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HIGHLIGHT

2022 Brazilian Thoracic Association recommendations for long-term home oxygen therapy

Determinants of death during the first wave of COVID-19

Lung cancer screening with low-dose computed tomography

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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Malignant mesothelioma: health care awareness and preparedness

Eduardo Mello De Capitani[1], Eduardo Algranti[2]

Malignant mesothelioma (MM) is a rare cancer. Malignant pleural mesothelioma (MPM) is the most prevalent primary cancer in the pleura.[1] MM is considered the hallmark of asbestos exposure. As it happens with rare diseases, the recognition of MM is strongly dependent on its regional incidence and on the awareness of the attending physician. A recent study linking Brazilian public health databases from 1996 to 2017 retrieved 2,405 records of MM as the underlying or contributing cause of death. It grossly corresponds to 200 deaths per year.[2]

In this number of the *Jornal Brasileiro de Pneumologia*, Gregorio et al.[3] retrospectively described the time spent from the onset of initial symptoms to death in 66 patients (52 men and 14 women) with MPM. The authors smartly have broken the analyses into four distinct stages: 1. from initial symptoms to referral to a specialized service; 2. during diagnostic workup; 3. during tumor staging and treatment options; and 4. from treatment to death. By breaking the analyses into time periods, they were able to identify and discuss diagnostic barriers in some of the stages.

First, the authors showed that in only 27/66 (41%) of the cases a history of asbestos exposure was retrieved.[3] Second, the median time from the onset of initial symptoms to referral to a specialized service was 6.5 months. After initiating specialized diagnostic workup, the median time for histopathological definition, disease staging, and beginning of treatment was 3.2 months. Finally, it took less than 11 months from the beginning of treatment to death.

The importance of retrieving a positive history of asbestos exposure is highlighted by the significant shorter time of referral of these patients to a specialized service, compared with those without a history of asbestos exposure (231.5 vs. 419.5 days).[3] What seems to be certain is that a history of occupational or nonoccupational asbestos exposure was not appropriately taken, or not even taken at all, since most health care workers are unfamiliar with it. Even when taken correctly, the occupational history can be flawed by the patient's recall bias related to past exposures, as MPM characteristically appears 30-50 years after the beginning of the exposure,[4] even after brief exposures. This information gap is supposed to improve with the current setting up of a Brazilian national database of all asbestos-exposed workers which includes individual occupational histories. Full access to this database (designated DATAMIANTO) will potentially be granted to any specialized health care unit in the country.[5] Thus, any diffuse pleural ailment or pleural effusion diagnosed in a patient with a record in that database might be suspected of MPM for being a former asbestos worker. Information on domestic indoor asbestos exposure due to occupational exposure of one member of the family can also be retrieved. It is well known that family members living in the same household can be exposed to considerable amounts of asbestos brought home on working clothes. Para-occupational (i.e., working not directly with asbestos but in workplaces where asbestos is manipulated) and environmental exposures to asbestos (e.g., living around asbestos mines or asbestos-cement plants, as well as other less conspicuous situations) will continue to be a difficult issue.

The delay in referring MPM cases to a specialized service was mainly caused by the absence of MPM suspicion and the performance of many nondiagnostic procedures, such as pleural fluid drainage to alleviate symptoms.[3] Only 27 (40.9%) of those patients were submitted to pleural biopsies prior to referral; of these, one quarter had false-negative results. Due to the lack of a previous diagnosis, insufficient biopsy materials, or negative results, 40 patients were biopsied at the specialized unit. Of these, 9 (22.5%) had false-negative results (by needle biopsy in 8 and by surgical biopsy in 1), leading to further procedures.[3] These findings reinforce the necessity of video-assisted thoracoscopy to obtain adequate pleural tissue samples for histopathology and immunochemistry workup, discouraging blind pleural biopsies, which have less sensitivity and specificity. This recommendation was highlighted in recent guidelines on MM and MPM diagnosis and management.[6-10]

Dealing with a clinically devastating neoplasm, the observed median of 9.7 months from the onset of initial symptoms to the beginning of specific treatment can be considered an excessive delay,[3] although this is in line with other series from developed countries.[6-8] However, several studies have showed a significant survival time in patients treated at initial stages, when clinical performance status is still satisfactory.[7,8,11]

Despite being a retrospective descriptive study,[3] the expressive number of cases of MPM brings us important information that sheds light on the necessity of creating diagnostic awareness among physicians and of following guidelines in order to utilize appropriate diagnostic procedures. Because asbestos production and consumption in Brazil peaked in the late 1980s, we are supposed to be at the beginning of an increase in the incidence of MM and MPM.[12]

CONFLICTS OF INTEREST

None declared.

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The COVID-19 challenge. What have we learned?

Adrian Ceccato[1,2,3], Carlos M Luna[4], Antonio Artigas[1,2,5]

Since COVID-19 (the disease caused by SARS-CoV-2) broke out in December of 2019 in China and became a pandemic in March of 2020, health care systems of every country have had the challenge of dealing with the disease. Specific conditions in Latin-American countries, such as previous shortcomings in the health care system, financial problems, the complexity in the geography and infrastructure of the region, and the emergence of new variants (gamma and lambda), hindered the fight against the pandemic.

Data collected and studies performed during the pandemic were important to investigate the performance of health care systems, evaluating their strengths and limitations.

Ranzani et al.[1] analyzed a large cohort of COVID-19-related hospitalized patients during the first months of the pandemic in Brazil and found that mortality was high and that the differences among regions were notable. The overall in-hospital mortality was 38%, whereas mortality in the ICU was 59%. Although mortality rates were comparable with those in other countries, younger patients were included in this cohort.

Data from other countries are available. In Mexico, the mortality rate reported in August of 2020 in patients receiving invasive mechanical ventilation was extremely high (73.7%).[2] Nevertheless, other reports coming from Latin-American countries showed mortality rates comparable with those from high-income countries. Reyes et al.[3] observed in an international cohort including patients from eight Latin-American countries an in-hospital mortality rate of 35%.

Many countries had to open new beds with access to ventilators in high-dependency care units or increase the number of beds in the ICU. Controversies about increased mortality have been observed in these units or during periods of high demands,[4,5] highlighting the importance of qualified personnel and appropriate resources.

In this issue of the *Jornal Brasileiro de Pneumologia*, Ramos et al.[6] reported data obtained from three ICUs in São Paulo, Brazil, during the first pandemic wave. Of the 645 patients included, about 10% acquired the disease in the hospital. Approximately 55% required invasive mechanical ventilation, 35% needed renal replacement therapy, and 52.2% received vasopressor therapy. The in-hospital mortality was high, reaching 42.4%, mainly in those patients who required organ support. Unlike other cohorts, septic shock and multiple organ dysfunction were the most common causes of death.[6]

Interestingly, the presence of complications, including liver failure, arrhythmias, hand/foot ischemia, hemorrhage, and health care-associated infections, were independently related to lower survival rates. Health care-associated infections have been reported to be high in COVID-19 patients, as well as the mortality associated with these infections.[7,8] It is not well known why the occurrence of secondary infections increased; however, immune tolerance in critically ill/septic patients, the use of corticosteroids, and the overwhelmed health care system during the pandemic could be related. According to the study,[6] only 46.8% of the patients received corticosteroids. Early in the pandemic, in March of 2020, an observational study showed that methylprednisolone was associated with lower mortality[9] in patients with ARDS; however, corticosteroids were not recommended because of concerns raised by the experience with other viral diseases, such as influenza or Middle East respiratory syndrome. Quickly, several studies evaluated the efficacy/effectiveness of corticosteroids in patients with COVID-19, the study designated RECOVERY[10] being the first to be published and showed a reduced risk of death only in those patients who required supplementary oxygen. Corticosteroids are cheap and widely available, even though they are not exempt from risk. Corticosteroids have been associated with an increased risk of secondary infections, mainly hospital-acquired pneumonia.[11] More studies are warranted to clarify which phenotypes could benefit from the use of corticosteroids and which ones should avoid the use of these medications because the risks would exceed the benefits. However, several drugs were prescribed in the early phase of the pandemic without a piece of clear evidence showing benefits. Data were extrapolated from in vitro studies or from the experience gathered with the first SARS. Ramos et al.[6] reported that more than 40% of the patients were exposed to drugs with low levels of evidence (or even none) that supported their use. Moreover, oseltamivir, an antiviral recommended for influenza, was associated with an increased risk of death in this population.

In summary, the COVID-19 pandemic has provided several lessons. First, infectious diseases are a constant threat, and governments should invest in research to be prepared to fight them. Second, although the health care system has shown the capacity to increase the number of beds for critically ill patients, the lack of availability of trained personnel to give support to severely/critically ill patients is an unresolved problem. Third, the prescription of off-label drugs might have increased the risk of harm

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without a clear benefit, and therefore physicians should act following recommendations based on evidence. Fourth, COVID-19 survivors can experience severe pulmonary sequelae and other morbidities. Finally, we have to highlight the quick response of the research community to the pandemic, based on basic, observational, and interventional collaborative studies. Appling new technologies and knowledge allowed the development of new vaccines in a short time, changing the course of the pandemic.

It is unclear whether the COVID-19 pandemic is about to end; however, we must continue learning from these experiences, aiming to improve our clinical practice and be ready for future epidemics.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL

Association of cardiovascular disease with COPD: cardiac function and structure evaluation

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COPD is defined as "a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation."[1] COPD is the leading cause of morbidity and mortality worldwide, and it was the third leading cause of death globally in 2019. Therefore, COPD burdens the society and economy as a whole.[1] COPD-related mortality is frequently found to be associated with cardiovascular comorbidities.[2,3] Evidence suggests that mortality due to cardiovascular disease (CVD) is more dominant than those related to respiratory failure in patients with COPD.[4,5]

The association between COPD and CVD was suggested to be due to several factors, including shared risk factors (cigarette smoking, aging), symptom overlap (dyspnea, exercise limitation), and pathophysiological processes (systemic inflammation, increased oxidative stress).[2,5-8] The heightened inflammatory response to cigarette smoke in patients with COPD contributes to atherosclerotic plaque formation, which leads to coronary heart disease.[7,8] In acute COPD exacerbations, respiratory tract infection induces an acute inflammatory stimulation, potentially leading to a high risk for an acute cardiovascular event.[7,9] In stable COPD, a higher circulating level of systemic inflammatory biomarkers was found and associated with an increased risk of cardiac injury.[10]

Other than the abovementioned chronic inflammation, several characteristics of COPD affect cardiac function and structure, such as airflow limitation, hyperinflation, and pulmonary hypoxia.[5,7,11] Lung hyperinflation resulting from chronic airflow limitation, together with increased pulmonary vascular resistance from hypoxic vasoconstriction, could directly increase pressure in the pulmonary artery (pulmonary hypertension), leading to right ventricular diastolic dysfunction.[3,11] Chronic rising pulmonary pressure in long-standing COPD leads to right ventricle (RV) dilation and hypertrophy, which usually preserve stroke volume.[5,12] During a COPD acute exacerbation, a sudden increase in RV pressure load can lead to acute *cor pulmonale*, which presents with acute RV dilation and RV failure.[12,13] Hyperinflation can also affect cardiac dimension, resulting in decreased diastolic filling and reduced systolic ejection fraction.[11]

The importance of CVD comorbidity in COPD has been recognized, and integrated care was suggested.[14] Management of CVD comorbidity in COPD has been addressed in the GOLD guidelines.[1] It has been shown that cardiac abnormalities are highly prevalent during a COPD exacerbation regardless of established cardiac disease or cardiovascular risk factors.[13] Therefore, an echocardiogram has been recommended to assess cardiac function and structure for CVD in COPD during both acute and stable stages.[5,14] Echocardiograms reveal several abnormal cardiac functions and structures, such as left ventricle systolic and diastolic dysfunction, right and left ventricle enlargement, left atrial dilatation, and pulmonary hypertension.[15] A pitfall of performing an echocardiogram for CVD in COPD is that air trapping may impede the echocardiographic acoustic window resulting in unsatisfactory images.[16]

In this issue of the *Jornal Brasileiro de Pneumologia*, Pereira et al.[17] tried to contrast cardiac function and structure between patients with stable COPD and those with recent exacerbated COPD using echocardiogram. However, the results showed no differences in cardiac function or structure between recently exacerbated (one month prior) and stable COPD patients regardless of their clinical conditions.[17] The authors suggested that the similarities in cardiac function and structure in these two populations was because the patients with a recent COPD exacerbation had no significant respiratory failure to the point that it could cause changes in cardiac function. The authors further explained that, within 30 days after an exacerbation, the cardiac changes could have been transitory and went back to normal. However, in the absence of differences in echocardiographic results between the two groups, Pereira et al.[17] found impaired left ventricular function, increased left ventricular posterior wall thickness, and reduced mitral peak early/late diastolic filling velocity ratio, which is an index to assess diastolic filling. However, whether modifications in the left ventricular structure could affect left ventricular systolic and diastolic function is still controversial. The relative results were still inconclusive when compared with previous studies.[13,15]

Pereira et al.[17] also aimed to verify the association between cardiac structure and function with exercise capacity. The authors found that exercise capacity was associated with left ventricular posterior wall thickness and right atrial volume index, suggesting ventricular stiffness and increased filling pressure, which resulted in limited exercise capacity.[17] However, the effect of cardiac structure and function on exercise capacity was not shown in this study due to the type of analysis performed (e.g., Pearson correlation coefficient). The effect of cardiac structure and function on exercise capacity should have been evaluated using regression analysis by accounting for the degree of airway obstruction and cardiac function as confounding factors.

It is known that limited exercise capacity is one of the shared symptoms found in COPD and CVD.[14] However,

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evidence supporting the association between exercise capacity and cardiac function and structure is limited. In advanced emphysema, limited exercise capacity can be a result of airflow limitation, gas exchange impairment, and muscle depletion.[18] A study[15] involving 342 COPD patients hospitalized due to their first COPD exacerbation found no association between the six-minute walk distance and the presence of echocardiography abnormalities, whereas Schoos et al.[19] found that a longer six-minute walk distance independently correlated with milder tricuspid valve regurgitation.[15,19] More studies are required about the association between cardiac function and structure and exercise capacity in patients with concomitant COPD and CVD.

The presence of cardiovascular comorbidities in COPD has long been recognized, and their coexistence yields worse outcomes in comparison with each condition alone.[3,6] Even though the precise mechanism of the influence of these two diseases is not fully understood, the management of CVD comorbidities is implied in the GOLD guidelines.[1] Therefore, a thorough assessment of the signs and symptoms of both diseases is encouraged.[5,14] An echocardiogram is one of the assessment tools suggested to be useful and should be considered in concomitant COPD and CVD.[5,14,15] Information on cardiac function and structure could lead to a better understanding of the mechanism and subsequently facilitate an improvement in the disease management and therapeutic approach.

AUTHOR CONTRIBUTIONS

SD: drafting of the manuscript. SD, WC, and PT: conception, revision, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Diffuse opacification of the hemithorax

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A 72-year-old male with a smoking history of 60 pack-years presented with a 1-year history of dry cough at night, together with a 3-month history of blood-streaked sputum, having lost 9 kg since the onset of those symptoms. A chest X-ray showed diffuse opacification of the right hemithorax, with preserved volume (Figure 1A). A CT scan of the chest showed obstruction of the right main bronchus, with partial collapse of the corresponding lung, as well as pleural effusion (Figure 1B).

Diffuse opacification of a hemithorax is known as an opaque hemithorax (OH). This condition is commonly seen in emergency departments, and the attending physician needs to make an immediate decision regarding the most appropriate course of action. The differential diagnosis is broad and is mainly based on the position of the mediastinum, which indirectly reflects the volume of the affected hemithorax.

Patients with OH can present with a reduction in the volume of the affected hemithorax (with the mediastinum shifted to that side), an increase in its volume (with the mediastinum shifted to the opposite side), or no change in its volume (with a centered mediastinum). In most cases, that differentiation is easily made by using ultrasound or CT. The main causes of OH with increased volume are massive pleural effusions and, less commonly, large thoracic masses occupying the entire hemithorax. Reduced-volume OH can be due to congenital anomalies (e.g., pulmonary agenesis or aplasia), surgical history (previous pneumonectomy), or total atelectasis. Although the causes of atelectasis are varied, bronchial obstruction—by a foreign body in children or by an endobronchial tumor in adults—is the most common etiology. The main differential diagnoses of OH with preserved volume are extensive pneumonia, in which an air bronchogram is frequently observed, and bronchogenic carcinoma, with a combination of atelectasis and pleural effusion, which have antagonistic effects on the volume of the affected hemithorax.[1,2]

In the case described here, we observed a right-sided OH with a centered mediastinum (i.e., a preserved-volume OH). The patient had no history of infection, nor was there an air bronchogram, which allowed us to rule out the hypothesis of extensive pneumonia. A chest CT showed obstruction of the right main bronchus, with partial atelectasis and with pleural effusion. Bronchoscopy showed a bronchogenic carcinoma obstructing the right main bronchus.

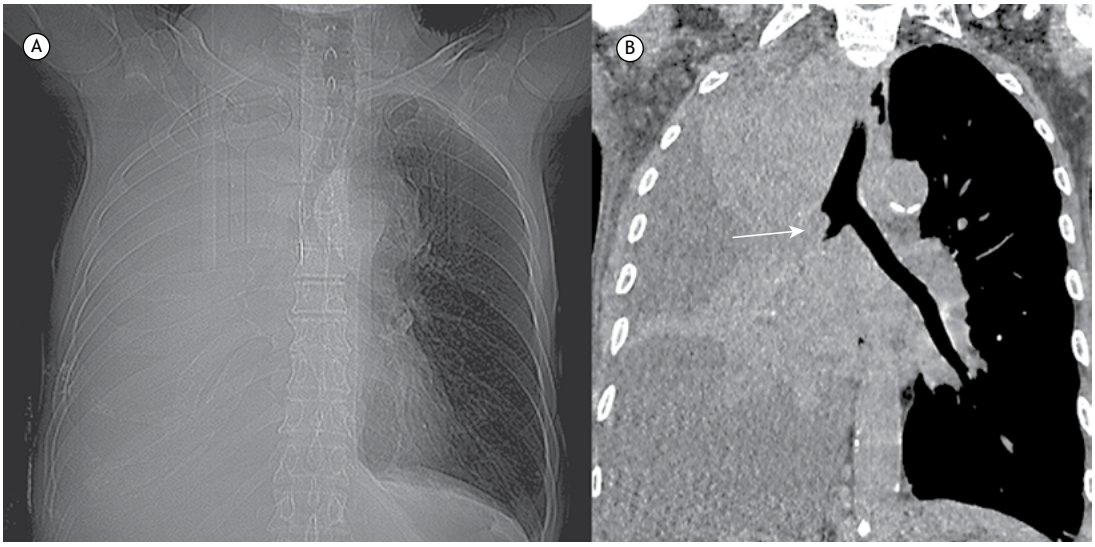

Figure 1. Anteroposterior chest X-ray (in A) showing diffuse opacification of the right hemithorax (opaque hemithorax). Note that the mediastinal structures, particularly the trachea, are centered and in a normal position. In B, coronal CT reconstruction showing obstruction of the right main bronchus (arrow). Note also that the lung is partially collapsed and that there is pleural effusion. These findings are characteristic of an opaque hemithorax with preserved volume.

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Why is conducting pragmatic clinical trials so important?

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PRACTICAL SCENARIO

Researchers in Finland have designed a randomized clinical trial (RCT) in which adults older than 65 years of age will be randomized (1:1) to receive either high-dose or standard-dose of a quadrivalent influenza vaccine. The main outcome is cardiorespiratory hospitalizations up to 6 months post-vaccination. They propose to use a pragmatic design and implement follow-up for up to 11 months post-vaccination using the Finnish national health registries. Here, we analyze the design of this pragmatic clinical trial (PCT) to discuss its importance in evidence-based decision-making.[1]

PCTS: ADVANTAGES AND DIFFERENCES FROM EXPLANATORY CLINICAL TRIALS

RCTs are the gold standard study design to determine the safety and efficacy of new interventions. However, the "ideal scenario" in which clinical trials are conducted may be far removed from the true needs and the decision-making process of health personnel and the population. RCTs can be classified as explanatory trials (also called phase III of drug development), in which the main objective is to confirm a clinical or physiological hypothesis in a very controlled environment, or as pragmatic trials, as part of the post-marketing phase or the so-called phase IV, with the objective of testing the new intervention in real-world scenarios, thus helping understand the true impact of the introduction of the drug or technology under study.[2]

Choosing a PCT over an explanatory clinical trial (ECT) depends on the stage of development of the intervention and the level of pragmatism desired to increase the generalizability of the results. This decision implies modifications to typical aspects of RCTs to improve the feasibility of the study.

ECTs are usually carried out in research centers with trained professionals, while PCTs can be carried out in multiple types of health care centers (hospitals, clinics, and private practices) and by different health professionals, several of whom without prior research training; in our example, the study takes place in over 40 health care stations.[1] This increases the generalizability of the results.

Participants in PCTs, as those in our example, tend to be a heterogeneous population with minimal criteria for

Table 1. Differences between explanatory clinical trials and pragmatic clinical trials.

	Explanatory clinical trials	Pragmatic clinical trials
General		
Objective	Efficacy and safety of a new intervention.	Effectiveness and long-term safety. Optimization of generalizability of trial results.
Recruitment	Active recruitment is needed.	Less strict. May utilize disease registries.
Participants	Highly selected (many exclusion criteria)	Similar to patients who would receive the intervention if it became standard of care.
Study design		
Delivery of the intervention	Requires frequent study visits for intervention administration and safety evaluations.	Trial procedures and data-collection requirements are minimized. Intervention is administered as in normal practice.
Safety endpoints	Precise collection and description of adverse events.	Long-term safety data in some cases, often less complex and similar to standard of care.
Randomization	Present. Removes significant differences between groups.	Can be more complex. Could be performed on a patient, cluster, or clinician level.
Risk of bias	Minimal.	Higher due to less control over other variables. Can be addressed.
Other		
Ethical considerations	Participants' informed consent, and Institutional Review Board and regulatory entities' approval are required.	Less complicated. Requirements may be waived in some cases
Funding	Usually by industry.	Variable. Co-financed by industry and government.

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their selection and with a wider age range, whereas participants in ECTs are frequently more homogeneous and highly selected or share a common pathology.[2]

Both types of clinical trials use a control group; however, PCTs usually utilize another active arm group, many times a standard-of-care group instead of a placebo group. In our example, the high-dose group is being compared against the standard-dose group. Endpoints in PCTs are usually patient-centered such as deaths, hospitalizations, symptoms, disability, and quality of life, which facilitates data collection with a more flexible surveillance system.[2] The follow-up of participants in ECTs typically requires multiple visits to the study site, while the follow-up in PCTs is less strict; in our example, the researchers periodically collect registry data provided by electronic health records of the public health care system. Other major characteristics of both studies are summarized in Table 1.

Due to concerns about adherence and less stringent follow-up in PCTs, high-quality data collection, robust statistical design, and blinding when defining and adjudicating the study endpoint are key to obtaining reliable results.[2] The Pragmatic Explanatory Continuum Indicator Summary (PRECIS-2)[3] is a useful tool on how to conduct and increase the robustness of PCTs.

KEY POINTS

1. PCTs are increasingly in use in clinical research because they offer evidence about interventions under real-life circumstances.
2. PCTs provide information of paramount importance for new interventions, development processes, and public health decision-making, informing clinical practice.
3. The correct implementation of PCTs with a robust statistical design, high-quality data collection, and follow-up are essential to increase their validity.

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Probing the old lung: challenges to pulmonary function testing interpretation in the elderly

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BACKGROUND

The number of elderly individuals (≥ 65 years of age) worldwide is projected to triplicate by 2050, with a quarter of these individuals being in the "oldest-old" age range (> 85 years of age).[1] The prevalence of chronic lung disease and comorbidities with the potential to influence pulmonary function tests increases with aging. Knowing the physiological effects of senescence on the respiratory system is paramount to avoiding under- or overdiagnosis of respiratory disease in the elderly.

OVERVIEW

A 77-year-old man with a smoking history of 50 pack-years—he had quit 10 years before—heart failure (left ventricular ejection fraction = 36%), and atrial fibrillation presented with progressive dyspnea (modified Medical Research Council scale score = 3) after a lower respiratory tract infection that was managed at home. A chest X-ray showed minor linear opacities in the right lower lobe. He was diagnosed with COPD on the basis of the following: a) $FEV_1/FVC < 0.7$ (but above the lower limit of normal); b) FEV_1/"slow" VC below the lower limit of normal; c) a borderline decrease in $FEF_{25-75\%}$, with some expiratory "scooping"; d) mildly increased RV; and e) slightly decreased DL_{CO}. Inhaled formoterol did not improve his dyspnea, being associated with palpitations and lightheadedness. Because of these undesirable side effects, formoterol was discontinued. His dyspnea eventually subsided after a few weeks of chest physiotherapy for secretion clearance.

Aging is associated with loss of lung elastic recoil and alveolar attachments to the small airways, both of

Table 1. Effects of aging on pulmonary function tests, with practical implications for interpretation. The effects are most pronounced in individuals over 75 years of age, being further accentuated in those in the oldest-old age range (> 85 years of age).

Directional change	Main putative mechanism	Potential interpretative mistake
Spirometry		
↓ FEV_1/FVC	Larger decrease in flows than in lung volumes as age progresses	False positive for obstructive lung disease
↓ FEV_1	↓ lung elastic recoil, upstream displacement of the choke point	Overestimation of functional impairment caused by underlying obstructive lung disease
↓ FVC	↑ RV and, secondarily, ↓ TLC	Overestimation of functional impairment caused by underlying restrictive lung disease
↑ SVC-FVC difference leading to ↓ FEV_1/SVC	↑ compressibility/collapsibility of the small airways in the forced maneuver	False positive for obstructive lung disease
↓ $FEF_{25-75\%}$	As above, and ↓ diameters of the lower bronchioles	False positive for small airway disease
Body plethysmography		
↑ RV and ↑ RV/TLC	↑ closing volume, enlarged distal airspaces (distended alveolar sacs, alveolar coalescence)	Overestimation of functional impairment caused by underlying obstructive lung disease
↑ FRC, ↑ FRC/TLC	↑ closing capacity, upward shift of the TLC-RV equilibrium volume	As above
↓TLC	Preponderance of chest wall stiffness relative to loss of lung elastic recoil	Overestimation of functional impairment caused by underlying restrictive lung disease
Airway resistance		
↑ sRaw	All of the above	False positive for obstructive lung disease
Gas exchange		
↓ DL_{CO}	↓ anatomical-functional area for gas exchange, heterogeneous ventilation distribution (↓ V_A)	Overestimation of functional impairment caused by underlying disease (including pulmonary vascular disease)
↓ PaO_2	As above	As above

↑: increased; ↓: decreased; SVC: slow vital capacity; FRC: functional residual capacity; sRaw: specific airway resistance; and V_A: alveolar volume.

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which contribute to decreasing the expiratory flows and, consequently, FEV_1 and $FEF_{25-75\%}$ (a-c above). Low mid- and tele-expiratory flow may create a slight concavity on the expiratory flow limb (c). An increase in the relaxation volume of the respiratory system and a tendency toward airway closure at a small lung volume cause an increase in functional residual capacity and RV (d), respectively. TLC may remain unchanged or decrease secondary to a stiffer chest wall, reducing inspiratory capacity and VC.[2] Given that the small airways tend to close earlier during a forced expiratory maneuver than during a "slow" expiratory maneuver, FVC decreases more than does VC; thus, FEV_1/VC diminishes to a greater extent than does FEV_1/FVC (a and b above).[3] Since the volume at which the small airways start to close during expiration increases more than does functional residual capacity, ventilation distribution inequalities may decrease pulmonary gas exchange efficiency. Airspace dilation without distinct alveolar destruction and reduced density of the membranous bronchioles suggest coalescence of smaller alveoli into larger alveoli, reducing the functional surface for gas exchange while increasing areas of a high ventilation-perfusion relationship.[2] The corollary is an age-related reduction in DL_{CO} (e) and PaO_2, as well as an increase in the alveolar-arterial oxygen gradient (Table 1).

CLINICAL MESSAGE

Several aging-related physiological changes can mimic the abnormalities induced by airway disease, including low expiratory flows, increased operating lung volumes, and ventilation distribution inequalities. Conversely, the dominance of chest wall stiffness relative to the loss of lung elastic recoil may raise unjustified concerns of restriction, particularly in the presence of moderate-to-severe obesity.[4] This scenario is further complicated by the lower accuracy of reference values in the extremes of age.[5] Special care should be taken to avoid overdiagnosis of respiratory disease (or overestimation of impairment caused by preexisting disease) in the elderly.

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ORIGINAL ARTICLE

Determinants of death in critically ill COVID-19 patients during the first wave of COVID-19: a multicenter study in Brazil

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Study carried out at the Hospital São Paulo, Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil; Hospital BP Mirante, São Paulo (SP) Brasil; and Hospital SEPACO, São Paulo (SP) Brasil.

ABSTRACT

Objective: To evaluate clinical outcomes and factors associated with mortality, focusing on secondary infections, in critically ill patients with COVID-19 in three Brazilian hospitals during the first pandemic wave. **Methods:** This was a retrospective observational study involving adult patients with COVID-19 admitted to one of the participating ICUs between March and August of 2020. We analyzed clinical features, comorbidities, source of SARS-CoV-2 infection, laboratory data, microbiology data, complications, and causes of death. We assessed factors associated with in-hospital mortality using logistic regression models. **Results:** We included 645 patients with a mean age of 61.4 years. Of those, 387 (60.0%) were male, 12.9% (83/643) had undergone solid organ transplant, and almost 10% (59/641) had nosocomial COVID-19 infection. During ICU stay, 359/644 patients (55.7%) required invasive mechanical ventilation, 225 (34.9%) needed renal replacement therapy, 337 (52.2%) received vasopressors, and 216 (33.5%) had hospital-acquired infections (HAIs), mainly caused by multidrug-resistant gram-negative bacteria. HAIs were independently associated with a higher risk of death. The major causes of death were refractory shock and multiple organ dysfunction syndrome but not ARDS, as previously reported in the literature. **Conclusions:** In this study, most of our cohort required invasive mechanical ventilation and almost one third had HAIs, which were independently associated with a higher risk of death. Other factors related to death were Charlson Comorbidity Index, SOFA score at admission, and clinical complications during ICU stay. Nosocomial COVID-19 infection was not associated with death. The main immediate causes of death were refractory shock and multiple organ dysfunction syndrome.

Keywords: COVID-19/mortality; Sepsis; Multiple organ failure.

INTRODUCTION

The COVID-19 pandemic has continued to impact health care systems around the world since cases were first reported in China in December of 2019. A significant number of patients with COVID-19 develops critical illness and requires ICU management.[1] ICU mortality rates range from 8.1% to 97% in those requiring mechanical ventilation, depending on the country or the period of the pandemic.[2-5]

Older age and preexisting chronic health conditions are strongly associated with in-hospital mortality.[1,6,7] However, the mortality rates of critically ill COVID-19 patients are related not only to the severity of the disease but also to modifiable factors, such as the strain in the ICU, hospital acquired infections (HAIs), and organizational aspects.[8-11] Information on causality and mechanism of death is unclear and conflicting.[12,13] The impact of hospital-acquired COVID-19 is also inconsistent.[14] Although the most worrisome clinical feature of COVID-19 is ARDS requiring invasive mechanical ventilation (IMV) and respiratory failure is usually reported as the major cause of death,[15] the role of COVID-19-related HAIs, bacterial sepsis, and multiple organ dysfunction syndrome (MODS) needs to be further clarified, mainly in low- and middle-income countries (LMICs).[16]

The objective of the present study was to investigate the clinical features and factors associated with in-hospital mortality, focusing on secondary infections, in critically ill COVID-19 patients.

METHODS

This was a retrospective study involving adult COVID-19 patients admitted to the ICUs in three different hospitals in the city of São Paulo, Brazil. Hospital São Paulo is a public teaching hospital from the Federal University of São Paulo with 35 ICU beds dedicated to COVID-19 patients, whereas Hospital SEPACO and Hospital BP Mirante are private hospitals with 40 and 14 ICU beds dedicated to COVID-19 patients, respectively. The three ICUs were active before the pandemic and had appropriate staff,

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supplies, and well-established routines such as daily multidisciplinary rounds and clinical protocols. The three institutions developed specific guidelines for the management of COVID-19 patients, including the main aspects of care such as admission criteria, personal protection equipment use, noninvasive ventilation (NIV) support, IMV support, hemodynamic management, sedation, analgesia, nutrition, use of steroids, and rehabilitation. The Research Ethics Committee of the Hospital São Paulo approved the study (Protocol n. 38065220.9.1001.5505). Informed consent was waived because of the retrospective nature of the study.

All consecutive adult patients admitted to the participating ICUs between the 10th of March and the 31st of August, 2020, were included in the study. All patients had a confirmed diagnosis of COVID-19 or a high clinical suspicion. Confirmed cases were those with positive RT-PCR results of samples obtained from nasopharyngeal swabs, BAL fluid, or nasopharyngeal/tracheal aspirates. Suspected cases were defined based on the presence of clinical symptoms, compatible clinical history, and CT results highly suggestive of COVID-19. There were no exclusion criteria.

Our primary outcome was in-hospital mortality. We also collected secondary outcomes such as source of SARS-CoV-2 infection (community-acquired or hospital-acquired), clinical complications, solid organ transplant mortality, major cause of death, prevalence of secondary infections, and microbiological profile.

We collected data using a web-based platform (REDCap—Research Electronic Data Capture) that was accessed on a site-by-site basis. We used data from electronic medical records and from an electronic administrative database (Epimed Solutions, Rio de Janeiro, Brazil). We collected data regarding demographic and clinical characteristics (age, gender, comorbidities, source of ICU admission, diagnosis, and presence of bacterial/fungal coinfection), source of COVID-19 infection (community-acquired or hospital-acquired), severity of illness as determined by the Simplified Acute Physiology Score 3 (SAPS 3) and the SOFA score at ICU admission for patients with community-acquired and hospital-acquired COVID-19, main medications administered during the first 48 h from ICU admission (oseltamivir, antiviral therapy, antibiotics, antifungal agents, and corticosteroids), laboratory data, and presence of frailty as defined by a Clinical Frailty Scale score > 4.[17] we recorded the use of resources such as oxygen therapy, NIV, high-flow nasal catheter, IMV, vasopressors, renal replacement therapy (RRT), prone positioning therapy, extracorporeal membrane oxygenation, and nitric oxide during the ICU stay. We also recorded the main complications during the ICU stay, focusing on HAIs and isolated bacteria and fungi in cultures. We defined HAIs according to medical records and positive cultures. Reported or suspected HAIs were confirmed or ruled out by the authors of this study. The attending physicians and the ICU team, together with family members or legal representatives of the patients and in accordance with the Brazilian ethical rules, decided on palliative care. Patients were followed until hospital discharge. Data on length of ICU and hospital stay and the main immediate cause of death in the ICU reported by the attending physician were collected. The main immediate cause of death (Chart S1) was also confirmed or disproved by one of our research team members using a structured form adapted from previous studies.[12,18] We reported our results in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[19]

Statistical analysis

No sample size calculations were performed for this exploratory, descriptive study. We used absolute and relative frequencies to describe categorical variables and medians and interquartile ranges or means and standard deviations to describe continuous variables. For comparisons between survivors and nonsurvivors, we used the Student's t test and the Mann-Whitney test for continuous variables with normal distribution and non-normal distribution, respectively. Categorical variables were compared with the Pearson's chi-square test.

