43.5)
46-65	-	2 (66.7)	2 (50)	1 (25)	5 (62.5)	6 (50)	2 (100)	5 (50)	7 (58)	2 (25)	4 (50)	6 (37.5)	2 (40)	4 (31)	6 (33)	7 (35)	20 (48)	27(43.5)
> 65	-	-	-	1 (25)	-	1 (8.3)	-	-	-	1 (12.5)	1 (12.5)	2 (25)	2 (40)	3 (23)	5 (28)	4 (20)	4 (9)	8 (13)
Race																		
White	-	-	-	-	3 (37.5)	3 (25)	-	3 (30)	3 (25)	5 (62.5)	3 (37.5)	8 (50)	-	5 (38)	5 (28)	5 (25)	14 (33)	19 (31)
Non-White	1 (100)	3 (100)	4 (100)	4 (100)	5 (62.5)	9 (75)	2 (100)	7 (70)	9 (75)	3 (37.5)	5 (62.5)	8 (50)	5 (100)	8 (62)	13 (72)	15 (75)	28 (67)	43 (69)
Education level, years of schooling																		
Illiterate	-	-	-	-	-	-	-	-	-	-	2 (25)	2 (13)	1 (20)	-	1 (6)	1 (5)	2 (5)	3 (5)
Literate, 1-8	1 (100)	3 (100)	4 (100)	1 (25)	3 (37.5)	4 (33)	-	4 (40)	4 (33)	1 (12.5)	4 (50)	5 (31)	2 (40)	5 (38)	7 (39)	5 (25)	19 (45)	24 (39)
Literate, > 8	-	-	-	3 (75)	5 (62.5)	8 (67)	2 (100)	6 (60)	8 (67)	7 (87.5)	2 (25)	9 (56)	2 (40)	8 (62)	10 (55)	14 (70)	21 (50)	35 (56)
Formal employment																		
Employed	-	1(33)	1 (25)	-	3 (37.5)	3 (25)	1 (50)	2 (20)	3 (25)	3 (37.5)	2 (25)	5 (31.2)	2 (40)	5 (38.4)	7 (39)	6 (30)	13 (31)	18 (29)
Unemployed because of tuberculosis	1 (100)	2 (67)	3 (75)	3 (75)	2 (25)	5 (41.7)	1 (50)	3 (30)	4 (33.3)	3 (37.5)	4 (50)	7 (43.8)	1 (20)	2 (15.4)	3 (16.6)	9 (45)	13 (31)	22 (35.5)
Unemployed for other reasons	-	-	-	1 (25)	3 (37.5)	4 (33.3)	-	5 (50)	5 (41.7)	2 (25)	2 (25)	4 (25)	2 (40)	6 (46.2)	8 (44.4)	5 (25)	16 (38)	22 (35.5)
Annual income, R$[b]																		
< 2,994.00	-	1 (33)	1 (25)	2 (50)	1 (12.5)	3 (25)	1 (50)	-	1 (8)	1 (12.5)	2 (25)	3 (19)	1 (20)	1 (8)	2 (11)	5 (25)	5 (12)	10 (16)
2,994.01-5,988.00	1(100)	-	1 (25)		1 (12.5)	1 (8)	-	3 (30)	3 (25)	3 (37.5)	2 (25)	5 (31)	-	2 (15)	2 (11)	4 (20)	8 (19)	12 (19)
> 5,988.00	-	2 (67)	2 (50)	2 (50)	6 (75)	8 (67)	1 (50)	7 (70)	8 (67)	4 (50)	4 (50)	8 (50)	4 (80)	10 (77)	14 (78)	11 (55)	29 (69)	40 (65)

Continue...▶

Table 1. Demographic, socioeconomic, and clinical characteristics of the study population.[a] (Continued...)

Characteristic	Vitória (ES) Participants			Campo Grande (MS) Participants			Recife (PE) Participants			Porto Alegre (RS) Participants			Manaus (AM) Participants			Brazil Participants		
	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total	Female	Male	Total
Family size																		
< 4	-	1 (33.3)	1 (25)	3 (75)	7 (87.5)	10 (84)	1 (50)	6 (60)	7 (58)	6 (75)	3 (37.5)	9 (56)	2 (40)	8 (62)	10 (55)	12 (60)	25 (59)	37 (60)
4	1 (100)	1 (33.3)	2 (50)	1 (25)	-	1 (8)	1 (50)	2 (20)	3 (25)	1 (12.5)	5 (62.5)	6 (37.5)	1 (20)	2 (15)	3 (17)	5 (25)	10 (24)	15 (24)
> 4	-	1 (33.3)	1 (25)	-	1 (12.5)	1 (8)	-	2 (20)	2 (17)	1 (12.5)	-	1 (6.5)	2 (40)	3 (23)	5 (28)	3 (15)	7 (17)	10 (16)
Family type																		
Joint	1 (100)	2 (67)	3 (75)	4 (100)	7 (87.5)	11 (92)	2 (100)	9 (90)	11 (92)	7 (87.5)	6 (75)	13 (81)	4 (80)	12 (92)	16 (89)	18 (90)	37 (88)	54 (87)
Nuclear	-	1 (33)	1 (25)	-	1 (12.5)	1 (8)	-	1 (10)	1 (8)	1 (12.5)	2 (25)	3 (19)	1 (20)	1 (8)	2 (11)	2 (10)	6 (12)	8 (13)
No. of income earners																		
≤ 1	1 (100)	1 (33)	2 (50)	3 (75)	5 (62.5)	8 (67)	1 (50)	4 (40)	5 (42)	5 (62.5)	4 (50)	9 (56)	3 (60)	6 (46)	9 (50)	13 (65)	20 (48)	33 (53)
> 1	-	2 (67)	2 (50)	1 (25)	3 (37.5)	4 (33)	1 (50)	6 (60)	7 (58)	3 (37.5)	4 (50)	7 (44)	2 (40)	7 (54)	9 (50)	7 (35)	22 (52)	29 (47)
Clinical																		
Type of tuberculosis																		
Pulmonary	-	3 (100)	3 (75)	2 (50)	4 (50)	6 (50)	2 (100)	9 (90)	11 (92)	4 (50)	8 (100)	12 (75)	4 (80)	11 (85)	15 (83)	12 (60)	35 (83)	47 (76)
Extrapulmonary	1 (100)	-	1 (25)	2 (50)	4 (50)	6 (50)	-	1 (10)	1 (8)	4 (50)	-	4 (25)	1 (20)	2 (15)	3 (17)	8 (40)	7 (17)	15 (24)
HIV status																		
Positive	-	-	-	1 (25)	4 (50)	5 (42)	-	-	-	1 (12.5)	1 (12.5)	2 (12.5)	-	2 (15)	2 (11)	2 (10)	7 (17)	9 (1)
Negative	1 (100)	3 (100)	4 (100)	3 (75)	4 (50)	7 (58)	-	4 (40)	4 (33)	7 (87.5)	5 (62.5)	12 (75)	2 (40)	7 (54)	9 (50)	13 (65)	23 (55)	36 (58)
Unknown	-	-	-	-	-	-	2 (100)	6 (60)	8 (67)	-	2 (25)	2 (12.5)	3 (60)	4 (31)	7 (39)	5 (25)	12 (28)	17 (27)
Comorbidities																		
Present	1 (100)	-	1 (25)	3 (75)	5 (62.5)	8 (67)	1 (50)	5 (50)	6 (50)	3 (37.5)	6 (75)	9 (56)	1 (20)	5 (38.5)	6 (33)	9 (45)	21 (50)	30 (48)
Absent	-	3 (100)	3 (75)	1 (25)	3 (37.5)	4 (33)	1 (50)	5 (50)	6 (50)	5 (62.5)	2 (25)	7 (44)	4 (80)	8 (61.5)	12 (67)	11 (55)	21 (50)	32 (52)

ES: Espírito Santo; MS: Mato Grosso do Sul; PE: Pernambuco; RS: Rio Grande do Sul; and AM: Amazonas. [a]Values expressed in n (%). [b]In 2019, 1 U.S. dollar = 3.9451 Brazilian reals.

Table 2. Components of costs incurred by patients in the pre- and post-diagnosis periods.

Component	Cost incurred, patients[a]		
	Yes	No	Mean cost, R$[b]
Pre-diagnosis			
Type of cost			
Direct cost			
Medical			
Tests	6 (10)	56 (90)	22.98
X-rays	7 (11)	55 (89)	13.76
Medications	22 (35)	40 (65)	157.62
Subtotal			194.36
Nonmedical			
Food	25 (40)	37 (60)	21.62
Travel	55 (89)	7 (11)	58.59
Accommodation	2 (3)	60 (97)	2.90
Administrative	3 (5)	59 (95)	6.37
Subtotal			89.48
TOTAL			283.84
Post-diagnosis			
Type of cost			
Direct cost			
Medical			
Follow-up	7 (11)	55 (89)	8.11
Hospitalization	11 (18)	51 (82)	7.43
Subtotal			15.54
Nonmedical			
Food	12 (19)	50 (81)	23.24
Travel	55 (89)	7 (11)	74.55
Accommodation	0	0	0.00
Administrative	0	0	0.00
Special foods	35 (56)	27 (44)	108.44
Subtotal			206.23
TOTAL			221.77
Indirect cost			
Loss of income	37 (60)	25 (40)	3,940.09
TOTAL			3,940.09
Caregiver (direct and indirect cost)	42 (68)	20 (32)	1,362.60

R$: Brazilian reals. [a]Values expressed in n (%). [b]In 2016, 1 U.S. dollar = 3.4901 Brazilian reals.

poverty worldwide[25,26] and pushes families deeper into poverty.[27,28]

Regarding the level of poverty, patients living in extreme poverty had a higher proportion of the annual household income spent on tuberculosis costs, incurring catastrophic costs. After the costs of tuberculosis disease, the number of patients living in nonpoverty decreased by 5%, the number of patients living in poverty increased by 6% and the number of patients living in extreme poverty increased by 5%. This shows that catastrophic costs continue to affect tuberculosis patients in Brazil, more predominantly the poor, thus contributing to increasing economic and social inequalities. In addition, these results highlight that access to tuberculosis diagnosis and treatment, available free of charge in the SUS, can be expensive for poor and extremely poor patients because high health costs imply a significant reduction in the resilience of families contending with high food and housing expenses.[3,29,30-36] This can result in increased stigmatization.[3,30,31]

In this context, it is important to highlight that the present study was carried out during the dismantling of social security and conditional cash transfer programs. This dismantling had a direct impact on tuberculosis-related social conditions, especially with regard to high indirect food costs. One study[37] showed that the *Programa Bolsa Família* alone had a direct effect on the outcomes of tuberculosis treatment and could greatly contribute to achieving the WHO End TB Strategy goals. Expanding the coverage of social protection programs can play an important role in alleviating extreme poverty and, indirectly, reducing the incidence of tuberculosis.[38]

More than 70% of the patients included in the present study were willing to pay more than three times the

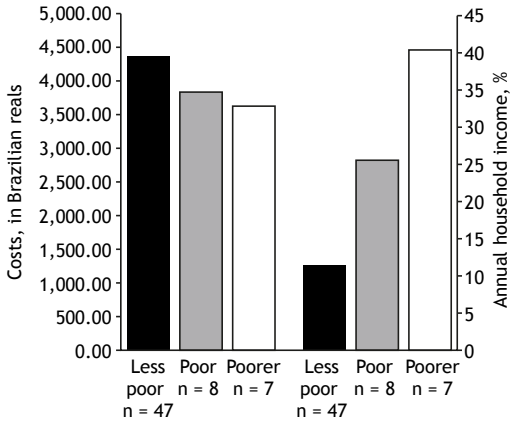

Figure 3. Overview of the household poverty level and cost burden of tuberculosis on the patient/household.

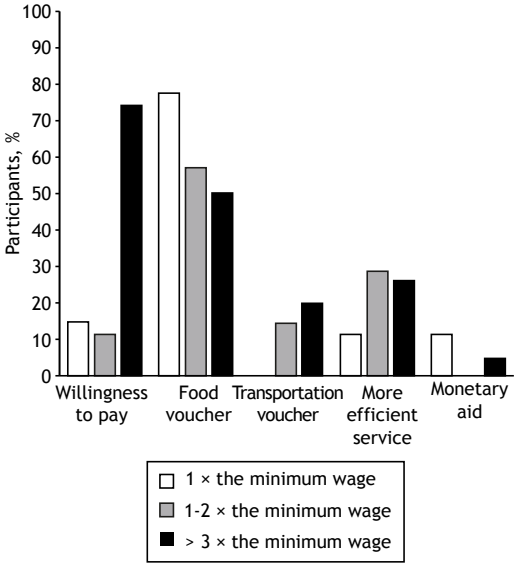

Figure 4. Willingness to pay to prevent tuberculosis and measures chosen to alleviate the burden of tuberculosis.

Brazilian national minimum wage to reduce the chance of an adverse health outcome. This is a useful indicator of how participants value life and health when social preferences are incorporated into public policies. The willingness-to-pay method is important because it seeks to assess indirect and intangible aspects of a disease or condition.[39] To reduce the economic burden of tuberculosis on the household,[11,40] social support measures must be implemented.

This is the first study in Brazil to assess the economic impact of tuberculosis on the household. The study has limitations. The number of participants included in the analysis of the costs of tuberculosis disease was lower because of logistical barriers to data collection, mainly due to the COVID-19 pandemic, and because of the death or migration of patients who were eligible for follow-up. This may have introduced a selection bias and therefore affected the study results.

The study participants incurred economic losses in the pre-diagnosis period and severe loss of income in the post-diagnosis period. These losses resulted in unemployment and social sequelae. National and global policies to mitigate catastrophic costs should include interventions planned by health care systems to ensure early diagnosis of tuberculosis patients (through active case finding and contact investigation); social support to patients receiving tuberculosis treatment, so as to minimize the loss of income; and social protection measures for tuberculosis patients with lower incomes, so as to interrupt the relationship between tuberculosis and poverty, and, consequently, eliminate the global tuberculosis epidemic by 2035—a WHO goal in line with the United Nations Sustainable Development Goals.

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AUTHOR CONTRIBUTIONS

RBL and ELNM conceptualized and designed the study. RBL, LMG, GF, and ELNM acquired, analyzed, and interpreted the data, and drafted the manuscript. SMVLO, DS, JSP, and DG critically reviewed the manuscript. RBL and ELNM had final responsibility to submit for publication. All authors agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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SPECIAL ARTICLE

Certainty of evidence, why?