Associations with in-hospital mortality were estimated using a logistic regression model. We included in the model all variables with a p value < 0.05 in the univariate analysis, including those at baseline and during evolution, as well as medications used during the ICU stay. In order to limit the number of variables to avoid overfitting, we assessed both biological plausibility and collinearity. We assessed collinearity first by examining the scatter plot matrix and Pearson's correlation coefficient for continuous variables or cross-tabulation for categorical variables. In the presence of collinearity (e.g., frailty score and age; type of infection and source of admission; and neutrophils and lymphocytes), the most clinically relevant variable was maintained in the model. Results were expressed an odds ratios and their respective 95% confidence intervals.

In all tests, significance was set at $p < 0.05$. Statistical analyses were carried out with the statistical software R 4.0 (R Core Team, 2018).

RESULTS

Between the 10th of March and the 31st of August, 2020, 645 adult patients diagnosed with COVID-19 and admitted to one of the participating ICUs were included in the study. The mean age was 61.4 ± 16.6 years. Most were men (387 [60.0%]) and White (434 [67.2%]). Demographic characteristics and comorbidities are described in Table 1. Hypertension and diabetes were the most common comorbidities (Charlson Comorbidity Index = 3.7 ± 2.6). Frailty was present in 20.4% of our patients, and 83 (12.9%) had a history of solid organ transplantation, mainly kidney transplant. The main source of admission was the emergency department (398 patients [62.1%]),

and 582 (90.8%) had community-acquired COVID-19. Table S1 shows laboratory data at admission.

Data regarding severity of disease and organ support during ICU stay are available in Table 2. The mean SAPS 3 was 53.8 ± 15.3, and the median SOFA score at ICU admission was 4.0 (2.0-7.0). Almost 21% (134/641) of our patients received vasopressors, and almost 30% (181/641) required IMV at ICU admission. The length of ICU stay was 13.9 ± 29.7 days, 55.7% (359/644) of our cohort received IMV, almost 30% (189/638) required prone positioning, and 35.1% (225/641) needed RRT. Table 3 describes the most common clinical complications during ICU stay. Overall, the ICU mortality rate was 39% (252/645). More than one third of our patients developed HAIs. Positive cultures were most commonly obtained from blood and tracheal aspirates, with *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* being the predominant gram-negative agents (Table 4). Data regarding drug resistance are presented in the supplementary material (Tables S2 to S6) and shows a high proportion of carbapenem resistance for both *Klebsiella pneumoniae* (> 90%) and *Pseudomonas aeruginosa* (50%).

In the multivariate analysis, the occurrence of HAIs was independently associated with a higher risk of death (OR = 3.57; 95% CI: 2.29-5.59; p < 0.001) even after adjustment for age and SOFA score. Patients with

Table 1. Demographic variables and comorbidities.[a]

Variable	In-hospital outcome		Total	OR	95% CI		p*
	Discharge (n = 371)	Death (n = 274)			2.5%	97.5%	
Age, years	58.1 ± 17.7	65.9 ± 13.9	61.4 ± 16.6	1,03	1.02	1.04	< 0.01
Skin color							
White	258/371 (69.5)	176/274 (64.2)	434/645 (67.3)	1 (ref)	-	-	-
Black	30/371 (8.1)	21/274 (7.7)	51/645 (7.9)	1,03	0.57	1.85	0.93
Brown	75/371 (20.2)	73/274 (26.6)	148/645 (22.9)	1,43	0.98	2.08	0.06
Yellow	8/371 (2.2)	4/274 (1.5)	12/645 (1.9)	0,73	0.22	2.47	0.62
Sex							
Men	220/371 (59.3)	167/274 (60.9)	387/645 (60.0)	1 (ref)	-	-	-
Women	151/371 (40.7)	107/274 (39.1)	258/645 (40.0)	0.93	0.68	1.28	0.67
Source of admission							
Emergency department	238/368 (64.7)	160/273 (58.6)	398/641 (62.1)	1 (ref)	-	-	-
Ward	93/368 (25.3)	73/273 (26.7)	166/641 (25.9)	1.17	0.81	1.68	0.1
Another ICU	10/368 (2.7)	29/273 (10.6)	39/641 (6.1)	4.31	2.05	9.10	< 0.01
Another hospital	27/368 (7.3)	11/273 (4.0)	38/641 (5.9)	0.61	0.29	1.26	0.18
COVID-19							
Community-acquired	348/368 (94.6)	234/273 (85.7)	582/641 (90.8)	1 (ref)	-	-	-
Hospital-acquired	20/368 (5.4)	39/273 (14.3)	59/641 (9.2)	2.90	1.65	5.10	< 0.01
Comorbidities							
Charlson Comorbidity Index	2.9 ± 2.5	4.7 ± 2.4	3.7 ± 2.6	1.33	1.24	1.42	< 0.01
Diabetes (not complicated)	75/371 (20.2)	53/274 (19.3)	128/645 (19.8)	0.95	0.639	1.401	0.78
Diabetes (complicated)	57/371 (15.4)	77/274 (28.1)	134/645 (20.8)	2.15	1.464	3.168	< 0.01
Chronic heart disease	46/370 (12.4)	74/272 (27.2)	120/642 (18.7)	2,63	1.75	3.96	< 0.01
Hypertension	221/371 (59.6)	201/272 (73.9)	422/643 (65.6)	1.92	1.37	2.70	< 0.01
Chronic kidney disease	58/371 (15.6)	76/271 (28.0)	134/642 (20.9)	2.10	1.43	3.09	< 0.01
Chronic neurologic disease	27/371 (7.3)	14/271 (5.2)	41/642 (6.4)	0.69	0.36	1.35	0.28
Dementia	21/371 (5.7)	10/271 (3.7)	31/642 (4.8)	0.64	0.30	1.38	0.25
Chronic hematologic disease	7/371 (1.9)	13/271 (4.8)	20/642 (3.1)	2.62	1.03	6.66	0.04
Smoking							
Current	16/274 (5.8)	22/236 (9.3)	38/510 (7.5)	1.84	0.94	3.63	0.08
Former	53/274 (19.3)	61/236 (25.8)	114/510 (22.4)	1.54	1.01	2.36	0.04
Obesity	90/371 (24.3)	41/273 (15.0)	131/644 (20.3)	0.55	0.37	0.83	< 0.01
BMI, kg/m²	27.6 ± 6.0	26.3 ± 6.3	27.0 ± 6.1	0.96	0.94	0.99	< 0.01
Solid organ transplant	28/371 (7.5)	55/272 (20.2)	83/643 (12.9)	3.10	1.91	5.05	< 0.01
Immunosuppressive therapy	38/371 (10.2)	71/270 (26.3)	109/641 (17.0)	3.13	2.03	4.81	< 0.01
Frailty (CFS > 4)				1.75	1.19	2.56	< 0.01
No	307/369 (83.2)	200/268 (74.6)	507/637 (79.6)				
Yes	62/369 (16.8)	68/268(25.4)	130/637 (20.4)				

ref: reference; and CFS: Clinical Frailty Scale. [a]Values expressed as n/N (%) or mean ± SD. *Fisher's exact test.

Table 2. Severity scores and treatment during ICU stay [a]

Variable	In-hospital outcome		Total	OR	95% CI		p*
	Discharge (n = 371)	Death (n = 274)			2.5%	97.5%	
First 24 h							
SAPS 3	47.5 ± 12.0	62.5 ± 15.2	53.8 ± 15.3	1.09	1.07	1.10	< 0.01
SOFA	2.0 [1.0-5.0]	6.0 [4.0-9.0]	4.0 [2.0-7.0][b]	1.39	1.31	1.48	< 0.01
Vasopressors	39/368 (10.6)	95/273 (34.8)	134/641 (20.9)	4.50	2.97	6.82	< 0.01
Renal replacement therapy	18/368 (4.9)	23/273 (8.4)	41/641 (6.4)	1.79	0.95	3.39	0.07
Oxygen therapy							
None	55/370 (14.9)	14/274 (5.1)	69/644 (10.7)	1 (ref)	-	-	-
Nasal catheter	213/370 (57.6)	117/274 (42.7)	330/644 (51.2)	2.16	1.15	4.05	0.02
High-flow nasal catheter	31/370 (8.4)	16/274 (5.8)	47/644 (7.3)	2.03	0.87	4.70	0.01
NIV	10/370 (2.7)	7/274 (2.6)	17/644 (2.6)	2.75	0.89	8.51	0.08
IMV	61/370 (16.5)	120/274 (43.8)	181/644 (28.1)	7.73	3.98	14.99	< 0.01
Medications within 48 h							
Oseltamivir	101/370 (27.3)	97/274 (35.4)	198/644 (30.7)	1.46	1.04	2.05	0.03
Ribavirin/lopinavir/ritonavir	100/371 (27.0)	97/274 (35.4)	197/645 (30.5)	1.49	1.06	2.08	0.02
Hydroxychloroquine	65/370 (17.6)	66/274 (24.1)	131/644 (20.3)	1.49	1.01	2.19	0.04
Azithromycin	168/371 (45.3)	120/274 (43.8)	288/645 (44.7)	0.94	0.69	1.29	0.71
Antibiotics	346/371 (93.3)	273/274 (99.6)	619/645 (96.0)	19.73	2.66	146.39	0.003
Antifungal therapy	2/371 (0.5)	9/274 (3.3)	11/645 (1.7)	6.27	1.34	29.24	0.02
Corticosteroids	154/371 (41.5)	148/274 (54.0)	302/645 (46.8)	1.66	1.21	2.27	0.002
Whole ICU stay							
Vasopressors	106/371 (31.5)	231/274 (68.5)	337/645 (52.2)	19.52	12.4	30.61	< 0.01
Renal replacement therapy	61/368 (16.6)	164/273 (60.1)	225/641 (35.1)	7.59	5.26	10.95	< 0.01
Ventilatory support							
High-flow nasal catheter	68/368 (18.5)	43/272 (15.8)	111/640 (17.3)	0.83	0.54	1.26	0.4
NIV	70/365 (19.2)	63/268 (23.5)	133/633 (21.0)	1.28	0.87	1.88	0.24
IMV	108/370 (29.2)	251/274 (91.6)	359/644 (55.7)	50.10	26.3	95.20	< 0.01
Duration of IMV, days	13.8 ± 13.6	13.6 ± 14.4	13.7 ± 14.1	-	-	-	0.9
Prone positioning	82/367 (22.3)	107/271 (39.5)	189/638 (29.6)	2.27	1.61	3.21	< 0.01
Nitric oxide	2/371 (0.5)	1/274 (0.4)	3/645 (0.5)	3.12	0.28	34.6	0.56
ECMO	0/367 (0.0)	2/273 (0.7)	2/640 (0.3)	-	-	-	0.18
Length of ICU stay, days	11.7 ± 29.2	16.8 ± 30.3	13.9 ± 29.7	-	-	-	0.03
Palliative care	3/370 (0.08)	44/272 (16.1)	47/642 (7.3)	12.67	0.98	162.25	0.07

SAPS 3: Simplified Acute Physiological Score; ref: reference; NIV: noninvasive ventilation; and IMV: invasive mechanical ventilation; and ECMO: extracorporeal membrane oxygenation. [a]Values expressed as n/N (%), mean ± SD, or median [IQR]. [b]N = 643. *Pearson's chi-square test, Student's t test, or Mann-Whitney test.

higher Charlson Comorbidity Index (OR = 1.15; 95% CI: 1.02-1.28; p = 0.02) and clinical complications, such as liver failure, cardiac arrhythmia, hand/foot ischemia, and hemorrhage, also had higher mortality rates (Table 5). The most common causes of death were refractory shock and MODS but not hypoxemia (Table 6).

DISCUSSION

In this retrospective study, we analyzed clinical and laboratorial characteristics, ICU support, clinical complications, and immediate cause of death in the ICU in a sample of 645 adult patients with COVID-19 admitted to the ICU. We found that most of our cohort required IMV and that almost one third needed RRT and had HAIs as a complication during their ICU stay. The main causes of death were refractory shock and MODS. Nosocomial infections as a complication at ICU admission were associated with higher mortality even after adjusting for baseline characteristics such as age, Charlson Comorbidity Index, solid organ transplant, and SOFA score.

The in-hospital mortality rate was 42.4% in our cohort. Several studies reported similar results, and patients who needed IMV and RRT had higher mortality rates (69.9% and 72.8% respectively).[2,3,5] In studies in Brazil, the reported mortality rates were usually high. Ranzani et al.[20] reported a high mortality rate (55%) in ICU patients in Brazil and an even higher rate for those on IMV (80%). However, severity of illness, as assessed by the use of organ support, is also high mainly in public hospitals. Ferreira et al.[5] reported the use of IMV, vasopressors, and RTT, respectively, in 79%, 73%, and 35% of the patients in a public referral hospital. Socolovithc et al.[4] reported data from

Table 3. Clinical complications during ICU stay.[a]

Variable	In-hospital outcome		Total	p*
	Discharge (n = 371)	Death (n = 274)	(N = 645)	
Acute coronary syndrome	0 (0.0)	2 (0.7)	2 (0.3)	0.15
Arrhythmias	23 (6.2)	79 (28.8)	102 (15.8)	< 0.01
Myocarditis/pericarditis	2 (0.5)	0 (0.0)	2 (0.3)	0.52
Deep vein thrombosis	11 (3.0)	11 (4.0)	22 (3.4)	0.64
Hand/feet ischemia	2 (0.5)	21 (7.7)	23 (3.6)	< 0.01
Hemorrhage	6 (1.6)	22 (8.0)	28 (4.3)	< 0.01
ICU readmission	16 (4.3)	17 (6.2)	33 (5.1)	< 0.01
Liver dysfunction	4 (1.1)	36 (13.1)	40 (6.2)	< 0.01
Hospital-acquired infection	70 (18.9)	146 (53.3)	216 (33.5)	< 0.01
Pleural effusion	4 (1.1)	7 (2.6)	11 (1.7)	0.12
Pneumothorax	8 (2.2)	16 (5.8)	24 (3.7)	0.06
Pulmonary embolism	9 (2.4)	12 (4.4)	21 (3.3)	0.37
Stroke	2 (0.5)	7 (2.6)	9 (1.4)	0.03
Seizures	8 (2.2)	12 (4.4)	20 (3.1)	0.06

[a]Values expressed as n (%). *Fisher's exact test or Pearson's chi-square test.

Table 4. Microbiological profile according to the source of infection.[a]

Agent	Sample					Total[b]
	Blood	Tracheal aspirate	Urine	Catheter tip	Blood from catheter	
Gram-negative bacteria						
Acinetobacter baumannii	2 (0.3)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)
Acinetobacter sp.	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Escherichia coli	5 (0.8)	2 (0.3)	7 (1.1)	1 (0.2)	0 (0.0)	14 (2.2)
Klebsiella pneumoniae	21 (3.3)	45 (7.0)	12 (1.9)	7 (1.1)	1 (0.2)	69 (10.7)
Pseudomonas aeruginosa	2 (0.3)	17 (2.6)	1 (0.2)	2 (0.3)	0 (0.0)	19 (2.9)
Other gram-negative bacillus	5 (0.8)	8 (1.2)	3 (0.5)	8 (1.2)	0 (0.0)	21 (3.3)
Gram-positive bacteria						
Enterococcus faecalis	3 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	6 (0.9)
Staphylococcus aureus	5 (0.8)	11 (1.7)	0 (0.0)	2 (0.3)	2 (0.3)	17 (2.6)
Other *Enterococcus* sp.	1 (0.2)	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	4 (0.6)
Other *Staphylococcus* sp.	50 (7.8)	1 (0.2)	0 (0.0)	6 (0.9)	7 (1.1)	56 (8.7)
Other *Streptococcus* sp.	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Fungi						
Aspergillus spp.	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Candida albicans	1 (0.2)	16 (2.5)	10 (1.6)	1 (0.2)	0 (0.0)	25 (3.9)
Candida glabrata	1 (0.2)	1 (0.2)	4 (0.6)	0 (0.0)	0 (0.0)	6 (0.9)
Candida sp.	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	3 (0.5)
Other yeasts	1 (0.2)	1 (0.2)	4 (0.6)	1 (0.2)	0 (0.0)	7 (1.1)
Other pathogens	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)

[a]Values expressed as n (%). Relative frequencies were calculated as number of positive samples divided by the total number of patients (N = 645) × 100. [b]A microorganism may have appeared in more than one culture.

a private hospital during the first wave of COVID-19 and observed lower rates of organ support with the use of IMV, vasopressors, and RTT, respectively, in 49.5%, 50.9% and 13.2% of the patients. We analyzed patients from both private and public hospitals and also demonstrated a high use of support for organ dysfunction. In our study, 55.7% of patients underwent IMV, approximately 20% used NIV or high-flow nasal catheter during ICU stay, and 35% needed RTT. Mortality rates are influenced by the severity of illness, and IMV and RRT are the interventions most commonly associated with death, being proxies for severity. We did not assess mortality according to the main source of income of hospitals, because previous studies in Brazil already demonstrated that convenience samples from public and private hospitals can bias the results.[21] In a previous random sample of patients admitted to Brazilian ICUs, mortality rates of septic patients showed no differences between public and private institutions.[21]

Table 5. Multivariate analysis of factors associated with in-hospital mortality.

Variable	OR (95% CI)	p
Oseltamivir use within 48 h after ICU admission	1.88 (1.19-2.94)	0.006
Liver failure	13.60 (4.12-44.51)	< 0.001
Cardiac arrhythmias	3.16 (1.76-5.67)	< 0.001
Hand/foot ischemia	12.55 (2.41-65.57)	0.003
Hospital-acquired infection	3.60 (2.33-5.56)	< 0.001
Hemorrhage	3.97 (1.36-11.71)	0.012
Age	1.02 (1.00-1.03)	0.065
SOFA score at admission	1.30 (1.21-1.38)	< 0.001
Charlson Comorbidity Index	1.21 (1.09-1.35)	< 0.001

We included in the model all variables with a p value < 0.05 on Tables 1 to 3 in the univariate model, in the presence of collinearity, we selected the most clinically relevant variable (in bold): type of infection and admission type; frailty and age; SAPS 3, use of vasopressors, renal replacement therapy, ventilatory support, platelets, creatinine, bilirubin at admission and SOFA score at admission; diabetes, chronic heart disease, hypertension, chronic kidney disease, chronic hematologic disease, history of smoking and Charlson Comorbidity Index; obesity and BMI; immunosuppressive therapy and solid organ transplant. We excluded laboratory variables with missing data.

Table 6. Causes of death (n = 269 patients).

Cause	n (%)
Refractory shock	175 (65.1)
Multiple organ dysfunction	37 (13.8)
Hypoxemia	16 (5.9)
Central nervous system failure	9 (3.3)
Acute myocardial infarction	7 (2.6)
Hemorrhagic shock	3 (1.1)
Pulmonary embolism	2 (0.7)
Other	20 (7.5)

Requião-Moura et al.[22] reported a mortality rate of 58.2% in kidney transplant patients with COVID-19 admitted to the ICU and a mortality rate of 75.7% in such patients if they had undergone IMV. Moreover, patients that required RRT had a mortality rate of 69.8%. Alberca et al.[23] analyzed the mortality among solid organ transplant patients and found that kidney and heart recipients presented with a higher risk of death when compared with liver recipients. Almost 35% of the patients in our cohort needed RRT, which is much higher than that reported in a previous study.[3] This finding could be explained by the number of patients with chronic kidney disease and kidney transplant recipients in our cohort. A multicenter study in Brazil included data from 35 kidney transplant centers, involving 1,680 hospitalizations and 577 COVID-19-related admissions to the ICU, and reported that 23.4% of the patients required RRT.[22] In part, our higher mortality rates in patients on IMV and RRT could be explained by the severity of the disease at ICU admission and the high proportion of transplant patients. Patients with a history of transplantation are immunosuppressed and at risk for more severe disease and HAIs.[24]

In our cohort there was a high incidence of HAIs (33.5%), *K. pneumoniae* and *P. aeruginosa* being the gram-negative bacteria most commonly isolated in cultures. Several studies have reported a high incidence of and mortality from secondary HAIs in patients with COVID-19.[9,25] Data from Italy on 774 adult patients with severe COVID-19 in 8 Italian hub hospitals showed that 359 patients (46%) developed 759 HAIs.[9] The authors reported a high prevalence of multidrug-resistant bacteria (35% of all isolated agents). As expected, ventilator-associated pneumonia, bloodstream infections, and catheter-associated bloodstream infections were the most common HAIs.[9] HAIs prolonged IMV and hospitalization, and HAIs complicated by septic shock almost doubled mortality. There is no robust data from LMICs regarding HAIs in COVID-19 patients. A systematic review reported 44% of nosocomial infection in patients with COVID-19 in China, suggesting that the impact might be greater in LMICs than in developed countries.[26] Our data showed that HAIs, which potentially can lead to sepsis, were associated with mortality even after adjusting for baseline characteristics, suggesting that preventive measures are key to reduce COVID-19-associated mortality in LMICs.

In the present study, 56 patients (9.2%) had hospital-acquired COVID-19. Read et al.[27] estimated that almost 11.3% of COVID-19 cases occurred after hospital admission in the United Kingdom. Earlier in the beginning of the COVID-19 pandemic, Wake et al.[28] described similar results. Recently, a meta-analysis reported that hospital-acquired COVID-19 is associated with a higher risk of mortality when compared with community-acquired COVID-19, especially in immunosuppressed patients.[14] In our study, we did not observe the same results. One of the potential reasons might have been the high mortality rates even for community-acquired COVID-19 in our population, which might have biased the results.

The most common causes of death in our cohort were refractory shock and MODS, differently from other studies in which respiratory failure was the main cause of death, with a smaller proportion of patients dying from shock and multiorgan failure.[13,15,29,30] Ketcham et al.[15] reported that the most common organ dysfunction prior to death was pulmonary failure (81.7%), septic shock being the primary cause of death in only 26.8% of the cases. Gupta et al.[30] analyzed the cause of death in 787 patients and found that 92.7% of those

died from respiratory failure; however, almost 40% also had septic shock. Data from LMICs are scarce, but Aggarwal et al.[11] recently reported sepsis and MODS as the major causes of death in COVID-19 patients in India, followed by ARDS and cardiogenic shock. One possible explanation for the inconsistency in mortality rates and main causes of death might be related to hospitals' financial resources, as previously reported for sepsis.[21,31] Main causes of death are influenced by the rates of bacterial and fungal sepsis as a consequence of HAIs, which probably lead to a higher frequency of refractory septic shock and MODS. Previous data already suggested that the rates for HAIs are higher in resource-poor settings.[32] In addition, overcrowding in ICUs, temporary ICU beds, lack of trained and experienced health care workers, low nurse-to-patient staffing ratios, burnout syndrome in staff, insufficient medical equipment and supplies, antibiotic stewardship, personnel workload, and infection prevention may contribute to increased rates of HAIs, antibiotic overuse, and increased multidrug resistance.[10]

Our study has some strengths. This was a multicenter study, with detailed data collection focused on the relevance of secondary infections in the outcome of COVID-19 patients, including data on microbiology and multidrug resistance. However, it also has some limitations. First, this was a retrospective study that collected data from electronic m-health reports concerning the first wave of the COVID-19 pandemic in Brazil. Second, we estimated HAIs according to medical records and positive culture results, but we did not use a specific criterion to confirm the infection.

In conclusion, the COVID-19-related mortality rate in our cohort was similar to that in international reports, being very high in patients on IMV and RRT. Mortality was associated with the presence of HAIs even after adjustment for known risk factors such as comorbidities, solid organ transplant, disease severity, and age. Reflecting the relevance of sepsis, the main cause of death was refractory shock. Measures to HAI prevention should be emphasized to improve outcomes.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

FJSR: guarantor of the article from inception to publication. FJSR, FCA, MAS, EMF, DYVT, ESP, FSCS, MJ, NFN, FSVA, TMLA, FRM, and FGRF: study design. FJSR, FCA, MAS, EMF, FRM, and FGRF: data collection. FJSR, FCA, MAS, EMF, DYVT, ESP, FSCS, MJ, NFN, FSVA, TMLA, FRM, and FGRF: data analysis and interpretation, as well as drafting and review of the manuscript. All authors: final approval of the manuscript.

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COVID-19 knowledge, attitudes, and practices among health care workers in Latin America

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ABSTRACT

Objective: To evaluate COVID-19 knowledge, attitudes, and practices among health care workers (HCWs) practicing in Latin American countries during the first surge of the COVID-19 pandemic. **Methods:** This was a multinational cross-sectional survey study, using an online self-administered questionnaire. The final version of the questionnaire comprised 40 questions, organized in five sections: demographic and professional characteristics; COVID-19 knowledge; attitudes toward COVID-19; COVID-19 practices; and institutional resources. **Results:** The study involved 251 HCWs from 19 Latin American countries who agreed to participate. In our sample, 77% of HCWs participated in some sort of institutional training on COVID-19, and 43% had a low COVID-19 knowledge score. COVID-19 knowledge was associated with the type of health center (public/private), availability of institutional training, and sources of information about COVID-19. Concerns about not providing adequate care were reported by 60% of the participants. The most commonly used ventilatory strategies were protective mechanical ventilation, alveolar recruitment maneuvers, and prone positioning, and the use of drugs to treat COVID-19 was mainly based on institutional protocols. **Conclusions:** In this multinational study in Latin America, almost half of HCWs had a low COVID-19 knowledge score, and the level of knowledge was associated with the type of institution, participation in institutional training, and information sources. HCWs considered that COVID-19 was very relevant, and more than half were concerned about not providing adequate care to patients.

Keywords: COVID-19; Health knowledge, attitude, practice; Health personnel; Latin America.

INTRODUCTION

In December of 2019, a new infectious disease caused by a beta coronavirus was identified in the province of Wuhan, China.[1-5] Since then, the virus has spread around the globe and infected nearly 174 million individuals and more than 3 million people have died as of June of 2021.[6]

Research studies from all over the globe described the modes of transmission, which are now known to include mainly contact with respiratory droplets and aerosols,[7,8] whereas clinical studies have revealed that the most common symptoms of COVID-19 were fever, cough, headache, myalgia, dyspnea, and fatigue.[9,10] Additionally, clinical manifestations ranged from mild to severe illness and death, although a significant proportion of subjects infected with the virus never developed symptoms.[11]

Health care workers (HCWs) are at highest risk of being infected since they provide direct care to infected patients.[8] The implementation of standard contact and respiratory precautions, as well as the use of adequate personal protective equipment (PPE), such as N95 masks, eye protection with goggles, and face shields; regular hand washing with soap or disinfection with alcohol hand sanitizer; maintenance of a distance of 1.5-2 m from other people; and avoidance of touching eyes, nose, and mouth constitute the major preventive measures against contamination.[4,8]

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Medical institutions in low-resource settings, such as Latin America, had limited access to PPE during the first surge of COVID-19 in early 2020.[12,13] In addition, the lack of institutional clinical protocols and training, increase in work hours, and shortage of resources, including ICU beds, medications, and ventilators, posed additional barriers to HCWs to care for patients with COVID-19 in those settings.

Adequate knowledge, attitudes, and practices (KAP) toward COVID-19-related diseases among HCWs may decrease the risk of infection and impact patient outcomes.[8,14-16] Therefore, institutions should ensure that frontline workers have access to information, adequate training, and emotional preparation, as well as access to PPE and resources, in order to provide evidence-based care to COVID-19 patients.[17,18]

The objective of this study was to evaluate COVID-19 KAP among HCWs practicing in Latin America countries during the first surge of the COVID-19 pandemic.

METHODS

Study design and sample

This was a cross-sectional survey study using an online self-administered questionnaire. The study was approved by the Research Ethics Committee of the University of São Paulo Medical School (approval numbers: SDC 5047/20/076 and CAAE 32048620.0.0000.0068), and informed consent was electronically obtained from all participants before their answering of the survey questions (written self-administered electronic informed consent).

The inclusion criterion was being an HCW in Latin America, and the exclusion criterion was refusal to sign the informed consent. Invitations to participate in the study were sent by the *Asociación Latinoamericana de Tórax* (ALAT, Latin American Thoracic Society) to all members, via email, between June and October of 2020. In addition, the investigators sent invitations using social media, with a link to access the questionnaire, using a snowballing strategy to reach a broader group of HCWs, including those who were not ALAT members.

KAP questionnaire design

The questions on the questionnaire were developed based on contents and recommendations by the US Centers for Disease Control and Prevention,[19] the *Associação de Medicina Intensiva Brasileira* (AMIB, Brazilian Critical Care Association),[20] and the WHO.[4] The questionnaire was developed in Portuguese and then translated into Spanish by bilingual researchers using the back-translation process.

A panel of experts, consisting of one infectious disease physician, one pulmonologist, one respiratory therapist, and one nurse, reviewed the questionnaire for comprehensiveness, clarity, and relevance. These experts also evaluated face and content validity of the questions.[21]

The final version of the questionnaire, after several rounds of review and expert evaluation, comprised 40 questions organized in five sections.

The first section focused on demographic and professional characteristics, including age, gender, job category (physician, respiratory therapist/physiotherapist, nurse, and other), work experience, and type of institution of employment (Table S1).

The second section evaluated knowledge about COVID-19. The knowledge section included 10 multiple choice questions on sources of information about COVID-19, training, prevention, diagnosis, and treatment. Correct answers to knowledge questions were given a score of 1, while incorrect or "I don't know" answers were given a score of 0. Hence, the maximum score on this section was 10. Participants with scores ≥ 6 were considered to have a high level of knowledge about COVID-19.

The third section assessed attitudes toward COVID-19 and comprised 10 questions. Five questions assessed the perception of relevance of COVID-19, using a Likert scale ranging from 1 (not important) to 5 (very important), and the subsequent 5 questions assessed fears or concerns regarding the disease, the first 4 questions using a Likert scale ranging from 1 (strong fear) to 5 (no fear), and 1 dichotomous (yes/no) question regarding fear of not providing adequate care to COVID-19 patients, scored as 5 and 0 points, respectively. When respondents answered "Yes" to this question, they were asked about the reasons for such fear with 6 additional yes/no questions, which did not count for the attitude score. Attitude scores ranged from 10 (worst attitude) to 50 (best attitude).

The fourth section included three subsections describing practices regarding COVID-19. The first subsection included 8 yes/no questions about COVID-19 clinical practices. The second subsection inquired about ventilatory strategies for patients on mechanical ventilation (MV) using a 4-point Likert scale ("Always", "Sometimes", "Never" and "I don't know"). The last subsection had 7 questions about treatment, including the use of specific medications for COVID-19, such as hydroxychloroquine/chloroquine, azithromycin, remdesivir, lopinavir/ritonavir, tocilizumab, systemic steroids, and convalescent plasma.

The fifth section assessed institutional resources available for patient care, such as numbers of hospital and ICU beds, number of mechanical ventilators, and PPE.

Statistical analysis

Data were collected and managed using the REDCap platform (Vanderbilt University, Nashville, TN, USA) hosted at ALAT.[22,23]

The study sample size was calculated based on the proportion of HCWs with a sufficient level of knowledge about COVID-19. A previous publication reported that 89% of HCWs had sufficient knowledge on COVID-19.[24] We predicted that 60% of HCWs would be considered

to have a sufficient knowledge, and we used a 5% margin of error (95% CI), resulting in a sample size of 150 participants.

Categorical variables were described as absolute and relative frequencies, as were continuous variables described as means and standard deviations in order to characterize the study population. We used the Fisher's exact test and chi-square tests for comparisons between participants with knowledge scores above and below the median.

All data were entered and analyzed using the R statistical package, version 4.0.3 ((The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

RESULTS

Between June and October of 2020, 251 HCWs from 19 Latin American countries agreed to participate in the study. The main characteristics of the study respondents are presented in Table 1. Respondents were mainly from Mexico, Brazil, Argentina, and Colombia. The participation was very low in some countries: Bolivia (1.2%), Costa Rica (1.2%), Guatemala (1.2%), Honduras (0.4%), Nicaragua (1.2%), and Panama (1.2%), which added up to 6% of the sample. The mean age was 48 ± 13 years, and 62% of the sample were male. The majority of respondents were physicians, with a long period of professional experience (> 15 years), and currently working in a hospital or in a health care center. Nearly half of the respondents worked in public institutions, and 77% reported having participated in some sort of COVID-19 institutional training. The most commonly used sources of COVID-19 information were scientific publications, scientific society recommendations, and official government websites.

Table 2 presents the proportion of correct answers for each of the 10 knowledge questions. The median knowledge score (range, 0 to 10) was 6 (IQR: 5-6). In our sample, 107 participants (43%) had low knowledge scores (score < 6). Among the participants who had an adequate knowledge score (score ≥ 6), 17 (7% of the overall sample) had a knowledge score ≥ 8. Knowledge about asymptomatic presentation of COVID-19, risk factors, diagnostic criteria, and prevention measures was high, but that on COVID-19 treatment, transmission, complications, and protective MV was low.

The results in the attitude section are summarized in Figure 1. The median score was 43 (IQR: 38-49). There was no significant association between scores and characteristics of respondents (Table S1). The majority of the participants believed that COVID-19 was a very relevant issue in their institution, their country, and worldwide. Participants were more concerned about infecting family members than about being infected. Overall, respondents were very afraid of not having access to testing (40%) or medical assistance (60%) if they had COVID-19. In addition, 60% reported being concerned about not providing adequate patient care,

Table 1. Characteristics of the respondents (N = 251).[a]

Country	Result
Mexico	48 (19)
Brazil	36 (14)
Argentina	29 (12)
Colombia	27 (11)
Chile	23 (9)
Ecuador	17 (7)
Peru	15 (6)
Venezuela	9 (4)
Cuba	6 (2)
Uruguay	6 (2)
El Salvador	5 (2)
Paraguay	5 (2)
Dominican Republic	5 (2)
Other	16 (6)
Age, years	48 ± 13
Sex - Male	156 (62)
Profession	
Physician	213 (85)
Respiratory therapist/physiotherapist	28 (11)
Nurse	4 (2)
Other	6 (2)
Experience, years	20 [12-31]
Currently working in a hospital or clinic	224 (89)
Hospital type	
Public	131 (52)
Private	67 (27)
University	20 (8)
Mixed	22 (9)
Philanthropic	2 (1)
Other	4 (2)
Direct care for COVID-19 patients	217 (87)
Working in the ICU	68 (27)
Working in the ER	53 (21)
Researcher	23 (9)
Academic supervisor	52 (21)
Chief of staff	32 (13)
Director	8 (3)
Previously tested positive for COVID-19	39 (16)
Institutional training on COVID-19	194 (77)
Sources of information on COVID-19	
Scientific publications in academic journals	213 (85)
Professional or scientific society recommendations	211 (84)
Official government websites	192 (77)
Recommendations from other institutions	100 (40)
Colleagues	90 (36)
Media (e.g., TV, radio, newspaper)	62 (25)
Social media (e.g., Facebook, Instagram, WhatsApp)	59 (24)
Family and friends	7 (3)
Other	13 (5)

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

the major reasons for that being lack of staff, lack of PPE, work overload, and ethical dilemmas.