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ABSTRACT

Optimal clinical decision-making requires understanding of evidence regarding benefits, harms, and burdens of alternative management options. Rigorously conducted systematic reviews and meta-analyses offer accurate summaries of the evidence. However, such summaries may review only low-certainty evidence, in the process highlighting that no single decision is likely to be best for all patients. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach offers a systematic and transparent method for rating certainty of evidence in systematic reviews. In this paper, we will address the importance of assessing the certainty associated with bodies of evidence; explain how the GRADE system rates the certainty of evidence from systematic reviews; and present the GRADE evidence to decision framework for moving from evidence to strong or weak recommendations in clinical practice guidelines.

Keywords: Systematic reviews as topic; Meta-analysis as topic; Evidence-Based Medicine; Decision making.

INTRODUCTION

When answering patient questions regarding treatment options, clinicians need to consider the relevant evidence regarding benefits, harms, and burdens. Systematic reviews and meta-analyses address structured clinical questions and, when done well, offer accurate summaries of the evidence. When the evidence is low certainty (also known as low quality), however, even rigorous evidence summaries will leave large uncertainty regarding benefits and harms. In this paper, we will address the importance of assessing the certainty of the evidence from interventional and diagnostic studies and explain the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to rating the certainty of evidence from systematic reviews and the strength of recommendations in clinical practice guidelines.

Patients, clinicians, and policymakers will often be misled if they do not consider the certainty of evidence. Consider the use of systemic glucocorticoids, until recently widely used in the management of idiopathic pulmonary fibrosis. The evidence supporting the benefit of glucocorticoid use in these patients was never better than low certainty, whereas high-certainty evidence exists for the multiple harms of this intervention.[1] Optimal practice for clinicians offering glucocorticoid therapy to patients would include making clear the speculative nature of any benefits and the high risk of substantial harm. Many patients, aware of the uncertain benefits and the high-certainty evidence of harms, would decline the intervention. Failure to recognize the low-certainty evidence of benefit would result in overuse of the intervention.

A formal assessment of the certainty of evidence is an effective strategy to prevent the overuse of interventions with questionable benefits. The GRADE approach offers a systematic and transparent method for rating certainty of evidence in systematic reviews (Chart 1), and for developing and determining the strength of recommendations in clinical practice guidelines.[2] More than 110 organizations, including the World Health Organization, the UK National Institute for Health and Care Excellence, the Cochrane Collaboration, and leading American professional organizations including the American Thoracic Society and the American College of Chest Physicians have adopted GRADE. Moreover, the world's leading electronic textbook, UpToDate, includes over 10,000 GRADE recommendations. GRADE now represents the gold standard approach to systematic reviews and guideline development.[3]

Applying the GRADE system of rating certainty of evidence requires the availability of rigorously conducting systematic reviews to address clinical questions. GRADE also offers evidence to decision (EtD) frameworks for guideline panels as they move from evidence to recommendations.[4] After considering all issues highlighted in the EtD framework, guideline panels will issue, in favor or against a treatment or diagnostic test, a strong or weak recommendation.

Naïve clinicians may be prematurely inclined to change their practice based on the results of a single randomized trial, neglecting considerations of risk of bias, imprecision due to limited sample size, and applicability if patients enrolled do not represent a close match to the patients under their care. Moreover, naïve clinicians may be

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Chart 1. Certainty of evidence: assessment criteria.

Study design	Confidence in estimates	Lower if	Higher if
Randomized trials	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational studies	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or
	Very low	Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	+1 Would suggest a spurious effect when results show no effect

ready to inappropriately change practice based on a systematic review and meta-analysis that yields only low-certainty evidence. The evidence may be low certainty if it comes exclusively from observational, non-randomized studies. Alternatively, the evidence may be low certainty, even if based on randomized trials, if those trials suffer from limitations in the study design and sample size; inconsistency in results; or limitations in applicability to the patients at hand. In the following sections of this review, we will expand on these limitations of randomized controlled trials (RCTs) and systematic reviews and meta-analyses in the clinical decision-making process, highlighting the importance of GRADE for rating the certainty of evidence and recommendations of treatment and diagnostic tests in clinical practice guidelines.

THE GRADE APPROACH IN SYSTEMATIC REVIEWS AND CLINICAL RECOMMENDATIONS

GRADE approach for rating certainty of evidence regarding interventions

The GRADE approach to the certainty of evidence begins with the acknowledgment that sound clinical decisions require rigorous systematic summaries of the highest quality available evidence regarding interventions under consideration. Once such a systematic review is available, the GRADE rating of the certainty of evidence begins with the study design: randomized trials begin as high-certainty evidence and observational studies as low-certainty evidence in GRADE's four-category system of certainty of evidence (high, moderate, low, and very low; Chart 1).[2] Following the study design, GRADE has identified five domains that warrant consideration when rating the certainty of evidence: risk of bias, inconsistency, indirectness, imprecision, and publication bias (Chart 1).[2]

Reviewers rate down the certainty of evidence by one level when they identify serious concerns and by two levels when they identify very serious concerns in any of these five domains. Reviewers can rate up the certainty of evidence from observational studies, primarily for large or very large magnitude of effect.[5] Reviewers assess the certainty of evidence not for individual studies but rather for entire bodies of evidence summarized in systematic reviews, and separately for each outcome. All patient-important outcomes receive a certainty rating.

We will now briefly describe considerations related to the five reasons for rating down the certainty of evidence. Concerning the risk of bias,[6] randomized trials may be limited by failure to conceal randomization; failure to blind patients, clinicians, data collectors, and adjudicators; and losing patients to follow-up. Randomized trials will also overestimate treatment effects if they are stopped early for large treatment effects, particularly if their sample size is small.[7]

Secondly, certainty decreases when there is unexplained inconsistency among results presented from different studies. Reviewers judge consistency through the similarity of point estimates and the extent of overlap of CIs. Statistical criteria may further inform judgments regarding inconsistency, including tests of heterogeneity (Can chance explain differences in results between studies?) and I^2, which quantifies inconsistency on a scale from 0 to 100.[8,9]

Thirdly, studies included in a systematic review should reflect the review question. When rating indirectness (the GRADE term related to the applicability of the evidence to the question at hand), reviewers consider whether patients, interventions, comparisons, and outcomes differ from those of interest.[10] Indirectness is even more important for guidelines than for systematic reviews.

Fourthly, GRADE considers the width of the CIs around the estimates of the absolute effects of treatment.[11] Rating down the certainty of evidence requires consideration of whether the CI crosses a threshold of interest. For instance, if the entire confidence is in the range of an important effect, one will not rate down for imprecision. If it crosses the threshold of importance, leaving uncertainty about whether an effect is trivial or important, reviewers will rate it down. Consider for example Figure 1: for intervention A, reviewers would rate down for imprecision, whereas, for intervention B, they would not.

Finally, trials that fail to show positive treatment effects may remain unpublished and thus result in overestimates of treatment effect, a phenomenon referred to as publication bias.[12] Review authors will suspect publication bias when a pharmaceutical company has sponsored all available studies, particularly if the sample size of the studies is small.

If a body of evidence from randomized trials suffers from several of these limitations, reviewers may rate down to moderate, low, or even very low certainty of evidence. Moreover, these limitations also apply to observational studies and may lead to rating down certainty from low to very low. On rare occasions, reviewers may rate up certainty for large or very large effects (e.g., insulin for diabetic ketoacidosis and dialysis for end-stage renal disease).

As with therapeutic interventions, systematic reviews should inform diagnostic clinical questions.[13] Most studies of diagnostic tests focus exclusively on diagnostic accuracy, and GRADE's five reasons for rating down apply to systematic reviews of such studies.[14] Ideally though, studies will focus on the impact of alternative diagnostic strategies on patient-important outcomes (e.g., mortality and quality of life) using randomized study designs.[15,16] For those studies, the certainty of evidence is assessed in the same way as the GRADE approach to clinical interventions.

How does GRADE inform moving from evidence to recommendations?

GRADE uses the EtD framework to help people use the evidence to inform clinical decisions. This framework includes considerations of the magnitude of benefits, harms, and burdens; the certainty of evidence regarding those benefits, harms, and burdens; patient values and preferences; and, sometimes, costs, feasibility, acceptability, and equity issues (Chart 2).[4] Clinical recommendations, after considering all these issues, should provide explicit statements on the best course of action.

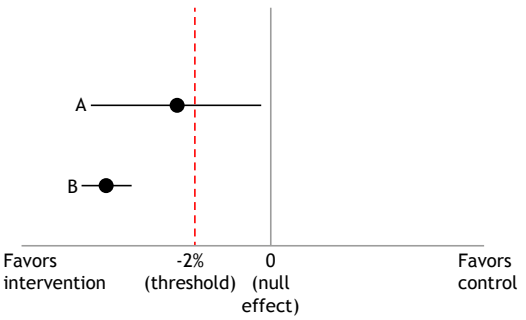

Figure 1. Rating imprecision: consideration of whether the confidence interval crosses a threshold of interest.

Guideline panels make strong recommendations when they conclude that all or almost all fully informed patients would choose the proposed intervention. In contrast, they make weak (also referred to as conditional) recommendations when they consider that patients presented with the treatment options would, as a result of different values and preferences, vary in their choices.[17]

Desirable and undesirable outcomes (estimated effects)

When benefits (desirable outcomes) are large, and harms and burdens (undesirable outcomes) are small in magnitude, guideline panels are more likely to issue a strong recommendation. In contrast, when the desirable and undesirable consequences are closely balanced, a weak recommendation is likely more appropriate.

Certainty of evidence

When evidence certainty is high or moderate, strong recommendations may be appropriate. When the evidence is low or very low certainty, high confidence that benefits outweigh harms and burdens (or the reverse) is very unlikely, and weak recommendations will almost always be appropriate.

Uncertainty or variability in values and preferences

Marking a recommendation involves determining the value one places on benefits versus harms and burdens. Although patients will have different views regarding these values, in making recommendations guideline panels must focus on typical or average patient values and preferences. Given this is the case, large variability in values and preferences in the relevant patient population will make a weak recommendation more likely, as will uncertainty regarding patient values and preferences. Although there is often limited evidence to inform patient preferences and values, clinical experience may leave a panel confident that values and preferences differ widely among patients.[14]

Resource use (costs), feasibility, acceptability, and equity

Treatment interventions or diagnostic tests may increase or decrease resource use when compared to an alternative. The impact of the cost may vary among settings and patients' socioeconomic situations. Additional, often secondary, considerations include resource use, feasibility, acceptability, and equity. Although these considerations are not always germane, they are sometimes important, particularly when guidelines take a public health or systems perspective rather than an individual patient perspective.

Chart 2. Domains that affect the strength of a recommendation.

- Desirable and undesirable outcomes (estimated effects)
- Certainty of evidence
- Uncertainty or variability in values and preferences
- Resource use (cost), feasibility, acceptability, and equity

How do clinicians interpret and apply GRADE recommendations to patient care?

Clinicians should be able to differentiate an untrustworthy recommendation from trustworthy recommendations; understand the meaning of the strength of the recommendation; and understand how to apply the recommendation to patient care.[18] A guide for health professionals to interpret and use recommendations in guidelines developed with the GRADE approach suggests specific criteria to interpret, critically assess, and apply GRADE recommendations (Chart 3).[17]

Understanding the meaning of the strength of the recommendation

Clinicians' interpretation of GRADE recommendations should include consideration of the strength of the recommendation and the certainty of the evidence. Guideline panels using the GRADE approach will issue either strong or weak/conditional recommendations. If a guideline panel is confident that desirable effects outweigh undesirable consequences, they will issue a strong recommendation, usually framed as "we recommend."[17] On the other hand, if the guideline panel is less confident about the balance between desirable and undesirable consequences in the proposed course, they issue a weak recommendation, usually framed as "we suggest."

Panels issue weak recommendations when they believe that the recommendation is unlikely to apply to all patients. In that case, clinicians should spend time to ensure that each patient receives the therapeutic option that reflects their values and preferences.[19]

Distinguishing between trustworthy and untrustworthy recommendations

Clinicians should not only understand the concepts of strength of the recommendation and certainty of the evidence but should also be able to choose trustworthy guidelines to inform their practice. Consideration of five domains may help in this choice (Chart 3).[17]

Were all of the relevant outcomes important to patients explicitly considered?

Balancing between desirable and undesirable in the proposed course will depend on what outcomes are considered. Clinicians should assess whether the guideline panel considered and included all relevant patient-important outcomes.

Was the recommendation based on the best current evidence?

The recommendation should be based on the best current evidence. Clinicians should assess the credibility of the guideline process based on whether a systematic review informed the recommendations. Ideally, the systematic review panels should be up to date.

Is the strength of the recommendation appropriate?

Guideline panels should consider all issues in the EtD framework in making their recommendations and seldom make strong recommendations when evidence is low certainty (Chart 2).

Is the recommendation clear and actionable?

The recommendation should provide the details of the recommended action, the situation to which the recommendations apply, to whom they apply, and the clinical action to which the intervention was compared.

Applying recommendations to patient care

Clinicians can apply strong recommendations to all or almost all patients without the necessity of a detailed discussion with the patient. For weak recommendations, clinicians should understand and be able to communicate the evidence to patients through shared decision-making.

FINAL CONSIDERATIONS

Neither individual RCTs nor systematic reviews of the best available evidence ensure high-certainty evidence; indeed, for RCTs and rigorous systematic reviews, the certainty of the evidence may be low. The GRADE approach offers a system for rating the certainty of evidence in systematic reviews and grading the strength of recommendations in clinical guidelines. In applying guidelines to clinical care, clinicians should understand the implications of strong and particularly weak recommendations that mandate considering

Chart 3. User guide to GRADE for health professionals, including interpretation, critical assessment, and use of GRADE recommendations in patient care.

Understanding the meaning of the strength of the recommendation
What does strength mean?
What does the certainty of the evidence mean?
Distinguishing between trustworthy and untrustworthy recommendations
Were all of the relevant outcomes important to patients explicitly considered?
Was the recommendation based on the best current evidence?
Is the strength of the recommendation appropriate?
Is the recommendation clear and actionable?
Does the recommendation provide the necessary additional information?
Applying recommendations to patient care
Strong recommendations
Weak recommendations

GRADE: Grading of Recommendations Assessment, Development, and Evaluation.

patient values and preferences in their decision-making process.

AUTHOR CONTRIBUTIONS

JPL, XC, and WT equally contributed to this work. JPL, XC, GHG, and WT: study conception and design. JPL, XC, and WT: drafting of the manuscript. JPL, XC, GHG, and WT: review and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Idiopathic pulmonary fibrosis: current diagnosis and treatment

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a devastating chronic lung disease without a clear recognizable cause. IPF has been at the forefront of new diagnostic algorithms and treatment developments that led to a shift in patients' care in the past decade, indeed influencing the management of fibrotic interstitial lung diseases other than IPF itself. Clinical presentation, pathophysiology, and diagnostic criteria are briefly addressed in this review article. Additionally, evidence regarding the use of antifibrotics beyond the settings of clinical trials, impact of comorbidities, and therapeutic approaches other than pharmacological treatments are discussed in further detail.