Table 2. Performance on the COVID-19 knowledge section (N = 251).[a]

Question and topic	Correct answer
K1: Incubation period	158 (63)
K2: Risk factors	231 (92)
K3: Diagnostic criteria	212 (85)
K4: Asymptomatic presentation	245 (98)
K5: Transmission	50 (20)
K6: Prevention measures	202 (81)
K7: Treatment	60 (24)
K8: Complications	47 (19)
K9: Indication of mechanical ventilation	158 (63)
K10: Protective mechanical ventilation	41 (16)

K: question in the COVID-19 knowledge section. [a]Values expressed as n (%).

Figure 2 summarizes the results in the practice section. Nearly all participants reported caring for patients in the ICU (95%) on MV (98%). Almost half of the respondents reported lack of beds, and one third reported lack of mechanical ventilators in the institutions they worked at. The most commonly used ventilatory strategies for COVID-19 patients were protective MV, alveolar recruitment maneuvers, and prone positioning. Regarding COVID-19 treatment, the use of drugs was mainly based on institutional protocols. Remdesivir, hydroxychloroquine, and convalescent plasma were the most commonly used drugs.

Comparing participants with a score in the knowledge section above the median with those with a score below the median, we found that those with higher scores more commonly worked in public institutions, had received institutional training on COVID-19, and used scientific publications, scientific society recommendations, and recommendations from other institutions as sources

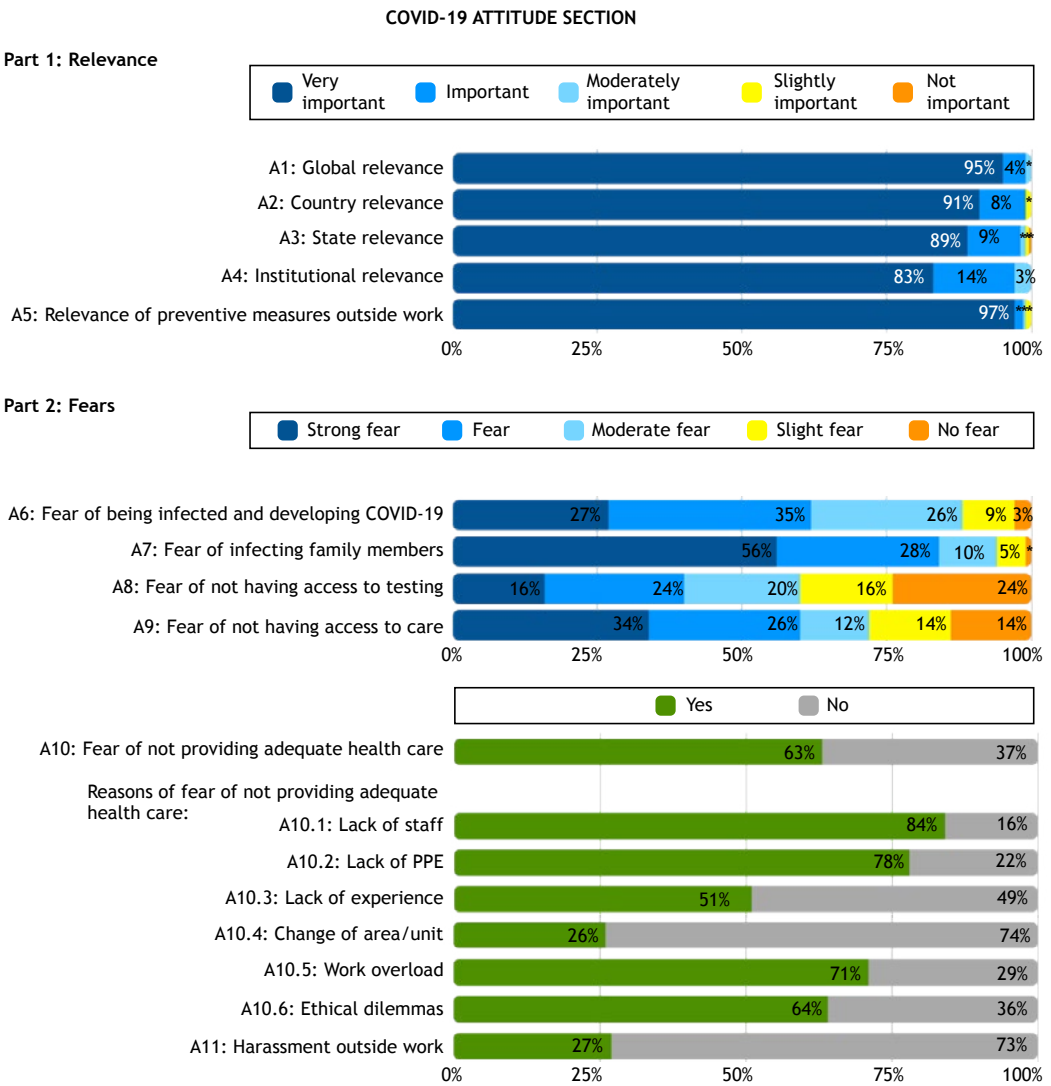

Figure 1. Attitudes toward COVID-19. The width of bars represents the proportion of respondents that marked each response. A: question in the attitude section; and PPE: personal protective equipment. *≤ 1%.

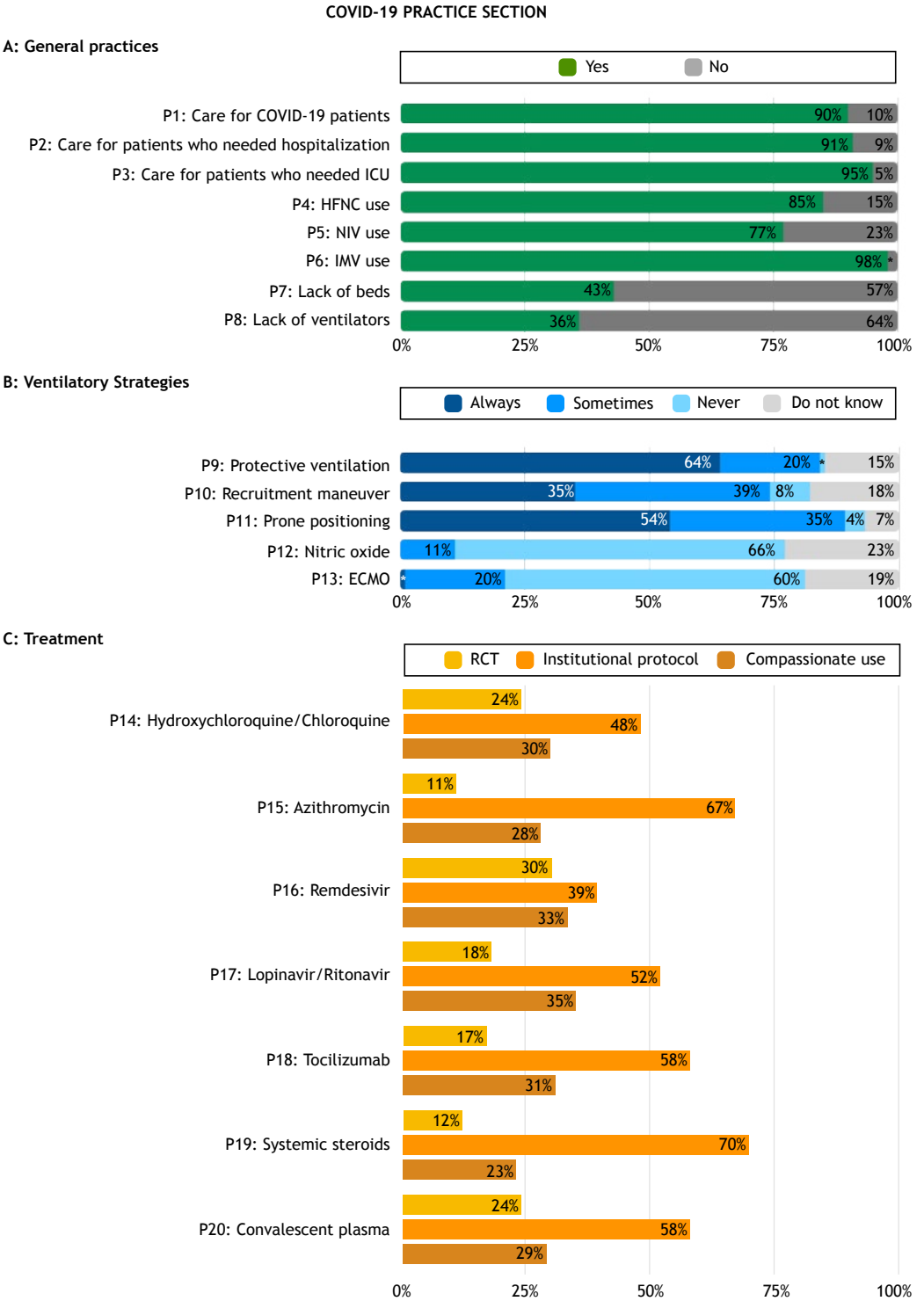

Figure 2. Practices regarding COVID-19. The width of bars represents the proportion of respondents that marked each response. P: question in the practice section; HFNC: high-flow nasal cannula; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; ECMO: extracorporeal membrane oxygenation; and RCT: randomized controlled trial. *≤ 1%.

of information about COVID-19. However, the scores showed no associations with working in the ICU/ER or testing positive for COVID-19 (Table 3).

The characteristics of the participants' institutions are presented in the supplementary material (Tables S2-S6). Regarding diagnostic imaging equipment, 20 (13%) and 34 (22%) of the respondents, respectively, reported that CT and ultrasound were unavailable in their institutions (Table S3). About one third of the participants reported that their institutions

had insufficient numbers of physicians, nurses, or physiotherapists (Table S4). Regarding PPE availability, 53 participants (47%) reported that employees only sometimes had access to N95 respirators in their institutions, whereas 5 (3%) reported having no access to this PPE (Table S6).

DISCUSSION

In this cross-sectional study we assessed COVID-19 KAP among HCWs in 19 countries in Latin America. We found that more than one third of HCWs in our sample participated in some sort of institutional training on COVID-19 and that 43% had a low level of knowledge about COVID-19. The median attitude score was high, but 60% of the participants reported concerns about not providing adequate care to their patients. Most participants reported caring for COVID-19 patients on MV, the most commonly used ventilatory strategies being protective MV, alveolar recruitment maneuvers, and prone positioning, and the use of drugs to treat COVID-19 was mainly based on institutional protocols. We also found that COVID-19 knowledge was associated with the type of institution, availability of institutional training, and the type of sources of information.

This is a comprehensive Latin American study that addressed COVID-19 KAP among HCWs. KAP studies are important to provide valuable insights into how public health initiatives can protect health at the population level better. Because HCWs are more exposed to hazards of SARS-CoV-2 infection, it is important to understand their KAP to establish strategic behavioral interventions to prevent infections in this population.[25-27]

Table 3. Factors associated with a high level of knowledge about COVID-19.[a]

Factor	Level of knowledge		p
	Low (n = 107)	High (n = 144)	
Age, years	49 ± 13	48 ± 13	0.35
Profession			0.70
Physician	93 (87)	120 (83)	
Respiratory therapist/ Physiotherapist	9 (8)	19 (13)	
Nurse	2 (2)	2 (2)	
Other	3 (3)	3 (2)	
Experience, years	20 [14-32]	20 [12-30]	0.38
Currently working in a hospital or clinic	90 (86)	134 (93)	0.09
Hospital type			0.01
Public	45 (44)	86 (60)	
Private	35 (34)	32 (22)	
University	5 (5)	15 (10)	
Mixed	14 (14)	8 (6)	
Philanthropic	1 (1)	1 (1)	
Other	2 (2)	2 (1)	
Direct care for COVID-19 patients	89 (86)	128 (90)	0.46
Working in the ICU	28 (27)	40 (27)	0.95
Working in the ER	20 (19)	33 (23)	0.56
Researcher	10 (9)	13 (9)	1.00
Academic supervisor	21 (20)	31 (22)	0.83
Chief of staff	16 (15)	16 (11)	0.48
Director	4 (4)	4 (3)	0.73
Previously tested positive for COVID-19	15 (14)	24 (17)	0.74
institutional training on COVID-19	75 (71)	119 (83)	0.05
Sources of information			
Scientific publications	84 (79)	129 (90)	0.03
Scientific society recommendations	82 (77)	129 (90)	0.01
Official government websites	81 (76)	111 (77)	0.92
Recommendations from other institutions	34 (32)	66 (46)	0.03
Colleagues	38 ((36)	52 (36)	1.00
Media	25 (23)	37 (26)	0.78
Social media	23 (22)	36 (25)	0.62
Family and friends	3 (3)	4 (3)	1.00
Other	4 (4)	9 (6)	0.56

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

Most participants reported having participated in institutional training on COVID-19, and that was associated with higher levels of knowledge. The COVID-19 pandemic had a significant impact on medical education all over the world, and webinars and online meetings have provided a great opportunity for teaching and learning during this period.[16] However, some HCWs reported feeling overwhelmed with the number and frequency of these events and had not attended all of these, reinforcing the importance of proposing effective training strategies, especially during the COVID-19 pandemic.[28]

Despite high training participation, almost half of HCWs had low levels of knowledge about COVID-19. Although it is difficult to estimate how much knowledge is enough to achieve desirable changes in health outcomes, it is known that the type of information source might influence the level of knowledge and, potentially, the clinical practice.[26,29] Our finding that knowledge about COVID-19 treatment, transmission, complications, and protective MV was low might be explained by the lack of scientific knowledge during the first wave of the pandemic, especially in relation to complications and treatment.[18,26]

HCWs had a high attitude score, believing that COVID-19 was very relevant. Previous studies have reported that the majority of HCWs have positive attitudes toward COVID-19, and that has been associated with age, gender, professional category, level of education, hospital type, and participation in online courses.[13,27,29-31]

We also found that 60% of HCWs were concerned about not providing adequate care, and the main reasons were concerns about the lack of staff, lack of PPE, work overload, and ethical dilemmas. Latin America has one of the highest COVID-19 infection rates in the world, and several risk factors have been suggested, including the lack of human and institutional resources,[13,32] which may explain the concerns of HCWs. Furthermore, a considerable proportion of respondents reported lack of beds and/or of mechanical ventilators at the institutions they worked at.

Respondents also reported a lack of diagnostic imaging equipment. Restricted access to CT in low- and middle-income countries (LMICs) may be expected considering the high costs of the equipment. However, ultrasound is a portable and a relatively low-cost technology, but 22% of the respondents had no access to it. Previous studies have also reported a lack of access to ultrasound, and they suggested that this might reflect inequality in the supply and acquisition of medical equipment and in medical equipment training in LMICs, especially in rural areas.[33,34]

The most commonly used ventilatory strategies for COVID-19 patients were protective MV, alveolar recruitment maneuvers, and prone positioning. This finding is in line with those of a scoping review that mapped MV strategies used in critically ill COVID-19 patients[35]; the authors found that ventilator settings, especially tidal volume, plateau pressure, and driving pressure were relatively consistent across the studies and generally followed evidence-based recommendations for lung protective ventilation, and that prone positioning was widely used.[35]

Regarding COVID-19 treatment, the respondents reported that the use of drugs was mainly based on institutional protocols. This might be explained by the fact that there were a very limited number of published randomized controlled trials on COVID-19 treatment published during the study period. The most commonly used drugs were remdesivir, hydroxychloroquine, and convalescent plasma. It is important to mention that, at the time the survey was distributed, there was no evidence of efficacy for these treatment strategies in COVID-19 patients.

We observed that the knowledge scores were higher among HCWs who worked at public institutions, those who had institutional training on COVID-19, and those who used scientific publications, scientific society recommendations, and recommendations from other institutions as sources of information. Other studies also reported a higher proportion of adequate knowledge among frontline HCWs working in public hospitals and those who received COVID-19 institutional training.[29] These findings emphasize the need for continuous medical training to guarantee access to evidence-based recommendations at all levels.

This study has several limitations. Knowledge was measured using a self-administered questionnaire and therefore may not reflect all aspects of medical knowledge about COVID-19. Our recruiting strategy was based on sending emails to ALAT members and invitations via social media, so the resulting sample may not be representative ofthe reality in all Latin American countries. In addition, because we used a snowballing strategy, it is possible that we had a sample clustering among well-trained staff, and we cannot estimate the response rate. The respondents of online surveys are most likely not representative of the whole universe of HCWs, since attitudes, risk perceptions, and knowledge may vary across countries and over time. Furthermore, self-reported behavior-related measures are subject to recall, response, and social desirability biases, and we lacked objective corroboration of real KAP among respondents. The majority of the participants in the survey were physicians, and other HCWs were not well represented. Since this was a cross-sectional study, we can only make assumptions for a single moment. Finally, our study design prevents us from making any assumptions about how the level of knowledge of the participants translated into patient outcomes. It is reasonable to expect that the level of knowledge varied throughout the COVID-19 pandemic, and it is important to consider that surges of cases during this first wave of the pandemic in the represented countries did not happen at the same time everywhere; there were peaks of COVID-19 cases in Argentina, Uruguay, and Paraguay after the survey period.

In conclusion, this multinational study involving several countries in Latin America showed that almost half of the HCWs surveyed had a low level of knowledge regarding COVID-19, and that was associated with the type of hospital that they worked at (public/private), their participation in institutional training, and their sources of information. HCWs considered that COVID-19 was very relevant, scoring high in the attitude section of the questionnaire, and more than half were concerned about not providing adequate care to patients. Our findings underscore the need for adequate institutional training on COVID-19, implementation of appropriate institutional measures to address frontline workers' concerns about the disease, including the provision of necessary resources and PPE, and dissemination of trustworthy sources of information about COVID-19.

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AUTHOR CONTRIBUTIONS

MLAS and ISS equally contributed to all aspects of the study. CMP, CATD, IZ, GEZ, RPP, FVV, and MC: conceptualization, methodology, and editing/revision of the manuscript draft. JCF: conceptualization; data curation; formal analysis; methodology; project administration; and drafting, editing, and review of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Factors underlying denial of and disbelief in COVID-19

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ABSTRACT

Objective: To investigate factors that influence or promote disbelief and negative attitudes toward COVID-19. **Methods:** This was cross-sectional study involving 544 males and females ≥ 18 years of age in Greece between December of 2020 and January of 2021. All participants were informed about the purpose of the study, protection of anonymity, and volunteer participation. Participants completed an online anonymous 40-item questionnaire. Analysis of data included the identification of correlations and use of t-tests and ANOVA. **Results:** The level of knowledge regarding COVID-19 transmission routes, manifestations, and prevention was high in our sample. Women appeared to have a more positive attitude toward COVID-19 prevention and management than did men ($p = 0.032$ and $p = 0.018$, respectively). Younger people (18-30 years of age) seemed to deny the validity of scientific data and mass media reports about ways to deal with the pandemic more commonly than did those > 30 years of age ($p = 0.003$ and $p = 0.001$, respectively). People who resided in cities more commonly believed in scientific announcements than did those living in villages ($p = 0.029$). **Conclusions:** In order to minimize cases of denial of and disbelief in COVID-19 and to promote vaccination, a series of actions are required. Governments should implement a series of measures to contain the disease, taking into consideration the psychological and social aspects of those policies.

Keywords: Vaccination; COVID-19; Health knowledge, attitudes, practice.

INTRODUCTION

In December of 2019, several cases of lower respiratory tract infections of unknown cause were reported in the city of Wuhan, province of Hubei, China. On January 7, 2020, a new coronavirus strain was identified as the cause of these infections and received a temporary name: 2019-nCoV. The continuous rise in the number of new cases worldwide forced the WHO to announce the characterization of the disease as a pandemic about two months after the identification of the infectious strain.[1]

Recently, scientists have faced threatening pandemic situations caused by different strains of the Coronavirus family, which they have successfully managed to contain. Specifically, Middle East respiratory syndrome was first reported in Saudi Arabia in September of 2012, and, according to the WHO, 2,519 cases and 866 deaths were reported worldwide by January of 2020. Severe acute respiratory syndrome was first reported in Asia in February of 2003 and rapidly spread across 26 countries before it was contained after approximately four months. During this period, more than 8,000 people were ill and 774 died. Since 2004, no cases of this syndrome have been reported.[2]

From the beginning of the COVID-19 pandemic to this writing, an attitude of denial of and disbelief in the disease has been observed, along with extreme questioning of preventive measures, disease manifestations, and management of suspected and confirmed cases all over the world. According to the results of a global study,[3] 13% of Americans disbelieved that COVID-19 was real, the highest rates of disbelieving the disease being found in Turkey and Poland (22% of the population), in Egypt and Saudi Arabia (19%), followed by Nigeria and Greece (17%).

The analysis of factors and reasons behind the adoption of a negative attitude toward COVID-19 is a complicated and tedious task. Reasons that have driven people to deny or downplay the existence and progression of the pandemic are mostly related to psychological, personal, social, and political factors. The first phase of this phenomenon started with the publication of epidemiological data, creating a feeling of imminent threat. A portion of people took a denialist stance as an innate survival mechanism against future difficulties in order to cope with the overload of information and the constant bombardment with medical terminology.[4-6]

Another important parameter that contributes to the spiraling of this phenomenon is the obligatory use of personal protective equipment (PPE) and the restriction of personal and social activities. The introduction of preventive PPE caused feelings of restraint, distress, and anxiety which translated into disbelief, possible

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violations of human rights, and outbursts of reactive behaviors. The mandatory use of PPE was exploited by many as an instrument of political opposition against government initiatives, resulting in an opportunity to promote political interests.[7,8]

Constant restrictions, long periods of social isolation, and consecutive large-scale pandemic waves caused the postponement or cancellation of important activities such as trips, excursions, athletic events, and celebrations, generating feelings of sorrow and indignation in the population, which in turn led people to downplay the disease and take a denialist viewpoint on the severity of the pandemic and the usefulness of restrictive measures.[9,10]

The aim of the present study was to investigate the factors that influence or promote disbelief and negative attitudes toward COVID-19.

METHODS

The present study had a cross-sectional design. The reason behind this choice was the credibility of the results produced, because this design is considered to be the most appropriate for collecting data from many participants. The study comprised a convenience sample of 544 adult participants (≥ 18 years of age). Initially, 600 participants expressed an interest in taking part of the study, yielding a response rate of 90.67%. Participants were initially informed about the purpose of the research, protection of anonymity, and volunteer participation. Then, the participants were asked to complete an online anonymous self-administered questionnaire. This study was conducted between December 1, 2020 and January 31, 2021.

In order to ensure the validity of the questionnaire content, relevant Greek and international literature was reviewed. After meticulous critical reading of the relevant literature, no measurement tools evaluating people's knowledge on and belief/disbelief in COVID-19 were found. As a result, we developed a questionnaire in Greek and pilot tested it with 15 people in order to assess the validity and reliability of the questionnaire.[11]

The internal consistency (reliability) of a questionnaire represents the extent to which subparts of the questionnaire measure the same characteristic. Reliability assessment is extremely useful because it evaluates the consistency of the questions and, by extension, that of the answers.

The validity of a questionnaire represents the extent to which the questionnaire measures what it was designed to measure. The measurements need to be relevant to the characteristics that the researcher wants to study. The different aspects of validity examined in our questionnaire were face validity and content validity.

The present study complied with national and institutional research ethics committee standards, as well as with the 1964 Helsinki Declaration and subsequent amendments or equivalent ethical standards. The study was designed and conducted in accordance with the ethical principles established by the University of Thessaly, Greece (no. 77 acceptance statement).

The final structure of the questionnaire included 8 questions on knowledge about the transmission, manifestations, and prevention of COVID-19; 10 questions on information sources; 10 questions on the trust in and acceptance of scientific data related to the disease; 10 questions on the influence of social environment on believing/disbelieving in the disease; and 10 questions on the attitudes and preferences regarding vaccination. Answers to the latter 30 questions were scored on a five-point Likert scale ranging from 1 (not at all/totally disagree) to 5 (absolutely/totally agree). Cronbach's alpha coefficient was 0.68, showing borderline internal consistency.

In the present study, descriptive and inferential statistics were employed. Descriptive variables were expressed as absolute and relative frequencies or as means and standard deviations. Inferential statistics were utilized considering the importance of the results; for that reason, independent tests were conducted together with parametric tests, since the results had a normal distribution. More specifically, the Student's t-test was applied for binary variables because larger samples are assumed to have normal distribution; for variables with three or more values, ANOVA was chosen in order to control for the impact of two or more independent variables on the dependent variable. Two-tailed statistical significance was set at $p \leq 0.05$. Data analysis was performed with the IBM SPSS Statistics software package, version 25.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The proportions of men and women in the sample were 17.8% and 82.0%, respectively. With regard to age distribution, 50.6% were in the > 30-year age group, whereas 49.4% were in the ≤ 30-year age group. The nationality of the majority of the participants was Greek (97.6%). Regarding the level of education, most participants were college undergraduates/graduates (43.0%); among these, 17.5% and 2.2% held a master's degree and a PhD degree, respectively. Most participants were employed (90.3%), and 39.0% reported working in the private sector. The unemployment rate was 9.7%. Regarding marital status, 30.7% were married, 65.1% were single, 3.3% were divorced, and 0.9% was widowed. Lastly, 82.4% lived in a city, 9.7% lived in a small town, and 7.9% lived in a village.

Regarding the knowledge of COVID-19, the overall proportion of correct answers was 89.1%. Specifically, questions on COVID-19 symptoms were correctly responded by 93.9% of the participants, as were those on, as follows: transmission routes, by 97.4%; clinical features of asymptomatic patients, by 97.6%; incubation period, by 93.6%; treatment, by 66.7%; prevention, by 68.2%; recognition of alarming symptoms, by 99.1%; and disease diagnosis, by

96.3%. A statistically significant difference was found regarding the question about whether there was a specific treatment for the disease: 68.6% of women and 57.7% of men correctly answered that there was no specific treatment. In addition, we noted that the higher the education level of the respondents was, the more likely they were to answer this question correctly, that is, there is no specific treatment. Regarding the question about the mean number of days between exposure to a confirmed COVID-19 case and symptom onset, we noticed a statistically significant correlation with age, since 96.3% of respondents > 30 years of age correctly answered that symptoms would start, on average, 5-6 days after a contact, compared with 3.7% of those ≤ 30 years of age, who answered 22-23 days after a contact. In the question about COVID-19 symptoms, "living in a city" or "living in a small town" correlated positively with the answer "weight loss is not one of the clinical signs of the disease" (in 94.6% and 96.2%, respectively). However, "living in a village" showed no correlation.

Table 1 shows statistically significant differences regarding opinions and attitudes toward COVID-19 between males and females. In general, women more often obtained information about the disease from mass media and more often believed in scientific announcements, although they believed that the guidelines for the treatment of and recovery from the disease were unclear. In addition, women more commonly followed protective recommendations during restrictive measures and were more concerned about side effects of vaccines. As for men, they were more prone to accepting data from scientific studies conducted abroad, because they considered them to be of greater validity.

Table 2 shows statistically significant differences regarding opinions and attitudes toward COVID-19 between the two age groups studied (18-30 years and > 30 years). In general, the participants in the > 30-year age group more frequently obtained information about the disease from mass media, supported the validity of published data, and believed that scientific studies were moving in the right direction toward the end of the pandemic. Furthermore, they more commonly followed protective recommendations during restrictive measures. As for those in the ≤ 30-year age group, they more often had negative opinions and attitudes toward information provided by mass media and scientific announcements, disregarding scientific studies conducted in Greece. They were more careless about following protective recommendations and restrictive measures, and their social environment more often influenced on their denial of and disbelief in the severity of COVID-19.

Regarding the level of education, we found that the higher that level is, the greater the variation in trust rates; people with tertiary education, except those with doctoral degrees, claimed that they trust the scientific community in relation to disease prevention guidelines, that they believe that scientific studies are moving in the right direction toward the end of the pandemic, that scientific announcements are greatly exaggerated, and that most of the scientific data cannot be implemented in Greece. They also comply with regulations and do not accept visitors or visit friends and relatives.

People who lived in a city or in a small town showed greater receptiveness toward scientific announcements by specialists regarding disease management when compared with people residing in a village. Conversely, people who lived in rural areas were more often influenced by their social environment regarding disease severity (Table 3).

DISCUSSION

The present study attempts to define factors that drive people within the community toward rejection of and disbelief in COVID-19. People's attitude toward health issues is related to their knowledge of the infectious

Table 1. Statistically significant differences between male (n = 97) and female (n = 446) participants regarding opinions and attitudes about COVID-19.

Parameter	Sex		p
	Male	Female	
Constant reference to and demonstration of protective measures by mass media has helped me protect myself from the disease.	2.24 ± 1.13	2.52 ± 1.16	0.032
I believe in scientific announcements of specialists regarding disease management.	3.52 ± 1.07	3.77 ± 0.93	0.018
Guidelines for the treatment of and recovery from the disease are unclear.	2.76 ± 0.94	3.10 ± 1.03	0.003
Scientific studies that are conducted abroad have greater validity than do those conducted by Greek scientists.	2.70 ± 1.25	2.40 ± 1.17	0.026
Due to the pandemic, I do not accept visitors or visit friends and relatives.	2.89 ± 1.28	3.26 ± 1.32	0.013
People I interact with take all necessary protective measures in order not to contract or transmit the disease.	3.56 ± 1.08	3.83 ± 0.86	0.007
I feel more comfortable when the people with whom I interact wear a mask.	3.34 ± 1.36	3.74 ± 1.20	0.004
I am worried about possible side effects of the vaccine.	3.25 ± 1.41	3.55 ± 1.37	0.05

agent, level of education, psychoemotional state, and sources of information, as well as the way facts are being disseminated and their previous personal experiences. In order to investigate the research hypothesis and the abovementioned reasons thoroughly, we examined the participants' knowledge, information sources, and attitudes related to COVID-19, as well as the influence of their social environment on their beliefs about COVID-19.

The level of knowledge on COVID-19 among the respondents was very high with 89.1% of them correctly answering questions on transmission routes, prevention, and clinical features of the disease. A similar study by Chen et al.[12] reported high rates of correct responses regarding disease symptoms such as cough (99.5%), fever (96.0%), droplet transmission (99.5%), airborne transmission (81.1%), and transmission through direct contact (92.3%). A high level of knowledge of COVID-19 protection was also documented by Siddiqui et al,[7] who reported that 84% of their sample knew the correct hand washing technique, 82% knew that the disease can be transmitted through handshaking, and 79% knew that they should maintain a distance of at least one meter from others.

The present study and those by Chen et al.[12] and Siddiqui et al.[7] all concluded that people's

Table 2. Statistically significant differences between respondents in the < 30-year age group (n = 275) and those in the ≥ 30-year age group (n = 269) regarding opinions and attitudes about COVID-19.

Parameter	Age group, years		p
	≤ 30	> 30	
I understand disease progression better from TV.	2.21 ± 1.03	2.41 ± 1.06	0.034
I feel safer getting informed on the course of the disease from the Internet.	2.93 ± 1.07	3.18 ± 1.02	0.005
Constant reference to and demonstration of preventive measures by mass media has helped me protect myself from the disease.	2.31 ± 1.12	2.63 ± 1.17	0.001
I am satisfied with the information that I get from mass media.	1.92 ± 0.97	2.27 ± 1.11	0.001
I support the validity of published data on the pandemic.	2.41 ± 1.06	2.66 ± 1.20	0.011
I believe that mass media overestimates COVID-19.	3.43 ± 1.23	3.15 ± 1.32	0.012
Reporters and TV presenters explain the pandemic progression in a comprehensible manner.	2.35 ± 0.92	2.53 ± 1.00	0.024
I think scientific studies are moving in the right direction toward the end of the pandemic.	3.31 ± 1.07	3.57 ± 1.00	0.003
Scientific studies that are conducted abroad have greater validity than do those by Greek scientists.	2.71 ± 1.16	2.20 ± 1.17	0.001
Due to the pandemic, I do not accept visitors or visit friends and relatives.	2.85 ± 1.19	3.54 ± 1.36	0.001
People with whom I interact take all necessary protective measures in order not to contract or transmit the disease.	3.68 ± 0.94	3.89 ± 0.87	0.007
I feel more comfortable when the people with whom I interact wear a mask.	3.39 ± 1.24	3.95 ± 1.18	0.001
Scientific announcements often show elements of exaggeration.	3.02 ± 1.26	2.64 ± 1.31	0.001
Much of the scientific data cannot be implemented in Greece.	2.89 ± 1.14	2.53 ± 1.18	0.001
When I am around friends or relatives, we do not wear a mask because we are not afraid of one another.	3.09 ± 1.41	2.53 ± 1.35	0.001
People from my social environment believe that the disease is much milder than what has been presented.	2.89 ± 1.22	2.65 ± 1.27	0.023
People from my social environment consider that State measures and policies to limit disease transmission are exaggerated.	3.25 ± 1.23	2.94 ± 1.36	0.006

Table 3. Statistically significant differences regarding opinions and attitudes about COVID-19 by area of residence of the respondents.

Area of residence	I believe in scientific announcements by specialists regarding disease management.	People from my social environment question the severity of the disease
City (n = 448)	3.75 ± 0.94	2.48 ± 1.11
Small town (n = 53)	3.75 ± 0.94	2.43 ± 1.14
Village (n = 44)	3.34 ± 1.13	2.98 ± 1.17
p	0.029	0.023

level of knowledge on prevention, clinical signs, and transmission routes of COVID-19 is particularly high. This increase in knowledge is most likely due to the efforts of health care workers to provide people with valid and scientific information, such as the high levels of COVID-19 morbidity and mortality globally and the people's need for protection.

Today, it is very easy to access and disseminate information. Mass media and the Internet seem to play an important role in informing the public about health issues. Their dynamic features vastly contribute to shaping people's opinions and attitudes regarding several diseases and their prevention.[13-15]

With regard to sources of information, women believed that the constant reference and demonstration of preventive measures by mass media has considerably helped them protect themselves from the disease, in contrast with men. At the same time, people > 30 years of age seemed to understand the disease progression better from television and feel safer getting informed on the course of the disease from the Internet, in contrast to those ≤ 30 years of age, who believed that mass media overestimate COVID-19.

In most countries, television is the most popular means of information, because the mean TV viewing time is two hours.[16] Over the last years, rapid advancement of technology has brought important changes in the way that children and adolescents live and get informed. Ownership of a computer and access to the Internet are now easier than ever and, along with the widespread use of smart devices, people have the opportunity to receive validated information rapidly.

The extensive use of the Internet as a major source for information about COVID-19 has been observed. According to the present study, knowledge obtained from mass media is more accepted by people > 30 years of age than those ≤ 30 years of age. A study by Dkhar et al.[17] on people's knowledge about COVID-19 mentions that 89% of the sample population used the Internet as their source of information. The interest of young people in searching medical information online is probably associated with the fact that they are more familiar with the Internet and, at the same time, they use it as a tool for most, if not all, daily activities such as education, shopping, and entertainment.

Various scientists believe that the rapid spread of information and, particularly, the publication of research protocols about prevention, treatment, and diagnostic approaches of the disease contributed to the immediate preparation of health care professionals and the faster acceptance of the disease in populations all over the world.[18] However, the large volume of information during the course of the pandemic seems to drive people to confusion and dead ends. A portion of medical evidence is ambiguous, promoting mixed messages. Unclear and not scientifically proven studies and practices are accepted by a group of people who encourage negative impressions, downplay the disease, and cultivate doubts in order to fulfill personal, political, and economic goals.[19]

The present study shows that the level of knowledge regarding COVID-19 transmission routes, manifestations and prevention was high in our sample. Women appeared to place more trust in information about preventing and managing COVID-19 than did men. Younger people were less likely to believe in the validity of scientific data and mass media reports about ways to deal with the pandemic, and people residing in cities were more likely to believe in scientific announcements when compared with those living in villages.

In order to minimize the number of cases of denial and disbelief regarding COVID-19, a series of actions are required. Governments should implement a series of measures to contain the disease, taking into consideration the psychological and social aspects of those policies. Scientific announcements and broadcastings should be simple, clear, and precise to avoid promotion of mixed messages. Mass media should inform people about current public health issues without any bias, personal opinions, or practices of persuasion.

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AUTHOR CONTRIBUTIONS

AV: conceptualization (lead), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (lead), project administration (equal), resources (equal), software use (equal), supervision (lead), validation (equal), visualization (equal), writing of original draft (equal), and review & editing of the manuscript (equal). NAP: conceptualization (equal), data curation (equal), formal analysis (supporting), funding acquisition (support), investigation (equal), methodology (support), project administration (equal), resources (support), software use (support), supervision (equal), validation (support), visualization (equal), writing of original draft (support), and review & editing of the manuscript (support). AT: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (support), investigation (equal), methodology (support), project administration (equal), resources (equal), software use (equal), supervision (support), validation (equal), visualization (equal), writing of original draft (support), and review & editing of the manuscript (support). DP: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (support), investigation (equal), methodology (equal), project administration (equal), resources (support), software use (support), supervision (equal), validation (equal), visualization (support), writing of original draft (support), and review & editing of the manuscript (support). KS: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal),

investigation (equal), methodology (equal), project administration (equal), resources (equal), software use (equal), supervision (equal), validation (equal), visualization (equal), writing of original draft (equal), and review & editing of the manuscript (equal). TP: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software use (equal), supervision (equal), validation (equal), visualization (equal), writing of original draft (equal), and review & editing of the manuscript (equal). EK: conceptualization (equal), data curation (equal), formal analysis (support), funding acquisition (equal), investigation (equal), methodology (equal), project administration (support), resources (support), software use (support), supervision (equal), validation (equal), visualization (equal), writing of original draft (support), and review & editing of the manuscript (equal). DM: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (support), investigation (support), methodology (equal), project administration (support), resources (support), software use (support), supervision (equal), validation (equal), visualization (equal), writing of original draft (equal), and review & editing of the manuscript (equal). All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Use of different reference values for handgrip strength in individuals with COPD: analysis of agreement, discriminative capacity, and main clinical implications

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ABSTRACT

Objective: To identify reference values for handgrip strength through a literature search and compare the agreement of reference values from Brazil with others for handgrip strength in a sample of COPD patients in Brazil, as well as to determine which set of reference values is more discriminative regarding differences in clinical characteristics between individuals with low handgrip strength and normal handgrip strength. **Methods:** To identify reference values for handgrip strength, a literature search was performed; a retrospective cross-sectional analysis of baseline-only data from two unrelated studies was then performed. Individuals were evaluated for handgrip strength, peripheral muscle strength, respiratory muscle strength, pulmonary function, body composition, exercise capacity, dyspnea, and functional status. **Results:** Of the 45 studies that were initially selected, 9 met the criteria for inclusion in the analysis, which included 99 COPD patients in Brazil (52% of whom were male with GOLD stage II-IV COPD). The prevalence of low handgrip strength varied across studies (from 9% to 55%), the set of reference values for handgrip strength in a sample of individuals in Brazil having classified 9% of the study sample as having low handgrip strength. The level of agreement between the reference values for a sample of individuals in Brazil and the other sets of reference values varied from weak to excellent. The reference values for a sample of individuals in Brazil showed the highest number of significantly different characteristics between individuals with low and normal handgrip strength. **Conclusions:** The level of agreement between national and international sets of reference values for handgrip strength varied from weak to excellent in COPD patients in Brazil. Reference values for handgrip strength with higher discriminative capacity are not necessarily those that identify more individuals as having low handgrip strength.

Keywords: Pulmonary disease, chronic obstructive; Hand strength; Muscle weakness; Muscle strength; Reference values.

INTRODUCTION

Handgrip strength has been described as an important prognostic factor, moderately strongly associated with mortality in the general population and in individuals with COPD.[1,2] Handgrip strength reflects well overall peripheral muscle strength in individuals with COPD,[3] and assessment of muscle strength in this population is common and highly encouraged because muscle dysfunction is expected as a systemic manifestation of the disease.[4] Reference values or prediction equations are useful tools to identify the presence of abnormal muscle function while accounting for differences in individual characteristics because muscle strength is somehow associated with such characteristics.[4] Correct identification of individuals with peripheral muscle weakness is essential so that those at risk can be referred for specific treatment.[5]

Since the publication of reference values for handgrip strength by Mathiowetz et al.[6] in 1985, various studies have reported normative data for handgrip strength. Normative ranges, cutoff points, and reference equations are available in the literature,[7-9] but there are differences across studies regarding age ranges and methods. In addition to population-based characteristics, technical issues such as patient positioning for assessment, the instrument used for assessment, the hand selected for assessment, and the number of attempts should be taken into consideration when choosing the most suitable reference values.[10]

The objectives of this study were threefold: to identify reference values for handgrip strength through a literature search; to determine the level of agreement between a set of reference values for handgrip strength from Brazil[11] and other sets of reference values for handgrip

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strength in a sample of COPD patients recruited in Brazil; and to determine which set of reference values is more discriminative regarding differences in clinical characteristics between individuals with low handgrip strength and normal handgrip strength.

METHODS

This was a retrospective cross-sectional study of baseline-only data from two unrelated studies: a previous study conducted by our research group[12] and an as yet unpublished study by our research group (NCT03127878, approved by the local research ethics committee [Protocol no. 1.730.247]). Data from the two studies were collected between 2006 and 2019 in the Laboratory of Research in Respiratory Physiotherapy at the State University of Londrina, located in the city of Londrina, Brazil. The inclusion criteria for the two studies were as follows: a clinical diagnosis of COPD in accordance with the GOLD criteria[13]; clinical stability, without infections or exacerbations in the previous month; no severe/unstable cardiac disease; and no orthopedic, neurological, or muscular impairment that could hinder the assessments. Participants were evaluated for handgrip strength, peripheral muscle strength (quadriceps, biceps, and triceps muscle strength), respiratory muscle strength, pulmonary function, body composition, exercise capacity, dyspnea, and functional status. All participants gave written informed consent prior to inclusion in the study.

Literature search

A literature search was undertaken in order to identify studies for analysis. Studies reporting reference values and/or prediction equations for handgrip strength were retrieved from the MEDLINE (PubMed) database on September 13, 2021. The search strategy and process of article selection are described in detail in the supplementary material.

Handgrip strength assessment

Handgrip strength was assessed for both hands with the use of a validated hydraulic hand dynamometer (SH50011; Saehan Corporation, Changwon, South Korea),[14] with the patient in a seated position with unsupported arms, shoulders in a neutral position along the body, elbows flexed to 90°, and wrists in a neutral position. Three maximal attempts were made for each hand, with 3 s of contraction and 30 s of rest between attempts; the highest value for each hand was used in the analysis.[15] Right- or left-hand dominance was self-reported.

Other assessments

Quadriceps, biceps, and triceps muscle strength was assessed by the one-repetition maximum test; pulmonary function was assessed by spirometry; body composition was assessed by bioelectrical impedance analysis and an equation proposed by Rutten et al.[16]; and exercise capacity was assessed by the six-minute walk test. All assessments were performed as previously described.[3]

Respiratory muscle strength was assessed by measuring maximum respiratory pressures (MIP and MEP) with a digital manometer (MVD 300; Globalmed, Porto Alegre, Brazil), in accordance with recommendations by Black & Hyatt[17] and population-specific reference values.[18] Dyspnea during activities of daily living and functional status were respectively assessed by the Portuguese-language versions of the Medical Research Council scale[19] and the London Chest Activity of Daily Living scale.[20] In addition, the BODE index[21] and the Age, Dyspnea, and airflow Obstruction (ADO) index[22] were calculated.

Statistical analysis

All statistical analyses were performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA) and Epidat, version 3.1 (*Dirección Xeral de Saúde Pública de la Consellería de Sanidade*, *Xunta de Galicia*, Santiago de Compostela, Spain). The normality of the data distribution was examined with the Shapiro-Wilk test. Normally distributed data were described as mean ± standard deviation, and non-normally distributed data were described as median (IQR). Individuals were classified as having normal or reduced handgrip strength in accordance with different sets of reference values, on the basis of the limits proposed by the authors of each study or the number of SDs below the mean and specific for each group of individuals (classified by sex, age, and height in some cases), with the limit of 2 SDs[23] or the 5th percentile if values of mean ± SD were not available. The level of agreement between sets of reference values was determined by calculating the kappa statistic, being classified as weak (< 0.20), fair (0.21-0.40), moderate (0.41-0.60), excellent (0.61-0.80), or almost perfect (0.81-0.99).[24] For comparison of clinical characteristics between individuals with normal and reduced handgrip strength (in accordance with each set of reference values), the Student's t-test or the Mann-Whitney test was used depending on the normality of the data distribution. A value of $p < 0.05$ was considered statistically significant for all analyses.

RESULTS

Thirty-seven studies were selected from a total of 895 articles retrieved from the MEDLINE (PubMed) database. An additional 8 were retrieved by manual search, adding up to a total of 45 studies. Of those, 9 were selected for analysis.[6,11,25-31] The selection process is shown in detail in Figure 1. Table 1 shows the characteristics of the 9 studies selected for analysis. The studies reported normative ranges for handgrip strength by sex and age, at least. General characteristics of the 36 studies that were not included in the analysis are shown in Table S1, including the reasons for not including them in the analysis (differences regarding

the assessment of handgrip strength and the lack of a representative sample, in most cases).

Table 2 describes the sample characteristics. Ninety-nine individuals with COPD were included in the analysis. Of those, 52% were men with moderate to very severe airflow obstruction and relatively preserved exercise capacity. As can be seen in Figure 2, the prevalence of low handgrip strength ranged from 9% in studies conducted in Brazil[11] and the UK[30] to 55% in a multinational study conducted in the USA, Australia, Canada, the UK, and Sweden.[25] Table 3 shows the kappa statistics for the level of agreement between the set of reference values for a sample of adults and elderly individuals in Brazil[11] and the other sets of reference values.[6,25-31] The values varied considerably, ranging from as low as 0.1481 in the multinational study[25] to as high as 0.7963 in a study conducted in Korea.[29] Table S2 shows the level of agreement among all sets of reference values except the one for a sample of adults and elderly individuals in Brazil,[11] the kappa values having also varied widely (from 0.02 to 0.90).

A comparison of individuals with normal handgrip strength and those with low handgrip strength in accordance with each set of reference values was performed in order to find meaningful clinical differences between these two groups (Table 4). The reference values for a sample of adults and elderly individuals in Brazil[11] had a high number of variables showing statistical differences between groups (15 of 19 variables), with all of the variables showing better results for individuals with normal handgrip strength. Differences were found regarding peripheral muscle strength, exercise capacity, body composition, dyspnea, functional status, the BODE index, and the ADO index (Table 4). In a study conducted in the Netherlands,[28] the number of variables showing statistical differences was the same as that in the study conducted in Brazil.[11] However, in the former study,[28] 32% of the individuals were classified as having low handgrip strength, whereas, in the latter,[11] 9% were classified as having low handgrip strength (Figure 2), the level of agreement between the two being low (0.3463; Table 3).

DISCUSSION

In the present study, we analyzed 9 different sets of reference values for handgrip strength. The proportion of COPD patients classified as having low handgrip strength varied substantially across studies, from 9% to 55%. Weak to excellent agreement was observed between reference values for a sample of adults and elderly individuals in Brazil[11] and those for individuals in other countries when classifying individuals with COPD as having low or normal handgrip strength. The reference values that revealed the highest prevalence of individuals with low handgrip strength did not necessarily show better discriminative capacity than did the other sets of values; that is, a greater number of significant differences in clinical characteristics between individuals with normal and low handgrip strength. The reference values proposed by Amaral et al.[11] were found to be the most discriminative when applied to a sample of individuals with moderate to very severe COPD in Brazil, together with the reference values proposed by Peters et al.,[28] although the level of agreement between the two sets of reference values was not good. This indicates that the reference values for handgrip strength with the highest discriminative capacity to identify individuals with worse clinical characteristics are not necessarily the same as those that identify the highest number of individuals as having low handgrip strength. These results also indicate that, although handgrip strength might be a good reflection of peripheral muscle strength,[32] it does not necessarily indicate worse clinical characteristics in a broader sense.

One hypothesis as to why the reference values for a sample of adults and elderly individuals in Brazil[11] classified considerably fewer individuals as having low handgrip strength in comparison with other sets of reference values is that the aforementioned reference values[11] were derived from individuals in a single state in northern Brazil, whereas our study sample comprises individuals in a single state in southern Brazil. Brazil is a very large country, with marked differences in population characteristics across regions (especially between the northern and southern regions of the country), and this might have affected the representativeness of the reference values. In countries of continental dimensions, as in the present case, multicenter samples are more likely to be representative of the population as a whole. In addition, the reference values that showed the lowest level of agreement with the reference values for a sample of adults and elderly individuals in Brazil[11] were those from a multinational study by Bohannon et al.,[25] who investigated independent samples of individuals in countries in various continents. However, all of the countries involved were well-developed countries. According to Dodds et al.,[33] normative values for handgrip strength derived from individuals in developing regions are considerably lower than those derived from individuals in developed regions. Although Bohannon et al. argue that there is homogeneity across studies,[25] reference values derived from individuals in developed countries can overestimate the number of individuals with lower handgrip strength in developing countries[33] and lead to a very low level of agreement.

Reference values derived from individuals in developed countries such as the USA, Australia, and the UK[6,27,30] are expected to classify a higher number of individuals as having low handgrip strength because the normal values for individuals in developed countries are greater than those for individuals in developing countries, such as Brazil. Factors other than the country of origin might explain this difference in handgrip strength, including genetic factors; body size and composition[33]; comorbidities; and nutritional status.

Table 1. Characteristics of the nine studies included in the analysis.

Study	Sample Age range, years	Country	Reference values	Method of handgrip strength evaluation	Criteria used in order to identify reduced handgrip strength
Amaral et al.[11]	n = 1,462 18-102	Brazil	Stratified by sex and age (10-year age groups)	Position in accordance with the ASHT recommendations; measurements were performed with the patient in a seated position, with the elbow at 90° and the handle adjusted to the second position; a familiarization with the instrument was allowed; the procedure was performed three times for each hand alternately, with an interval of 1-min between measurements; a hydraulic hand dynamometer (SH50011; Saehan Corporation, Changwon, South Korea) was used; values were expressed in kg; the highest handgrip strength value for each hand was used.	2 SDs below the mean and group-specific (by sex and age)
Bohannon et al.[25]	n = 3,317 20-75[a]	USA, Australia, Canada, UK, and Sweden	Stratified by sex and age (5-year age groups)	Position in accordance with the ASHT recommendations; a Jamar dynamometer (Patterson Medical/Sammons Preston, Bolingbrook, IL, USA) was used. Most of the studies included in the meta-analysis used the mean of three trials and assessed both hands.	Values below the 5th percentile and group-specific (by sex and age)
Frederiksen et al.[26]	n = 8,342 45-102	Denmark	Stratified by sex, height (5-cm height groups), and age (5-year age groups)	Measurements were performed in a series of three measurements with the elbow at 90° and the upper arm tight against the trunk; a Smedley dynamometer (TTM, Tokyo, Japan) was used; the width of the handle was adjusted to fit the hand size; the second phalanx should rest against the inner stirrup; three trials were performed for each hand, with each hand in two cohorts of the study and three trials for the preferred hand in the other study cohort; values were expressed in kg.	2 SDs below the mean and group-specific (by sex, height, and age)
Massy-Westropp et al.[27]	n = 2,629 20-70	Australia	Stratified by sex and age (10-year age groups)	Measurements were performed with the patient in a seated position, with the elbow by the side and flexed to right angles, as well as with a neutral wrist position; the dynamometer handle was on position II, and there was provision of support underneath the dynamometer; a Jamar dynamometer (Patterson Medical/Sammons Preston) was used; three trials were performed for each hand; the mean value for each hand was used.	2 SDs below the mean and group-specific (by sex and age)
Mathiowetz et al.[6]	n = 628 20-94	USA	Stratified by sex and age (5-year age groups, the eldest individuals being > 75 years of age)	Measurements were performed with the patient in a seated position, with shoulders adducted and neutrally rotated, elbows flexed at 90°, forearms in a neutral position, and wrists between 0° and 30° of dorsiflexion and between 0° and 15° of ulnar deviation; a Jamar dynamometer (Patterson Medical/Sammons Preston) was used, being set at the second handle position for all individuals; three successive trials were performed for each hand; values were expressed in pounds; the mean of three trials was used.	2 SDs below the mean and group-specific (by sex and age)

Continue...▶

Table 1. Characteristics of the nine studies included in the analysis. (Continued...)

Study	Sample Age range, years	Country	Reference values	Method of handgrip strength evaluation	Criteria used in order to identify reduced handgrip strength
Peters et al.[28]	n = 720 20-96	The Netherlands	Stratified by sex and age (10-year age groups)	Position in accordance with the ASHT recommendations; a Jamar dynamometer (Patterson Medical/Sammons Preston) was used; three trials were performed for each hand; the mean value for each hand was used.	Values below the 5th percentile and group-specific (by age and sex)
Shim et al.[29]	n = 366 13-77	Korea	Stratified by sex and age (10-year age groups)	Measurements were performed with the patient in a seated position, with the shoulders adducted and neutrally rotated, the elbows flexed at 90°, the forearms in a neutral position, and the wrists between 0° and 30° of flexion and between 0° and 15° of ulnar deviation; a Jamar hand dynamometer (Patterson Medical/Sammons Preston) was used; three consecutive trials were performed for each hand, 1 min apart; values were expressed in kg.	2 SDs below the mean and group-specific (by sex and age)
Spruit et al.[30]	n = 224,852 39-73	UK	Stratified by sex, height (5-cm height groups), and age (5-year age groups)	Measurements were performed with the patient in a seated position, with the elbow of the arm holding the dynamometer against the side of the patient and bent to a 90° angle, the forearm pointing forward, and the thumb in the uppermost position; the wrist was straight so that the hand was either pointing forward or bent slightly outward; a Jamar hydraulic hand dynamometer (Patterson Medical/Sammons Preston) was used; three trials were performed for each hand; values were expressed in kg.	Values below the 5th percentile and group-specific (by sex, height, and age)
Werle et al.[31]	n = 1,023 18-96	Switzerland	Stratified by sex and age (5-year age groups, the eldest individuals being > 85 years of age)	Position in accordance with the ASHT recommendations; a Jamar dynamometer (Patterson Medical/Sammons Preston) was used and set at the second handle position; both hands were assessed; the mean of three trials was used; values were expressed in kg.	2 SDs below the mean and group-specific (by sex and age)

ASHT: American Society of Hand Therapists. [a]The eldest individuals were at least that age. Beyond that, the maximum age was not clear.

Table 2. Characteristics of the study sample (N = 99).[a]

Variable	Result
Age, years (min-max)	65 ± 8 (47-89)
Height, m	1.58 [1.52-1.67]
Weight, kg	70 ± 17
BMI, kg/m^2	27 ± 6
GOLD stage II/III/IV COPD, n (%)	39/45/15 (39/46/15)
FEV_1, L	1.19 [0.81-1.53]
FEV_1, % predicted	46 ± 15
FVC, L	2.33 [1.91-2.99]
FVC, % predicted	74 ± 20
FEV_1/FVC	51 ± 13
Handgrip strength, kg	26 ± 10
Quadriceps muscle strength, kg	17 [9-23]
Biceps muscle strength, kg	12 [10-15]
Triceps muscle strength, kg	14 [11-17]
Six-minute walk distance, m	453 [388-500]
Six-minute walk distance, % predicted	85 [72-95]
MIP, cmH_2O[a]	74 ± 25
MIP, % predicted[a]	81 ± 26
MEP, cmH_2O[a]	101 ± 32
MEP, % predicted[b]	111 ± 36
Fat-free mass, kg[c]	46 ± 10
Fat-free mass, % of body weight[c]	66 [60-72]
Fat-free mass index, kg/m[c]	18 ± 3
Fat mass, kg[c]	23 ± 10
Fat mass, % of body weight[c]	34 [27-39]
MRC scale score	3 [2-4]
LCADL scale - total[b]	23 [18-30]
LCADL - self-care	6 [5-8]
LCADL - domestic	9 [5-13]
LCADL - physical	4 [3-5]
LCADL - leisure	4 [3-6]
BODE index	3 [2-5]
ADO index	4 [4-6]

LCADL: London Chest Activity of Daily Living; MRC: Medical Research Council; and ADO: Age, Dyspnea, and airflow Obstruction. [a]Values expressed as mean ± SD or median [IQR], except where otherwise indicated. [b]n = 96. [c]n = 97.

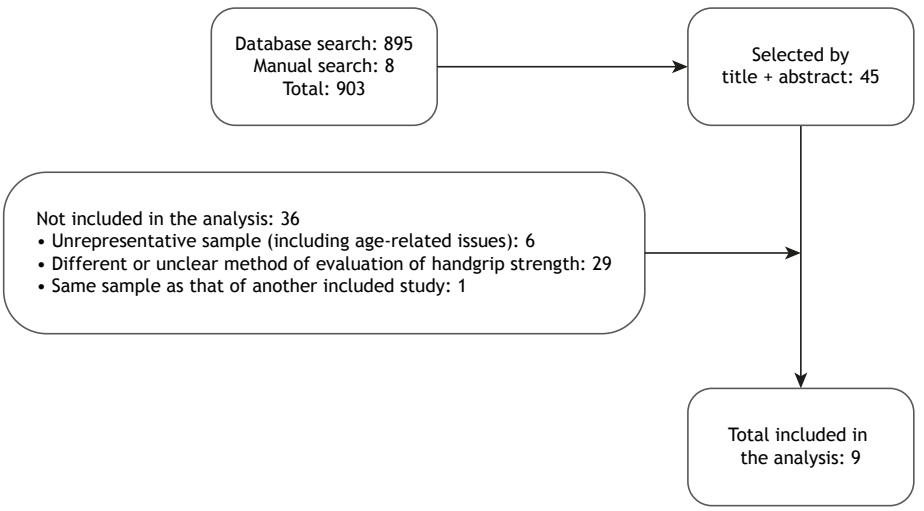

Figure 1. Flow chart of study selection for inclusion in the analysis.

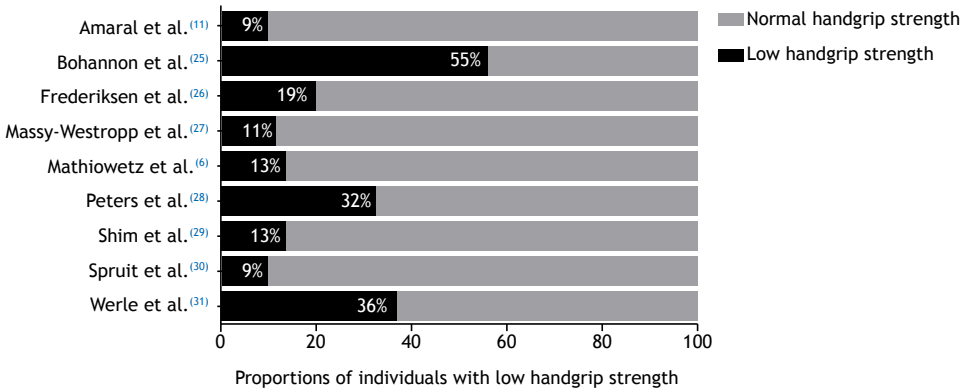

Figure 2. Proportions of individuals classified as having low handgrip strength in accordance with different sets of reference values.

Table 3. Level of agreement between a set of reference values proposed by Amaral et al.[11] for a sample of adults and elderly individuals in Brazil and other sets of reference values when classifying individuals with COPD in Brazil as having low handgrip strength.

Amaral et al.[11] vs.	Kappa statistic
Bohannon et al.[25]	0.1481
Frederiksen et al.[26]	0.4913
Massy-Westropp et al.[27]	0.7778
Mathiowetz et al.[6]	0.6944
Peters et al.[28]	0.3463
Shim et al.[29]	0.7963
Spruit et al.[30]	0.7090
Werle et al.[31]	0.2979

Discrepancies in the proportions of individuals with low handgrip strength in accordance with reference values for different populations might also have been due to the population profile, with different occupational physical demands, activities of daily living, and leisure activities,[34] for example. This profile can vary depending on the country or region of origin, as well as on how recent the reference values are.[34] This is due to the fact that many influencing characteristics can change over the decades, and this might explain the finding that most of the sets of reference values that had a lower level of agreement with the reference values for a sample of adults and elderly individuals in Brazil[11] originated from studies[25,26,31] published prior to most of the studies presenting sets of reference values that had a higher level of agreement[29,30] with those for the sample in Brazil,[11] with the exception of the reference values derived from individuals in the USA, proposed by Mathiowetz et al.[6]

All of the aforementioned factors can lead to underestimation or overestimation of a sample analyzed in accordance with reference values based on different population characteristics and time frames. Regardless of differences in the proportions of individuals classified as having reduced handgrip strength, reference values should be discriminative. Despite having classified fewer individuals as having reduced handgrip strength, the reference values for the sample in Brazil,[11] together with those proposed by Peters et al. in the Netherlands,[28] showed the highest discriminative capacity regarding differences in clinical variables between individuals with normal handgrip strength and those with reduced handgrip strength. Furthermore, the classifications made by the Brazilian reference values[11] and the Dutch reference values[28] were the only ones that showed differences in dyspnea and functional status between individuals with normal handgrip strength and those with low handgrip strength, with the Brazilian reference values[11] also showing differences regarding other London Chest Activity of Daily Living scale domains and the ADO index. These results constitute further evidence of the discriminative capacity of these sets of reference values, suggesting that they were an appropriate choice for use in the present sample. Moreover, the fact that these two sets of reference values had similarly high discriminative capacity suggests that, in the absence of national, population-specific reference values, there might be an acceptable alternative, i.e., reference values for a population whose characteristics more closely resemble those of the sample to be assessed and/or reference values that have similar discriminative capacity.

All of the studies analyzed in the present study provided reference values in table format, stratified at least by sex and age, showing values of mean ± SD,[6,11,26,27,29,31] mean and 95% CI,[25] or 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles.[30] Three sets of reference values[25,28,30] were developed on the basis of the lower limit of the confidence interval (5th percentile) rather than 2 SDs.[6,11,26,27,29,31] It is of note that two of the sets of reference values on the basis of which the prevalence of low handgrip strength was highest[25,28] were developed on the basis of the lower limit (5th percentile). Therefore, we speculate that reference values developed on the basis of the lower limit of the confidence interval constitute another factor leading to a difference in prevalence between the reference values proposed by Peters et al.[28] and those proposed by Amaral et al.,[11] despite a clear similarity in discriminative capacity between these two sets of reference values.

Table 4. Comparison between individuals with normal handgrip strength and those with low handgrip strength in accordance with each set of reference values.

Variable	Amaral et al.[11]		Bohannon et al.[25]		Fredericksen et al.[26],b	
	Normal handgrip strength (n = 90)	Low handgrip strength (n = 9)	Normal handgrip strength (n = 44)	Low handgrip strength (n = 55)	Normal handgrip strength (n = 66)	Low handgrip strength (n = 16)
Quadriceps muscle strength, kg	17 [10-24]	9 [3.25-11.75]*	20 [16-29]	12 [7-18]*	18 [11.35-24]	8 [5-17.75]*
Biceps muscle strength, kg	15.5 [10-15]	2.5 [1.75-7.75]*	12.5 [10-18]	12 [10-14]*	12.5 [10-15]	11.5 [3.1-13.9]
Triceps muscle strength, kg	13.5 [11.87-17.75]	5.5 [1.75-10]*	15 [12-20]	12 [10-15]*	13.5 [12-17]	11 [6.515.87]*
Handgrip strength, kg	26 [20.75-34]	10 [4-14.5]*	29 [24-42]	20 [16-28]*	26 [21-36]	24.5 [10-29.5]*
FEV_1, % predicted	46 [35-57]	42 [35-46]	49 [41-63]	43 [31-54]*	47 [35-62]	41 [30-53]
MIP, % predicted	80 [66-98]	66 [57-97]	90 [74-106]	72 [58-92]*	80 [65-99]	66 [57-77]*
MEP, % predicted	107 [89-134]	82 [62-119]	107 [89-133]	108 [83-134]	108 [90-134]	97 [65-124]
6MWD, m	458 [399-506]	345 [237-456]*	465 [404-500]	437 [351-510]	459 [401-506]	415 [258-470]*
6MWD, % predicted	86 [75-96]	60 [43-82]*	87 [79-97]	80 [64-93]*	86 [77-97]	68 [46-84]*
FFMI, kg/m^2	18.09 [16.22-20.82]	16.03 [14.07-17.01]*	19.23 [17.35-21.24]	16.48 [15.38-19.77]*	17.80 [16.06-20.91]	16.26 [15.80-19.78]
FMI, kg/m^2	9.78 [7.12-12.01]	8.35 [5.34-8.02]*	10.23 [7.39-11.82]	8.76 [6.06-11.19]	9.52 [7.00-12.00]	7.45 [4.06-9.87]
MRC scale score	3 [2-4]	4 [3.5-5]*	3 [2-4]	3 [2-4]	3 [2-4]	4 [2.25-4.75]
LCADL scale, total	22 [17-28]	31 [26-42]*	21 [16-28]	23 [20-31]	22 [17-28.75]	23 [18-28.5]
Self-care	5 [5-7]	9 [6.5-10.5]*	5 [5-7]	6 [5-9]	5 [5-7]	6.5 [5-8.75]
Domestic	9 [5-12]	15 [8.5-23.5]*	7 [4-12]	9 [6-15]	8.5 [4.25-13]	7 [4-11.25]
Physical activity	4 [3-5]	5 [4-5]*	4 [3-5]	4 [3-5]	4 [3-5]	4 [3-5]
Leisure	4 [3-6]	6 [4-6.5]	4 [3-5]	5 [4-6]*	4 [3-5]	5 [4-6]
BODE index	3 [2-5]	6 [3-7]*	3 [1-3]	4 [2-6]*	3 [2-4]	4 [3-7]*
ADO index	4 [3-5]	6 [4-7]*	4 [3-5]	5 [4-6]	4 [4-5]	4 [3-7]
	Massy-Westropp et al.[27]		Mathiowetz et al.[6]		Peters et al.[28]	
	Normal handgrip strength (n = 88)	Low handgrip strength (n = 11)	Normal handgrip strength (n = 86)	Low handgrip strength (n = 13)	Normal handgrip strength (n = 67)	Low handgrip strength (n = 32)
Quadriceps muscle strength, kg	17 [10.6-24]	8 [2-11]*	17.5 [11.37-24]	8 [3.5-10.5]*	18 [11-24]	11 [8-17]*
Biceps muscle strength, kg	12.5 [10-15]	3.5 [2-12]*	12.5 [10-15.2]	10 [2-12]*	12 [10-16]	10 [5-12]*
Triceps muscle strength, kg	13.5 [12-18.25]	8 [5-12]*	13.75 [12-18.5]	10 [5.25-12]*	14 [12-19]	11 [7-15]*
Handgrip strength, kg	20 [20.25-34]	11 [4-20]*	26 [21-34]	15 [6.5-19]*	28 [24-36]	18 [14-23]*
FEV_1, % predicted	46 [35-58]	40 [33-46]	47 [36-58]	38 [28-45]*	50 [38-62]	40 [31-46]*
MIP, % predicted	80 [66-99]	73 [53-93]	80 [66-98]	73 [49-97]	88 [67-100]	70 [57-91]*
MEP, % predicted	109 [91-135]	82 [64-101]*	109 [91-135]	82 [66-113]*	114 [95-142]	92 [74-118]*
6MWD, m	457 [398-504]	388 [220-472]	458 [396-506]	428 [244-468]	465 [403-510]	424 [283-465]*
6MWD, % predicted	86 [74-97]	74 [42-82]*	86 [74-97]	76 [43-84]*	88 [77-97]	76 [83-85]*
FFMI, kg/m^2	18.21 [16.30-20.86]	16.03 [14.15-16.70]*	18.48 [16.39-20.96]	16.01 [14.20-16.48]*	18.61 [17.02-21.24]	16.26 [14.42-19.76]*
FMI, kg/m^2	9.78 [7.15-11.99]	6.13 [4.96-8.96]*	9.88 [7.17-12.01]	6.13 [5.22-8.86]*	10.23 [7.20-12.17]	8.49 [5.72-9.88]*
MRC scale score	3 [2-4]	4 [3-4]	3 [2-4]	4 [2.5-4.5]	3 [2-4]	4 [2.5-4]*
LCADL scale, total	22 [17-28.5]	29 [20-42]	22 [17-28]	29 [20.5-42]	21.5 [17-26.7]	28 [20.2-36]*
Self-care	5 [5-7.5]	8 [5-10]	5 [5-7]	8 [5-10.5]	5 [5-7]	6.5 [5-9]
Domestic	9 [5-13]	10 [7-20]	8 [5-13]	10 [8-19]	7 [5-11]	9.5 [6.25-18]*

Continue...▶

Table 4. Comparison between individuals with normal handgrip strength and those with low handgrip strength in accordance with each set of reference values. (Continued...)