Keywords: Idiopathic pulmonary fibrosis/diagnosis; Idiopathic pulmonary fibrosis/physiopathology; Idiopathic pulmonary fibrosis/therapy; Idiopathic pulmonary fibrosis/rehabilitation.

INTRODUCTION

Interstitial lung diseases (ILDs) comprise a heterogeneous group of non-neoplastic diseases with various degrees of inflammation and/or fibrosis. Some have known causes; others have a set of recognizable risk factors and pathogenic pathways but not a single identifiable etiology, the so-called idiopathic interstitial pneumonias—among which figures idiopathic pulmonary fibrosis (IPF), its most prominent member, and regarded as the prototypical fibrotic disease.[1,2]

IPF is a chronic progressive fibrotic disease restricted to the lungs that affects adult patients, mainly elderly individuals (> 50 years of age, but usually > 65 years), in a 2-3:1 male to female ratio, most commonly with a history of concurrent or previous smoking.[1,3]

Epidemiological data are scarce, especially in low/medium-income countries, but its incidence and prevalence appear to be rising, reaching annual rates of more than 8 and 28 cases per 100,000 population per year, respectively.[4] In Brazil, Baddini-Martinez and Pereira[5] estimated, based on data from the USA, an annual incidence of 3.5-5.1/100,000 population and a prevalence of 7.1-9.4 per 100,000 population. Mortality is high, and most patients have an estimated survival of 3-5 years without treatment, which is comparable to cancers with poor prognosis.[1]

Over the last decade, important advances regarding IPF physiopathology, consensus diagnostic criteria, and development of target medications have led to a new era of understanding and treatment of ILDs.[6]

PATHOPHYSIOLOGY

Although not entirely known, IPF is believed to derive from recurrent epithelial injury in the lungs that are susceptible to cellular aging and aberrant repair, resulting in intense deposition of collagen through activated myofibroblasts.[7]

Short telomeres, determinants of cellular senescence, associated with oxidative stress, mitochondrial dysfunction, and protein dysregulation, are also part of fibrosis initiation and progression, which occurs through several mediators, such as TGF-β, IL-1β, IL-6, and IL-8.[8] Up to one third of patients with IPF, either in its familial or sporadic presentation, have recognizable genes associated with pulmonary fibrosis (including, but not only, IPF), most notably those related to telomere length mutations (such as *TERC*, *TERT*, *PARN*, and *RTEL1*) and a single nucleotide polymorphism (rs35705950) of the promoter region of the *MUC5B* gene.[1,2]

Although specific causes for IPF development are unknown, some risk factors have been widely recognized for their association with the disease, especially age, male sex, and smoking. Other risk factors include gastroesophageal reflux disease (GERD), obstructive sleep apnea, air pollution, occupational exposures throughout life (not leading to a specific pneumoconiosis), chronic viral infections (such as hepatitis C and Epstein-Bar virus), and a family history of ILD.[1]

CLINICAL PRESENTATION AND NATURAL COURSE

IPF must be considered in adult patients (generally > 50 years of age) with an insidious course of progressive dyspnea on exertion, dry cough, and "Velcro" crackles on inspiration, sometimes with digital clubbing. Signs of pulmonary hypertension, such as limb edema and jugular vein distention, may be apparent in later stages of disease.

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Constitutional symptoms should prompt the investigation of alternative etiologies or associated comorbidities, such as cancer. Additionally, a thorough history of exposures (both environmental and occupational), drugs, and infections as a cause of ILD must be ruled out before a diagnosis of IPF can be confidently made.[1,2]

Pulmonary function tests should be performed in all patients, both for diagnostic purposes and especially for prognosis and follow-up. A restrictive pattern with low FVC, TLC, and DL_{CO} is the rule. FVC is the most well studied parameter for mortality prediction, and a relative decline ≥ 10%, along with an absolute decline > 5%, is used as a surrogate for disease progression[9] and has been employed as an endpoint for randomized controlled trials.

Prognostication in IPF can be challenging since the disease course, although usually progressive, might be unpredictable. Classically, patients present with a slow and sustained loss of FVC over time, but some might present with an accelerated decline in functional capacity or even periods with stabilization.[2,6]

The most widely validated prognostic tool was developed in 2012 by Ley et al,[10] the GAP index, which comprises Gender, Age, and Physiology (FVC and DL_{co}). Field tests, such as the six-minute walk test (6MWT) and cardiopulmonary exercise testing, might also be employed as surrogates for severity. Hypoxemia on exertion occurs early in the disease course and can also reflect disease progression.

Rarely might patients also present with an acute exacerbation of IPF (AE-IPF), defined as a recent worsening of dyspnea (usually within the last 30 days or less), with new bilateral superposing consolidation or ground-glass opacities on chest X-ray or HRCT to previous fibrotic areas, excluding pulmonary edema as a sole cause. AE-IPF is either triggered by a known cause (such as infection, aspiration, or drugs) or idiopathic (untriggered). This condition is associated with poor prognosis and is responsible for most IPF-related hospitalizations.[11]

DIAGNOSIS

Multidisciplinary meetings remain the gold standard for ILD diagnosis, including IPF. Ideally, patients should be evaluated at an ILD specialized center involving at least a group of clinicians, radiologists, and pathologists. Accurate early diagnosis remains suboptimal, delaying therapy initiation and frequently submitting patients to incorrect treatments for other conditions (such as COPD or congestive heart failure) or with the use of proven harmful drugs (such as corticosteroids and immunosuppressants).

A diagnosis of IPF requires definite exclusion of ILDs with known causes, such as drug-related ILD, fibrotic hypersensitivity pneumonitis (fHP), or connective tissue disease-associated ILD. Once other causes of ILD have been ruled out and/or IPF is suspected based on clinical suspicion, a combination of clinical and radiological features should be employed to determine the probability of IPF. Eventually, if lung biopsy is performed (usually after a first multidisciplinary meeting discussion), histopathological features are added to the probability estimation.

A morphological pattern of usual interstitial pneumonia (UIP), either a radiological or a histopathological one, is required to establish an IPF diagnosis. On the other hand, a UIP pattern has been associated with other conditions, such as asbestosis, fHP, and rheumatoid arthritis. Therefore, the exclusion of alternative diagnoses remains central, even with a typical UIP pattern on HRCT.[2]

HRCT has become central to the diagnosis of IPF (Table 1). The radiological appearance of UIP (or typical UIP) has a strong correlation with histological UIP, precluding the need for invasive procedures (Figure 1). In other patterns, such as probable or indeterminate UIP, BAL or lung biopsy could be performed in order to improve diagnostic accuracy, although a probable UIP pattern in an appropriate clinical context of high suspicion of IPF is accepted by most thoracic/respiratory societies as diagnostic for IPF without biopsy (Figure 2), and some patients might be unsuitable for invasive procedures.[3,6]

Differentiating IPF from other diseases has gained importance with current treatment approaches, but it is usually easier said than done, especially when dealing with diseases that might present with similar behavior and radiological appearance, such as fHP. Therefore, a provisional diagnosis with higher or lower confidence is acceptable in many practical clinical scenarios; however, the pursuit of alternative diagnosis should be restless.[12,13]

When needed, lung sampling may be obtained either through open lung biopsy (preferably video-assisted thoracoscopy) or transbronchial cryobiopsy, which has become increasingly available. Choosing the best procedure should consider center expertise (both for the procedure and the pathological interpretation), individual contraindications, and preferences of patients. Some biomarkers for molecular diagnosis have shown promising results for a noninvasive diagnosis of a UIP pattern; however, they have not been incorporated into clinical practice and are not recommended as a standard of care yet.[3,14]

In summary, the diagnostic criteria include the exclusion of alternative diagnosis of ILD (extensively investigated) and a UIP pattern on HRCT and/or lung biopsy or a combination of HRCT and/or histological patterns.[3]

TREATMENT

Pharmacological treatment

The IPF treatment journey has been remarkable in terms of the number of failures in almost 25 years of clinical trials without positive results.[15] This has been motivated by an early (and, nowadays,

Table 1. HRCT findings in idiopathic pulmonary fibrosis (in relation to the usual interstitial pneumonia pattern).

	UIP	Probable UIP	Indeterminate for UIP	Alternative Diagnosis
Distribution	• Subpleural inferior predominance • Might be asymmetrical and heterogeneous	• Subpleural inferior predominance • Frequently heterogeneous	• Diffuse (without subpleural predominance)	• Peribronchovascular • Perilymphatic • Upper or mid lung • Subpleural sparing

HRCT characteristics	• Honeycombing (with or without traction bronchiectasis)
	• Irregular thickening of interlobular septa
	• Superimposed to reticular pattern
	• Mild GGO
	• Might have pulmonary ossification
		• Reticular pattern with traction bronchiectasis
		• May have mild GGO (usually near areas of bronchiectasis)
		• Absence of subpleural sparing
			• HRCT features of lung fibrosis that do not suggest any diagnosis	• Lung findings:
				  • Cysts
				  • Mosaic attenuation
				  • GGO predominance (might be found if diagnosed during an AE-IFP)
				  • Centrilobular micronodules
				  • Nodules
				  • Consolidations
				• Mediastinal findings:
				  • Pleural plaques
				  • Dilated esophagus

Based on Raghu et al.[3] UIP: usual interstitial pneumonia; GGO: ground-glass opacities; and AE-IPF: acute exacerbation of idiopathic pulmonary fibrosis.

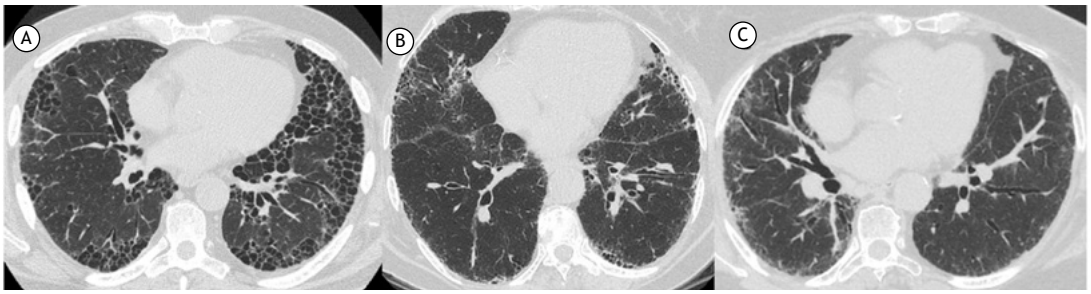

Figure 1. HRCT patterns in relation to usual interstitial pneumonia (UIP). In A, UIP pattern, showing exuberant honeycombing. In B, probable UIP pattern, with traction bronchiectasis and typical subpleural inferior distribution. In C, indeterminate for UIP, showing mild reticular and ground-glass opacities.

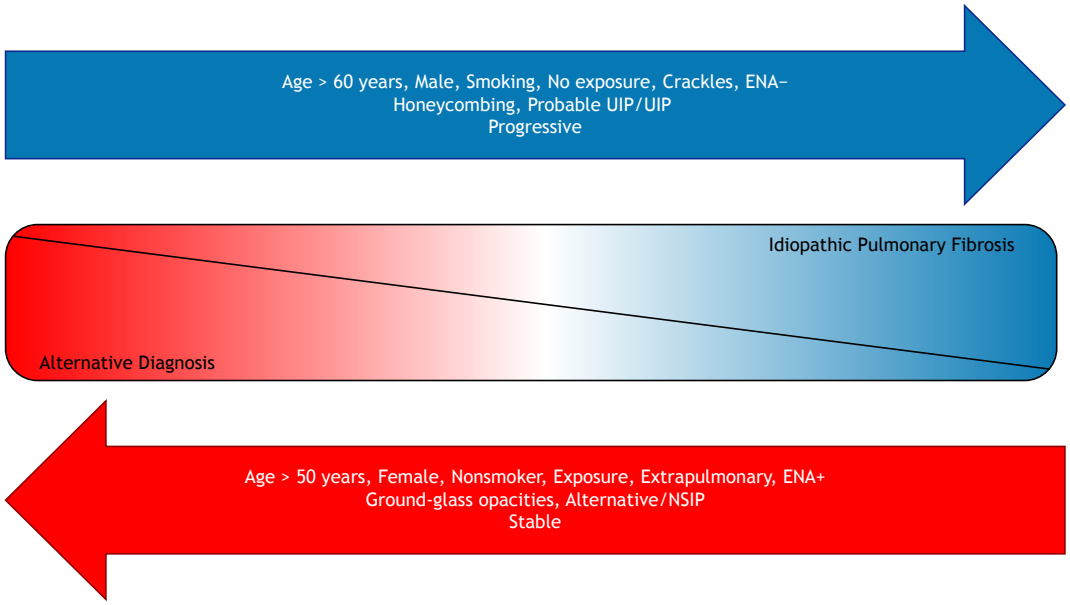

Figure 2. Probability of idiopathic pulmonary fibrosis based on clinical and radiological features. ENA: extractable nuclear antigen; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia.

abandoned) hypothesis that IPF could be the final pathway to persistent overt inflammation—most notably due to a changing practice clinical trial, the famously known PANTHER-IPF trial, that revealed an excessive death rate in the group of patients treated with a combination of prednisone, azathioprine, and N-acetylcysteine.[15] Anticoagulants and pulmonary circulation vasodilators have also been extensively studied with no convincing evidence of efficacy.[15]

The understanding of IPF as a mostly fibrotic disease with minimal or no inflammation has inaugurated the antifibrotic era with two currently approved drugs: pirfenidone and nintedanib. Both have been FDA-approved in 2014, after concomitant publication of their phase III trials, although pirfenidone had already been used in Europe and Asia based on previous trials.[16,17] Recently, the "ILD world" has witnessed the growth of antifibrotic indications beyond IPF, the prototypical fibrotic disease, including their use for systemic sclerosis, unclassifiable ILD, and the progressive fibrotic phenotype.

Pirfenidone

The mechanism of action of pirfenidone is yet to be completely understood, but it is believed to reduce pro-fibrotic mediators, fibroblastic proliferation, and myofibroblast differentiation, mainly through TGF-β downregulation.

The recommended dosage is three 267-mg capsules thrice a day. The most common adverse reactions include cutaneous rash or photosensitivity and gastrointestinal effects (mainly nausea or vomiting). Hepatic function should be monitored after treatment initiation owing to the risk of toxicity.[18]

Nintedanib

Nintedanib is a tyrosine kinase inhibitor that acts mainly through three receptors: fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDFGR) and vascular endothelial growth receptor (VEGFR).