Physical activity	4 [3-5]	5 [3-5]	4 [3-5]	5 [3-5]	4 [3-5]	4 [3-5]
Leisure	4 [3-6]	5 [4-6]	4 [3-6]	5 [4-6.5]	4 [3-5]	5 [4-6]
BODE index	3 [2-4]	5 [3-7]*	3 [2-4]	5 [3-7]*	3 [1-4]	4 [3-6]*
ADO index	4 [3-5]	5 [4-6]	4 [3-5]	5 [4-6]	4 [3-5]	5 [4-7]
	Shim et al.[29]		Spruit et al.[30]		Werle et al.[31]	
	Normal handgrip strength (n = 86)	Low handgrip strength (n = 13)	Normal handgrip strength (n = 90)	Low handgrip strength (n = 9)	Normal handgrip strength (n = 63)	Low handgrip strength (n = 33)
Quadriceps muscle strength, kg	17 [10.37-24]	9 [3.5-12.75]*	17 [10-24]	9.50 [4.12-15.75]*	19.5 [14-25.5]	10.75 [6.25-17]*
Biceps muscle strength, kg	12.5 [10-15.25]	3.5 [2-12]*	12.50 [10-15]	3.25 [1.87-13.5]*	12.5 [10-16]	11 [7.37-13.37]*
Triceps muscle strength, kg	13.5 [12-18.5]	8 [3.75-12]*	13.5 [11.75-17]	7 [2.15-17]*	14 [12.5-18.5]	11.5 [8.62-14.75]*
Handgrip strength, kg	26 [21.75-34]	11 [6.5-20]*	26 [20-34]	10 [4-21]*	28 [24-36]	20 [16-27.5]*
FEV_1, % predicted	47 [35-58]	40 [34-46]*	46 [34-57]	43 [37-47]	47 [37-62]	43 [30-54]
MIP, % predicted	80 [66-98]	66 [49-97]	84 [66-99]	57 [68-40]*	86 [68-100]	70 [57-91]*
MEP, % predicted	107 [90-134]	85 [66-119]	107 [87-135]	111 [72-129]	107 [91-135]	108 [83-130]
6MWD, m	459 [401-510]	370 [237-453]*	458 [394-507]	412 [265-467]	461 [400-505]	439 [316-490]*
6MWD, % predicted	86 [75-97]	74 [43-81]*	85.87 [73.94-95.5]	75.32 [49.31-83.01]*	86 [76-97]	79 [58-89]*
FFMI, kg/m^2	18.09 [16.22-20.96]	16.26 [14.62-18.57]*	17.92 [16.15-20.82]	16.26 [14.07-19.69]	18.52 [16.53-21.10]	16.48 [15.66-19.78]*
FMI, kg/m^2	9.67 [7.12-11.85]	8.49 [5.66-9.86]	9.67 [7.03-13.01]	8.49 [5.93-9.33]	9.80 [7.15-12.06]	8.90 [5.92-10.64]
MRC scale score	3 [2-4]	4 [3-4.5]	3 [2-4]	4 [2-4.25]	3 [2-4]	3.5 [2-4]
LCADL scale, total	22 [17-28]	30 [19.5-41]	22 [18-29.25]	26 [16.75-40.5]	22 [17-28]	24 [18-32.5]
Self-care	5 [5-7]	8 [5.5-9.5]	6 [5-8]	6.5 [5-9.5]	5 [5-7.75]	6 [5-9]
Domestic	9 [5-12]	12 [6.5-21.5]	9 [5-13]	9.5 [3.75-20.75]	9 [5-12.75]	9 [5.25-16.5]
Physical activity	4 [3-5]	4 [2-5]	4 [3-5]	4 [3-5]	4 [3-5]	4 [3-5]
Leisure	4 [3-6]	5 [3.5-6]	4 [3-6]	5 [3-6]	4 [3-5]	5 [3.25-6]
BODE index	3 [2-4]	5 [3-7]*	3 [2-5]	4 [2-6]	3 [1-4]	4 [2-6]
ADO index	4 [3-5]	5 [4-6]	4 [4-5]	5 [4-7]	4 [4-5]	4 [3-6]

6MWD: six-minute walk distance; FFMI: fat-free mass index; FMI: fat mass index; MRC: Medical Research Council; LCADL: London Chest Activity of Daily Living; and ADO: Age, Dyspnea, and airflow Obstruction. [a]Values expressed as median [IQR]. [b]n = 82 (i.e., those who fit into the categories of height, sex, and age). *p < 0.05 in comparison with individuals with normal handgrip strength.

The present study has limitations. The retrospective nature of the study did not allow us to analyze adequately studies providing predictive equations, because it was impossible to assess some of the predictive variables in those equations. In addition, we did not evaluate comorbidities. Evaluation of comorbidities could have provided additional information on impaired handgrip strength. Furthermore, characteristics of the study sample resulted in the fact that many studies (80% of the studies that were initially retrieved) were not included in the analysis, because of methodological differences such as very specific populations[35] or a very limited age range.[36] Another limitation is that only one reviewer selected the articles, and this is not the ideal methodological scenario. Moreover, despite the high number of studies retrieved from the literature search, a stricter standardization of handgrip strength assessment might be required in order to allow more comprehensive and reliable comparisons between studies and populations.

In summary, a large number of studies providing reference values were identified through a literature search, and there was large variation in the level of agreement (i.e., from weak to excellent) between national and international sets of reference values for handgrip strength used in order to classify individuals with moderate to very severe COPD as having normal or low handgrip strength. Although the set of reference values for a sample of adults and elderly individuals in Brazil[11] classified fewer individuals as having low handgrip strength than did almost all other sets of values, it was one of the sets with the highest discriminative capacity (showing significant differences in clinical characteristics between individuals with

normal handgrip strength and those with low handgrip strength), together with the set of reference values for individuals in the Netherlands, which classified a higher proportion of individuals as having low handgrip strength. Therefore, reference values for handgrip strength with higher discriminative capacity to identify individuals with worse clinical characteristics are not necessarily those that identify more individuals as having low handgrip strength.

AUTHOR CONTRIBUTIONS

JF, FVCM, and FP: study conception, statistical analysis, and interpretation of results. LCS: drafting and revision of the manuscript. All authors revised and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Comparing cardiac function and structure and their relationship with exercise capacity between patients with stable COPD and recent acute exacerbation: a cross-sectional study

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ABSTRACT

Objective: Patients with COPD are prone to cardiac remodeling; however, little is known about cardiac function in patients recovering from an acute exacerbation of COPD (AECOPD) and its association with exercise capacity. The aim of this study was to evaluate the cardiac function and structure and to compare their relationship with exercise capacity in patients with a recent AECOPD and patients with clinically stable COPD. **Methods:** This was a cross-sectional study including 40 COPD patients equally divided into two groups: recent AECOPD group (AEG) and clinically stable COPD group (STG). Echocardiography was performed to assess cardiac function and chamber structure. The six-minute walk distance (6MWD) and the Duke Activity Status Index (estimated V_{O_2}) were used in order to assess exercise capacity. **Results:** No significant differences in cardiac function and structure were found between the groups. The 6MWD was associated with early/late diastolic mitral filling velocity ratio ($r = 0.50$; $p < 0.01$), left ventricular posterior wall thickness ($r = -0.33$; $p = 0.03$), and right atrium volume index ($r = -0.34$; $p = 0.04$), whereas V_{O_2} was associated with right atrium volume index ($r = -0.40$; $p = 0.02$). **Conclusions:** Regardless of the clinical condition (recent AECOPD vs. stable COPD), the cardiac function and structure were similar between the groups, and exercise capacity (determined by the 6MWD and V_{O_2}) was associated with cardiac features.

Keywords: Pulmonary disease, chronic obstructive; Echocardiography; Walk test; Pulmonary medicine.

INTRODUCTION

COPD is already the third leading cause of death worldwide, causing 3.23 million deaths in 2019.[1] Acute exacerbation of COPD (AECOPD) is a common event in the clinical course of the disease, imposing a general increase in physiological stress toward a homeostatic imbalance,[2] and has been associated with an increased risk of cardiovascular events.[3] In a recent study[3] with a cohort of 16,485 COPD patients, the greatest risk was demonstrated especially within the first 30 days after the exacerbation; high concentrations of circulating proinflammatory biomarkers, which can be slow to return to baseline levels, are one of the plausible explanations.

Echocardiography findings have also demonstrated that lung hyperinflation affects pulmonary hemodynamics and, consequently, cardiac function.[4,5] In a study of hospitalized patients with AECOPD, evidence of pulmonary arterial hypertension was found in all patients evaluated, and there was evidence of right ventricle (RV) enlargement and decline in RV systolic function.[6] In a previous study in which COPD patients were evaluated at least three months after hospital discharge from their first admission for an exacerbation, cardiac alterations were found in 64% of the patients (left and right cardiac disorders in 27% and 48%, respectively), and the

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most common abnormalities were RV enlargement (in 30%) and pulmonary hypertension (in 19%).[7] The authors showed that echocardiographic abnormalities were unrelated to COPD severity and that they were highly prevalent in patients with moderate-to-severe COPD, even among those with unknown cardiac disease or cardiovascular risk factors other than smoking.

Previous studies[8,9] have shown that an AECOPD has a negative impact on physical activity, and although there is improvement after hospital discharge, it still remains low in relation to clinically stable patients. This decrease in physical activity levels found in patients with an AECOPD increases the risk of a new hospital admission and has a negative impact on the emergence and advance of comorbidities.[10]

In this context, regardless of the clinical status, there is evidence of impaired cardiac function and structure in COPD patients[6,7]; however, to the best of our knowledge, no studies investigated the period shortly after an AECOPD and its possible relationship with exercise capacity. These results can support rehabilitation and health care strategies for COPD patients at different stages of the disease. Therefore, the aim of this study was to evaluate both cardiac function and structure and to compare their relationship with exercise capacity in patients with clinically stable COPD and patients with a recent AECOPD. We hypothesized that patients recovering from an AECOPD would have a similar cardiac structure but worse cardiac function when compared with patients with clinically stable COPD. Furthermore, we hypothesized that cardiac function and structure would be significantly associated with exercise capacity.

METHODS

Study design and population

This was a cross-sectional study including 40 patients diagnosed with COPD[2] and ≥ 40 years of age regardless of the sex. Patients were evaluated between February of 2016 and March of 2020 and allocated into two groups: recent AECOPD group (AEG) and clinically stable COPD group (STG). Groups were matched in terms of age and sex. No patients were allocated into the two groups at any time.

The AEG comprised recently hospitalized patients who received standard pharmacological therapy during hospitalization[2] without requiring ICU admission or mechanical ventilation; these patients were screened at the University Hospital of the Federal University of São Carlos, located in the city of São Carlos, Brazil. The STG consisted of patients with no exacerbation episodes for at least three months who were selected at the *Ambulatório de Pneumologia do Centro de Especialidades Médicas* (Pulmonology Outpatient Clinic of the Center of Medical Specialties) in the city of São Carlos, at the *Unidade Saúde Escola* (Health School Unit), or from the *Laboratório de Fisioterapia Cardiopulmonar* (Laboratory of Cardiopulmonary Physiotherapy) database, the latter two being part of the Federal University of São Carlos.

The exclusion criteria were as follows: being heavy alcohol drinkers; having uncontrolled hypertension, uncontrolled diabetes mellitus, concomitant respiratory diseases, unstable angina, recent cardiac events (within the last six months), reduced left ventricular (LV) ejection fraction (< 50%), heart valve disease, cardiac pacemaker, cardiac arrhythmias, chronic kidney disease, cancer, neurological conditions, or orthopedic conditions; participating in a regular exercise program within the last six months; and being unable to perform experimental procedures.

This study is in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee at the Federal University of São Carlos (no. 46431415.0.0000.5504; approval no. 2015/1220983). All patients gave written informed consent.

Experimental procedures

Assessments were performed on two separate days with an interval of 24-48 h between them. On the first day, patients underwent an initial evaluation comprising anamnesis, physical examination, electrocardiogram, modified Medical Research Council dyspnea scale,[11] COPD Assessment Test (CAT),[12] Saint George's Respiratory Questionnaire (SGRQ),[13] Duke Activity Status Index (DASI),[14,15] and pulmonary function test. On the second day, patients underwent transthoracic echocardiography and the six-minute walk test (6MWT). For the AEG, the first assessment was preferably carried out 30 days after hospital admission due to the AECOPD, and a period of up to three days later was tolerated. All procedures were carried out in the afternoon, and the patients were instructed to abstain from caffeinated and alcoholic beverages or any other stimulants the night before and on the day of evaluation, as well as not to perform activities requiring moderate-to-heavy physical exertion the day before the application of the procedures.

Pulmonary function test

The pulmonary function test was performed using a calibrated spirometer (CPFS/S; Medical Graphics, Saint Paul, MN, USA). The parameters (FVC, FEV_1 and FEV_1/FVC ratio) were obtained 20 min after inhaling albuterol sulfate (400 µg).[16] The results were compared with the predicted values,[17] and COPD was confirmed when $FEV_1/FVC < 0.7$[2]; all of the patients were classified by severity of airflow limitation in accordance with the GOLD.[2]

Transthoracic echocardiography

To assess cardiac function and structure, transthoracic echocardiography was performed by a cardiologist, using an ultrasound device—a 3-MHz mechanical sector transducer—(HD11 XE; Phillips, Bothell, WA, USA) following the manufacturer recommendations.[18]

The aortic root diameter, left atrium (LA) diameter, LV end-diastolic diameter, LV end-systolic diameter,

interventricular septum (IVS) thickness, LV posterior wall thickness, and RV diameter were measured. The LA volume and right atrium (RA) volume were obtained and indexed by the body-surface area (LA volume index and RA volume index).[19] The LV mass index was calculated using the following formula[20]:

$$\text{LV mass index} = 0.8 \times \{1.04 \times [(\text{IVS thickness} + \text{LV end-diastolic diameter} + \text{LV posterior wall thickness})^3 - (\text{LV end-diastolic diameter})^3]\} + 0.6/\text{body surface area}$$

Data were presented in absolute values, and reference values were presented for comparison purposes.[21,22]

Tissue Doppler imaging was performed, and LV and RV functions were assessed; early diastolic mitral or tricuspid filling velocity (E wave) and late diastolic mitral or tricuspid filling velocity (A wave) were measured, and the E/A ratios were calculated. In addition, the S wave (atrial relaxation wave) and early diastolic mitral or tricuspid annular velocity (E' wave) were obtained; then, the ratios between the mitral and tricuspid E and E' velocities (E/E' ratios) were calculated. The LV ejection fraction was calculated using the Teichholz method. Data were presented in absolute values, and reference values were presented for comparison purposes.[18.21]

Exercise capacity—DASI and 6MWT

Exercise capacity was evaluated by the six-minute walk distance (6MWD) and by the estimated V_{O_2} derived from the DASI questionnaire (V_{O_2} = 0.43 × DASI score + 9.6).[15]

The 6MWT was performed following international recommendations.[23] Dyspnea and lower limb fatigue were assessed by the 0-10 Borg scale.[24] HR was monitored with an HR monitor (Polar, Kempele, Finland), and SpO_2 was measured by pulse oximetry (UT-100 MR; Rossmax Inc. Ltd., Shanghai, China) at rest, at every minute, at peak, and 1 min after recovery. Blood pressure was measured at rest and at peak with a sphygmomanometer (BD, São Paulo, Brazil).

The 6MWD was presented in meters and in % of the predicted values.[25] The criteria for test termination were as follows: chest pain, intolerable dyspnea, leg cramps, excessive diaphoresis, pale or ashen appearance, HR > 85% of maximum HR (220 – age for men; 210 – age for women), or SpO_2 < 85% (oxygen was administered in these cases).[23]

Statistical analysis

Using the G*Power software package, version 3.1.9.2 (Kiel, Germany), the sample size was calculated based on pilot studies using the association between the mitral E/A ratio and the 6MWD (10 patients in each group). To reach statistical significance ($p < 0.05$) at a power of 80%, a minimum sample of 16 patients (8 in each group) was required. Due to the fact that this study is part of a more extensive one, we chose to include a larger sample (n = 40) than necessary, thus making the results more robust.

For all statistical analysis, the SigmaPlot, version 11.0, was used (Systat Software, San Jose, CA, USA). The Shapiro-Wilk test was used in order to investigate data distribution. Continuous quantitative variables were expressed as means ± standard deviations or medians (interquartile ranges), whereas discrete quantitative variables were expressed as absolute and relative frequencies. To compare continuous quantitative variables between the groups, the unpaired Student's t-test was used, whereas to compare discrete quantitative variables, the Fisher's exact test was used. The Pearson's correlation analysis was applied to assess the association of cardiac function and structure with exercise capacity. A value of $p < 0.05$ was considered significant.

RESULTS

We observed a prevalence of male patients in both groups. The AEG had lower values in weight, diastolic blood pressure, CAT scores, DASI scores, estimated V_{O_2}, FVC (in % of predicted values), and FEV_1 (in absolute and in % of predicted values), and it had higher values in SGRQ scores (symptoms, activity, and total score) when compared with the STG. The number of patients with mild disease, in accordance with the GOLD classification, and of those receiving short-acting β-agonists or long-acting β-agonists was higher in the STG in comparison with the AEG. Regarding the 6MWT, both groups presented low values of 6MWD (in % of predicted); however, the AEG had a lower 6MWD mean both in absolute and in % of predicted values when compared with the STG (Table 1).

Echocardiographic data for both groups are shown in Table 2. No significant differences were observed in the values obtained in terms of cardiac function and structure between the groups.

By means of the relationship of cardiac function and structure with exercise capacity, we found a positive correlation between the mitral E/A ratio and the 6MWD ($r = 0.50$; $p < 0.01$) and negative correlations between the LV posterior wall thickness and 6MWD ($r = -0.33$; $p = 0.03$), between RA volume index and 6MWD ($r = -0.34$; $p = 0.04$), and between RA volume index and estimated V_{O_2} ($r = -0.40$; $p = 0.02$; Figure 1).

DISCUSSION

The present study evaluated the cardiac function and structure and compared their relationship with exercise capacity in two groups of patients in different clinical phases of COPD: those who were recently recovering from a recent AECOPD and those who were clinically stable. Our findings demonstrated that the cardiac function and structure were similar in patients recovering from an AECOPD (30 days after the exacerbation) and in those who had been clinically stable (for at least three months). Additionally, a positive association

Table 1. Characteristics of the patients studied (N = 40).[a]

Characteristic	Total	Group		p
		AEG n = 20	STG n = 20	
Age, years	67.6 ± 8.7	68.9 ± 8.3	66.4 ± 9.3	0.38
Male sex	22 (55)	11 (55)	11 (55)	1.00
Anthropometry				
Weight, kg	66.9 ± 18.2	60.0 ±12.1	73.7 ± 20.8*	0.01
Height, m	1.61 ± 0.09	1.60 ± 0.10	1.61 ± 0.08	0.55
BMI, kg/m²	25.7 ± 7.2	23.5 ± 4.6	27.9 ± 8.8	0.05
Clinical data				
HR, bpm	78.5 ± 14.0	82.4 ± 16.9	74.6 ± 9.2	0.07
Systolic BP, mmHg	120.7 ± 15.3	119.8 ± 17.3	121.7 ± 13.4	0.69
Diastolic BP, mmHg	76.8 ± 10.0	73.1 ± 10.0	80.4 ± 8.7*	0.01
SpO_2, %	93.1 ± 3.9	92.9 ± 4.0	93.3 ± 3.8	0.68
Supplemental oxygen	3 (7.5)	3 (15.0)	0 (0.0)	0.23
Risk factors				
Hypertension	22 (55)	12 (60)	10 (50)	0.75
Diabetes mellitus	3 (8)	2 (10)	1 (5)	1.00
Myocardial infarction	1 (2.5)	1 (5.0)	0 (0.0)	1.00
Current smokers	14 (35)	8 (40)	6 (30)	0.74
Former smokers	26 (65)	12 (60)	14 (70)	0.74
Smoking history, pack-years	60.4 ± 61.2	56.1 ± 47.3	64.4 ± 73.2	0.67
mMRC score	2 [1-2]	2 [1-3]	1 [1-2]	0.14
CAT score	15.4 ± 8.5	18.5 ± 6.9	12.65 ± 8.9*	0.03
SGRQ score				
Symptoms domain	41.0 ± 22.4	54.3 ± 20.4	31.1 ± 18.6*	< 0.01
Activity domain	61.4 ± 25.8	73.1 ± 19.1	52.6 ± 27.1*	0.01
Psychosocial impact domain	35.2 ± 20.2	38.8 ± 20.9	32.4 ± 19.7	0.36
Total	44.2 ± 18.4	51.8 ± 14.1	38.4 ± 19.4*	0.03
DASI				
Estimated Vo_{2max}, mL · kg^{-1} · in^{-1}	21.8 ± 5.8	19.4 ± 4.9	24.1 ± 5.7*	< 0.01
DASI score	28.3 ± 13.4	22.9 ± 11.5	33.7 ± 13.2*	< 0.01
Pulmonary function				
FVC, % of predicted	84.0 ± 25.0	70.0 ± 20.1	95.7 ± 22.9*	< 0.01
FEV_1, L	1.3 ± 0.6	1.0 ± 0.3	1.5 ± 0.7*	0.01
FEV_1, % of predicted	53.6 ± 20.5	43.8 ± 11.8	63.8 ± 22.9*	< 0.01
FEV_1/FVC	50.6 ± 15.0	48.2 ± 16.6	53.0 ± 12.9	0.32
GOLD 1	6 (15)	0 (0)	6 (30)*	0.02
GOLD 2	12 (30)	5 (25)	7 (35)	0.73
GOLD 3	20 (50)	13 (65)	7 (35)	0.11
GOLD 4	2 (5)	2 (10)	0 (0)	0.48
Medications				
Inhaled corticosteroid	4 (10)	4 (20)	0 (0)	0.10
SAMA	2 (5)	2 (10)	0 (0)	0.48
LAMA	6 (15)	4 (20)	2 (10)	0.66
SABA	17 (42.5)	4 (20)	13 (65)*	< 0.01
LABA	8 (20)	1 (5)	7 (35)*	0.04
Beta-blocker	2 (5)	0 (0)	2 (10)	0.48
Calcium channel blocker	1 (2.5)	1 (5)	0 (0)	1.0
ACE inhibitor	3 (7.5)	2 (10)	1 (5)	1.0
Diuretic	3 (7.5)	3 (15)	0 (0)	0.23
Hypoglycemic agent	3 (7.5)	2 (10)	1 (5)	1.0
6MWD, m	357.0 ± 121.5	305.2 ± 109.9	408.7 ± 112.1*	< 0.01
6MWD, % predicted	67.2 ± 22.6	57.9 ± 20.9	76.5 ± 20.7*	< 0.01

AEG: recent acute exacerbation of COPD group; STG: clinically stable COPD group; BP: blood pressure; mMRC: modified Medical Research Council dyspnea scale; CAT: COPD Assessment Test; SGRQ: Saint George's Respiratory Questionnaire; DASI: Duke Activity Status Index; SAMA: short-acting muscarinic antagonist; LAMA: long-acting muscarinic antagonist; SABA: short-acting β-agonist; LABA: long-acting β-agonist; ACE: angiotensin converting enzyme; and 6MWD: six-minute walk distance. [a]Values expressed as n (%), mean ± SD, or median [IQR]. *Unpaired Student's t-test and Fisher's exact test.

Table 2. Echocardiographic data of the patients studied (N = 40).[a]

Variable	Reference values	Total	Group		p*
			AEG n = 20	STG n = 20	
Structure					
Aortic root diameter, mm	22-36	33.1 ± 5.5	32.9 ± 6.2	33.4 ± 4.9	0.75
LA diameter, mm	F: 27-38 M: 30-40	36.6 ± 8.4	35.3 ± 7.0	37.9 ± 9.6	0.33
LV end-diastolic diameter, mm	F: 37.8-52.2 M: 42.0-58.4	45.3 ± 6.3	44.8 ± 5.6	45.9 ± 7.0	0.56
LV end-systolic diameter, mm	F: 21.6-34.8 M: 25.0-39.8	29.0 ± 5.8	28.2 ± 6.8	29.8 ± 4.6	0.37
IVS thickness, mm	F: 6-9 mm M: 6-10 mm	10.3 ± 2.0	10.7 ± 2.3	11.9 ± 8.0	0.52
LV mass index, g/m^2	F: 44-88 M: 50-102	103.5 ± 41.7	104.1 ± 39.2	102.9 ± 45.3	0.92
LV posterior wall thickness, mm	F: 6-9 mm M: 6-10 mm	11.3 ± 5.9	10.6 ± 2.2	10.1 ± 1.7	0.50
RV diameter, mm	25-41 mm	33.7 ± 7.2	35.6 ± 7.7	31.6 ± 6.2	0.09
LA volume index, mL/m^2	16-34	20.3 ± 7.7	21.2 ± 9.9	19.6 ± 5.3	0.56
RA volume index, mLl/m^2	F: 21 ± 6 M: 25 ± 7	16.5 ± 5.3	18.2 ± 6.3	15.3 ± 4.1	0.11
LV function					
LV ejection fraction, %	≥ 50	67.4 ± 8.2	67.9 ± 9.3	66.9 ± 6.8	0.74
Mitral S wave, cm/s	≥ 8.2 ± 1.3	9.0 ± 2.3	8.9 ± 2.3	9.2 ± 2.3	0.75
Mitral E/A ratio	≥ 0.8 to ≤ 2.0	0.8 ± 0.2	0.7 ± 0.2	0.8 ± 0.2	0.30
Mitral E/E' ratio	< 14	7.5 ± 2.8	7.6 ± 2.6	7.4 ± 3.1	0.82
RV function					
Tricuspid S wave, cm/s	≥ 9.5	13.7 ± 4.6	14.0 ± 6.1	13.4 ± 2.9	0.70
Tricuspid E/A ratio	≥ 0.8 to ≤ 2.0	1.0 ± 0.4	1.0 ± 0.5	0.9 ± 0.3	0.43
Tricuspid E/E' ratio	≤ 6	4.0 ± 1.9	4.3 ± 2.3	3.7 ± 1.5	0.41

AEG: recent acute exacerbation of COPD group; STG: clinically stable COPD group; LA: left atrium; F: female; M: male; LV: left ventricular; IVS: interventricular septum; RV: right ventricle; RA: right atrium; S wave: atrial relaxation wave; E/A: early diastolic mitral or tricuspid filling velocity/late diastolic mitral or tricuspid filling velocity; E/E': early diastolic mitral or tricuspid filling velocity/early diastolic mitral or tricuspid annular velocity. [a]Values expressed as mean ± SD. *Unpaired Student's t-test.

between the mitral E/A ratio and the 6MWD was demonstrated, as were negative associations between LV posterior wall thickness and 6MWD, between RA volume index and 6MWD, and between RA volume index and estimated V_{O_2}.

The use of transthoracic echocardiography, which is a noninvasive and relatively inexpensive imaging technique, in the evaluation of COPD patients may help reveal more specific information about the right side of the heart, the presence of pulmonary arterial hypertension,[26] changes in LV geometry,[27] and, consequently, the cardiac function. These findings will contribute to the foundation of future interventional proposals, such as cardiopulmonary rehabilitation aimed at these different clinical phases of COPD. Furthermore, we were unaware of any study evaluating cardiac function and structure and their relationship with exercise capacity by comparing patients recently recovering from a recent AECOPD with clinically stable COPD patients, which made our findings extremely relevant, because this is an important subject for clinical practice in order to increase cardiovascular health care and attention in patients with pulmonary disease.

Although cardiac abnormalities are often associated with RV dysfunction due to underlying pulmonary hypertension in COPD patients,[26] the LV can also be impaired.[28] According to a recent study[28] that evaluated patients with clinically stable COPD, those with concentric LV hypertrophy were associated with an increase in the LA volume index, which represents an increase in the LV filling pressure as a consequence of diastolic dysfunction. Regarding cardiac damage due to AECOPD, one study[29] showed that this leads to pulmonary arterial hypertension, which negatively affects the RV, although the patients had no overt clinical RV failure. Pulmonary arterial hypertension stimulates RV hypertrophy in a compensatory attempt to maintain cardiac output; however, there may be an eventual maladaptive remodeling causing RV dilation in some patients.[30] Although we found no significant difference between the groups regarding the RV basal diameter (AEG: 35.6 mm vs. STG: 31.6 mm; p = 0.09), the AEG presented a higher mean value even after the 30-day period after the exacerbation. RV diameter is an extremely important parameter because it is able to identify patients with high-risk lung disease and

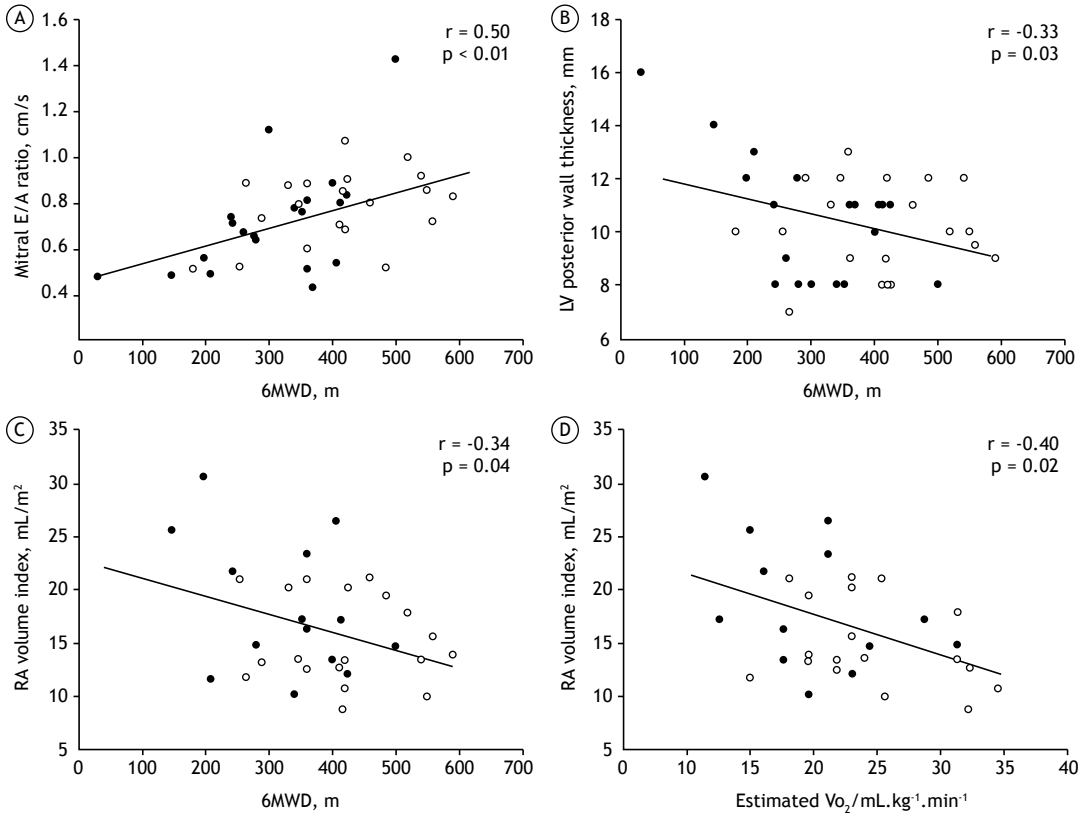

Figure 1. Correlations* between the group of patients with a recent acute exacerbation of COPD (●) and the group of patients with clinically stable COPD (○). In A, mitral E/A (early diastolic mitral filling velocity/late diastolic mitral filling velocity) ratio vs. the six-minute walk distance (6MWD). In B, left ventricular (LV) posterior wall thickness vs. 6MWD. In C, right atrium (RA) volume index (RA volume/body surface area) vs. 6MWD. In D, RA volume index vs. estimated Vo_2 estimated from the Duke Activity Status Index. *Pearson's correlation coefficient.

provides incremental prognostic information beyond that provided by clinical data.[31]

Our hypothesis was formulated because AECOPD imposes a general increase in physiological stress marked by increased airway resistance (due to bronchospasm, mucosal edema, and hypersecretion), which leads to an increase in end-expiratory lung volume above normal and, consequently, to dynamic lung hyperinflation.[32] As a result, cardiovascular effects can be observed, such as cardiac compression, intrathoracic hypovolemia, and reduced venous return due to the recruitment of abdominal expiratory muscles, impeding the normal increase in cardiac output during exercise.[33] A previous study[34] showed that LV and RV performance is impaired in patients with very severe COPD because of a small LV end-diastolic diameter and, consequently, a decreased biventricular preload, which was attributed to the intrathoracic hypovolemia caused by hyperinflated lungs. These findings led us to hypothesize that patients recovering from an AECOPD would have worse cardiac function when compared with patients in a stable clinical condition. However, no significant differences were found in cardiac function and structure between the patients who were recovering from a recent AECOPD and those who were clinically stable. One possible explanation for our findings may be the fact that the hospitalized patients did not have respiratory failure that was significant enough to require invasive ventilatory support, causing little or no change in cardiac function. Therefore, the counterpoint is part of our hypothesis—that patients recovering from an AECOPD would have worse cardiac function when compared with stable patients. Furthermore, the cardiac changes mentioned in a previous study[6] of COPD patients during the hospital phase could possibly have been transitory, and the period of 30 days after the exacerbation in our study may have been enough for these findings to normalize. On the other hand, another study[7] that evaluated patients at least three months after hospital discharge from their due to the first admission for a COPD exacerbation revealed a high prevalence of both left and right echocardiographic abnormalities, even after excluding those with cardiovascular risk factors, and this prevalence was unrelated to COPD severity.

Our results clearly showed that, regardless of the clinical condition, COPD patients in general present with an impairment in the LV structure, as observed by the high values of IVS thickness (AEG: 10.7 mm vs. STG: 11.9 mm; p = 0.52), LV mass index (AEG: 104.1 g/m² vs. STG: 102.9 g/m²; p = 0.92), and LV posterior wall thickness (AEG: 10.6 mm vs. STG: 10.1 mm; p =

0.50) in comparison with the predicted values.[18] We also observed a reduced value for the mitral E/A ratio in the AEG (i.e., 0.7) in comparison with the reference values (≥ 0.8), indicating an incipient/initial alteration in diastolic function.[21]

A particularly relevant finding of our study was the association of cardiac structure and ventricular function with exercise capacity regardless of whether the patients were recovering from an exacerbation or were clinically stable; regarding the cardiac structure, negative associations between LV posterior wall thickness and 6MWD, between RA volume index and 6MWD, and between RA volume index and estimated V_{O_2} were found. The LV posterior wall thickness is a determinant factor of the stiffness and of the diastolic pressure of the LV, directly influencing ventricular relaxation[35]; the RA volume index is an independent predictor of morbidity and can serve as a quantitative marker of RV dysfunction.[36] Thus, our results suggest that ventricular stiffness and increased filling pressure in both ventricular chambers may negatively influence exercise capacity, which was assessed by the 6MWD and V_{O_2} (estimated from the DASI score).

We also observed a positive association between the mitral E/A ratio and the 6MWD; this result might indicate the possible influence of LV diastolic dysfunction on exercise capacity since a low mitral E/A ratio is indicative of impaired LV relaxation. Reduced exercise capacity in diastolic dysfunction results from a number of pathophysiological alterations, such as slow myocardial relaxation, reduced myocardial distensibility, elevated filling pressures, and reduced ventricular suction forces. These alterations limit the increase in ventricular diastolic filling and cardiac output during exercise, leading to pulmonary congestion.[37]

Our results regarding the perception of dyspnea (modified Medical Research Council scale score) showed that the two groups were similar. On the other hand, the AEG had worse health status (CAT score and SGRQ symptoms, activity, and total scores) and worse estimated exercise capacity (DASI score and estimated V_{O_2}) when compared with the STG, corroborating a previous study.[8] With respect to CAT, both groups were classified as moderate (a score of 10-20 points) according to the impact of COPD on the patient's life[12]; however, the AEG presented a significant difference in the lowest score (5.85; $p = 0.03$) in comparison with the STG. Our results showed that even 30 days after an AECOPD, health status and exercise capacity continued to be affected.

As for exercise capacity, we also observed that patients who had recently recovered from an AECOPD had worse 6MWD when compared with clinically stable patients, even 30 days after hospital discharge. A recent study[38] showed that performance on the 6MWT is able to predict exacerbations in COPD patients over two years, and patients with a 6MWD ≤ 80% of the predicted value have more than twice the chance of having an exacerbation within two years when compared with those whose exercise capacity was preserved. Our results showed that both groups had a 6MWD < 80% of the predicted, but the AEG presented a value of 18.6%, which was significantly lower in relation to that of the STG ($p < 0.01$), representing an absolute difference of 103.5 m. ($p < 0.01$). Thus, our results showed that a recent AECOPD further affected the reduction in exercise capacity, showing a minimal clinically important difference between the groups (estimated at 26 ± 2 m for COPD patients).[39] At the same time, another possible factor influencing these findings is the severity of COPD, as the AEG had the lowest FEV_1 (in absolute and in % of predicted values) when compared with the STG, a condition that has already been reported in a previous study[40] in which a positive association between the severity of COPD and the 6MWD was demonstrated.