The suggested posology consists of 150 mg twice daily. The most common adverse reactions include gastrointestinal side effects, mainly diarrhea (about 60% of patients). Loperamide or dose reduction is usually effective in its management. Liver enzymes should also be monitored because of the increased risk of toxicity. It should also be administered with caution in patients with recent cardiovascular events or concomitant use of anticoagulants owing to its mechanism of action (including an exclusion criterion for these populations in pivotal trials).[18]

The pivotal trials that culminated in the new paradigm of IPF treatment used a surrogate endpoint of FVC decline over 52 weeks, demonstrating an attenuation of functional loss by approximately 50% in a year. However, aggregated data from studies and, more recently, real-world cohort studies (mainly from world registries from different regions of the globe) have consistently shown mortality reduction, augmented progression-free survival, and reduced acute exacerbations, with sustained long-term effects.[19,20]

Nathan et al.[21] evaluated aggregated data from three main pirfenidone randomized trials (CAPACITY 004, CAPACITY 006, and ASCEND trials) and found a 52-week mortality reduction.[20-22] Similarly, the combination of phase II (TOMORROW) and phase III (INPULSIS I and INPULSIS 2) trials of nintedanib have also shown mortality reduction in 52 weeks, when compared with placebo, as well as a delayed time to a first acute exacerbation and a borderline (not significant) reduction of mortality from all causes.[19,23] A further analysis that included the extended open-label trial (INPULSIS-ON)[24] and an exploratory phase IIIb trial (combined for more than 1,000 patients) suggested a 5-year extended survival in the treated group of patients (median survival of 3 years in the placebo group and of 8 years in the treated group).

Outside the clinical trial settings, evidence also supports the use of antifibrotics. Dempsey et al.[25] evaluated a large database of over 8,000 patients in the USA using propensity score matching and found a global mortality reduction and fewer hospitalizations in the treated group. No differences were found between both the available medications, suggesting a similar efficacy. A Korean group of researchers conducted a similar analysis with longer follow-up and found a similar reduction in mortality, respiratory hospitalizations, acute exacerbations, and annual mortality rates at 1, 3, and 5 years.[26]

Several national or regional registries with real-world data have corroborated these findings. The Australian IPF Registry, which included patients with several comorbidities, a wide range of disease severity, and older age (i.e., patients usually left out of randomized trials), found better survival in the patients treated with antifibrotics regardless of disease severity at baseline.[27] Accordingly, the Finish IPF registry encompassed 28 centers and found a survival benefit in patients who received at least 6 months of treatment, even when taking account of between-group differences due to access to treatment (medication was reserved for patients with FVC between 50-90% of predicted values).[28] The Swedish IPF registry also found a survival benefit and longer transplant-free survival in patients with more severe disease (GAP index ≥ 2).[29]

The 2-year follow-up analysis of the German IPF registry likewise found a significant reduction in mortality from 87% in the treated group against 46% in patients without treatment in 1 year, and from 62% against 21%, respectively, in the 2-year period. Curiously, these findings remained significant even after a multivariate analysis that failed to demonstrate any difference in lung function loss in the period between the two groups, suggesting that antifibrotic treatment benefits in mortality reduction might occur regardless of FVC and DL_{co} trajectories.[30]

More recently, a systematic review and meta-analysis of 26 studies[31] comprising almost 13,000 patients have shown a reduction in mortality from all causes, with a relative risk of 0.55 (95% CI, 0.45-0.66) favoring antifibrotics. The effect was consistent across a sensitivity analysis and in different subgroups, including study type (randomized trial or cohort study), risk of bias, duration of follow-up, and studied drug. The same study suggested a reduction in AE-IPF risk of the same magnitude (hazard ratio [HR] = 0.63; 95% CI, 0.53-0.76).[31]

Given the rarity of the disease and the costs and restraints of conducting randomized controlled trials in this population of patients, although findings of aggregated populations and real-world data are largely subject to bias,[32] one might anticipate that the current evidence is almost definitive. Therefore, it should be regarded as enough to reassure a probable survival benefit and a significant reduction in mortality due to IPF, while further studies should assess the effects of new drugs currently under development or waiting for evidence-based analysis in combination with the current standard of care (Table 2).[16,17,19-28,30,31,33-41]

GERD treatment

The latest IPF guidelines[3] have withdrawn an early conditional recommendation of universal GERD treatment for IPF patients (even without symptoms) with antacid therapy. The prevalence of GERD in IPF patients is high, but evidence for its treatment (regarding lung disease) is conflicting. A recent meta-analysis failed to demonstrate any effect on mortality, number of hospitalizations, or functional decline in patients treated with proton pump inhibitors.[42] Reflux surgery has also been proposed; however, although safe, the primary endpoint was not reached in a randomized controlled trial.[43] Therefore, GERD treatment in the IPF population should follow recommendations from GERD guidelines.[3]

Special situations

Early or late disease

The efficacy of antifibrotic therapy (AFT) seems to be ubiquitous, working just as well in the subset of patients with early disease as in those with more advanced disease.[35,44,45] Early initiation of AFT is advocated due to its effect of attenuating functional loss (although not reversing any), but this decision should also consider diagnostic confidence, safety profile, life expectancy, and quality-of-life issues. However, the unpredictable course of the disease and the risk of AE-IPF warrant a prompt decision (without long watchful waiting periods). On the other hand, patients with more advanced disease (such as those with FVC < 50%) are still AFT candidates, since the effect of treatment is of the same magnitude, but greater mortality and increased risk of adverse effects should guide therapeutic decisions.

Elderly

IPF is an elderly disease, with rare exceptions (mostly in the context of familial IPF). However, patients > 75 years of age have an increased risk of adverse effects and higher discontinuation rates. Therefore, AFT should be used with more caution in this population.[46] Notwithstanding, frailty, as a measure of functional age, is very common in elderly IPF patients[47] and seems to have a greater impact on adverse events than biological age itself (even when adding measurement of telomere length to the analysis).[48] Hence, identifying patients with a critical state of frailty may be a better option than using age alone when selecting appropriate therapeutic strategies.

Switching

Although severe adverse events are rare and most side effects are manageable, some patients discontinue medication due to intolerance. Additionally, some patients may have their medication switched due to inefficacy (usually defined as a > 10% decline in FVC in 1 year or an acute exacerbation). Switching AFT appears to be safe, but evidence of its efficacy is scarce. In addition, AFT efficacy does not seem to disappear after an event of progression; therefore, continuity seems to be a reasonable option (and preferred over discontinuation alone).[49-51]

Accessibility

AFT in some countries, including Brazil, is restricted and, sometimes, exacerbates social disparities in access to health care (for instance, due to its prohibitive costs or in situations where medication is obtained only through litigation). European registries show that treatment availability rates vary from 26% to 78% for patients at different sites.[28,52] The Latin-American IPF registry (REFIPI) showed that 72% of participants were on some antifibrotic medication; however, underrepresentation of most populated countries/regions and selection bias probably overestimated access.[41] Many international regulation agencies, including those in Canada (CADTH), Australia (PBS), Portugal (Infarrmed), and the United Kingdom (NICE), have incorporated access to antifibrotics in their standard of care.

Comorbidities

Comorbidity incidences surpass what would be expected for IPF patients even after taking into account shared risk factors (such as smoking and age) and have a negative impact on prognosis.[53] In addition to GERD (addressed above), some comorbidities deserve special attention (Figure 3).

Lung cancer

The risk of lung cancer is increased in IPF patients, and this is one of the leading causes of mortality in this population.[28] The most frequent histology is squamous cell carcinoma, and most cancers are found in the lower lobes (as opposed to adenocarcinomas and

Table 2. Main studies evaluating the impact of antifibrotics on idiopathic pulmonary fibrosis regarding mortality and acute exacerbation of idiopathic pulmonary fibrosis.

Study	Study Type	Year	Antifibrotic	Outcome	Main Findings	Mortality Reduction	Effect on Acute Exacerbation
SHIONOGI Phase 2 - Research Group for Diffuse Lung Diseases Azuma et al.[17]	Randomized phase II trial	2005	Pirfenidone	Lowest oxygen saturation during 6MWT	Negative for the primary endpoint, but pirfenidone significantly reduced the decline in vital capacity at 9 months and reduced the incidence of acute exacerbations when compared with placebo.	No	Yes
SHIONOGI Phase 3 - Pirfenidone Clinical Study Group Taniguchi et al.[16]	Randomized trial	2010	Pirfenidone	FVC decline	Pirfenidone reduced the decline of lung function and improved progression-free survival.	No	No
CAPACITY-004 and CAPACITY-006 Noble et al.[22]	Randomized trial	2011	Pirfenidone	FVC decline	Pirfenidone reduced the rate of decline in FVC at 72 weeks in CAPACITY-004 (but not in CAPACITY-006) and reduced the mean change from baseline in 6MWD and improved progression-free survival in the pooled analysis.	No	N/A
TOMORROW Richeldi et al.[19]	Randomized phase II trial	2011	Nintedanib	FVC decline	Nintedanib reduced annual decline in FVC, incidence of acute exacerbations, and SGRQ score (improved quality of life)	No	Yes
INPULSIS-1 and INPULSIS-2 Richeldi et al.[23]	Randomized trial	2014	Nintedanib	FVC decline	Nintedanib reduced the annual rate of decline in FVC by 51% ($p < 0.001$)	No	Yes[a]
ASCEND King Jr. et al.[20]	Randomized trial	2014	Pirfenidone	FVC decline	Pirfenidone reduced change in FVC from baseline and improved progression-free survival (defined as death, decrease in FVC, or decrease in 6MWD).	No	N/A
Washington Group Canestaro et al.[33]	Systematic Review and Meta-analysis	2016	Pirfenidone + Nintedanib	All-cause and respiratory-specific death	Negative for primary endpoint, but pirfenidone and nintedanib had effects approaching significance under a fixed-effects model for all-cause mortality.	No	N/A
Combined CAPACITY and ASCEND trials Noble et al.[34]	Pooled analysis	2016	Pirfenidone	FVC decline or death	Pirfenidone reduced decline in lung function and improved other measures such as progression-free survival, 6MWD, and dyspnea.	Yes	N/A
Combined TOMORROW and INPULSIS Richeldi et al.[23]	Pooled analysis	2016	Nintedanib	FVC decline, acute exacerbation, SGRQ, and mortality in 52 weeks	Nintedanib reduced FVC decline, time to first acute exacerbation and on-treatment (but not all-cause) mortality	No	Yes
RECAP Costabel et al.[35]	Open-label extension study	2016	Pirfenidone	Long-term safety	Pirfenidone was deemed to be safe. Sustained effect on FVC decline and a median on-treatment survival of 77.2 months was observed.	N/A	N/A

Continue...▶

Table 2. Main studies evaluating the impact of antifibrotics on idiopathic pulmonary fibrosis regarding mortality and acute exacerbation of idiopathic pulmonary fibrosis. (Continued...)

Study	Study Type	Year	Antifibrotic	Outcome	Main Findings	Mortality Reduction	Effect on Acute Exacerbation
Combined SHIONOGI, CAPACITY and ASCEND trials Nathan et al.[21]	Pooled analysis	2017	Pirfenidone	Long-term mortality (120 weeks)	Pirfenidone was associated with a reduced relative risk of death for patients for all mortality outcomes (all-cause mortality, treatment-emergent all-cause mortality, idiopathic-pulmonary-fibrosis-related mortality, and treatment-emergent idiopathic-pulmonary-fibrosis-related mortality).	Yes	N/A
AIPFR Jo et al.[27]	Real-life Registry from Australia	2017	Pirfenidone + Nintedanib	Baseline characteristics	Improved survival in patients taking antifibrotics even after multivariate analysis adjusted for age, gender, smoking, BMI, and baseline lung function.	Yes	N/A
INSTAGE Kolb et al.[36]	Randomized trial	2018	Nintedanib + sildenafil	Change in SGRQ	Addition of sildenafil to nintedanib did not improve dyspnea and similar percentages of patients had at least one acute exacerbation or died.	No	No
Post-hoc CAPACITY and ASCEND trials Nathan et al.[37]	Pooled data analysis	2018	Pirfenidone	Continued effect of pirfenidone after a disease progression event	Patients receiving pirfenidone who experienced an initial absolute or relative decline in percent predicted FVC were less likely to experience further decline in lung function or death in the subsequent 6 months compared with those receiving placebo.	Yes	Yes[b]
INPULSIS-ON Crestani et al.[24]	Open-label extension study	2018	Nintedanib	Safety and long-term efficacy	Nintedanib had a safety profile consistent with that observed in the INPULSIS trials and effect on slowing progression persisted beyond 4 years.	N/A	N/A
Post-hoc TOMORROW, INPULSIS, INPULSIS-ON and Phase IIIb trial Lancaster et al.[38]	Pooled data analysis	2019	Nintedanib	Safety and survival	Treatment with nintedanib was considered safe. Survival was estimated as 11.6 years in the treated group (versus 3.7 in the placebo group).	Yes	N/A
EMPIRE Zurkova et al.[39]	Real-life registry from Czech Republic	2019	Pirfenidone	Overall survival and FVC decline	Pirfenidone increased overall 5-year survival versus no-antifibrotics (55.9% vs. 31.5% alive, respectively, p = 0.002).	Yes	No
FinnishIPF Kaunisto et al.[28]	Real-life registry from Finland	2019	Pirfenidone + Nintedanib	Demographics and survival	Patients who received ≥ 6 months of treatment had better survival compared with those who did not receive treatment in the unadjusted analysis.	Yes	N/A
Insurance Database Dempsey et al.[25]	Retrospective cohort	2019	Pirfenidone + Nintedanib	Mortality and hospitalization	Lower risk of all-cause mortality and hospitalization compared with no treatment.	Yes	Yes[b]

Continue...▶

Table 2. Main studies evaluating the impact of antifibrotics on idiopathic pulmonary fibrosis regarding mortality and acute exacerbation of idiopathic pulmonary fibrosis. (Continued...)

Study	Study Type	Year	Antifibrotic	Outcome	Main Findings	Mortality Reduction	Effect on Acute Exacerbation
IPF-PRO Snyder et al.[40]	Real-life registry	2019	Pirfenidone + Nintedanib	Predictors of death or lung transplant	The authors were unable to evaluate associations between the use of antifibrotic therapy at enrollment and death or lung transplant.	N/A	N/A
INSIGHTS-IPF Registry Behr et al.[30]	Real-life registry in Germany	2020	Pirfenidone + Nintedanib	Survival and FVC decline	Survival was significantly higher in IPF patients on antifibrotic therapy, but the course of lung function parameters was similar in patients on antifibrotic therapy or not.	Yes	N/A
Korean Cohort Kang et al.[26]	Retrospective cohort	2020	Pirfenidone + Nintedanib	Mortality, hospitalization, and acute exacerbation	Antifibrotic treatment significantly reduced the risks of mortality [hazard ratio (HR) = 0.59], all-cause hospitalization (HR = 0.71), respiratory-related hospitalization (HR = 0.67), acute exacerbation (HR = 0.69), and mortality after acute exacerbation (HR = 0.60).	Yes	Yes
Petnak et al.[31]	Systematic review and meta-analysis	2021	Pirfenidone + Nintedanib	Mortality and acute exacerbations	Antifibrotic treatment appears to reduce the risk of all-cause mortality and acute exacerbations.	Yes	Yes
REFIPI Caro et al.[41]	Real-life registry	2022	Pirfenidone + Nintedanib	Demographic, clinical, serological, functional, tomographic, histological, and treatment variables	Most patients in the REFIPI received antifibrotics, which were well tolerated and associated with a lower rate of adverse events than that reported in clinical trials.	N/A	N/A

IPF: idiopathic pulmonary fibrosis; AE-IPF: acute exacerbation of IPF; 6MWT: six-minute walking test; SGRQ: Saint-George's Respiratory Questionnaire; and 6MWD: six-minute walk distance. [a]Only INPULSIS-1 showed a reduction in the incidence of AE-IPF. [b]Respiratory-related hospitalization was analyzed as a surrogate for AE-IPF.

upper lobe predominance in the general population). The concomitancy of diagnosis is associated with poor prognosis (worse than the sum of each isolated condition), even with potentially resectable nodules (i.e., early disease), and treatment can be very challenging, since all treatment modalities (chemotherapy, radiotherapy, or surgery) are associated with increased risks, especially that of AE-IPF.[6,54] Some experts recommend screening patients with HRCT annually, even if clinically stable, due to the augmented risk of lung cancer; however, the frequency of screening, concerns with unnecessary radiation exposure, and clear benefits of this strategy remain unknown.

Pulmonary hypertension

Pulmonary hypertension (PH) is a common IPF complication and has long been associated with increased mortality risk.[6,55] Several pulmonary circulation vasodilators have been studied for IPF treatment (even without concomitant PH); however, although these medications appear to be safe, they have not been demonstrated to benefit the disease course. Inhaled therapies (specifically treprostinil) have shown promising results, with increased walk distance on 6MWT, longer time to clinical worsening, and decrease in brain natriuretic peptide when compared with placebo in a clinical trial.[56] However, the short follow-up period and high discontinuation rates highlight the need for confirmation of these promising results in future trials.

Cardiovascular disease

ILDs in general, and IPF in particular, increase the risk of cardiovascular disease, mainly acute myocardial infarction (MI) and chronic coronary artery disease (CAD). A cohort study of over 68,000 patients suggested that IPF is an independent risk factor for CAD (even after taking into account other risk factors such as age and smoking), especially in the population of patients between 60 and 79 years of age.[57] Although chronic CAD was more common in men, women had a higher risk of acute MI. A particular challenge is the differential diagnosis of worsening dyspnea in IPF patients (since CAD can lead to dyspnea or fatigue as an anginal equivalent) and exercise-induced hypoxia that could lead to increased ischemic events; therefore, a high index of suspicion from doctors is needed to diagnose CAD and MI in this population.[57]

Sleep disorders

Obstructive sleep apnea is extremely common in IPF patients, with a prevalence ranging from 50% to 90%. Some authors have suggested a common physiopathology of the two entities, with high-pressure swings, intermittent hypoxia, and association with GERD (and microaspirations) as possible etiologies for IPF due to recurrent injury. Most patients have less typical symptoms (such as excessive daytime sleepiness, snoring, and witnessed apnea). Likewise, lower BMI and higher desaturation indices, sometimes even in the absence of obstructive events, are found. Treatment with positive pressure (CPAP) seems challenging, with lower adherence and uncertainty regarding its efficacy.[58]

Mood disorders

Patients with IPF are at an increased risk for anxiety and depression. Symptoms of both disorders may be present in up to two-thirds of patients, even without fulfilling criteria for a specific mental illness. These symptoms correlate with respiratory symptoms (i.e., cough and dyspnea) and with disease severity, GAP index, and walk distance on the 6MWT.[59]

Emphysema

IPF and COPD share many risk factors, especially age and smoking; therefore, emphysema findings on HRCT are common (in up to 30% of IPF patients). However, the clinical impact of this finding will come

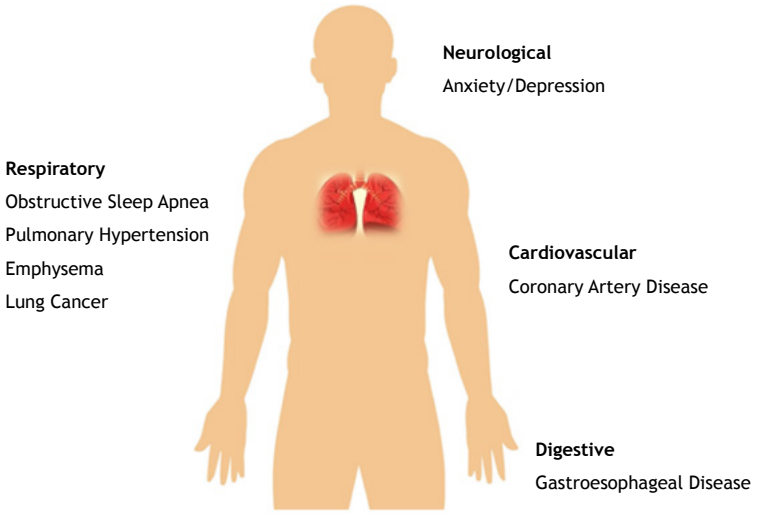

Figure 3. Main comorbidities in idiopathic pulmonary fibrosis.

down to the extension of both diseases—the upper predominance of emphysema and lower predominance of fibrosis constitutes a separate entity, frequently referred to as "combined pulmonary fibrosis and emphysema" or CPFE. The North-American IPF registry estimated the prevalence of CPFE in IPF patients to be approximately 13%. CPFE has some important distinct characteristics, such as pulmonary function pseudonormalization (with relative preservation of flows and volumes and accentuated loss of DL_{CO}), which impairs the use of FVC in the follow-up of this population. Besides that, PH seems to be more prevalent in this subgroup and has been associated with worse prognosis, although it can probably be explained by the sum of the extension of the two major components (emphysema and fibrosis).[6,60]

Acute exacerbation

AE-IPF, as previously defined, is a rather frequent and life-threatening event in IPF patients, accounting for a number of IPF-related deaths. Prognosis is poor, with mortality rates as high as 50%. Baseline disease severity negatively impacts the risk of AE-IPF.

No treatment has been shown to be effective, and corticosteroids remain the treatment of choice; however, evidence for this suggestion relies mainly on retrospective data and expert opinion. Several immunomodulatory therapies have already been employed as well, with conflicting results and relying a lot on single-center experiences.[11] Prevention of AE-IPF with antifibrotics remains the sole best evidence-based treatment, although many patients may still experience an AE-IPF event while on AFT (although with a delayed time to the first event and decreased frequency).

Acute or acute-on-chronic respiratory failure in these patients can be incredibly challenging. Mechanical ventilation (MV) in this population shares many features with ARDS, with greater lung heterogeneity but no lung recruitability, making protective ventilation strategies almost impossible in some cases (Figure 4). Employment of higher PEEP values has been associated with increased mortality, probably due to greater hyperinflation of healthy (with better compliance) lung portions, although no causality has been established. Owing to the high mortality rates, some authors have considered IPF a contraindication to MV, unless in the context of a bridge to lung transplant (LTx), but it might be employed in other situations, such as elective surgeries (e.g., surgical lung cancer treatment), when patients' initial presentation of the disease is an AE-IPF, and even in some special conditions (such as COVID-19 in a patient with early or moderate disease, which is thought to be reversible in an expected time frame). Noninvasive ventilation seems to be an alternative, but with a greater risk of barotrauma. The use of high-flow nasal cannula is a feasible option, with decreased work of breathing and delivery of high F_{IO_2} with better tolerability; however, evidence for its use (regarding clinical endpoints) is also lacking.[61]

Lung transplantation

Every patient with IPF should be considered for referral to a LTx center at diagnosis due to its poor prognosis, unless contraindications are readily identified, although inclusion in waiting lists must take account of the disease course (including hospitalizations) and the presence of comorbidities such as PH. ILD has surpassed COPD as the primary indication for LTx in the USA since an allocation score system has been adopted. Adequate selection of candidates is crucial, involving the impact of comorbidities, adherence to treatment, social and emotional aspects, and general risk profiling in order to achieve better outcomes, especially in settings of scarce supply of donors. Median survival is approximately 5 years, and many complications may arise after the procedure, particularly infection and chronic lung dysfunction; however, it has been demonstrated that LTx increases survival and improves symptoms in patients with advanced IPF.[3]

Rehabilitation

A pulmonary rehabilitation program (PRP) appears to be safe and is associated with improvement in symptoms, exercise capacity, and general quality of life. Data regarding long-term effects and mortality are still lacking, but it may be considered for any symptomatic patient with IPF. PRPs are also frequently employed perioperatively in LTx to improve outcomes.[62]

Symptom management and advanced disease

Disease course modifying drugs, such as AFT, have changed IPF treatment paradigms, but are not ideal, since disease course is still inexorable, besides having little or no impact on quality of life; therefore, caring for patients with IPF must include general measures, such as education about the disease course, smoking cessation strategies (when applicable), and immunization, along with palliative care (Figure 5). Palliative care is defined as symptom-based treatments aimed at improving quality of life and relief from suffering when indicated. It is often applied only to end-of-life care, but its use in early stages of diseases has been associated with extended survival and better quality of life in patients with lung cancer and refractory dyspnea from different causes.[63] Advanced care planning is key, preferably when patients are still able to make active decisions regarding their treatment strategies.[64]

Indications for ambulatory oxygen therapy generally follow those for COPD patients (Spo_2 below 88% at room air or between 88% and 90% when associated with polycythemia and/or PH), although evidence is limited for IPF patients. Exercise-induced hypoxia starts earlier in the course of disease, and oxygen use may alleviate symptoms, increase walk distance, and even improve short-term quality of life; however, health care costs and the burden of oxygen delivery systems should be weighed against their potential benefits.[65]

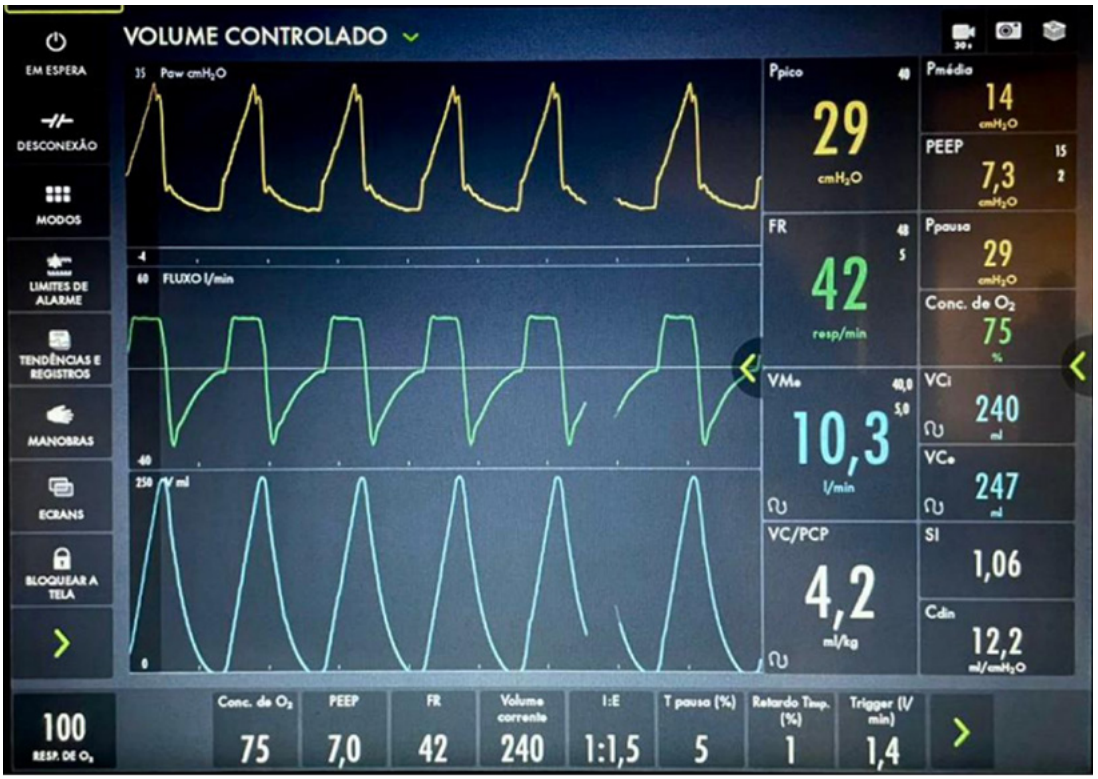

Figure 4. Mechanical ventilation parameters in a patient with acute exacerbation of idiopathic pulmonary fibrosis. Mechanical ventilation in this setting can be very challenging: note the high concentrations of oxygen (F_{IO_2} = 75%) and low static lung compliance (estimated on 11 mL/cmH_2O), with high driving pressure swings (22 cmH_2O) even with high respiratory rates (42 breaths/min) to prevent severe respiratory acidosis.

Dyspnea is usually the most debilitating symptom and can be effectively treated with opioids (e.g., morphine), alongside oxygen therapy, and PRP when indicated. Other nonpharmacological strategies such as breathing techniques, a hand-held fan, pacing guidance, and access to a breathlessness support service have been employed with great success in the treatment of refractory patients.[66] Cough is another important symptom and is sometimes very intense, and opioids are also first-line options, although codeine is usually preferred over morphine. Other strategies include treatment of comorbidities (such as GERD and rhinitis) and several options with lower quality evidence (such as gabapentin, corticosteroids, and even pirfenidone).

Perspectives

IPF remains the prototypical fibrotic ILD and, although AFT has been expanded to other ILDs, its long-standing history of trials, the validation of FVC as a surrogate endpoint, its presentation as an almost exclusively fibrotic disease, and its poor survival (which makes it suitable for shorter term studies) makes it an ideal candidate for trying out new therapies. In addition, current treatments, although effective, are far from perfect, since their effect on ameliorating lung function decline might be considered mere palliation, even if prolonged survival is indeed achieved.

Three recent drugs have shown promising results in phase II trials: pamrevlumab, a monoclonal antibody against connective-tissue growth factor, which reduced FVC decline in 48 weeks[67]; recombinant human pentraxin-2 protein, which showed a sustained effect on attenuating functional and walking distance declines in 24 weeks,[68] although a phase III open-label trial evaluating its safety and efficacy was terminated early due to an interim analysis indicating futility[69]; and a phosphodiesterase 4B inhibitor that prevented lung function decline at 12 weeks.[70] Currently, at least 15 randomized controlled trials are underway to evaluate the treatment of patients with chronic IPF or AE-IPF.