Regarding future prospects, our findings contribute to future studies that address other aspects of cardiac comorbidity and the effects of rehabilitation on cardiac function outcomes. Further studies should investigate COPD patients with a recent, more severe exacerbation (e.g., ICU admission and use of mechanical ventilation), in whom a greater ventilatory impact, such as increased ventilatory work and air trapping, might have a more deleterious effect on cardiac function, cardiac structure, and exercise capacity.

Some limitations of our study should be considered. The study had a cross-sectional design, making firm conclusions about causality to be impossible. In addition, groups were initially matched for age and gender, but not for severity of the disease. Another limitation was that it was not possible to determine the presence of air trapping or lung hyperinflation in the patients. Finally, echocardiographic assessments were not performed prior to the exacerbation episode, and therefore we had no information on the cardiac chamber structure and LV/RV functions prior to the AECOPD in order to understand the real impact of their worsening on the clinical condition of patients.

In conclusion, our results demonstrated that, regardless of the clinical condition, patients with clinically stable COPD and those with a recent AECOPD had similar cardiac function and structure, and that cardiac characteristics, that is, mitral E/A ratio, LV posterior wall thickness, and RA volume index, were associated with exercise capacity (determined by the 6MWD and estimated V_{O_2}. Although the follow-up of those patients was not the focus of the current study, we suggest that future studies should consider using a longitudinal design, since this would also be very interesting.

AUTHOR CONTRIBUTIONS

MBCMP, VCS, and RGM: study design and planning; interpretation of evidence; drafting the preliminary version; and revision and approval of the final version. ADH: data collection and cataloging; interpretation of evidence; drafting the preliminary version; and revision and approval of the final version. EZK and NSS: data collection and cataloging; drafting the preliminary

version; and revision and approval of the final version. MGR and ABS: drafting the preliminary version; and revision and approval of the final version.

CONFLICTS OF INTEREST

None declared.

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Mesothelioma in a developing country: a retrospective analysis of the diagnostic process

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ABSTRACT

Objective: To evaluate the process of diagnosing patients with malignant pleural mesothelioma (MPM) at a tertiary care hospital. **Methods:** This was a retrospective study involving patients referred to a tertiary-care cancer center in Brazil between 2009 and 2020. The diagnostic process was divided into four steps: onset of symptoms, referral to a specialist visit, histopathological diagnosis, and beginning of treatment. The intervals between each phase and the factors for delays were evaluated. Data including clinical status, radiological examinations, staging, treatment modalities, and survival outcomes were collected. **Results:** During the study period, 66 patients (mean age = 64 years) were diagnosed with MPM and underwent treatment. Only 27 (41%) of the patients had knowledge of prior exposure to asbestos. The median number of months (IQR) between the onset of symptoms and the first specialist visit, between the specialist visit and histopathological characterization, and between definite diagnosis and beginning of treatment was, respectively, 6.5 (2.0-11.4), 1.5 (0.6-2.1), and 1.7 (1.2-3.4). The knowledge of prior asbestos exposure was associated with a shorter time to referral to a specialist (median: 214 vs. 120 days; p = 0.04). A substantial number of nondiagnostic procedures and false-negative biopsy results (the majority of which involved the use of Cope needle biopsy) were found to be decisive factors for the length of waiting time. The mean overall survival was 11.9 months. **Conclusions:** The unfamiliarity of health professionals with MPM and the patient's lack of knowledge of prior asbestos exposure were the major factors to cause a long time interval between the onset of symptoms and beginning of treatment. An overall survival shorter than 1 year is likely to have been due to the aforementioned delays.

Keywords: Mesothelioma; Mesothelioma, malignant; Pleural effusion, malignant; Pleural diseases.

INTRODUCTION

Malignant pleural mesothelioma (MPM) has a proven association with prior asbestos exposure. Despite this correlation, most countries in Latin America (LA) have yet to adopt broad restrictions on asbestos mining and processing industries.[1] For decades, Brazil was the third largest asbestos producer in the world, accounting for 15.1% of global asbestos production in 2015.[2] Nevertheless, between 1980 and 2010, only 3,718 deaths caused by asbestos exposure were reported to the Brazilian National Mortality Information System, and such deaths were reported to have been caused by some type of pleural cancer, including but not limited to mesothelioma. In contrast, 2,497 deaths caused by asbestos exposure were reported in the United States in 2013 alone, where asbestos mining has been banned since 2002.[3]

Studies of mesothelioma in LA are scarce and usually limited to case reports, case series, or brief epidemiological studies.[4,5] In addition, despite the historically critical position regarding asbestos production, Brazil was only responsible for 22 of the 6,907 articles on asbestos and mesothelioma that were published between 1988 and 2011.[4]

The lack of data hinders a more effective and targeted intervention for the general population and health professionals who still have difficulties in identifying the disease, causing the current underdiagnosis and underreporting.[1] As descriptive studies are pivotal for the development of improved health care policies and progress of research, the objective of the present study was to evaluate the process of diagnosing patients referred to a public, tertiary-care cancer center in Brazil.

METHODS

This was a retrospective study conducted at a cancer center located in the city of São Paulo, Brazil. All patients diagnosed with MPM and treated between July of 2009 and December of 2020 had their medical records reviewed. Only

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patients with a histopathological diagnosis of MPM were included. Data including demographic characteristics, past medical history, diagnostic procedures, radiological examinations (including CT and 18F-FDG PET/CT), histopathological reports, disease staging, treatment modalities, and mortality were collected.

To evaluate the diagnostic process of MPM for each patient, the medical records were specifically reviewed for the following four events: onset of symptoms; first specialist visit (with a pulmonologist, a thoracic surgeon, or an oncologist); adequate histopathological characterization; and beginning of treatment, including chemotherapy, radiotherapy, or surgery—extended pleural decortication (EPD) or extended pleuropneumonectomy (EPP).

Performance status was classified using the ECOG scale.[6] Since this study involves a time interval when two different TNM editions (7th and 8th) were in use, each medical record based on the 7th edition was reviewed and reclassified in accordance with the 8th edition.

Data were assessed for normality of distribution using the Shapiro-Wilk test and described as means and standard deviations or as medians and interquartile ranges, respectively, when distribution was normal or non-normal. The association between categorical and continuous variables with non-normal distribution was analyzed using the Mann-Whitney U test. The correlation between non-normal continuous variables was tested with Spearman's correlation coefficient. The Kaplan-Meier estimator and the log-rank test were adopted for survival analysis.

All statistical analyses were conducted using the R software, version 4.1.1, and R Studio, version 3 (R studio, Boston, MA, USA). A significance level of $p < 0.05$ was adopted.

The local institutional review board approved this study (Protocol no. 02213612.8.0000.0068). Individual patient consent was waived due to the retrospective nature of the research and the fact that all data were managed anonymously.

RESULTS

Between 2009 and 2020, a total of 66 patients were treated. The medical records of all these patients were reviewed, and some of the characteristics evaluated are summarized in Table 1. The male-to-female ratio was 3.7:1.0, and the subjects had a mean age of 64.3 ± 11.3 years at diagnosis. Twenty-six patients had an ECOG score of 2 or higher. Remarkably, 30 (45%) and 11 (17%) of the subjects were smokers and former smokers, respectively. Also, less than a half of the patients (41%) had knowledge of prior exposure to asbestos.

Epithelioid mesothelioma was the main histopathological subtype, accounting for 88% of the cases, and predominated on the right side (in 56%). The mean standardized uptake value (SUV) for half of the patients who underwent 18F-FDG PET/CT was 8.60 ± 4.05.

Table 1. Characteristics of patients (N = 66) and disease at diagnosis.[a]

Characteristic	Result
Age, years	64.3 ± 11.3
Gender	
Male	52 (78)
Female	14 (22)
BMI, kg/m^2	24.3 ± 4.8
ECOG at first medical visit	
0	14 (21)
1	35 (53)
2	10 (15)
3	4 (6)
4	3 (5)
Smoking status	
Current smoker	30 (45)
Former smoker	11 (17)
Never smoker	25 (38)
Asbestos exposure	
Yes	27 (41)
No	39 (59)
Histological subtype	
Epithelioid	58 (88)
Sarcomatoid	4 (6)
Biphasic	4 (6)
TNM staging	
I	15 (22.7)
II	5 (7.6)
III	25 (37.9)
IV	21 (31.8)
PET-CT	33 (50)
PET-CT, SUV	8.60 ± 4.05
Laterality	
Right	37 (56)
Left	29 (44)

SUV: standardized uptake value. [a]Values expressed as n (%) or mean ± SD.

The number of months spent in each stage of the diagnostic process is outlined in Figure 1. After the onset of symptoms, a median of 6.5 months (2.0-11.4 months) lapsed before the patient had a specialist visit. Prior to undergoing pleural biopsy or being referred to our cancer center, the patients had undergone a median of 2 procedures (range, 0-5), majorly thoracentesis, with the sole purpose of relieving symptoms since oncologic cytology had rarely been requested. The Mann-Whitney U test was used in order to test the hypothesis that there was a correlation between knowledge of previous asbestos exposure and shorter time to referral. The median number of days to referral was 214 vs. 120 days (Mann-Whitney U test:: 231.5 vs. 419.5 days; $p = 0.04$) for the group with no knowledge of prior asbestos exposure and the group with that knowledge. The correlation between the number of

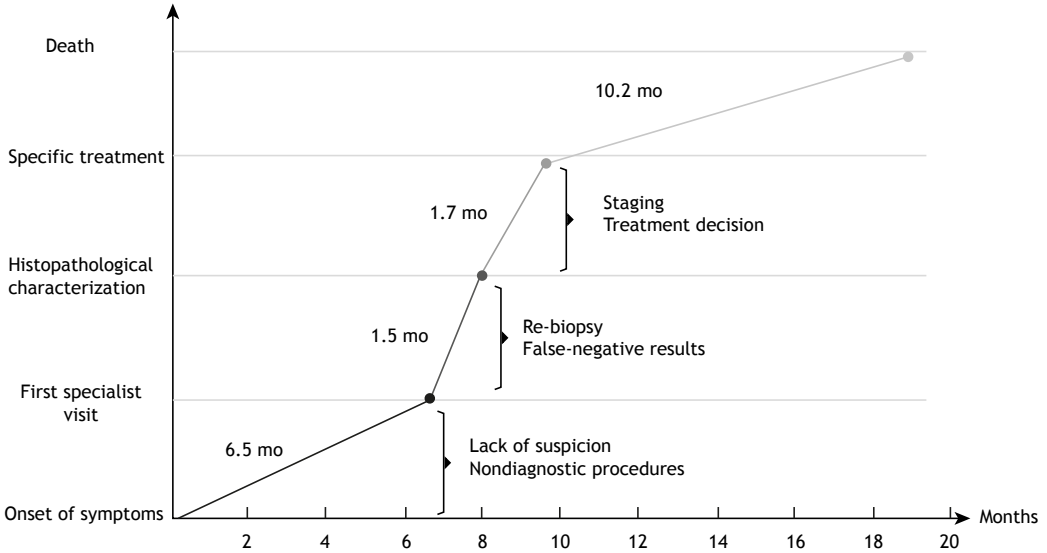

Figure 1. Timeline of the process of diagnosing patients with malignant pleural mesothelioma. mo: months.

procedures prior to a specialist visit and the number of days to referral was analyzed using the Spearman's correlation coefficient. A nonsignificant small negative relationship was found (ρ = −0.07; 95% CI: −0.39 to 0.26; p = 0.68).

The median time to adequate histopathological characterization of the neoplasm was 1.5 months (0.6-2.1). Only 27 (40.9%) of the patients had undergone pleural biopsy prior to referral, 7 (25.9%) of whom having been reported as negative for any kind of neoplastic processes. Due to inadequate histopathological examination or lack of histopathological diagnosis, 40 patients underwent pleural biopsy (surgical biopsy, in 23; Cope needle biopsy, in 14; and radiologically guided biopsy, in 3) after being referred to our cancer center. Of those, 9 had a negative biopsy result which was later diagnosed as MPM—8 who underwent Cope needle biopsy (false-negative rate of 57.1%); and 1 of those who underwent surgical biopsy (false-negative rate = 4.3%). Cytological pleural effusion analysis prior to pleural biopsy was carried out in 26 patients, 15 of whom (57.7%) had a negative result.

Disease staging and treatment decision required a median of 1.7 months (1.2-3.4) before the beginning of treatment. Only 15 patients were oncologically and/or clinically suitable for any major surgical treatment; therefore, EPP and EPD could be performed in 11 and 4 patients, respectively. In our sample, 44 patients received chemotherapy, 15 received chemotherapy and radiotherapy, and 1 was treated with immunotherapy. However, 6 patients were unable to undergo any kind of treatment and received supportive care only.

The overall survival time after diagnosis was 11.9 months (95% CI: 8.4-15.3). Survival analyses considering all subjects and according to disease staging are set forth in Figures 2 and 3, respectively. A survival analysis based on histological subtypes was not carried out due to the small number of patients with sarcomatoid and biphasic subtypes, and thus no attempt was made to compare those groups statistically.

DISCUSSION

Unfortunately, few cancer centers in LA have a reasonable number of MPM cases to allow for an optimal experience with the disease. In 2019, the largest observational study of mesothelioma in LA was published, including 302 patients from nine different countries/centers.[7] The analysis was focused on the overall response rate to first-line chemotherapy and on progression-free, survival-related factors. Although the study[7] provided pivotal information about clinical and pathological features, it compiled data from countries with distinct features, such as diverse health care systems and different types of asbestos fibers to which the populations were exposed.[5]

To date, the present study is the largest observational study in Brazil evaluating clinical and pathological features of MPM. The demographic characteristics, such as the male-to-female ratio and age, are similar to those in a report based on the WHO database concerning MPM patients.[8] In contrast, 45% of the patients in our study were smokers, which is considerably higher than the Brazilian national rate of smokers between 2008 and 2019, which decreased from 18.5% to 12.6% over that period.[9] The trend toward a stronger smoking habit among MPM patients was observed in several studies, which may be explained by a greater prevalence of smoking among asbestos workers.[10,11] Additionally, due to the high latency between asbestos exposure and development of mesothelioma, the patients treated tend to be older, and this part of the population is generally more prone to smoking.[12] The correlation between a previous environmental exposure and a pathological condition is a milestone in terms of improving the diagnostic

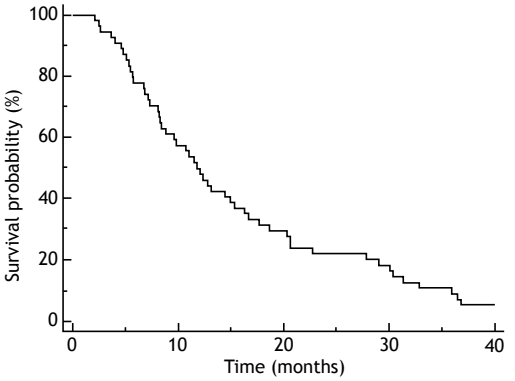

Figure 2. Survival analysis of the patients included in the study (N = 66).

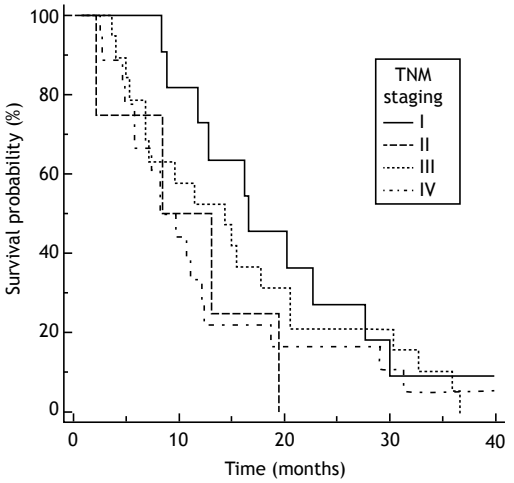

Figure 3. Survival analysis of the patients (N = 66) according to TNM staging.

process of occupational diseases.[13] Surprisingly, less than half of the patients in the present study had any knowledge of prior exposure to asbestos, according to their medical records, which contradicts current world statistics that associates 80% of the cases of MPM with exposure to asbestos.[14] The disparity can certainly be explained by the patients' unawareness of their environmental exposure that has happened throughout their lives. Unfortunately, such disparity may have consequences for the diagnosis of such patients since a significantly shorter time to referral to a specialist was observed among the patients who were aware of their prior exposure when compared with those who were unaware of such exposure.

On average, patients waited more than 6 months after the onset of symptoms to seek medical assistance. During this time, they underwent a median of two procedures before being referred to a specialist visit. A possible reason behind this delay was the use of procedures that had no clear diagnostic intention, mainly thoracentesis, performed in primary and secondary health care centers prior to referral. Moreover, despite the abovementioned delay, over 60% of the patients were referred without a definitive biopsy result/diagnosis. Although this finding may contain inaccuracies related to imprecise patient reporting their past medical history, it may provide valuable information for policy makers to develop targets for improvement of the recognition of the disease.

After the first specialist visit (with a thoracic surgeon, an oncologist, or a pulmonologist), an additional waiting time of almost 2 months was necessary to reach the diagnosis of MPM. As stated above, more than half of the subjects were referred without an established diagnosis, and therefore pleural biopsy had to be performed. However, there were an unexpected number of re-biopsies due to false-negative results. MPM has been a diagnostic challenge to pathologists even with the advances of immunohistochemistry over the last decades.[15] Two critical prospective studies have evaluated the diagnostic yield of different biopsy methods.[16,17] One prospective study analyzed 188 patients with MPM between 1973 and 1990 and showed that the diagnosis was confirmed using thoracoscopy, pleural fluid cytology, and needle biopsy in 98%, 26%, and 21% of the subjects, respectively,[16] and one randomized clinical trial compared Abram's needle biopsy and CT-guided biopsy and showed a significant superiority of the latter method regarding sensitivity (47% vs. 87%) and negative predictive value (40% vs. 80%).[17] Such findings support the fact that Cope needle biopsy had the highest false-negative rate among the pleural biopsy methods used in the present study.

Video-assisted thoracoscopy is the procedure with the highest sensitivity to diagnose MPM when compared with image-guided biopsy or Cope needle biopsy. Furthermore, it allows for the removal of a sufficient amount of tissue in order to perform all kinds of molecular analyses which are crucial for oncology today.[16,17] In the present study, although only a few cases of image-guided biopsies were analyzed, the same superiority of thoracoscopy regarding false-negative results was observed when it was compared with Cope needle biopsy. The recently released Brazilian national guidelines for the diagnosis of MPM states that there are advantages of thoracoscopy over other modalities. Therefore, thoracoscopy should be considered the mainstay method for the diagnosis of MPM as it may reduce eventual delays in terms of achieving proper histopathological characterization.[18]

Although epithelioid mesothelioma was the most frequent subtype in our sample, its proportion (88%) was higher than that reported in previous research, in which the presence of this subtype ranged from 60-75%.[19] The high frequency of epithelioid mesothelioma may have improved the overall survival rate, despite the adversities mentioned above with respect to the diagnostic process, since epithelioid morphology remains one of the dominant prognostic factors, together with TNM staging.[20,21]

To our knowledge, this is the first study to describe the mean SUV (8.6) of 18F-FDG PET/CT in MPM patients from a Latin American country. The use

of this radiological parameter as a tool to predict several outcomes and to help the differentiation of MPM from benign pleural diseases is currently under development.[22] However, in countries where infectious diseases are most of the times the main differential diagnoses of pleuropulmonary diseases, the SUV may have a different clinical implication. As such, the SUV data gathered in the present study may guide further research in those locations.

A well-known randomized feasibility study[23] that compared surgical treatment with systemic therapy alone found a lower survival rate (adjusted hazard ratio = 2.75) in patients who underwent trimodal therapy (including EPP) than in patients who received only systemic therapy. There was a great deal of criticism about that study, including the use of an underpowered sample size and poor compliance with the indication criteria for surgery.[23] On the other hand, a study[24] that included 14,228 patients with MPM found an improved survival rate (adjusted hazard ratio = 0.64) for patients who received cancer-directed surgery.

Even if we consider the uncertainty of the benefits of surgery in MPM, the current guidelines recommend surgical therapy for those who have resectable disease and are fit for surgery.[25] In the present study sample, due to advanced staging and poor performance status, less than 20% of the patients could undergo EPD or EPP. Consequently, aside from a lower overall survival rate when compared with other studies, poor baseline conditions also prevented those patients from receiving the recommended treatment modalities such as surgery, which could potentially be beneficial.[26]

The current stagnation of treatment options offered to MPM patients can be identified by a comparison between the results of the present study and those of a study carried out in Brazil 14 years ago.[27] That retrospective study, which reviewed the medical records of 17 patients treated for MPM between 2000 and 2005, found a low proportion of MPM patients who could undergo surgical treatment, and the mean overall survival was 11 months. The present study, carried out more than 10 years later, found very similar results, corroborating the lack of improvement in the management of the disease.

It is expected that mesothelioma in Brazil will reach its peak incidence by the year 2026, but health care systems are still not properly prepared to manage MPM.[28] Several factors, including the patient's lack of awareness of previous asbestos exposure and unfamiliarity of health professionals with this disease, threaten the capacity to offer the best available treatment for this type of cancer in Brazil.[18] Therefore, it is critical that progressive improvements in the abilities to recognize MPM be made in order to increase the survival rate of these patients, which today is very low.

AUTHOR CONTRIBUTIONS

PHPG: study design; data analysis; and reviewing of the manuscript. RMT: study design; and reviewing of the manuscript. LPL: data collection; and drafting of the manuscript. PMPF: study conception and design; and reviewing of the final manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Genetic polymorphisms and their effects on the severity of silicosis in workers exposed to silica in Brazil

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Study carried out at the Universidade Federal Fluminense, Niterói, the Universidade do Estado do Rio de Janeiro, Rio de Janeiro, and the Fundação Oswaldo Cruz, Rio de Janeiro (RJ) Brasil.

ABSTRACT

Objective: Silicosis is a pneumoconiosis characterized by fibrosis of the lung parenchyma caused by inhalation of silica particles. Genetic factors might play a role in the severity silicosis. We sought to evaluate the influence of polymorphisms in the *ACE*, *FAS*, *FASLG*, *NOS2*, *IL1RN*, *FAM13A*, *TGFB1*, and *TNF* genes on the severity of silicosis. **Methods:** Nine polymorphisms were genotyped by PCR in a sample of 143 patients with silicosis in the state of Rio de Janeiro, Brazil. **Results:** Fifty-seven patients (40%) were classified as having simple silicosis and 86 (60%) were classified as having complicated silicosis. The TT genotype of rs1800469 in the *TGFB1* gene showed a protective effect for complicated silicosis (OR = 0.35; 95% CI, 0.14-0.92; p = 0.028) when compared with the other two genotypes (CC+CT). The polymorphic T allele of rs763110 in the *FASLG* gene (OR = 0.56; 95% CI, 0.31-0.99; p = 0.047), as well as a dominant model for the T allele (TT+**CT:** OR = 0.37; 95% CI, 0.15-0.96; p = 0.037), also showed a protective effect. When patients with simple silicosis despite having been exposed to silica for a longer time (> 44,229 hours) were compared with patients with complicated silicosis despite having been exposed to silica for a shorter time, the T allele of rs763110 in the *FASLG* gene (OR = 0.20; 95% CI, 0.08-0.48; p < 0.0001), as well as dominant and recessive models (OR = 0.06; 95% CI, 0.00-0.49; p = 0.01 and OR = 0.22; 95% CI, 0.06-0.77; p = 0.014, respectively), showed a protective effect against the severity of silicosis. **Conclusions:** It appears that rs1800469 polymorphisms in the *TGFB1* gene and rs763110 polymorphisms in the *FASLG* gene are involved in the severity of silicosis. Given the lack of studies relating genetic polymorphisms to the severity of silicosis, these results should be replicated in other populations.

Keywords: Silicosis; Polymorphism, genetic; Genetic association studies; Cytokines.

INTRODUCTION

Silicosis is the most prevalent pneumoconiosis in the world, being characterized by fibrosis of the lung parenchyma caused by inhalation of silica particles.[1] Silicosis is an occupational disease that can affect workers in the mineral extraction industry, mineral processing industry, manufacturing industry, cosmetics industry, and sandblasting industry, among others.[2,3] The development of silicosis is related to the duration and degree of exposure to silica particles; deficiencies in the immune systems; impaired pulmonary clearance; smoking; the concentration of silica particles; personal protective equipment (PPE) use (or lack thereof); and genetic factors.[4,5] Genetic factors might explain distinct phenotypic expressions of the disease in patients with a similar exposure history.[4,5]

In the alveolar space, silica particles trigger various inflammatory mechanisms and pathways responsible for the pathogenesis of silicosis, represented by cycles of injury and healing. These cycles generate intense epithelial damage causing severe impairment of gas exchange by deposition of collagen fibers in the alveolar space, being divided into the following stages: direct cytotoxicity; generation of reactive oxygen species and reactive nitrogen species; intense production of cytokines; deposition of collagen fibers; fibrosis; apoptosis of alveolar cells; and release of crystals in the alveolar space, restarting the cycle.[1]

Silica particles lead to intensive production of reactive oxygen species and reactive nitrogen species, mainly by alveolar epithelial cells and macrophages. Inducible nitric oxide synthase activity is fundamental to this oxidative

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environment because it acts in the production of nitric oxide.[6] This intense oxidative environment promotes the release of several interleukins. IL-1 (IL-1α and IL-1β) acts in the activation of fibroblasts and in the deposition of collagen fibers in the alveolar space. However, IL-1 receptor antagonist (IL1RA) acts by blocking the action of IL-1.[7] TNF-α acts in fibroblast recruitment and proliferation, and as a ligand for apoptosis receptors.[1] TGFB1 acts in cell proliferation, differentiation, migration, inflammation, and apoptosis, as well as in tissue repair.[8] Angiotensin-converting enzyme (ACE), released by several epithelial cells and by macrophages, is an important biomarker of lung injury.[9] Family with sequence similarity 13 member A (FAM13A) is expressed in the airways in type II epithelial cells and alveolar macrophages, and seems to play a role in the pathogenesis of idiopathic pulmonary fibrosis.[10]

Alveolar macrophage apoptosis also contributes to the pathogenesis of silicosis, through increased expression of Fas cell surface death receptor (FAS) and its ligands (Fas ligand [FASLG] and TNF-α). Alveolar macrophage apoptosis releases inflammatory mediators, promoting new recruitment of inflammatory cells and repeated activation of inflammatory pathways.[1]

Silicosis is an irreversible and incurable disease. The identification of genetic polymorphisms is essential for early identification of patients who are more likely to present with increased disease severity, making it possible to establish appropriate follow-up strategies and decide on the use of antifibrotic drugs.[11] The objective of the present study was to evaluate the influence of polymorphisms in the *ACE* (rs4646994), *FAS* (rs2234767), *FASLG* (rs763110), *nitric oxide synthase 2—NOS2*—(rs2297518), *IL1RN* (rs419598 and rs2234663), *FAM13A* (rs2609255), *TGFB1* (rs1800469), and *TNF* (rs1800629) genes on the severity of silicosis in patients in Brazil.

METHODS

Patients

The study sample consisted of 143 patients diagnosed with silicosis on the basis of an occupational history of exposure to silica particles and radiological findings consistent with silicosis, in accordance with the International Labour Organization (ILO) International Classification of Radiographs of Pneumoconioses.[12] Patients with occupational lung diseases other than silicosis were excluded.

The patients included in the study were treated at the Fluminense Federal University Antônio Pedro University Hospital, the State University of Rio de Janeiro Pedro Ernesto University Hospital, or the Oswaldo Cruz Foundation School of Public Health, all of which are located in the state of Rio de Janeiro, Brazil. All patients were removed from work due to confirmed silicosis.

On the basis of chest X-rays findings, patients were classified as having simple silicosis (or small opacities, i.e., opacities smaller than 1.0 cm) or complicated silicosis (or large opacities, i.e., at least one opacity greater than 1.0 cm), in accordance with the ILO International Classification of Radiographs of Pneumoconioses.[12] The radiographs were obtained with the use of an LX30 X-ray machine (Siemens AG, Erlangen, Germany) and were evaluated separately by three ILO-certified readers. All of the study participants gave written informed consent, and the study was approved by the local research ethics committees.

Sociodemographic characteristics, clinical characteristics, and lung function parameters

Sociodemographic and clinical characteristics such as age (in years), occupation, weight (in kg), height (in m), BMI (in kg/m^2), total number of years of silica exposure, total number of hours worked per week, total number of hours of silica exposure, time elapsed since removal of exposure (in years), smoking history (in pack-years), use of PPE, and tuberculosis were assessed by means of a questionnaire.

Lung function parameters were obtained by spirometry, which was performed with an MS-PFT spirometer (Jaeger, Würzburg, Germany) and in accordance with the American Thoracic Society/European Respiratory Society standards[13] and the Brazilian Thoracic Association standardized methods.[14,15] FEV_1, FVC, and the FEV_1/FVC ratio were evaluated in all patients.

Genotyping

For genetic material collection, cell samples were obtained from the oral cavity by rinsing with 5 mL of saline solution (0.5% NaCl) for 60 s. The samples were then identified and immediately stored in a freezer at −4°C. Genomic DNA extraction was performed in accordance with Aidar & Line.[16]

Genotyping was performed by PCR. Standard PCR was used in order to analyze 2018T/C (rs419598) and 86 bp variable number tandem repeats (rs2234663) in the *IL1RN* gene, as well as Ins/Del (rs4646994) in the *ACE* gene. PCR conditions and primers were as previously described.[9,17,18] For *ACE* rs4646994, the alleles consisted of a 190-bp fragment (D allele) and a 490-bp fragment (I allele), detected by electrophoresis of PCR products on 2% agarose gel. For rs2234663 in the *IL1RN* gene, genotypes were established according to the sizes of PCR products on 2.5% agarose gel: IL1RN*1 410 bp (four repeats); IL1RN*2 240 bp (two repeats); IL1RN*3 500 bp (five repeats); IL1RN*4 325 bp (three repeats); and IL1RN*5 595 bp (six repeats).

Genotyping of the rs419598 polymorphism was performed by PCR, followed by RFLP with 1 U of MspI, in accordance with the manufacturer instructions (New England Biolabs, Ipswich, MA, USA). Electrophoresis on 3% agarose gel showed three PCR fragment sizes: 123 bp and 233 bp (C allele), and 356 bp (T allele).

Genotyping of *FAM13A* rs2609255, *FAS* rs2234767 (−1377G/A), *FASLG* rs763110 (−844C/T), *NOS2* rs2297518 (Ser608Leu), *TGFB1* rs1800469 (−509C/T), and *TNF* rs1800629 (−308G/A) was performed by real-time PCR with predesigned and validated TaqMan® assays (C_15906608_10, C_12123966_10, C_3175437_10, C_11889257_10, C_8708473_10, and C_7514879_10, respectively; Thermo Fisher Scientific, Waltham, MA, USA). The genotyping protocol followed the manufacturer instructions (Thermo Fisher Scientific), and the samples were run in a CFX96 real-time PCR system (Bio-Rad Laboratories, Inc., Hercules, CA, USA).

Statistical analysis

Allele frequencies were obtained by gene counting. Deviations from the Hardy-Weinberg equilibrium were evaluated by the chi-square test. Association analyses between gene polymorphisms and silicosis severity (simple vs. complicated) were evaluated by the chi-square test or Fisher's exact test. Quantitative data with normal distribution (as determined by the Kolmogorov-Smirnov test) were evaluated by a t-test, whereas quantitative data with non-normal distribution were evaluated by the Mann-Whitney test. Values were presented as mean ± standard deviation. The total number of hours of silica exposure was obtained by adjusting the total number of hours worked per week in each month (11 months of work) and multiplying it by the total number of years worked. The time elapsed since removal of exposure (in years) was calculated by the difference between the year of silicosis diagnosis (and sick leave) and the year of sample collection and classification as simple silicosis or complicated silicosis.

A multivariate logistic regression analysis was used in order to assess the ORs and 95% CIs for independent predictors of complicated silicosis. The logistic regression model included the following independent variables: polymorphisms significantly associated with silicosis severity, total number of hours of silica exposure > 44,229, time elapsed since removal of exposure (in years), and no use of PPE. The level of significance was set at $p < 0.05$. All statistical tests were performed with the IBM SPSS software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Sociodemographic characteristics, clinical characteristics, and lung function parameters

Of the 143 patients, 57 (40%) were classified as having simple silicosis and 86 (60%) were classified as having complicated silicosis. Sandblasting was the most common occupation, in 66 patients (46%), followed by marble work, in 21 (14.7%), and hammering, in 18 (12.6%). Seventy-six patients (53%) had a history of smoking. Of those, 27 (35.5%) had simple silicosis and 49 (64.5%) had complicated silicosis ($p = 0.260$). With regard to tuberculosis, 70 patients (49%) had a history of tuberculosis. Of those, 25 (35.7%) had simple silicosis and 45 (64.3%) had complicated silicosis ($p = 0.321$). With regard to the use of PPE, 54 (37.8%) reported not using PPE at work. Of those, 20 (37%) had simple silicosis and 34 (63%) had complicated silicosis ($p = 0.101$). Other clinical and demographic characteristics are presented in Table 1.

A statistically significant difference was observed between patients with simple silicosis and those with complicated silicosis regarding the time elapsed since removal of exposure ($p = 0.023$). With regard to lung function parameters, a statistically significant difference was observed between patients with simple silicosis and those with complicated silicosis regarding percent predicted FVC ($p = 0.007$), FEV_1 ($p = 0.0001$), and FEV_1/FVC ($p = 0.001$; Table 1).

Association analysis between gene polymorphisms and silicosis severity

Genotype frequencies of all polymorphisms in the total sample showed no significant deviation from the Hardy-Weinberg equilibrium. Associations between the severity of silicosis (simple silicosis vs. complicated silicosis) and the genetic polymorphisms investigated in the present study were significantly different for −844C>T (rs763110) in the *FASLG* gene and −509C>T (rs1800469) in the *TGFB1* gene (Table 2). The polymorphic T allele of rs763110 in the *FASLG* gene showed a protective effect for complicated silicosis (OR = 0.56; 95% CI, 0.31-0.99; $p = 0.047$). In a dominant model, carriers of the T allele (TT+CT) also showed this protective effect (OR = 0.37; 95% CI, 0.15-0.96; $p = 0.037$; Table 2).

The −509C>T (rs1800469) polymorphism in the *TGFB1* gene showed a significant protective effect in a recessive model of the T allele. As can be seen in Table 2, the TT genotype was more common than the other two genotypes (CC+CT) in patients with simple silicosis (OR = 0.35; 95% CI, 0.14-0.92; $p = 0.028$). For the remaining polymorphisms, no significant associations were observed (Table 2).

No significant differences were observed between patients with simple silicosis and those with complicated silicosis regarding the other polymorphisms: *ACE* rs4646994 ($p = 0.171$), *FAS* rs2234767 ($p = 0.709$), *FAM13A* rs2609255 ($p = 0.402$), *IL1RN* rs419598 ($p = 0.804$), *IL1RN* rs2234663 ($p = 0.978$), *NOS2* rs2297518 ($p = 0,221$), and *TNF-a* rs1800629 ($p = 0.289$; data not shown).