The future of IPF treatment, therefore, holds new perspectives of integrating early, less invasive diagnosis (with an essential role of biomarkers, which have been at the forefront of a great deal of research) and therapies aimed at restraining disease progression, most probably based on personalized or precision medicine (through targeting of genetic modification, for instance).[71]

AUTHOR CONTRIBUTIONS

AFA: conception, literature search, writing, and reviewing the manuscript. PFBC: literature search and writing the manuscript. RAK: conception and reviewing the manuscript. All authors have approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

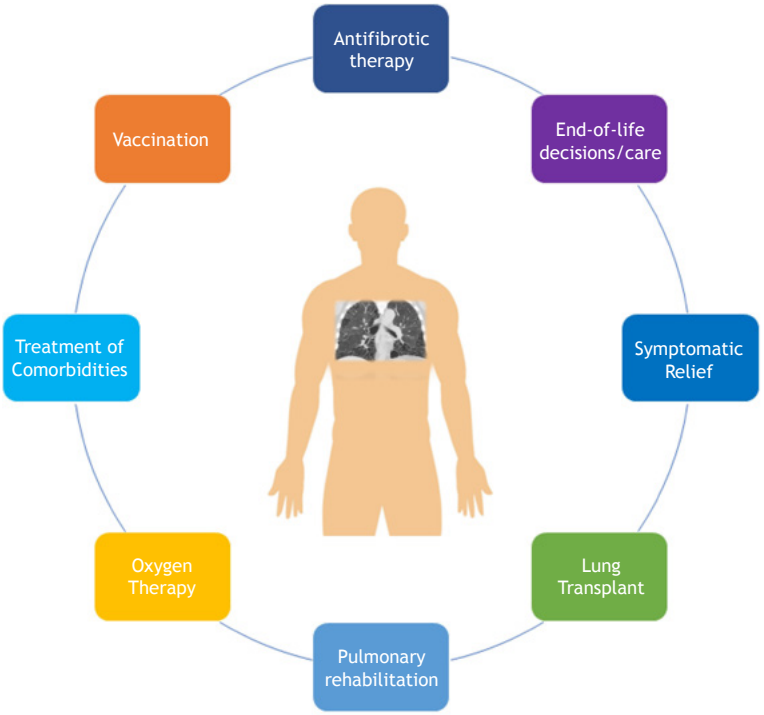

Figure 5. Management of patients with idiopathic pulmonary fibrosis.

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Veno-venous extracorporeal membrane oxygenation in patients with SARS-CoV-2 pneumonia in Brazil: a case series

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ABSTRACT

Objective: The world has been suffering from the COVID-19 pandemic. Some COVID-19 patients develop severe viral pneumonia, requiring mechanical ventilation and measures to treat refractory hypoxemia, such as a protective ventilation strategy, prone positioning, and the use of veno-venous extracorporeal membrane oxygenation (VV-ECMO). We describe a case series of 30 COVID-19 patients who needed VV-ECMO at the *Hospital Alemão Oswaldo Cruz*, located in the city of São Paulo, Brazil. **Methods:** We included all patients who required VV-ECMO due to COVID-19 pneumonia between March of 2020 and June of 2021. **Results:** Prior to VV-ECMO, patients presented with the following median scores: SOFA score, 11; APPS score, 7; Respiratory ECMO Survival Prediction score, 2; and Murray score, 3.3. The 60-day-in-hospital mortality was 33.3% (n = 10). **Conclusions:** Although our patients had a highly severe profile, our results were similar to those of other cohort studies in the literature. This demonstrates that VV-ECMO can be a good tool even in a pandemic situation when it is managed in an experienced center.

Keywords: Extracorporeal membrane oxygenation; COVID-19; SARS-CoV-2; Respiratory distress syndrome.

INTRODUCTION

ARDS is a challenging condition in intensive care, and if it is left untreated, it can lead to multiple organ failure and death. It can be defined as an acute condition of hypoxemia, whose pathophysiology is defined by immune-mediated disruption of the alveolar-capillary interface and noncardiogenic edema formation.[1] Since December of 2019, the world has been suffering from COVID-19, caused by the new SARS-CoV-2 virus. Most patients have mild to moderate symptoms; however, some develop severe viral pneumonia, requiring mechanical ventilation and measures to treat refractory hypoxemia, such as a protective ventilation strategies and prone positioning. However, mortality can be as high as 60%, which makes extracorporeal membrane oxygenation (ECMO) a therapeutic option in some cases.[2,3]

Our goal was to present a case series of patients with ARDS caused by COVID-19 treated at the *Hospital Alemão Oswaldo Cruz* (HAOC), a private hospital in the city of São Paulo, Brazil, who needed veno-venous ECMO (VV-ECMO).

METHODS

We included all patients admitted to the HAOC who required VV-ECMO due to COVID-19 pneumonia, confirmed by nasal swab PCR testing, and were cannulated by the hospital ECMO team between March of 2020 and June of 2021.

The HAOC is a private hospital located in the city of São Paulo and is an accredited ECMO center by the Extracorporeal Life Support Organization (ELSO). Patients were cannulated when ECMO material was available and there was an indication for VV-ECMO in accordance with the ELSO guidelines,[4] as follows: hypoxemia, defined as a Pao_2/Fio_2 ratio lower than 80 for at least 6 h or lower than 50 for at least 3 h after using a neuromuscular blocker and prone positioning; and/or hypercapnia, defined as a pH lower than 7.25 associated with a pCo_2 above 60 mmHg for at least 6 h. Patients could have already been admitted to our service or been cannulated by the ECMO Travel Team and transferred to our institution.

Patients were managed in accordance with our institutional protocol, using volume-controlled ventilation in the initial phase of ventilation, aiming at obtaining protective ventilation, defined by V_T less than or equal to 6 mL/kg of the predicted weight and plateau pressure below 30 cmH_2O. PEEP was defined in accordance with the lower-PEEP table provided in a clinical trial.[5] Other ventilation modes such as pressure-regulated volume control or other PEEP definition methods, such as PEEP titration, were used as an exception when protective

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ventilation was not achieved by means of the standard protocol. During the ventilatory weaning phase, pressure-controlled ventilation and pressure support ventilation were used. Regarding sedation, given the prolonged ventilation and sedation time, midazolam and fentanyl were the standard medications, propofol being used in cases with more difficult sedation. Other sedatives could be used as a strategy for weaning from sedation, such as ketamine and dexmedetomidine. Patients received neuromuscular blockers when they had a Pao_2/FIO_2 ratio below 150 or asynchrony unresolved with ventilatory adjustment. The selection of the neuromuscular blocker varied based on its availability. At the beginning of the study, four intensive care physicians formed the ECMO team, which had had four years of experience. They were also assisted by trained ECMO management nurses even when cannulation was performed in another site by the ECMO travel team. Cannulation was usually performed by two physicians and a nurse, preferably through the right jugular vein and the right femoral vein using an ultrasound-guided puncture when available. Contraindications of ECMO and indications of decannulation were guided in accordance with the ELSO guidelines.[4]

Data were collected retrospectively using the electronic medical record system, including laboratory tests from admission until discharge, death, transfer, or 60 days after ECMO, whichever came first. Categorical data are displayed as absolute and relative frequencies, whereas discrete and continuous data are displayed as medians and interquartile ranges considering a non-normal distribution.

RESULTS

Thirty patients who underwent VV-ECMO were included in this case series. The demographic characteristics of the patients are summarized in Table 1. Male and female patients were 16 (53.3%) and 14 (46.7%), respectively. Most patients were cannulated at our hospital, and only 2 patients were cannulated at another site by our ECMO travel team and then transferred to our hospital. The median age of the sample was 53 years (41-60 years), ranging from 26 to 73 years. Obesity was the most prevalent comorbidity, in 20 patients (66.7%), followed by hypertension, in 9 (30.0%), and hypothyroidism, in 6 (20.0%). There were at least two comorbidities in 15 (50.0%) of the cases. Only 1 patient had a previous COVID-19 vaccination record. However, the use of any medication under study for COVID-19 at the time was high, azithromycin being the most common, in 13 patients (43.3%), followed by colchicine, in 6 (20.0%), and hydroxychloroquine, in 4 (13.3%). There was also a high prevalence of antibiotic use. Only 2 patients had not used them before ECMO.

The median ventilation days before ECMO was 4 (1-10), whereas the median duration of symptoms was 19 days (13-24 days), and the length of hospital stay was 11 days (5-15 days). The clinical characteristics of the patients before ECMO are summarized in Table 2, including rescue therapy used before cannulation. As for severity, patients had a median SOFA score of 11 (8-12); a median APPS (acronym for Age, Pao_2/FIO_2 ratio, and Plateau pressure measured at 24 h after diagnosis of ARDS Score) of 7 (7-8); a median Respiratory ECMO Survival Prediction (RESP) score of 2 (2-5); and a median Murray score of 3.3 (3.3-3.0). As for ventilatory characteristics, patients had a median pulmonary compliance of 20 cmH_2O (14-24 cmH_2O) and required a median plateau pressure of 28.5 cmH_2O (25-32 cmH_2O). All patients were treated with a neuromuscular blocker (median duration = 48 h [5-144 h]), 23 patients also used the prone position maneuver, and only 1 patient used inhaled nitric oxide. Regarding laboratory characteristics, the median Pao_2/FIO_2 ratio was 66 (54-75), and there was a high prevalence of lymphopenia with a median lymphocyte count of 680 cells/mm^3 (550-990 cells/mm^3). The median pH was 7.31 (7.23–7.40).

The main indication for ECMO was hypoxemia, in 25 patients (83.3%), and hypercapnia was the sole indication in only 1 (3.3%), whereas both were present in 4 (13.3%). The characteristics of ECMO are summarized in Table 3. The median diameter of the inflow cannula was 25 Fr (23-29 Fr), whereas that of the outflow cannula was 19 Fr (19-21 Fr).

Table 1. Characteristics of the sample (N = 30).[a]

Characteristic	Result
Sex	
Male	16 (53.3)
Female	14 (46.7)
Location	
In site	28 (93.3)
ECMO travel team	02 (06.7)
Age, years	53 [41-60]
Comorbidities	
Hypertension	09 (30.0)
Diabetes	05 (16.7)
Asthma	04 (13.3)
Hypothyroidism	06 (20.0)
Obesity	20 (66.7)
BMI, kg/m^2	
< 25.0	05 (16.7)
25.0-29,9	05 (16.7)
30.0-34,9	12 (40.0)
35.0-39,9	07 (23.3)
> 40.0	01 (03.3)
Vaccinated for COVID-19	01 (03.3)
Prior drug use	
Any antibiotic	28 (93.3)
Tocilizumab	01 (03.3)
Hydroxychloroquine	04 (13.3)
Azithromycin	13 (43.3)
Remdesivir	01 (03.3)
Colchicine	06 (20.0)

ECMO: extracorporeal membrane oxygenation. [a]Values expressed as n (%) or median [IQR].

Table 2. Clinical characteristics of the patients before the use of extracorporeal membrane oxygenation (N = 30).[a]

Characteristic	Result
Time to ECMO, days	
First symptoms to ECMO	19 [13-24]
Hospital admission to ECMO	11 [5-15]
Intubation to ECMO	4 [1-10]
Total SOFA score[b]	11 [8-12]
Vasoactive-inotropic score[b]	6 [0-25]
APPS[b]	7 [7-8]
RESP score[b]	2 [2-5]
Murray score	3.3 [3.3-3.5]
Ventilation parameters	
FIO_2, %[b]	100 [100-100]
PEEP, cmH_2O[b]	10 [10-10]
RR, breaths/min	34 [30-36]
Plateau pressure, cmH_2O[c]	28.5 [25-32]
Driving pressure, cmH_2O[c]	17 [13-24]
Pulmonary compliance, cmH_2O[c]	20 [15-24]
Laboratory analysis	
pH[b]	7.31 [7.23-7.40]
PaO_2/FIO_2[b]	66 [54-75]
pCO_2, mmHg[b]	55 [47-68]
Plasma bicarbonate, mmol/L[e]	27 [22-32]
Arterial lactate, mg/dL	14 [11-20]
White cell count, cells/mm^3[c]	12.920 [9.510-15.300]
Lymphocytes, cells/mm^3[c]	680 [550-990]
Serum creatinine, mg/dL[c]	0.90 [0.57-1.36]
Rescue therapy before ECMO	
Neuromuscular blockade, h[d,f]	48 [5-144]
Prone positioning	23 (76.7)
Inhaled nitric oxide	01 (3.3)

ECMO: extracorporeal membrane oxygenation; APPS: acronym for Age, PaO_2/FIO_2 ratio, and Plateau pressure measured at 24 h after diagnosis of ARDS Score; and RESP: Respiratory ECMO Survival Prediction score. [a]Values expressed as n (%) or median [IQR]. [b]n = 29. n = 28. [d]n = 27. [e]n = 24. [f]All patients used neuromuscular blockers, but only 27 patients had the total number of hours of treatment recorded.

Table 3. Characteristics of extracorporeal membrane oxygenation use (N = 30).[a]

Characteristic	Result
ECMO indication criteria	
Hypoxemia	25 (83.3)
Hypercapnia	01 (03.3)
Both	04 (13.3)
Diameter of inflow cannula. Fr	25 [23-29][b]
Diameter of outflow cannula. Fr	19 [19-21][b]
ECMO parameters on ECMO Day 1	
ECMO blood flow. L/min	4.5 [4.2-5.0]
Sweep gas flow. L/min	5 [4-6][c]
FmO_2. %	100 [100-100]
Ventilation parameters on ECMO Day 1	
FIO_2. %	30 [30-40]
PEEP. cmH_2O	10 [8-10]
RR. breaths/min	10 [10-12]
Plateau pressure. cmH_2O	23 [21-26][d]
Driving pressure. cmH_2O	14 [12-15][d]
Drug use	
Antibiotics for any reason	29 (96.7)
Corticosteroids	30 (100.0)
Anticoagulation drugs	29 (96.7)
Vasoactive drugs	24 (80.0)
Tracheostomy during ECMO	14 (46.7)
Renal replacement therapy during ECMO	11 (36.7)

ECMO: extracorporeal membrane oxygenation; and FmO_2: membrane fraction of oxygen. [a]Values expressed as n (%) of patients or median [IQR]. [b]n = 28. [c]n = 29. [d]n = 21.

Regarding ventilatory characteristics, there was a reduction in plateau pressure, with the median value of 23 cmH_2O (21-26 cmH_2O). However, these data were missing in 9 patients (30%). Antibiotic use remained high, in 29 (96.7%) of the patients. All of the patients used corticosteroids, and only 1 patient received no anticoagulation therapy. Dialysis during ECMO was required in 11 patients (36.7%), and so was tracheostomy, in 14 (46.7%).

The 60-day-in-hospital mortality was 33.3% (n = 10). Among the survivors, 13 (43.3%) were discharged, 5 (16.7%) were still hospitalized off of ECMO, 1 (3.3%) was still hospitalized on ECMO, and 1 (3.3%) was transferred to another hospital for lung transplantation (still on ECMO). The main cause of death was septic shock, in 7 patients (23.3%), and hemorrhagic stroke, in 3 (10.0%). Outcomes and complications are summarized in Table 4. The median duration of ECMO was 12 days (8-22 days). The most common complications were microbiologically confirmed infection, in 23 patients (76.7%); major bleeding, in 10 (33.3%); severe thrombocytopenia, in 7 (23.3%); and tachyarrhythmia requiring electrical cardioversion, in 4 (13.3%). Anticoagulation was discontinued in 16 patients (53.3%). Regarding infections, 17 patients (56.6%) had ventilator-associated pneumonia; 6 (20.0%) had bloodstream infection, and 3 (10.0%) had urinary tract infection. There was a necessity to change the ECMO circuit in only 5 patients (16.6%), adding a second inflow cannula in 3 patients (10%), adding a second membrane in 1 (3.3%), and replacing the pump and membrane due to clotting, in 1 (3.3%).

DISCUSSION

In this case series, we describe the cases of 30 patients with COVID-19 pneumonia who required VV-ECMO support due to hypoxemia and/or hypercapnia, representing the experience in our center during the pandemic. The 60-day mortality rate in this sample was 33.3%. Mortality in VV-ECMO cohorts due to COVID-19 has great variability in the literature. The first annual report of the cases found in the ELSO registry comprised a sample of 1,035 patients in early 2020 and demonstrated a 90-day mortality rate of 37%,[6] which is close to what was found in our series.

Table 4. Outcomes and complications (N = 30).[a]

Variable	Result
Outcome in 60 days	
Death	10 (33.3)
Hospital discharge	13 (43.3)
Still hospitalized off of ECMO	05 (16.7)
Still hospitalized on ECMO	01 (3.3)
Transfer for transplant	01 (3.3)
Cause of death	
Septic shock	07 (23.3)
Hemorrhagic stroke	03 (10.0)
Days on ECMO	12 [8-22]
Complications	
Major bleeding	10 (33.3)
Severe thrombocytopenia	07 (23.3)
Tachyarrhythmia	04 (13.3)
Microbiologically confirmed infections[b]	23 (76.7)
Ventilator-associated pneumonia	17 (56.7)
Bloodstream Infection	06 (20.0)
Urinary tract infection	03 (10.0)
Circuit changes	05 (16.7)
Second inflow cannula	03 (10.0)
Second membrane	01 (3.3)
Membrane change	01 (3.3)
Pump change	01 (3.3)

ECMO: extracorporeal membrane oxygenation. [a]Values expressed as n (%) of patients or median [IQR]. [b]It refers to the number of patients who had some clinically overt infection with the infectious agent identified in a culture compatible with the focus of the infection. Even when the patient had more than one type of infection, he/she was counted only once.

Also, an American cohort study involving 130 patients reported a similar 60-day mortality rate of 34.6%,[7] as did a British cohort study involving 43 patients (32.6%),[8] and a cohort of 76 patients in Marseille, France (38%).[9] However, the second annual ELSO registry report showed that, among the 3,777 new cases reported, the 90-day mortality rate rose up to 51.9% in centers that had already participated in the first report and to 58.9% in new centers,[10] which is considerably higher than the rate found in our series. Similarly to these data, a cohort study in Warsaw involving 75 patients reported a 30-day mortality rate of 61.3%,[11] and a cohort study with 302 patients in Paris showed a 90-day mortality rate of 54%.[12] Pre-COVID mortality rates in patients undergoing VV-ECMO also showed high variability. Combes et al.[3] reported a 60-day mortality rate of 35%. However, a large German cohort study that collected data between 2010 and 2016 showed, in a sample of 12,572 patients on VV-ECMO, much higher mortality rates, varying each year from 53% to 66%.[13]

Some factors may explain this difference. In a systematic review and meta-analysis on the use of ECMO in COVID-19 involving 16 cohorts and 706 patients, Chong et al.[14] reported that survivors were younger, had fewer comorbidities, had higher pH, and used renal replacement therapy or vasoactive drugs less frequently. In that study, survivors had a mean age of 51.28 years vs. 55.15 years in nonsurvivors.[14] Our series had a mean age of 51 years and a median age of 53 years. Chong et al.[14] reported that patients with less than two comorbidities and those with two or more comorbidities presented with mortality rates of 23% and 31%, respectively. In our sample, 50% of cases had two or more comorbidities. The mean pH of survivors and nonsurvivors was 7.33 and 7.26, respectively, in that review,[14] whereas the mean and median of pH in our series were 7.3 and 7.31, respectively. In that study, renal replacement therapy was necessary in 21% and 39% of survivors and nonsurvivors, respectively,[14] whereas our patients required renal replacement therapy in 36.7% of the cases (considering the whole sample, regardless of their being survivors or nonsurvivors). Finally, vasoactive drug use was required in 76% of the survivors and in 92% of nonsurvivors in that study,[14] while vasoactive drugs were used in 80% of our cases. Table 5 compares our results with those of other four cohort studies regarding the use of ECMO in COVID-19 patients and demonstrates that our case series presented with either similar or worse risk factors than did those studies with similar mortality rates, and sometimes they were comparable to cohorts with higher mortality rates.

In addition to these factors, when analyzing the pre-ECMO data from our case series, we realized that the sample represents a group of patients who, despite having been cannulated relatively early, presented with high clinical severity and severe ARDS in a very advanced state. Our patients presented with median values as follows: SOFA score, 12; RESP score, 2; APPS score, 7; Murray score, 3.3; ventilation days before ECMO, 4 days; compliance, 20 cmH_2O; and Pao_2/F_{IO_2} ratio, 66. These data demonstrate a more severe patient profile than do other cohorts with similar mortality rates, which is comparable to the severity found in cohorts with higher mortality rates. This comparison is also shown in Table 5.

Another important aspect of our series was anticoagulation. All of the patients were maintained on or started anticoagulation during cannulation. However, 33.3% of them had major bleeding (defined as clinically overt bleeding which was fatal, or associated with a reduction in hemoglobin level of 2 g/dL, or transfusion of at least two units of packed red blood cells), including 3 cases of lethal hemorrhagic stroke (representing 10% of the sample and 30% of the deaths), and 23.3% had severe thrombocytopenia, causing anticoagulation to be suspended in 53.3% of the cases. However, only 1 patient had circuit clotting that required circuit replacement, and there was no diagnosis of clinical thrombosis such as deep vein thrombosis or pulmonary thromboembolism after cannulation. These data greatly diverge from those in the literature. Ripoll et al.[15] found in their observational study the occurrence of thrombosis in 66.7% of 30 patients with COVID-19 on VV-ECMO even without circuit clotting. It is noted, however, that this difference may be due

Table 5. Comparison among studies on the topic.[a]

Characteristic	Study				
	Shaefi et al.[7]	Zhang et al.[8]	Daviet et al.[9]	Lebreton et al.[12]	Present study
Participants, N	130	43	76	302	30
Country	USA	UK	France	France	Brazil
Mortality rate	34.6%	32.6%	38%	54%	33.3%
Age, years	45	49	61	52	53
More than two comorbidities	31.6%	N/A	N/A	N/A	50%
pH	N/A	N/A	7.30	7.31	7.31
Renal replacement therapy	21.8%	37.9%	33%	43%	36.7%
Use of vasoactive drugs	N/A	79.3%	N/A	N/A	80%
SOFA score	N/A	6	7	12	11
RESP score	3	4	1	N/A	2
Ventilation use before ECMO, days	2	5	6	5	4
Pao_2/Fio_2	85	67.5	71.5	61	66
Pulmonary compliance, cmH_2O	28	N/A	23	N/A	20
Thrombosis	22.6%	N/A	N/A	N/A	0
Circuit coagulation	N/A	N/A	15%	10%	3.3%
Major bleeding	24.7%	18.6%	57%	43%	33.3%
Hemorrhagic stroke	4.2%	N/A	N/A	12%	10%
Severe thrombocytopenia	N/A	N/A	N/A	18%	23.3%

ECMO: extracorporeal membrane oxygenation; and RESP: Respiratory ECMO Survival Prediction. [a]Values expressed as median, except where otherwise indicated.

to their active diagnosis,[15] something that was not performed in our series. Specifically, the occurrence of hemorrhagic stroke in the ELSO report varied from 5% to 7% between the groups.[6] Table 5 also shows the comparison of the occurrence of coagulation and anticoagulation complications between our study and four other cohorts.[7-9,12] Although the ELSO guidelines still indicate the use of anticoagulation in VV-ECMO,[5,16] there is a current tendency to use less anticoagulation even though there is no formal contraindication for it.[17] The results of our series corroborate this trend.

Because the present study is a case series, the main limitations are related to the design of the study itself. Series of cases, since they are observational studies, but mostly because they have no comparison groups, are especially subject to bias, selection bias being the most relevant one. Our study is also retrospective, which ends up contributing to this limitation. Another important factor to be mentioned was the atypical situation imposed by the pandemic that generated a lack of resources; therefore, the availability of ECMO machines, membranes, and circuits were limited, which demanded an extremely criterial decision-making prior to cannulating a patient.

In conclusion, we herein present our experience of 30 cases of patients with COVID-19 who underwent VV-ECMO. Although our patients had a highly severe profile, we obtained similar results than those in other cohort studies in the literature. This demonstrates that VV-ECMO can be a good tool even in a pandemic situation when it is managed in an experienced center.

AUTHOR CONTRIBUTIONS

FAD and FLF co-supervised the study. LMCRB and GNA: data collection and drafting the manuscript. GBFD: data collection. DI and LMCRB: data analysis. All of the authors actively participated in study conception and review of the manuscript, as well as approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Continuing health education as a tuberculosis control strategy in the prison system

Karine Zenatti Ely[1,2], Victor Göttems Vendrusculo[3], Isabela Frighetto[3], Andréia Rosane de Moura Valim[2], Lia Gonçalves Possuelo[2]

TO THE EDITOR:

Tuberculosis remains a challenge to global public health, particularly in prisons, where the risk of contracting the disease is 30 times higher.[1] The state of Rio Grande do Sul, Brazil, has more than 40,000 prison inmates and coverage by *equipes de Atenção Primária Prisional* (eAPP, prison primary care teams) of approximately 54.4% of closed prison inmates. Currently, there are 45 eAPP distributed in penal institutions throughout the state of Rio Grande do Sul, most of which are overcrowded.[2]

The need to expand and improve actions related to tuberculosis care, tuberculosis surveillance, and management of tuberculosis control, as recommended by national and international health agencies,[3,4] encouraged the development of continuing health education activities focused on prison inmates.[5] The *Programa de Educação Permanente em Saúde – Sistema Prisional* (PEPSSP, Continuing Health Education Program – Prison System) took place from July 6 to December 14, 2021, targeting prison system staff, managers, social control representatives, and the academic community. The COVID-19 pandemic prompted a virtual format, with 11 virtual lectures and 6 virtual roundtable discussions being offered. The virtual lectures were streamed live on YouTube and remain available to the public.[6]

The live-streamed virtual lectures covered topics related to tuberculosis in the prison system, tuberculosis/HIV coinfection, rapid testing at prison entry, and analysis of indicators for monitoring and evaluation of tuberculosis, among other topics. The virtual roundtable discussions were motivated by triggering questions, identifying the daily work challenges to control tuberculosis in prisons.

To complement the theoretical activities of the PEPSSP, the first *Competição em Saúde contra a Tuberculose no Sistema Prisional* (COMPETI-TB, Health Competition against Tuberculosis in the Prison System) was developed.[7] This competition took place from March 23 to May 4, 2022, and involved the participation of 19 teams linked to prisons in Rio Grande do Sul and 1,400 prison inmates, who were directly or indirectly involved. The launch of the first COMPETI-TB, which addressed the theme "Challenges of controlling tuberculosis in the prison system," was streamed live on YouTube on March 23, 2022. The registered teams were mixed, including professionals from both the health and security sectors. Multidisciplinary teams from prisons with enabled eAPP and other teams providing healthcare services for incarcerated individuals participated. The first COMPETI-TB consisted of 10 challenges and 2 bonus activities involving tuberculosis control that fostered competition between prisons. The completion of these challenges and bonus activities was proven electronically, with photos, reports, and videos; deadlines and scores were stipulated; and at the end, the teams with the highest scores and the outstanding teams from each penitentiary region of the state were awarded.

The proposed challenges had a diverse range of scores, with tasks considered to present with a low level of difficulty being worth 10 points, those with an intermediate level of difficulty being worth 25 points, and those with a high level of difficulty being worth 50 points. Bonus activities were worth additional points and served as tie-breakers.

Through posters, brochures, banners, and the *Pedágio da TB* (TB toll), teams discussed the concept of the disease, its transmission, and ways to prevent it, as well as how to identify individuals with respiratory symptoms. A discrepancy was observed between protocols and their implementation, which led to a movement towards standardization of actions and practices, such as use of an appropriate place for sputum collection and use of tuberculosis screening strategies, including active search for individuals with respiratory symptoms and rapid testing for infectious diseases at entry into the prison system.

The teams replicated continuing health education activities in their daily contexts through lectures, roundtable discussions, preparation of informational materials and educational games, such as the *Bingo da TB* (TB bingo), questionnaires, and lessons on the topic, all of which targeted prison staff and prison inmates. Several prisons established partnerships with educational institutions as part of the proposed challenges. There was an assessment of tuberculosis and HIV control indicators, application of the annual active case-finding score by the World Health Organization, and updating of or getting acquainted with registries of individuals with respiratory symptoms, as recommended by the Brazilian National Ministry of Health.[3]

The final challenge was the completion of an evaluation form by the participating teams. This made it possible to confirm the importance of the PEPSSP for correctional institutions, as it not only disseminates technical knowledge through practical activities, but also enables the integration between professionals with diverse knowledge.

This intervention proposal is part of an umbrella project called "Contributions to state prison health management:

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2. Programa de Pós-Graduação em Promoção da Saúde, Universidade de Santa Cruz do Sul, Santa Cruz do Sul (RS) Brasil.
2. Curso de Medicina, Departamento de Ciências da Saúde, Universidade de Santa Cruz do Sul, Santa Cruz do Sul (RS) Brasil.

monitoring and evaluation, continuing education, and health technologies," which has been approved by the Health Ethics Committee of the *Universidade de Santa Cruz do Sul* (Protocol no. 4.251.658). The first COMPETI-TB closing and award ceremony also took place through a live stream,[8] in which a compilation of activities developed during COMPETI-TB was presented and a Joint Informational Note on tuberculosis surveillance and control in the prison system was issued.[9]

This letter to the editor presents innovative strategies, reporting on what has been accomplished so far, and strongly recommends active case finding and systematic screening for tuberculosis in prisons.[10] This recommendation aligns with the United Nations 2030 Agenda for Sustainable Development, which includes tuberculosis control. The results presented here demonstrate the effectiveness of the implementation of the continuing health education policy. The PEPSSP reflects the dynamism and comprehensiveness of the Brazilian Unified Health Care System and promotes the value of experiences, the exchange of experiences, and meaningful learning, proving to be essential for solving problems in the daily life of prisons and for addressing tuberculosis and other complexities affecting prison inmates.