Association analysis between gene polymorphisms and silicosis severity, based on the total number of hours of silica exposure

Using the mean number of hours of silica exposure in the sample as a whole (44,229 hours), we compared genotype and allele distributions between simple silicosis patients with > 44,229 hours of exposure to silica and complicated silicosis patients with <

Table 1. Sociodemographic characteristics, clinical characteristics, and lung function parameters, by silicosis severity (i.e., simple or complicated silicosis).[a]

Variables	Total	Group		p
		Simple silicosis	Complicated silicosis	
	(N = 143)	(n = 57; 40%)	(n = 86; 60%)	
Age, years	59.98 ± 8.81	58.45 ± 9.31	61.00 ± 8.36	0.091*
BMI, kg/m^2	23.92 ± 4.53	24.05 ± 6.19	23.84 ± 3.01	0.403†
Duration of exposure, years	21.55 ± 9.31	22.88 ± 10.01	20.67 ± 8.77	0.192†
Total number of hours worked per week	47.06 ± 9.37	46.40 ± 8.06	47.50 ± 10.16	0.451†
Duration of exposure, hours	44,229 ± 19,939	46,763 ± 21,254	42,549 ± 18,958	0.217*
Time elapsed since removal of exposure, years	14.00 ± 10.19	11.78 ± 10.36	15.49 ± 9.87	0.023†
Smoking history (pack-years)	36.15 ± 30.52	36.39 ± 35.38	36.02 ± 27.87	0.480†
FVC, % predicted	86.62 ± 21 ± 81	87.61 ± 20.35	77.65 ± 21.96	0.007*
FEV_1, % predicted	68.42 ± 23.71	77.88 ± 23.16	62.15 ± 22.05	0.0001*
FEV_1/FVC	65.02 ± 17.84	70.01 ± 16.64	61.71 ± 17.93	0.001†

[a]Values expressed as mean ± SD. *t-test (Kolmogorov-Smirnov: p > 0.05). †Mann-Whitney test (Kolmogorov-Smirnov: p < 0.05).

Table 2. Genotype and allele distribution of *FASLG* and *TGFB1* gene polymorphisms between simple and complicated silicosis.

Polymorphism	Group				Total	p	OR (95% CI)
	Simple silicosis		Complicated silicosis				
FASLG rs763110	41		56		97		
CC	8	(0.20)	22	(0.39)	30	0.114	1.00
CT	19	(0.46)	20	(0.36)	39		0.38 (0.14-1.07)
TT	14	(0.34)	14	(0.25)	28		0.36 (0.12-1.09)
C	35	(0.43)	64	(0.57)	99	0.047	1.00
T	47	(0.57)	48	(0.43)	95		0.56 (0.31-0.99)
CC	8	(0.20)	22	(0.39)	30	0.037	1.00
TT+CT	33	(0.80)	34	(0.61)	67		0.37 (0.15-0.96)
TGFB1 rs1800469	56		83		139		
CC	24	(0.43)	39	(0.47)	63	0.084	1.00
CT	19	(0.34)	36	(0.43)	55		1.17 (0.55-2.48)
TT	13	(0.23)	8	(0.10)	21		0.38 (0.14-1.05)
C	67	(0.60)	114	(0.69)	181	0.129	1.00
T	45	(0.40)	52	(0.31)	97		0.68 (0.41-1.12)
CC+CT	43	(0.77)	75	(0.90)	118	0.028	1.00
TT	13	(0.23)	8	(0.10)	21		0.35 (0.14-0.92)

44,229 hours of exposure to silica. Our objective was to compare patients with simple silicosis despite longer exposure to silica and those with complicated silicosis despite shorter exposure to silica. We found a significant association between the two groups of patients and the rs763110 polymorphism in the *FASLG* gene.

The T allele showed a protective effect against complicated silicosis with increased exposure to silica (OR = 0.20; 95% CI, 0.08-0.48; p < 0.0001). This was also observed in dominant and recessive models of the T allele (OR = 0.06; 95% CI, 0.00-0.49; p = 0.01 and OR = 0.22; 95% CI, 0.06-0.77; p = 0.014, respectively; Table 3).

Multivariate logistic regression analysis

Table 4 shows the results of the multivariate logistic regression analysis of independent predictors of silicosis severity. *FASLG* TT+TC genotypes were found to be predictors of protection against complicated silicosis after controlling for risk factors (OR = 0.15; 95% CI, 0.03-0.75; p = 0.021), whereas no effect was observed for *TGFB1* TT genotype. No use of PPE and a longer time elapsed since removal of exposure were also important independent risk factors for complicated silicosis (OR = 6.40; 95% CI, 1.47-27.86; p = 0.013 and OR = 1.09; 95% CI, 1.01-1.17; p = 0.027, respectively).

DISCUSSION

A history of exposure to silica particles is the most important of all environmental factors related to silicosis.[19] However, phenotypic differences could be explained by individual responses to exposure, and genetic variations could influence these responses.[4,19] In this study, we evaluated the association of several polymorphisms with the severity of silicosis in workers exposed to silica in Brazil and found significant

Table 3. Association analysis between *FASLG* rs763110 and silicosis severity, based on the total number of hours of silica exposure.*

Polymorphism	Group		Total	p	OR (95% CI)
	Simple silicosis > cutoff exposure time	Complicated silicosis < cutoff exposure time			
FASLG rs763110	19	31	50		
CC	1 (0.05)	15 (0.48)	16		1.00
CT	8 (0.42)	10 (0.32)	18	0.002	0.08 (0.00-0.84)
TT	10 (0.53)	6 (0.19)	16		0.04 (0.00-0.43)
C	10 (0.26)	40 (0.65)	50	<	1.00
T	28 (0.74)	22 (0.35)	50	0.0001	0.20 (0.08-0.48)
CC	1 (0.05)	15 (0.48)	16	0.001	1.00
TT+CT	18 (0.95)	16 (0.52)	34		0.06 (0.00-0.49)
CC+CT	9 (0.47)	25 (0.81)	34	0.014	1.00
TT	10 (0.53)	6 (0.19)	16		0.22 (0.06-0.77)

*Cutoff point: 44,229 hours.

Table 4. Multivariate logistic regression analysis of independent predictors of complicated silicosis.

Variable	β	SE	Wald	df	p	OR	95% CI
TGFB1 (TT)	−2.20	1.24	3.15	1	0.076	0.11	0.01-1.26
FASLG (TT+TC)	−1.89	0.82	5.34	1	0.021	0.15	0.03-0.75
No use of PPE	1.86	0.75	6.13	1	0.013	6.40	1.47-27.86
Silica exposure duration > 44,229 hours	0.00	0.00	1.57	1	0.211	1.00	1.00-1.00
Time elapsed since removal of exposure, years	0.08	0.04	4.86	1	0.027	1.09	1.01-1.17

PPE: personal protective equipment; and df: degrees of freedom.

associations between disease severity and the *TGFB1* and *FASLG* genes.

TGFB1 is a multifunctional cytokine that regulates the proliferation and differentiation of various cell types and is directly involved in fibrosis of the lung parenchyma. This cytokine can bind to at least three receptors (types I, II, and III). The effects of TGFB1 on extracellular matrix synthesis and deposition are mediated by type I receptors; the effects of TGFB1 on cell growth and proliferation are mediated by type II receptors; and type III receptors inhibit the binding of TGFB1 to cell membrane receptors, inhibiting its action.[20] Fibrosis represents a pathological event of a normal tissue repair process. Therefore, excessive or sustained production of TGFB1 becomes a key point for tissue fibrosis. In animal and human models, limited tissue injury is accompanied by a transient increase in TGFB1, without progression to fibrosis. In the presence of repetitive injury, TGFB1 production is maintained, leading to progressive extracellular matrix deposition and fibrosis.[20] The mechanism involved in the maintenance of TGFB1 expression as a result of repetitive injury is still poorly understood.[20]

The rs1800469 (−509C/T) promoter polymorphism in the *TGFB1* gene alters the levels of TGFB1 production and secretion.[21] Plasma levels of TGFB1 are twice as high in patients homozygous for the T allele in comparison with individuals homozygous for the C allele, with heterozygotes showing intermediate production.[21,22] In a meta-analysis performed by Deng et al. and including seven studies (a total of 4,333 patients with pneumoconiosis and 3,478 controls), a significant association was found between the rs1800469 polymorphism and the risk of pneumoconiosis.[8] Wu et al. conducted an association study of the rs1800469 polymorphism in 183 patients with silicosis and 111 controls and observed no significant association.[21] In our study, we observed that the TT genotype represented a protective factor for silicosis severity.

The divergence in results might be due to the fact that TGFB1 also acts as an anti-inflammatory agent in silicosis, playing an important role in the initiation and termination of tissue repair after an aggression, leading to tissue remodeling.[20] This was confirmed by Barbarin et al.,[23] who demonstrated that the pathogenesis of silicosis involves a complex interaction of inflammatory and anti-inflammatory pathways. TGFB1 stimulates fibroblasts and smooth muscle cells to produce elastin, as well as stimulating the production of inflammatory mediators.[24] TGFB1 also acts as an anti-inflammatory agent, promoting extracellular matrix accumulation by decreasing collagenase synthesis; repressing the stimulatory effects of growth factors on collagenase gene expression; and increasing the production of collagenase inhibitors.[24] Moreover, TGFB1 acts in all stages of tissue repair, inhibiting T and B cells and their products (TNF-α and IL-1), as well as modulating macrophage cytotoxicity, including suppression of superoxide and nitric oxide production.[25]

Experimental studies have demonstrated that administration of TGFB1 results in normalization of the tissue damage process.[26] In addition, the different expressions of its receptors (I, II, and III)

and interactions with TGFB1 may cause an imbalance between the inflammatory and anti-inflammatory pathways. There are no studies evaluating the association of *TGFBR1* polymorphisms with silicosis or other pneumoconioses. There are also no studies evaluating the association of *TGFB1* and *TGFBR1* polymorphisms with silicosis or other pneumoconioses. However, some studies have investigated other diseases. Grigorova et al.[27] evaluated the association of the rs1800469 polymorphism in the *TGFB1* gene and the rs3087465 polymorphism in the *TGFBR2* gene with frequent episodes of disease activity in patients with multiple sclerosis. The authors found a higher concentration of TGFB1 determined by the *TGFB1* genotype in combination with the *TGFBR2* genotype and concluded that this combination acted as a protective factor for relapsing-remitting multiple sclerosis.[27] Jin et al.[28] analyzed the association of the aforementioned polymorphisms with esophageal squamous cell carcinoma. The authors concluded that individuals carrying variant genotypes of these polymorphisms had a significantly reduced risk of esophageal squamous cell carcinoma.

Apoptosis plays an important role in the pathophysiology of silicosis.[29] The FAS receptor, located at 10q24.1, is a potent member of the apoptosis receptor family, playing a key role in signaling for apoptosis of several cells. This receptor interacts with its ligand (FASLG), initiating the cell death cascade by apoptosis.[30] In the FAS/FASLG system, the FAS receptor is expressed in several cells of various tissues, whereas FASLG is restricted to cells of the immune system, such as activated T cells and natural killer cells.[31] Borges et al.[32] investigated the role of FASLG in silicosis and found that FASLG-deficient guinea pigs were resistant to silicosis because of reduced macrophage apoptosis. In addition, treatment with an FASLG antagonist antibody prevented the development of the disease.[32]

In the present study, the T allele of the rs763110 polymorphism in the *FASLG* gene showed a protective effect on disease severity, even when we compared patients with simple silicosis and longer exposure to silica with those with complicated silicosis and shorter exposure to silica. Studies have shown that the T allele of this polymorphism leads to lower *FASLG* expression[33] because the TT genotype also leads to suppression of apoptosis by reduced binding of the *FASLG* promoter to transcription factors.[34] Cooke et al. demonstrated that the C allele of this polymorphism causes higher basal expression of FASLG than does the T allele.[35] Wu et al.[4] analyzed the influence of this polymorphism on susceptibility to silicosis and found no significant association. In contrast, in our study, the protective effect of rs763110 in *FASLG* for the severity of silicosis might be due to reduced apoptosis caused by the presence of the T allele in patients with simple silicosis.

Our multivariate logistic regression analysis of independent predictors of silicosis severity revealed that *FASLG* TT+TC genotypes constituted an independent protection factor for complicated silicosis (OR = 0.15; 95% CI, 0.03-0.75; p = 0.021). It also revealed that no use of PPE (OR = 6.40; 95% CI, 1.47-27.86; p = 0.013) was an independent risk factor for complicated silicosis. Recently, Requena-Mullor et al. studied silicosis in artificial stone workers and demonstrated that using only a simple mask and not using the PPE provided by the company represented a greater risk for silicosis.[36] Our multivariate analysis also revealed that a longer time elapsed since removal of exposure was also an independent risk factor for complicated silicosis (OR = 1.09; 95% CI, 1.01-1.17; p = 0.027). In silicosis, fibrosis can progress as a result of the inflammatory process caused by silica dust, even after removal of exposure. Therefore, silicosis tends to progress even in patients who have been away from occupational exposure for a long time.

The present study has limitations, including the impossibility of analyzing all of the pathogenic pathways of silicosis, including IL receptors; the presence of memory bias (the exact duration of exposure and number of hours worked per week); appropriate PPE and its use; and the small sample size. Another limitation is that we analyzed chest X-rays and classified the findings on the basis of the ILO International Classification of Radiographs of Pneumoconioses.[12] However, several studies have shown greater sensitivity with the use of chest CT scans in the assessment of profusion of lung parenchymal opacities in patients with silicosis.[37-39] Yet another limitation is related to the inclusion of patients with tuberculosis, which is known to promote progression of parenchymal lesions caused by silicosis. However, the exclusion of these patients would have resulted in a small sample size and would have misrepresented the profile of silicosis patients in Brazil.

In conclusion, the pathophysiology of silicosis is extremely complex, encompassing inflammatory and anti-inflammatory pathways. Polymorphisms in genes related to several immune mechanisms could cause an imbalance between inflammatory and anti-inflammatory factors, explaining the expression of distinct phenotypes. This study identified a statistically significant difference in the prevalence of *TGFB1* and *FASLG* gene polymorphisms, which were found to act as protective factors for disease severity. Further studies should be carried out in an attempt to expand the sample size and analyze the associations between genetic polymorphisms and pathophysiological mechanisms.

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CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

FBK and ASFN: study concept and design; MCSC, ASFN, KCRS, HC, PC, WC, and FBK: sample collection; MCSC, KCRS, JFBS, CBMN, and FBK: data collection, analysis, and interpretation; MCSC, JMR, and FBK: drafting of the manuscript and critical revision of the manuscript for important intellectual content; MCSC, ASFN, KCRS, JFBS, JMR, HC, PC, WC, CBMN, and FBK: final approval of the submitted version.

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Lung cancer screening with low-dose CT integrated with pulmonary care in a public hospital in southern Brazil: results from the first 712 patients

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ABSTRACT

Objective: To describe the performance of a pulmonologist-led lung cancer screening program using low dose CT (LDCT) in a cohort of outpatients with stable respiratory diseases in the Brazilian public health care system. **Methods:** This was a retrospective analysis of the first two rounds of lung cancer screening of patients enrolled in the program. Inclusion criteria were being between 55 and 80 years of age, being a current or former smoker (smoking cessation ≤ 15 years), and having a smoking history ≥ 30 pack-years. LDCT results were interpreted in accordance with the Lung CT Screening Reporting and Data System, and those with a score of 3 or 4 were considered positive screening. Incidental pleuropulmonary findings were sought in all reports. **Results:** LDCTs were requested for 791 patients during the study period, and 712 patients (90%) met the screening criteria. The mean patient age was 63 years, and most participants were current smokers (56%) with emphysema (78.5%) and other pleuropulmonary findings on CT (64%). Screening was positive in 14.0% and 5.6% of the cases in the first and second screening rounds, respectively. Lung cancer was detected in 1.5% of the patients in both first and second rounds (positive predictive value: 11.0% and 26.6%, respectively). The rate of early-stage (TNM I or II) screen-detected non-small cell carcinoma was 64.3%. Of the patients with positive screening, 19% were lost to follow-up before investigation was complete. **Conclusions:** The results of this screening program suggest its adequate performance in a cohort of patients with significant respiratory morbidity. The loss to follow-up rate highlights the need for constant monitoring and interventions to ensure adherence.

Keywords: Lung neoplasms; Diagnostic screening programs; Early detection of cancer; Brazil; Tuberculosis.

INTRODUCTION

Lung cancer causes more deaths than any other neoplasms worldwide, and a substantial and growing proportion of cases occur in regions of middle and low socioeconomic development.[1] In Brazil, advanced-stage lung cancer is identified in about 70% of diagnosed cases,[2] and the estimated number of deaths is 28,000 every year.[3] Low-dose CT (LDCT) screening in high-risk patients, followed by an appropriate diagnostic and therapeutic approach, reduces mortality from this disease by 20% or more, as demonstrated by large clinical trials in the United States and in Europe.[4,5] However, factors associated with the clinical-epidemiological profile of the screened population, as well as the local health care system, can potentially alter the benefits of screening.[6] Current international guidelines recommend continuing to study this strategy in different scenarios, as well as collecting data with a view to improving local programs.[6,7]

This study describes the results of a screening program developed for patients at high risk of lung cancer who were being followed up for lung diseases in a large public hospital in southern Brazil. Because the hospital is located in an area with a high incidence of granulomatous diseases, especially tuberculosis (89.9/100,000 population in the city of Porto Alegre and 46.6/100,000 population in the State of Rio Grande do Sul)[8] but also paracoccidioidomycosis[9] and silicosis,[10] there is specific interest in the potential large number of positive screenings associated with inflammatory nodules. In addition, little is known about the feasibility of a lung cancer screening program in the Brazilian public health care system.

METHODS

This was a retrospective analysis of all patients who underwent LDCT at the institution between the implementation of the lung cancer screening program

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(June of 2014) and December of 2019. The centralized registry of all LDCTs allowed the location of all patient records for review. In the program's care routine, pulmonologists requested LDCTs during outpatient visits of patients with lung diseases and smokers who were already being followed at the hospital. Data on demographics and clinical history, in addition to spirometry test results and imaging controls, were available in the electronic medical records and were collected using a structured form. Clinical data from the examination request and previous consultations were reviewed to confirm the intent to screen. The main follow-up diagnosis was recorded as reported by the pulmonologist in the medical records. COPD was confirmed by spirometry, but patients with evidence of chronic bronchitis were also considered COPD cases. Data were recorded anonymously and the project's ethical and methodological aspects were approved by the institution's research ethics committee (CAAE 73309317.5.0000.5530). Partial results of the present study have been previously presented as a poster at a conference.[11]

LDCT protocol

The acquisition and processing of images followed the American College of Radiology recommendations.[12] In summary, LDCT was performed with a 16-channel scanner (BrightSpeed; GE Healthcare, Waukesha, WI, USA) without the use of intravenous contrast, according to the following parameters: 120 kVp; 60 mA; gantry rotation time, 0.5 s; and pitch, 1.375. A single acquisition was performed during inspiration, and subsequent reconstructions were performed with 20-mm collimation, 5-mm increment, and 1.25-mm thickness. Effective radiation doses ranged between 0.8 and 1.3 mSv, with a dose-length product between 69 and 86 mGy•cm. The results were interpreted in accordance with the Lung CT Screening Reporting and Data System (Lung-RADS) standards,[13] and the revised assessment categories (version 1.1; 2019) were used whenever relevant. The reports were completed by radiologists from the institution under the supervision of a certified radiologist, who had developed the program and had specific training in thoracic radiology. The reports included the Lung-RADS classification score, as well as information on the presence of emphysema and other incidental pleuropulmonary findings. These findings included all acute or chronic interstitial, parenchymal, and pleural abnormalities that were described in the report but not used for the Lung-RADS classification.[13] Findings about other thoracic and extrathoracic organs, although described in the report, were not recorded in the present study.

Inclusion criteria were being between 55 and 80 years of age; having a smoking history of at least 30 pack-years; and being a current smoker or a former smoker (cessation ≤ 15 years). Exclusion criteria were having a pulmonary or systemic disease that would limit the diagnostic investigation or a possible surgical treatment for lung cancer (defined by the attending physician at the time of requesting the exam); having symptoms or signs compatible with clinical suspicion of lung cancer at the time of LDCT request; and having had lung cancer previously.

The procedures for investigation after positive screening (including control CT, biopsy, or referral for surgery) were at the discretion of the attending pulmonologist, although suggestions on the LDCT report in accordance with the Lung-RADS standards[13] were also considered. As part of the program's routine, most control CTs were also LDCTs, and their reports also followed the Lung-RADS standards.[13] Regular multidisciplinary sessions were not a formal part of the screening program, and difficult cases were individually discussed between the radiologist, the thoracic surgeon, or both, as the routine practice at the institution.

The analysis of the present study refers to the outcomes in the first (T0) and second (T1) rounds of screening. Clinical and radiological outcomes were evaluated for every patient after a positive screening, including control CT results and final results of additional diagnostic workup (cancer or benign disease). The Lung-RADS standards[13] were used in order to determine the stability or regression of the lesion in control CTs. The medical records of patients with positive screening were reviewed until diagnostic definition or follow-up loss/closure. Additional data from patients diagnosed with cancer by screening were collected, including histological type and details on staging and treatment.

The parameters adopted to evaluate the program's performance were defined as follows: rate of positive screens—number of patients with a Lung-RADS score of 3 or 4 divided by the number of patients screened, the rate being calculated for T0 and T1 separately; prevalence of lung cancer—number of patients with confirmed lung cancer in T0 divided by the number of screened patients in T0; incidence of lung cancer—number of patients with confirmed lung cancer in T1 divided by the number of screened patients in T1; and positive predictive value—number of patients with confirmed lung cancer divided by the number of patients with positive screening.

As an additional element of investigation, non-small cell carcinoma cases detected by screening were compared with cases diagnosed outside the program at the same institution (patients whose investigation was initiated due to symptoms or incidental findings). This comparative sample consisted of all cases diagnosed outside the screening program in 2017, which was the midpoint of the study period.

Statistical analysis

Descriptive statistics (absolute and relative frequencies; means and standard deviations; and medians and interquartile ranges) were used for reporting data on the prevalence of positive screenings and neoplasms, as well as clinical-epidemiological variables. The chi-square test was used for comparison

of frequencies of positive screening between patients with and without additional CT findings, as well as for comparison of early-stage lung cancer between screened and unscreened patients (comparative sample). The significance level was set at 0.05 for all results.

RESULTS

During the study period, LDCT was performed in 791 patients. In 79 of these patients (10%), LDCT was not requested for screening purposes or the patient did not meet the inclusion criteria of the program. The reasons for excluding these patients are detailed in Figure 1. Of the 712 patients who underwent the first round of screening (T0), 266 (37.3%) underwent the second round (T1) by the end of the study period. Clinical and demographic data of the patients are shown in Table 1. Briefly, the mean age was 63 years, and there was a slight predominance of men (51.5%) and current smokers (56%). The most common diagnosis was COPD, which was the main diagnosis in 69.3% of the patients. The mean FEV_1 was 64.9% of the predicted value.

The rate of positive screenings in T0 was 14%, with a similar distribution between Lung-RADS scores of 3 and 4 (Table 2). In T1, among 266 patients, 15 (5.6%) of the screenings were positive. Overall, 16 cases of cancer were identified in the study: 15 were cases of primary lung cancer and 1 was a case of metastatic breast cancer (the primary tumor had not been diagnosed prior to screening). Of the 15 primary lung malignancies, 11 were identified in T0 (n = 721; cancer prevalence of 1.5%), as were 4 in T1 (n = 266; cancer incidence of 1.5%). The positive predictive value for positive screening in T0 was 11% (11 confirmed neoplasm cases/99 positive screenings). Considering only a Lung-RADS score of 4, the positive predictive value was 23.9% (11/46). In T1, the positive predictive value was 26.6% (4/15) for positive screening and 50% (4/8) for Lung-RADS 4.

Details on the patients diagnosed with lung cancer, including staging and treatment, are shown in Table 3. The most common histological type was adenocarcinoma (13/15 patients), and treatment with curative intent (surgery or ablative radiotherapy) was offered to all stage I or II patients. A comparison of staging of non-small cell carcinoma detected in the screening program with those detected outside the screening program in 2017 (n = 134) is shown in Figure 2. TNM staging I-II was found in 64.3% and 22.4% of screened and unscreened patients, respectively (percentage point difference = 41.9%; 95% CI: 15.2-62.2; p = 0.0007).

Table 4 shows the outcome of the 114 positive screenings (T0 and T1), including the proportion of cases in which the Lung-RADS score regressed on subsequent CTs. One important finding was that 19.3% (n = 22/114, T0 and T1 combined) of the patients with positive screening were lost to follow-up without completing the investigation: 18.3% with a Lung-RADS score of 3 and 20.3% with a Lung-RADS of 4 (T0 and T1 combined).

Incidental pleuropulmonary findings (in addition to emphysema) were described in 64% of the CT scans, including parenchymal bands/cicatricial atelectasis in 37.9% of the cases. The frequencies of positive screening between patients with and without incidental LDCT findings were similar (16.4% and 12.5%, respectively; percentage point difference = 3.9; 95% CI: −1.3 to 9.6; p = 0.15). There was no statistically significant difference between patients with and without emphysema on LDCTs (15% and 9.8%, respectively;

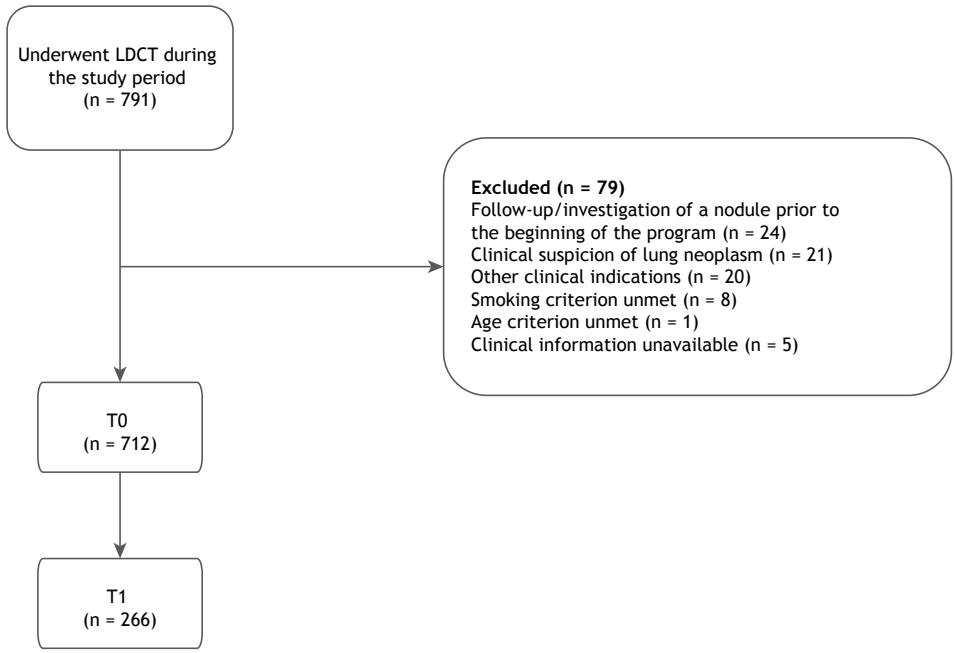

Figure 1. Flow chart of the participant selection process. LDCT: low-dose CT; T0: first round of screening; and T1: second round of screening.

Table 1. Characteristics of screened patients (N = 712).[a]

Characteristic	Result
Age bracket, years	
55-59	188 (26.4)
60-64	219 (30.7)
65-69	169 (23.7)
70-74	101 (14.2)
75-80	35 (4.9)
Age, years	63.0 ± 5.7
Sex	
Female	346 (48.5)
Male	366 (51.5)
BMI, kg/m^2	27.9 ± 5.4
< 30	438 (61.5)
≥ 30	198 (27.8)
Missing	76 (10.6)
Smoking	
Current	398 (56)
Former	296 (41)
Missing data	18 (2)
FEV_1, L	1.67 ± 0.69
FEV_1, % predicted	
≥ 80	188 (26.4)
50-79	274 (38.4)
30-49	164 (23)
< 30	33 (4.6)
Missing data	53 (7.4)
Main diagnosis[b]	
COPD[c]	494 (69.3)
Smoking cessation/counseling[d]	72 (10.1)
Tuberculosis sequelae	28 (3.9)
Asthma + COPD	26 (3.6)
Dyspnea assessment	24 (3.3)
Asthma	19 (2.7)
Previous pulmonary nodule[e]	8 (1.1)
Screening only	8 (1.1)
Interstitial disease	7 (0.9)
Bronchiectasis	5 (0.7)
Sleep apnea	4 (0.5)
Chronic cough	4 (0.5)
Preoperative screening	3 (0.4)
Chest pain	3 (0.4)
Silicosis	2 (0.3)
Sarcoidosis	1 (0.1)
Active tuberculosis	1 (0.1)
Paracoccidioidomycosis	1 (0.1)
Thrombophilia	1 (0.1)
Unreported/unavailable data	26 (3.6)

[a]Values expressed as n (%) or mean SD. [b]More than one diagnosis present in 25 patients. [c]Includes clinical diagnosis of chronic bronchitis, as well as cases associated with another diagnosis, except for asthma, which was described as ACOS. [d]Treatment/counseling as the main reason for outpatient follow-up. [e]Patients whose nodules had been identified and diagnosed as benign right before the beginning of the screening program were included in the study..

Table 2. Results obtained after the first round of low-dose CT (N = 712).[a]

Finding	Result
Negative screening	613 (86)
Lung-RADS 1	342 (48)
Lung-RADS 2	271 (38)
Positive screening	99 (14)
Lung-RADS 3	53 (7.4)
Lung-RADS 4	46 (6.5)
4A	26 (3.6)
4B	14 (2)
4X	6 (0.8)
Emphysema detected on LDCT	559 (78.5)
Incidental pleuropulmonary findings on LDCT[b]	
Any[c]	456 (64.0)
Parenchymal bands/cicatricial atelectasis	270 (37.9)
Compatible with respiratory bronchiolitis	118 (16.6)
Inflammatory opacities, other	70 (9.8)
Bronchiectasis	51 (7.2)
Interstitial abnormalities	33 (4.6)
Pleural thickening/calcification	10 (1.4)
None	256 (36.0)

Lung-RADS: Lung CT Screening Reporting and Data System score; and LDCT: low-dose CT. [a]Values expressed as n (%). [b]Except emphysema and pulmonary nodules included in Lung-RADS description. [c]More than one finding may occur in each patient.

percentage point difference = 5.2%; 95%CI: −1.15 to 10.1; p = 0.09).

DISCUSSION

Our study reports the initial results of a lung cancer screening program in a cohort of patients with specific characteristics that differ from others: it was developed in a setting of high prevalence of granulomatous diseases and conducted by pulmonologists for patients being already followed up for chronic stable respiratory diseases in the context of the Brazilian public health care system.

Although our inclusion criteria were practically the same as were those in the National Lung Screening Trial (NLST),[4] the patients included in our study had a different clinical profile, as expected in a cohort of patients with previous lung diseases in a different epidemiological context. In fact, in our study, emphysema was reported in 78.5% of the patients during the first round of LDCTs, which was much higher than that reported in the NLST (30.7%).[14] Similarly, only 10.6% had a history of COPD/emphysema in that study,[14] whereas, in our study, the main reason for respiratory follow-up was COPD (69.3%). Parenchymal bands/cicatricial atelectasis were also very frequent in our cohort, probably reflecting previous infections, including locally prevalent granulomatous diseases.

Despite these differences, the positive screening rates were quite similar according to the Lung-RADS classification: The proportion of Lung-RADS 3 or 4 was 13.6% and 14%, respectively, in the NLST reanalysis[15] and in our study. The same occurred with the prevalence of cancer: 1% and 1.5%, respectively.

In a context similar to that in this study, Grover et al.[16] evaluated a screening program in a population previously followed up for COPD in the United Kingdom public health care system. The prevalence of cancer was 2% and, more importantly, 66.7% of these cases were diagnosed at stage I or II. In our study, the proportion of early cases was similar (64.3%), and, of note, that was significantly higher than was the

Table 3. Description of 15 cases of primary lung cancer confirmed after positive screening.

Sex, Age (years)	Lung-RADS	Histology	TNM	Staging	Treatment
Positive screening (first round)					
Female, 59	4X	Adenocarcinoma	cT3 cN3 M1c	IVB	Chemotherapy
Female, 72	4A	Adenocarcinoma	pT1pN0M0	IA	Surgery
Female, 64	4A	Adenocarcinoma	pT1cN0M0	IA3	Surgery
Male, 63	4X	Adenocarcinoma	cT1b cN0 M0	IA2	Radiotherapy, curative intent (VMAT)
Female, 58[a]	4A	Adenocarcinoma	T1aN2M1c	IVB	Palliative radiotherapy
Female, 78	4B	Adenocarcinoma	cT1b cN0 M0	IA2	Surgery
Female, 61	4X	Small cell carcinoma	-	Extensive disease	? (oncology evaluation outside the screening center)
Female, 74	4B	Poorly differentiated carcinoma (probable squamous cell carcinoma)	cT3 CN3 M1b	IVA	Chemotherapy + targeted therapy (research protocol)
Female, 63	4B	Adenocarcinoma	pT3pN0M0	IIB	Surgery
Male, 77	4B	Adenocarcinoma	cT2aN0M0	IB	Initially refused treatment. Subsequent treatment outside the center.
Female, 55	4B	Adenocarcinoma	pT2aN0M0	IB	Surgery
Positive screening (second round)					
Male, 71	4B	Adenocarcinoma	pT1b pN0 M0	IA2	Surgery
Female, 55[b]	4X	Adenocarcinoma	T3N3M1a	IVA	? (oncology evaluation outside the screening center)
Male, 60	4A	Adenocarcinoma	pT2apN0M0	IB	Surgery
Female, 56	4B	Adenocarcinoma	T2 cN2 M1c	IV	Chemotherapy

Lung-RADS: Lung CT Screening Reporting and Data System score; and VMAT: volumetric modulated arc therapy. [a]Diagnosis/staging delayed for 13 months. [b]Delay between control CT and further investigation (suggestion, 6 months; completion, 22 months). Note: One case of breast cancer metastasis was not included in this analysis.

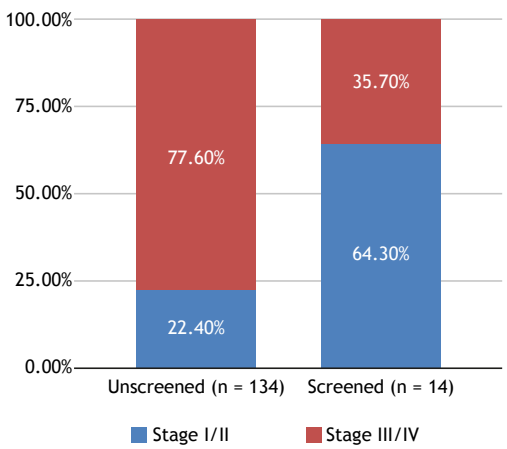

Figure 2. Staging of non-small cell lung carcinoma in patients participating in the screening program during the study period (2014-2019) and those not participating in the program in 2017 (midpoint of the study period).

proportion of cases detected outside the screening program in our institution (22.4%) and nationwide.[2] In fact, our results might have underestimated the potential benefit of screening, because a careful review of data revealed that in 2 of the stage IV cases, there was an unintentional delay in performing a control CT and diagnostic workup. Indeed, we cannot be sure whether avoiding these delays would have resulted in more favorable staging, and we understand that these situations may reflect real-life difficulties of a screening program.