AUTHOR CONTRIBUTIONS

KZE, VGV, IF, ARMV, and LGP: manuscript design, data collection, data analysis, drafting of the manuscript, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Pulmonary emphysema associated with skin nodules

Luciana Volpon Soares Souza[1], Arthur Soares Souza Jr[1,2], Edson Marchiori[3]

A 55-year-old nonsmoking female patient with a known diagnosis of neurofibromatosis type 1 (NF1) since adolescence presented with a two-month history of dyspnea and cough. During adolescence, she developed subcutaneous and cutaneous neurofibromas predominantly on the chest wall (Figure 1A). In addition, she had café au lait spots on the skin. The patient's brother also had NF1. She denied fever. Laboratory test findings, including alpha-1 antitrypsin levels, were normal. No pulmonary function testing was performed. A chest X-ray showed multiple soft-tissue nodules on the chest wall (Figure 1B). Chest CT demonstrated bilateral emphysematous changes with subpleural bullae, predominantly in the upper lobes, along with several cutaneous and subcutaneous nodules (Figures 1C and 1D). A diagnosis of neurofibromatosis-associated diffuse lung disease was established.

NF1 or von Recklinghausen's disease is a genetic disorder characterized by multiple tumors of ectodermal and mesodermal tissues. The disease has a varied clinical presentation, with subcutaneous and cutaneous neurofibromas, café au lait spots on the skin, and iris

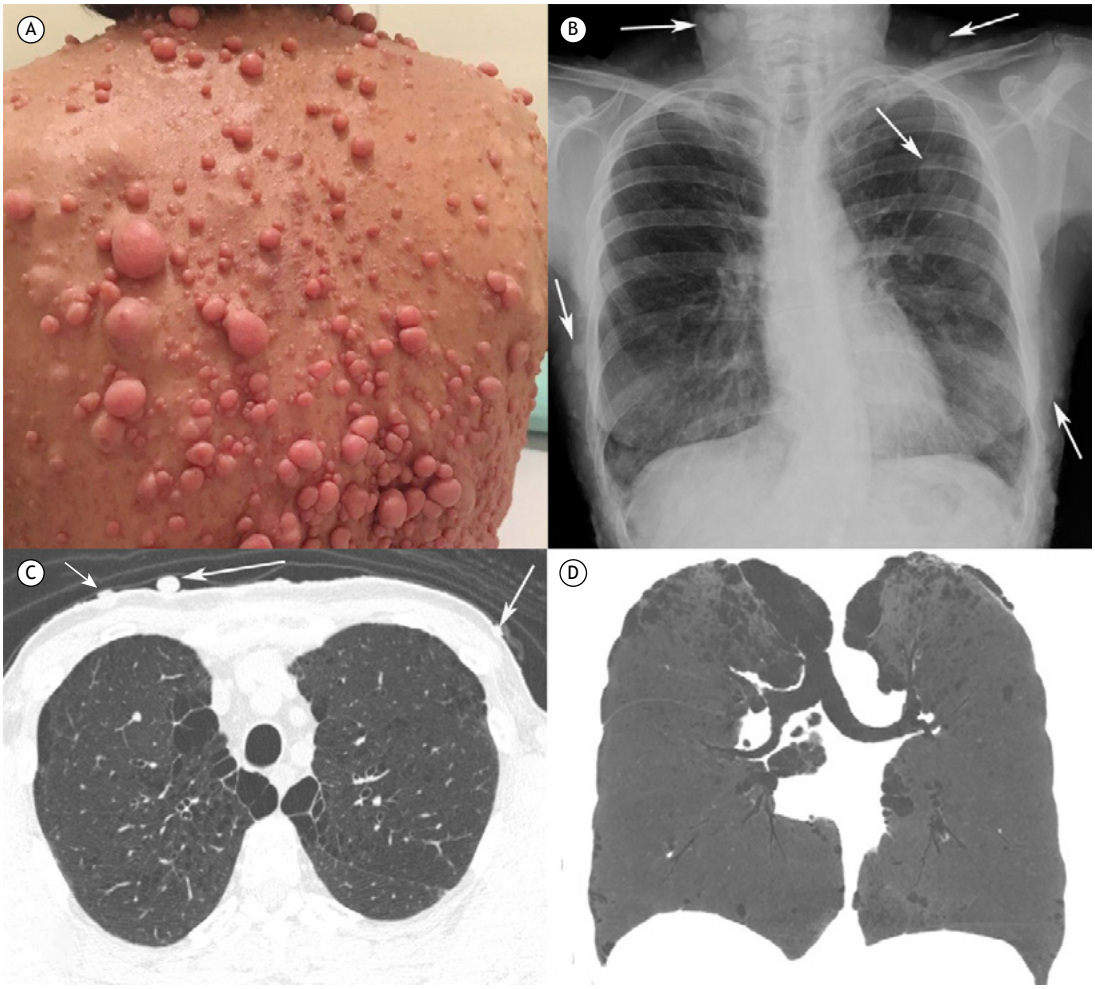

Figure 1. In A, a photograph of the dorsal region of the chest showing multiple cutaneous neurofibromas. In B, a chest X-ray shows multiple soft-tissue nodules on the chest wall (arrows). In C and D, respectively, an axial chest CT image (lung window) at the level of the upper lobes and a coronal minimum intensity projection image show emphysematous lesions predominantly in the upper lobes. Note also nodules (neurofibromas) on the chest wall (arrows in C).

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hamartomas (Lisch nodules) being most common. Diffuse lung disease associated with NF1 consists of an emphysematous, cystic, or bullous process with upper lobe predominance. Varying amounts of fibrosis and ground-glass opacity are also present.[1-3]

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

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Something is missing in the bronchus—Williams-Campbell syndrome

Felipe Marques da Costa[1], Augusto Kreling Medeiros[2], Antonio Carlos Portugal Gomes[2]

A 60-year-old female who was a former smoker was admitted with a five-day history of progressive dyspnea, cough, sputum production, and fever. She had a history of recurrent pneumonia since her childhood. Physical examination revealed expiratory wheezes and an SpO_2 of 91% on room air. A chest CT scan was performed (Figure 1). On the basis of the radiological findings and the exclusion of other causes, the patient was diagnosed with Williams-Campbell syndrome (WCS). After 10 days of antibiotic therapy, she was discharged with improved symptoms.

WCS is a rare congenital disorder characterized by the absence of cartilage in subsegmental bronchi, leading to bronchiectasis.[1,2] The pathophysiology of WCS involves airway collapse caused by deficiency of cartilage, resulting in chronic respiratory symptoms such as dyspnea and recurrent pulmonary infections.[1] Diagnosis is typically based on clinical manifestations and characteristic radiological findings on chest HRCT scans, as well as on exclusion of other causes of bronchiectasis.[3] Management of WCS remains challenging because of its rarity, being based on the use of antimicrobials. Treatments such as noninvasive positive pressure ventilation have shown promise in managing respiratory failure, and lung transplantation may be considered in severe cases.[1,2]

AUTHOR CONTRIBUTIONS

FMC and ACPG: study conception, planning, and design; data collection; and drafting of the manuscript. FMC, ACPG, and AKM: revision of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

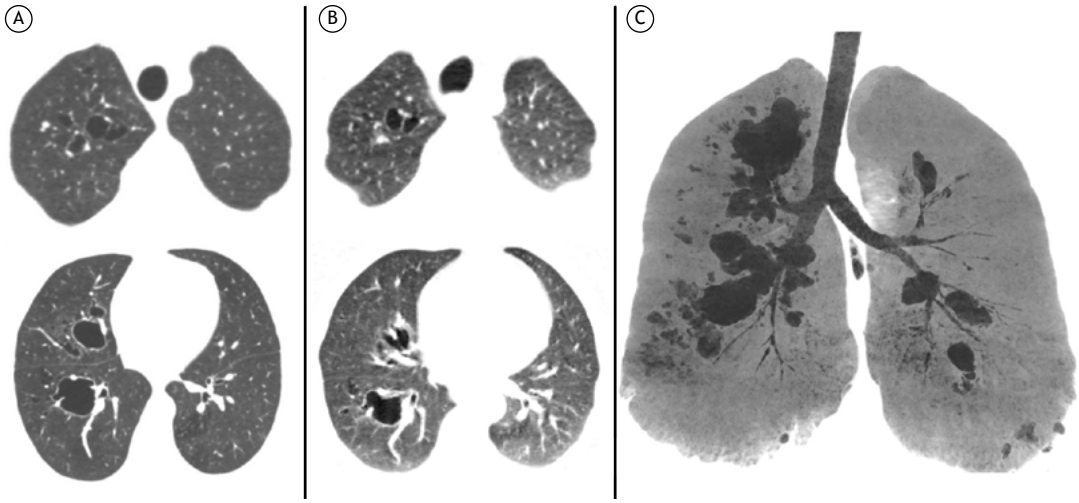

Figure 1. Axial CT scans of the chest taken during inhalation (in A) and exhalation (in B). Note complete or partial airway collapse during exhalation. In C, coronal CT scan of the chest with minimum intensity projection to improve visualization of the airways. Note bronchiectasis in both lungs, involving fourth- to sixth-order bronchi. The peripheral and central airways, including the trachea, main bronchi, and lobar bronchi, remain unaffected by bronchiectasis.

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Transfusion-related acute lung injury: an uncommon cause of pulmonary edema

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

A 14-year-old girl with the diagnosis of hereditary spherocytosis was admitted to the emergency department with intense fatigue, episodes of dizziness, and palpitations. A blood count revealed that the patient's hemoglobin level was 7.0 g/dL and her hematocrit was 23%. Blood transfusion was performed, with the patient receiving 300 mL packed red blood cells. Two hours later, she presented fever, cough, tachypnea, cyanosis, and hypotension. Her oxygen saturation level in room air was 93.9%. She also presented hypoxemia (pO_2: 65.8). A chest X-ray showed bilateral consolidations (Figure 1A). CT scanning revealed bilateral ground-glass opacities associated with interlobular septal thickening and bilateral pleural effusion (Figures 1B–1D). The diagnosis of transfusion-related acute lung injury (TRALI) was suggested. After 12 days of hospitalization, she presented good evolution, with significant clinical and radiological improvement.

TRALI is a severe post-transfusion reaction that manifests as acute lung injury occurring during or within 6 h after blood transfusion. CT may show irregular opacities, which can progress to bilateral interstitial and alveolar infiltrates. These findings, although nonspecific and usually indistinguishable from those of hydrostatic pulmonary edema, suggest the diagnosis of TRALI in the clinical context of recent transfusion of blood products.[1-3] In conclusion, the diagnosis of TRALI syndrome needs to be considered in patients who develop sudden respiratory distress after blood transfusion.

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

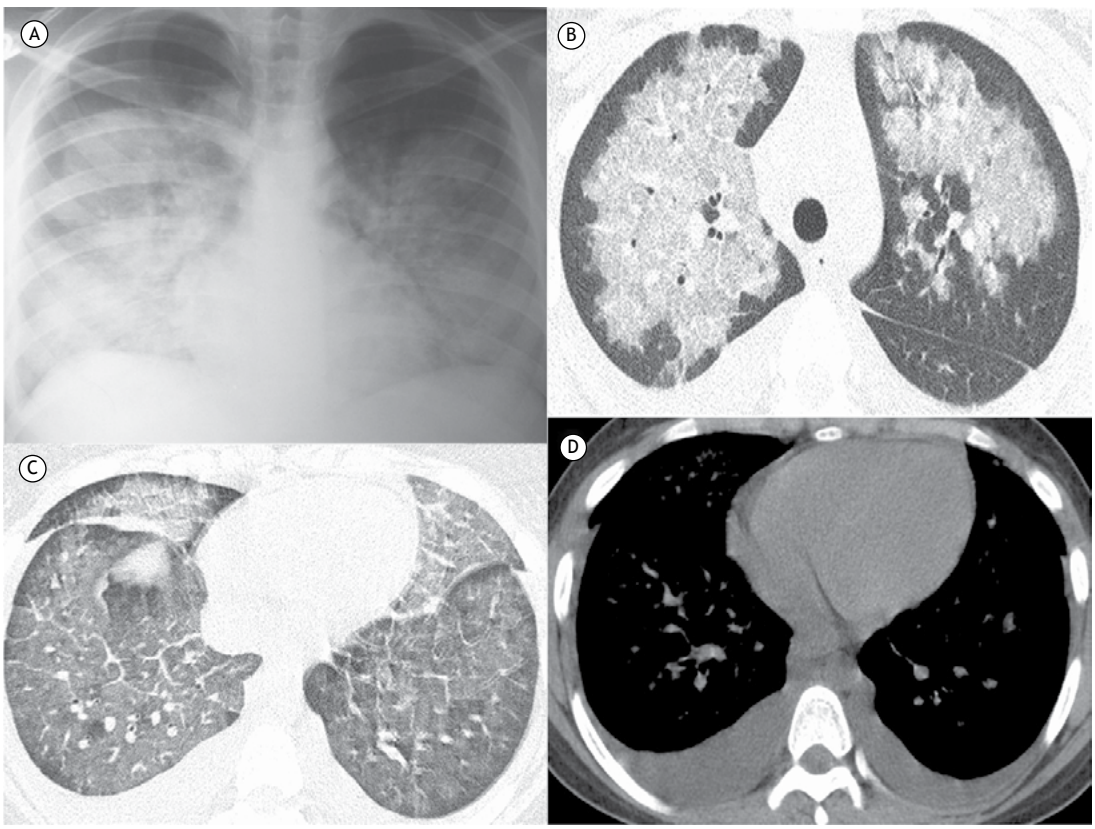

Figure 1. In A, a chest X-ray showed bilateral consolidations, predominantly in the central regions of the lungs. In B–D, CT scans revealed bilateral ground-glass opacities, predominantly in the central portions of the lungs, associated with interlobular septal thickening and bilateral pleural effusion.

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Abstracts

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

Chapter in a Book

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

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

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

Electronic publications

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

Homepages/URLs

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

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Referências:

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

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

Chegou: EGURINEL® (pirfenidona)

O primeiro similar de pirfenidona do Brasil!

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

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

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

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