One important concern is that patients with lung diseases and impaired lung function may present with a limited potential to treatment with curative intent. In our study, with the exception of 1 patient who refused treatment, all patients at TNM I or II received treatment with curative intent (surgery or ablative radiotherapy). Despite the significant number of patients with impaired lung function, including more than a quarter of the participants with FEV_1 < 50% of the predicted value, we believe that patients carefully selected on the basis of their overall clinical context may be suitable candidates for screening even at such levels of lung function impairment.

Screening with LDCT in developing countries is challenging, and efforts to study and implement it are still incipient.[17,18] Nevertheless, studies such as that by dos Santos et al.[19] demonstrate that cancer detection rates and the need for invasive investigation may be similar to those in developed countries. In fact, in a recent study by Hochhegger et al.,[20] who retrospectively evaluated the screening results of 3,470 patients in Brazil (88% from the private health care system), the results were quite encouraging: the prevalence of cancer was 2.1% and, more importantly, early staging was identified in 70.3% of these cases.

Table 4. Final clinical and/or radiographic outcomes after a positive screen (T0 and T1).[a]

Outcome after Lung-RADS 3	T0 (n = 53)	T1 (n = 7)	Total (n = 60)
Regression on early CT (up to 6 months)	28 (53.8)	3 (42.8)	31 (51.7)
Regression on CT (1 year)	8 (15.0)	1 (14.2)	9 (15.0)
Diagnosis of neoplasm	1[b] (1.9)	0 (0.0)	1 (1.7)
Diagnosis of benign disease	1 (1.9)	1 (14.2)	2 (3.3)
Loss to follow-up	9 (17.0)	2 (28.5)	11 (18.3)
Refused subsequent workup	0 (0.0)	0 (0.0)	0 (0.0)
Expectant treatment	6 (11.3)	0 (0.0)	6 (10.0)
Outcome after Lung-RADS 4	**T0 (n = 46)**	**T1 (n = 8)**	**Total (n = 54)**
Regression on early CT (up to 6 months)	12 (26.0)	3 (37.5)	15 (27.8)
Regression on CT (1 year)	3 (6.5)	0 (0.0)	3 (5.5)
Diagnosis of neoplasm	12[c] (26.0)	3 (37.5)	15 (27.8)
Diagnosis of benign disease	6 (13.0)	0 (0.0)	6 (11.1)
Loss to follow-up	10 (21.7)	1 (12.5)	11 (20.3)
Refused subsequent workup	2 (4.3)	1 (12.5)	3 (5.5)
Expectant treatment	1 (2.2)	0 (0.0)	1 (1.9)

T0: first round of screening; and T1: second round of screening. [a]Values expressed as n (%). [b]Control stability for 6 months; evolution to Lung-RADS 4 in 1 year, later diagnosed with neoplasia. [c]Includes one case of breast cancer metastasis.

These results are similar to those in international studies, and the authors concluded that the local prevalence of granulomatous diseases did not increase the number of lung biopsies. The results in our study are in the same direction and significantly increased the number of patients screened in the public health care system (401 in Hochhegger et al.[20] vs. 721 in this study). Even with the limitations inherent to the public health care system context, our early staging rates were similar to those of Hochhegger et al.[20] (64.3% vs. 70.3%), which represents a very important advance in relation to the usual rates without screening. We believe that the expertise of large-volume or academic centers in a multidisciplinary context with specialists familiar with the local epidemiology and management of granulomatous diseases can contribute to satisfactory results, such as those obtained in the present study, without unnecessary investigations.

Finally, the rate of loss to follow-up was a significant limitation. This is a constant concern in clinical screening practice in real-life situations.[21] A recent meta-analysis by Lopez-Olivo et al.[22] included 15 American studies (16,863 patients) and found an overall adherence rate of only 55%. The authors[22] found that the following factors had important associations with low adherence: current smoking, ethnic minorities, age < 65 years, low educational level, and decentralized screening programs. In our study, the reasons for the low rate of T1 screenings were not evaluated and may have been due to either the physician's or the patient's decision, which were beyond the scope of this study. However, all positive screenings were carefully reviewed, and our loss to follow-up was approximately 20%. Unfortunately, our retrospective study could not identify causes of nonadherence to the visits or of the failure to carry out the investigations requested after a positive screening. In addition to the usual causes of poor adherence, one possible factor is that some patients with positive screening at the end of 2019 may have had difficulties in scheduling control CTs or medical visits due to restrictions caused by the COVID-19 pandemic (from March of 2020). Although the high rate of patients lost to follow-up is worrisome, we understand that the adherence issues in our study are similar to those reported in real-life studies[22,23] and that detecting such limitations may help improve the program, including strategies to contact missing patients and improve "navigation" after a positive result. We also believe that patients who are already linked to outpatient care may have better adherence to subsequent rounds of screening.

In conclusion, a lung cancer screening program for patients undergoing respiratory follow-up in the Brazilian public health care system in an area with a high incidence of granulomatous diseases and with a high rate of residual inflammatory findings on CT obtained satisfactory results that are comparable to results in other cohorts in different contexts. The high rate of early staging is encouraging and suggests a beneficial impact on the number of treatments with curative intent. The frequency of incomplete investigations after positive screening points to the need for constant monitoring and interventions to ensure adherence to screening.

AUTHOR CONTRIBUTIONS

FMS, MMRL, APGS, RSG, and CFA: conceptualization. FMS, MMRL, and CFA: data curation. FMS and CFA: formal analysis. CTMO, RUB, FMS, RSG, ACC, APGS, and MMRL: investigation. FMS: drafting of the manuscript. FMS, CFA, RSG, MMRL, and APGS: editing and review of

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

CONFLICTS OF INtEREST

None declared.

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2022 Brazilian Thoracic Association recommendations for long-term home oxygen therapy

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ABSTRACT

Some chronic respiratory diseases can cause hypoxemia and, in such cases, long-term home oxygen therapy (LTOT) is indicated as a treatment option primarily to improve patient quality of life and life expectancy. Home oxygen has been used for more than 70 years, and support for LTOT is based on two studies from the 1980s that demonstrated that oxygen use improves survival in patients with COPD. There is evidence that LTOT has other beneficial effects such as improved cognitive function, improved exercise capacity, and reduced hospitalizations. LTOT is indicated in other respiratory diseases that cause hypoxemia, on the basis of the same criteria as those used for COPD. There has been an increase in the use of LTOT, probably because of increased life expectancy and a higher prevalence of chronic respiratory diseases, as well as greater availability of LTOT in the health care system. The first Brazilian Thoracic Association consensus statement on LTOT was published in 2000. Twenty-two years later, we present this updated version. This document is a nonsystematic review of the literature, conducted by pulmonologists who evaluated scientific evidence and international guidelines on LTOT in the various diseases that cause hypoxemia and in specific situations (i.e., exercise, sleep, and air travel). These recommendations, produced with a view to clinical practice, contain several charts with information on indications for LTOT, oxygen sources, accessories, strategies for improved efficiency and effectiveness, and recommendations for the safe use of LTOT, as well as a LTOT prescribing model.

Keywords: Oxygen; Hypoxia; Oxygen inhalation therapy; Delivery of health care.

INTRODUCTION

Chronic respiratory diseases can cause resting or exercise-induced hypoxemia, being among the main causes of decreased quality of life and life expectancy. Because especially of their infectious complications and their related hospitalizations, chronic respiratory diseases result in high costs for public and supplementary health care, as well as for patients and their families. For those who develop hypoxemia, the prescribing of long-term home oxygen therapy (LTOT) may provide benefits, such as a decrease in perceived dyspnea, improved exertional tolerance, and increased life expectancy.

Home oxygen has been used empirically for more than 70 years, and support for LTOT is based on two landmark studies from the 1980s, one by the Nocturnal Oxygen Therapy Trial Group[1] and one by the Medical Research Council Working Party.[2] Both studies demonstrated that oxygen use improves survival in COPD patients.

Improved survival with LTOT has been demonstrated in patients with stable COPD and severe, chronic hypoxemia.[3-6] In recent decades, accumulated evidence has shown that LTOT has other beneficial effects, such as reduced depression, improved cognitive function, improved quality of life, improved exercise capacity, and reduced hospitalizations.[7-16] In addition, LTOT can stabilize or even reverse

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pulmonary hypertension (PH) and decrease both cardiac arrhythmias and myocardial ischemia in patients with COPD.[17,18] However, the use of LTOT in other respiratory diseases that cause severe hypoxemia is based on extrapolation of COPD-related data, largely supported by knowledge of respiratory physiology and cellular respiration, which are identical regardless of the disease causing the hypoxemia, as well as its systemic effects.

The first Brazilian Thoracic Association consensus statement on LTOT was published in 2000 and remains a reference for many oxygen therapy protocols in Brazil.[19] In the last 22 years, there has been a large increase in the use of LTOT, partly because of increased life expectancy and an increasing number of patients diagnosed with chronic lung diseases, notably COPD and interstitial lung diseases (ILDs), as well as the fact that the availability of LTOT in the health care system has increased. In addition, in the last 2 years, a proportion of COVID-19 survivors needed to use oxygen during a transition period or became chronic oxygen users.

In Brazil, the protocols for provision of LTOT for free are municipal and state protocols, and this is one of the reasons why we do not have reliable national data on the total number of LTOT users. In the USA, more than 1.5 million patients were receiving LTOT in 2018.[20]

In Brazil, access to LTOT is guaranteed by the Brazilian Unified Health Care System's Organic Laws (Federal Laws no. 8080/90 and no. 8142/90) that regulate the conditions for health promotion, protection, and recovery and for guaranteeing this right to every citizen.

We brought together 16 pulmonologists with expertise in oxygen therapy, who conducted a nonsystematic review of the literature and international guidelines for scientific evidence on LTOT in the various diseases that cause hypoxemia and on oxygen use in specific situations (i.e., sleep, exercise, and air travel). With a view to clinical practice, we created several charts to facilitate patient management, with information on main indications for LTOT; different sources of oxygen supply and necessary accessories; strategies for increased adherence, efficiency, and effectiveness; cost reduction; and recommendations for the safe use of LTOT; as well as a LTOT prescribing model (Charts 1-10 and Figure 1). In these recommendations, we chose to use the term LTOT, although we understand that the meaning intended here is broader, that is, it is oxygen supplementation for outpatients, for use during any activity, inside or outside their home.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF HYPOXEMIA

Oxygen is essential in oxidative phosphorylation, promoting ATP synthesis for energy production. Arterial oxygen content is dependent on the partial pressure of inspired oxygen, which, in turn, is dependent on atmospheric pressure, ventilation, the actual gas exchange, and hemoglobin concentration and affinity for oxygen.[21]

Only a small fraction (less than 2%) of arterial oxygen content is dissolved in plasma and is free from hemoglobin. At sea level, an SpO_2 of 96-98% corresponds to approximately 20 mL of oxygen for every 100 mL of blood.[22] The delivery of oxygen to the tissues, in turn, is dependent on arterial oxygen content and cardiac output. The lower the oxygen concentration, the greater the hemoglobin-oxygen affinity, and, consequently, the more decreased the delivery of oxygen to the tissues. An increase in body temperature, acidosis from any cause, or an increase in 2,3-diphosphoglycerate produces a shift in the hemoglobin dissociation curve to the right, decreasing hemoglobin-oxygen affinity and increasing the delivery of oxygen to the tissues.[23]

Hypoxemia can be assessed by calculating the alveolar-arterial oxygen tension difference ($P[A\text{-}a]O_2$) or by calculating the oxygenation index (PaO_2/FiO_2). In hypoxemic patients with $P(A\text{-}a)O_2$ within the normal range, the likely pathophysiological mechanism is the presence of hypoventilation. In those with increased $P(A\text{-}a)O_2$ and persistent hypoxemia despite oxygen supplementation or with increased FiO_2, the presence of cardiac or intrapulmonary shunt is suggested. In those who respond to supplemental oxygen, ventilation-perfusion (V/Q) mismatch or altered diffusion should be considered.[24]

Acute or chronic hypoxemia induces various physiological responses aimed at maintaining adequate delivery of oxygen to the tissues. When PaO_2 is below 60 mmHg, there is an increased ventilatory stimulus, increasing PaO_2 and reducing $PaCO_2$. The vascular beds irrigating the hypoxic tissue dilate, inducing compensatory tachycardia to increase cardiac output and improve oxygen delivery. The pulmonary vasculature contracts to improve the V/Q ratio in the affected areas. If hypoxemia does not resolve, renal activation will occur to increase erythropoietin production and stimulate erythrocytosis, increasing oxygen transport and delivery capacity. These initial benefits may have harmful long-term effects, since long-term vasoconstriction, erythrocytosis, and increased cardiac output can cause PH and right ventricular failure, decreasing survival. In addition, the energy cost of increased ventilation and increased oxygen demand may contribute to malnutrition in COPD patients.[21-24]

DEFINITION OF HYPOXEMIA

At sea level, barometric pressure is 760 mmHg (or 1 atm), FiO_2 is 0.21 (or, as per clinical practice, 21%, a term that is used in scientific papers and will be used in this document), and PaO_2 is 80-100 mmHg in healthy individuals. Therefore, PaO_2 is dependent on altitude, although it should also be adjusted for age (with aging, there is a progressive reduction in PaO_2). Hypoxemia is defined as a PaO_2 below the lower limit

Chart 1. Indications for home oxygen therapy.[a]

Treatment modality and parameters to recommend its use
Assumptions Strong evidence based on studies of COPD and on use of supplemental oxygen for more than 15 h/day Oxygen therapy increases survival and improves pulmonary hemodynamics, quality of life, sleep quality, and cognition. It does not reduce the frequency of exacerbations. Use of supplemental oxygen for 24 h has an additional effect on survival in comparison with use of supplemental oxygen for 12-15 h. Oxygen therapy is available free of charge under the auspices of the Brazilian SUS municipal and state programs. The indication for use of oxygen therapy should be evaluated when patients are in a stable phase of their disease and receiving optimal treatment, with an SpO_2 of ≤ 92%. The indication for use of oxygen therapy should be confirmed by arterial blood gas analysis performed with the patient at rest in a sitting position and breathing room air. Correction of hypoxemia (SpO_2 ≥ 90-92%) should be confirmed, and increases in $PaCO_2$ should be monitored. Indications A PaO_2 of ≤ 55 mmHg (7.3 kPa) or an SpO_2 of ≤ 88% A PaO_2 of 56-59 mmHg (7.4-8.0 kPa) or an SpO_2 of ≤ 89% associated with PH, edema caused by heart failure, or hematocrit > 55%
Ambulatory oxygen therapy (during exercise and physical activity) An SpO_2 of ≤ 88% during physical activity and improved exercise tolerance with the use of oxygen Ambulatory oxygen therapy contributes to increasing the number of hours of daily oxygen therapy use. Although ambulatory oxygen therapy improves exercise capacity, there are conflicting results regarding improved quality of life. Ambulatory oxygen therapy can improve training duration and intensity during rehabilitation.
Nocturnal oxygen therapy An SpO_2 of ≤ 90% on ≥ 30% of the recording and evidence of PH or erythrocytosis (improvement in SpO_2 should be confirmed) One study[155] showed no benefit in patients who did not meet criteria for long-term home oxygen therapy (low power and adherence).
Oxygen therapy during air travel (see Chart 9) Indications: an SpO_2 of < 92% or an SpO_2 of 92-95% and ≤ 84% on a 6MWT or HAST
Palliative oxygen therapy Palliative oxygen therapy is generally not indicated for patients with advanced disease and dyspnea without hypoxemia. Oxygen is less effective than opioids in relieving dyspnea.

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] Lacasse et al.,[155] and the Global Initiative for Chronic Obstructive Lung Disease.[156] SUS: *Sistema Único de Saúde* (Unified Health Care System); PH: pulmonary hypertension; 6MWT: six-minute walk test; and HAST: hypoxia altitude simulation test.

of normal; however, this does not necessarily mean that oxygen supplementation will be required.

Classically, the prescribing of LTOT in patients with chronic respiratory diseases other than COPD relies on extrapolation of data from COPD studies. Pulse oximetry is used to screen patients for resting hypoxemia; when SpO_2 is ≤ 92%, a request for arterial blood gas analysis on room air is indicated; in addition, the presence or absence of hypercapnia should be evaluated. :The indications for LTOT are as follows: severe hypoxemia with a PaO_2 ≤ 55 mmHg or an SaO_2 ≤ 88% or a PaO_2 ≤ 59 mmHg or an SaO_2 ≤ 89% in the presence of edema, *cor pulmonale* (PH), or polycythemia (hematocrit > 55%).[6,20,25] The daily duration of LTOT should be at least 15 h/day, including the sleep period, and the oxygen flow rate should be high enough to raise PaO_2 above 60 mmHg or raise SpO_2 above 90%.[6,20,25]

≥Exercise-induced hypoxemia is defined as a reduction ≥ 4 points in exertional SpO_2, even if baseline SpO_2 is within the normal range. LTOT in patients with exercise-induced hypoxemia remains controversial in the literature, it being advisable to consider the magnitude of the decrease in perceived dyspnea after oxygen supplementation or to consider its use in pulmonary rehabilitation.

The mechanisms of action of supplemental oxygen are beyond the correction of hypoxemia and the improvement of oxygen delivery to the cells. In healthy individuals exposed to hypoxic conditions, the accumulation of hypoxia-inducible factors in the cell nucleus upregulates several genes responsible for the physiological responses to hypoxia, including remodeling of the pulmonary vasculature, culminating in PH and increased erythropoiesis.[26,27] Limited evidence from animal models suggests that some of the therapeutic effects of LTOT are mediated by inhibition of hypoxia-inducible factors.[28]

LTOT IN PATIENTS WITH COPD

Although observational studies have suggested benefits of using supplemental oxygen in COPD, two randomized clinical trials (RCTs) were critical in establishing the basis for the use of LTOT.[1,2] The study by the Medical Research Council Working Party[2] followed 87 COPD patients for 5 years who had

Chart 2. Sources of high-pressure oxygen.[a]

Sources	Advantages	Disadvantages
	Stationary cylinders - 20-50 L in general (30-75 kg)	
	• Are available nationwide • Are available free of charge in the Brazilian SUS • Can store O_2 for days • Require no power supply • Can deliver high O_2 flow rates	• Are heavy and difficult to transport • Require support for transportation • Pose a risk of falls and explosions • Have low autonomy: a 50-L cylinder delivering an O_2 flow rate of 1 L/min 24 h/day would last an average of 125 h (a refill every 5 days) • Are expensive because multiple monthly refills are required • Keep patients bound to their homes
		
	Portable cylinders - 3-5 L in general	
	• Facilitate use outside the home (outpatient use) • Weigh 3.5-5.5 kg	• Low autonomy depending on pressure and size: a 3-L cylinder delivering an O_2 flow rate of 1 L/min would last 4.5 h • Depending on size, weight, and degree of dyspnea, a wheeled cart might be needed in order to help patients move around.
		

Notes:
• 1 bar = 0.988 atm; 1 kgf/cm^2 = 0.97 atm; and 1 atm = 760 mmHg. In practice, 1 atm = 1 bar = 1 kgf/cm^2
• A 50-L cylinder at 200-bar pressure expands to 10,000 L (10 m^3) in the atmosphere
• Duration in minutes = (N of liters in the cylinder × pressure on the manometer)/N of L/min of O_2
• A cylinder delivering 10,000 L in the atmosphere at a flow rate of 2 L/min: autonomy of 5,000 min or 83.3 h (3.4 days)
• A portable cylinder delivering up to 270 L in the atmosphere (3 L × 90 bar) at a flow rate of 1 L/min: autonomy of 270 min or 4.5 h
• A total of 90 L of O_2 are consumed when nebulized O_2 is delivered at a flow rate of 6 L/min for 15 min.

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] O'Driscoll et al.,[124] Hardavella et al.,[157] and the Chest Foundation.[158] SUS: *Sistema Único de Saúde* (Unified Health Care System); and atm: standard atmospheres.

severe hypoxemia, hypercapnia, and *cor pulmonale*. Patients were randomized into two groups: placebo (no supplemental oxygen) and intervention (LTOT for at least 15 h/day). At the end of follow-up, mortality was 45.2% in the oxygen group and 66.7% in the control group.[2] The study by the Nocturnal Oxygen Therapy Trial Group[1] randomized 203 hypoxemic COPD patients into two groups: continuous supplemental oxygen and 12-h nocturnal supplemental oxygen. The follow-up period was 12 months, and mortality was higher in the nocturnal oxygen group (hazard ratio = 1.94; p = 0.01).

Studies that have demonstrated increased survival with LTOT involved patients with severe hypoxemia (PaO_2 ≤ 55 mmHg or SaO_2 ≤ 88%). In contrast, the use of LTOT in COPD patients with moderate hypoxemia showed no survival benefit.[29-31] Other studies of individuals with COPD also demonstrate that LTOT has other benefits in severely hypoxemic COPD patients, such as improvement in quality of life, exercise capacity, and cognitive function, as well as a reduction in pulmonary vascular resistance, right atrial pressure, cardiovascular morbidity, and hospitalizations.[13,15-18,32-34]

As previously mentioned, the mechanisms of action of supplemental oxygen are beyond the correction of hypoxemia and the improvement of oxygen delivery to the cells. In healthy individuals exposed to hypoxic conditions, the accumulation of hypoxia-inducible factors in the cell nucleus upregulates several genes responsible for the physiological responses to hypoxia, including remodeling of the pulmonary vasculature, leading to PH and increased erythropoiesis.[26,27] Limited evidence from animal models suggests that some of the therapeutic effects of LTOT are mediated by inhibition of hypoxia-inducible factors.[28]

LTOT is indicated for COPD patients with persistent severe hypoxemia who are clinically stable and have been on optimal drug therapy for at least one month. Those who are clinically unstable, for example, after a recent exacerbation, should receive temporary oxygen supplementation until clinical reassessment 1-3 months after decompensation, since approximately 50% will not require LTOT at follow-up.[35,36] It is recommended that all patients assess the need to increase the oxygen flow rate during exercise and sleep. Excessive oxygen flows should be avoided in order to minimize the side effects of oxygen, especially a worsening of hypercapnia in patients with carbon dioxide retention, with an increase in the risk of sensorial depression and, in extreme cases, of coma due to carbon dioxide narcosis,[37] and it is suggested that SpO_2 be maintained at 90-92%.

Chart 3. Sources of liquid oxygen (stored at −183°C; 1 L of liquid oxygen = 860 L of gaseous oxygen).[a]

Sources	Advantages	Disadvantages
	Stationary aluminum cylinders/tanks for home use (volume, 20-40 L; weight, 40-65 kg)	
	• Require no power supply • Are noise-free • Tanks equipped with wheels make it easier to move around the house • Refill portable cylinders • Have good autonomy, with refills every 8-20 days depending on the volume of the tank and on the O_2 flow rate • Deliver O_2 flow rates of up to 7 L/min	• Size and weight make them difficult to transport • Make it difficult for patients to move around the house • Pose a risk of frostbite, especially when refilling portable cylinders • Available only in major cities • Are relatively expensive, albeit less so than gaseous O_2 cylinders
	Small, portable aluminum cylinders (volume, 0.5-1.2 L; weight, 2.5-3.9 kg)	
	• Are small and light • Make it easier for patients to go outside their homes and move around • Have autonomy to deliver an O_2 flow rate of 1 L/min (range, 5-14 h) • Can be transported by patients • Can be refilled by stationary cylinders/tanks for home use	• Have low autonomy when delivering O_2 flow rates ≥ 3 L/min • Are not available in the Brazilian SUS • Are expensive

[a]Based on Hardinge et al.,[6] the Brazilian Thoracic Association,[19] González-Moro et al.,[25] O'Driscoll et al.,[124] Hardavella et al.,[157] and the Chest Foundation.[158] SUS: *Sistema Único de Saúde* (Unified Health Care System).

Pulse oximetry is used to screen patients for hypoxemia; when SpO_2 is ≤ 92%, arterial blood gas analysis is indicated. Arterial blood gas analysis is necessary for prescribing LTOT and is also useful for detecting hypercapnia. As previously mentioned, the indications for LTOT include a PaO_2 ≤ 55 mmHg or an SaO_2 ≤ 88% or a PaO_2 ≤ 59 mmHg or an SaO_2 ≤ 89% in the presence of edema, PH, *cor pulmonale*, or polycythemia (hematocrit > 55%).[6,20,25]

Hypoxemic patients with suspected obstructive sleep apnea (OSA) syndrome or alveolar hypoventilation should be referred for polysomnography. It should be emphasized that in such cases correction of hypoxemia may be achieved with noninvasive ventilation alone, even without supplemental oxygen.[38]

Smokers should be referred to smoking cessation programs and instructed not to smoke while using oxygen, not because oxygen is flammable, but because it accelerates combustion and increases the risk of fires and explosions.[39] In addition, smoking increases blood levels of carbon monoxide, which has a high affinity for hemoglobin and reduces oxygen transport.[6,25,27]

Adherence to treatment is essential for achieving the expected benefits of LTOT. Adherence can range from 45% to 70% and can be improved by identifying barriers, facilitators, and prescriber attitudes.[40] Many patients use oxygen for less than 15 h/day, use oxygen flows lower than those prescribed by their doctors, or both, because they lack guidance about their illness and about the role of oxygen in the treatment, have little improvement in their symptoms, or are afraid of becoming dependent on LTOT.[6,20,25,41,42] High-quality support from the health care team improves patient adherence to the correct use of oxygen (Chart 6). The decision to prescribe LTOT should be carefully considered, as should the decision to discontinue it. Oba et al.[43] observed that only 35% of patients were reassessed correctly and that the rate of appropriate reassessment was significantly higher among pulmonologists than among general practitioners (65% vs. 17%).

LTOT IN PATIENTS WITH CHRONIC LUNG DISEASES OTHER THAN COPD

Cystic fibrosis

In patients with cystic fibrosis (CF), chronic airway infection causes lung damage that results in chronic

Chart 4. Oxygen concentrators (oxygen from room air).[a]

Concentrators	Advantages	Disadvantages
	Stationary concentrators for continued home use	
	• Are medium-sized and are equipped with wheels that make it easier for patients to move around the house • There are dozens of brands available at different price ranges. • Newer models are virtually noise-free • Newer models can deliver O_2 flow rates of up to 10 L/min • An hour meter[b] makes it easier to assess treatment adherence	• Are expensive (5,000-15,000 Brazilian *reais*) • High power consumption (Patients should ask for a discount on electricity bills.) • Older models are larger and noisier. • Most deliver an O_2 flow rate of ≤ 5 L/min
	Portable concentrators	
  	• Are small • Relatively light (weighing 3-5 kg) • Make it easier for patients to go outside their homes and move around • Are approved for in-flight use by most airlines • Pulse flow: reduced O_2 consumption and increased autonomy	• Battery life ranges from 3 h to 12 h. • Continuous O_2 flow rates of ≤ 2 L/min in most cases • Are expensive (10,000-20,000 Brazilian *reais*): a longer battery life translates to a higher cost, as does a lower weight. Portable concentrators equipped with pulse flow modes (i.e., O_2 delivered at inhalation) are also more expensive.

[a]Based on Hardinge et al.,[6] the Brazilian Thoracic Association,[19] González-Moro et al.,[25] O'Driscoll et al.,[124] Hardavella et al.,[157] the Chest Foundation,[158] the American Association for Respiratory Care,[159] and Tanni et al.[160]
[b]The hour meter shows how long the concentrator has been used.

hypoxemia, with respiratory failure being the leading cause of death.[44,45] The proportion of CF patients receiving oxygen is unknown, and the impact of LTOT on the survival and quality of life of these patients remains unclear.[45] A review[45] of 11 studies on oxygen use in patients with CF, only one of which assessed its long-term benefit, concluded that LTOT had no discernible effect on mortality, hospitalization, or disease progression when compared with no oxygen therapy, although it reduced absenteeism from school and work.

There is little evidence for prescribing LTOT in patients with advanced CF, although in the short term some improvement in PaO_2 during sleep and exercise has been demonstrated.[46] The Cystic Fibrosis Foundation guidelines[47] suggest that patients with advanced CF be annually evaluated for exertional hypoxemia, nocturnal hypoxemia, hypercapnia, and PH, as well as recommending oxygen use in patients with an SpO_2 ≤ 88% during sleep or during exercise. The British Thoracic Society guidelines[6] recommend that the indications for LTOT in CF be the same as those in COPD.

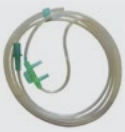
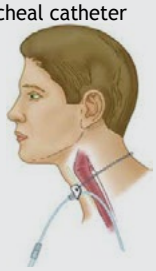
ILDs

COPD and ILDs are the main indications for LTOT.[48] Recent large RCTs of idiopathic pulmonary fibrosis concluded that 21-28% of study participants received supplemental oxygen therapy.[49,50] However, those rates did not differentiate between resting hypoxemia and exertional hypoxemia. A retrospective study of 400 patients conducted in Australia in specialist ILD clinics reported a prevalence of resting hypoxemia of 3.5%.[51]

Definitions of exertional hypoxemia vary widely, but regardless, exertional hypoxemia is common in ILD patients, being more severe in ILD than in COPD when compared with the severity of lung function impairment. In addition, exertional hypoxemia is a marker of poor prognosis for these patients.[52-55] Nocturnal hypoxemia affects approximately 27% of patients, and the association with sleep-disordered breathing may increase this prevalence.[56]

The benefit of LTOT in ILD patients is uncertain. A systematic review[57] found no consistent effects on exertional dyspnea, although exercise capacity

Chart 5. Devices and accessories for long-term home oxygen therapy.[a]

Options	Advantages	Disadvantages
Nasal cannulas • A low O_2 flow rate at a large volume of air • Every 1 L/min adds 3-4% of O_2 to the inhaled air. • For an O_2 flow rate of 1-6 L/min, an FiO_2 of 24-50% 	• Are light • Silicone cannulas are more comfortable than plastic cannulas. • Are more convenient for patients • Do not interfere with speech • Facilitate oral feeding	• O_2 concentration varies depending on the disease and breathing pattern • Variations in FiO_2 depending on the O_2 flow rate (e.g., for an O_2 flow rate of 2 L/min, FiO_2 is 24-35%) • An O_2 flow rate > 4 L/min can cause discomfort. • Can irritate the nostrils • Severe nasal obstruction can interfere with the flow of O_2.
(Simple) face masks • Translucent plastic • Small volume • Fastened by elastic bands 	• Do not irritate or hurt the nostrils • For an O_2 flow rate of 5-10 L/min, an FiO_2 of 35-55%	• Cover the nose and mouth • Interfere with oral communication • Need to be removed before oral feeding • Can cause discomfort and suffocation (claustrophobia)
Other options • Venturi masks  • Nonrebreather masks  • Transtracheal catheter 	• Indicated for situations requiring precise O_2 concentrations (high concentrations in patients with severe hypoxemia and low concentrations in CO_2 retainers) • Increased cost because of the need for higher O_2 flow rates • O_2 flow rates vary depending on the manufacturer; in general, 4-15 L/min for an O_2 concentration of 24-60%. • Widely used in patients with acute respiratory failure requiring high O_2 flow rates • An O_2 flow rate of 10-15 L/min - an FiO_2 of 80-95% (an O_2 flow rate of < 10 L/min can cause the reservoir to collapse) • Improves patient cosmesis and reduces O_2 consumption • Transtracheal insertion carries a small risk of complications. • Can have adverse effects if it remains in the airway for a prolonged period of time • Should not be used in hypersecretory patients	

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] O'Driscoll et al.,[124] Hardavella et al.,[157] the Chest Foundation,[158] and Schwartz et al.[161] Note: at O_2 flow rates of ≤ 5 L/min, the use of a hose of ≤ 30 m does not affect O_2 flow rates or FiO_2.(Aguiar et al.).[162]

improved. Studies on the use of LTOT in ILD patients have a high risk of bias, and it is therefore not possible to estimate the impact of LTOT on survival.[57] Current clinical guidelines have consistently recommended LTOT for ILD patients on the basis of the same criteria as those used for COPD patients.[4,6,58-62]

PH

Precapillary PH is a hemodynamic diagnosis that includes pulmonary arterial hypertension (PAH, group I), PH due to respiratory diseases (group III), and chronic thromboembolic PH (group IV), and can cause hypoxemia.[63] Several pathophysiological mechanisms, such as decreased cardiac output in patients with PH, V/Q mismatch, right-to-left shunt, and decreased oxygen diffusion capacity, are involved in hypoxemia, which may be increased by pulmonary vasoconstriction.[64-66]

A study conducted by Ulrich et al.[64] demonstrated that the use of supplemental oxygen in patients with PAH or chronic thromboembolic PH resulted in benefit

Chart 6. Strategies to improve the efficacy of long-term home oxygen therapy.

- Educate patients on their disease and the role of O_2
  - Emphasize the importance of adhering to pharmacological treatments and using O_2 correctly (at least 15 h/day, including the sleep period)
  - Explain that the outcome of LTOT is an increase in quality of life and life expectancy
  - Advise patients on symptoms of CO_2 retention
  - Advise patients on how to operate the devices
  - Advise patients on how to avoid or reduce the risks of using O_2 (see details in Chart 7)
- Correctly fill out the health department protocols
- Provide patients using a concentrator with a report for exemption from or a discount on electricity bills
- In conjunction with patients and on the basis of current recommendations, personal preferences, availability, and costs, decide on the following:
  - O_2 source: a gaseous O_2 cylinder, a liquid O_2 cylinder, or an O_2 concentrator
  - O_2 delivery interface: a cannula, a catheter, or a mask
  - Need for humidification (strong evidence is lacking)
    - Absence of indication for use of low O_2 flow rates (of < 5 L/min)
    - Use of heat and moisture exchangers (at 32-36°C) in patients requiring high O_2 flow rates and in tracheostomized patients
    - Use of a (non-heated) humidifier bottle (there is no evidence of its benefits, and it increases the risk of infections)
- By means of consultations, home visits, home-made photographs/videos, emails, apps, or social media, monitor and advise on the following:
  - Treatment adherence, by means of direct or indirect evaluation, as follows:
    Talk to patients and their families.
    - Check power consumption (in the case of patients using stationary O_2 concentrators).
    - Check the duration of and time elapsed between refills of stationary cylinders.
    - Read the hour meter (in the case of patients using O_2 concentrators).
    - Check for reduced hematocrit and treatment response.
  - Proper handling and hygiene of O_2 sources and accessories
    - Accessories: wash with soap and water; clean with a water/vinegar solution (10:1) and, subsequently, rinse with hot water; and allow to air dry
    - Change cannulas and masks regularly
    - Clean the concentrator filters in accordance with the manufacturer instructions
  - Select the appropriate O_2 flow rate for target SpO_2
    - Attention to decalibration and variations in flows across flow meters
- Periodically check whether or not patients should continue to receive O_2 therapy, especially in the following cases:
  - In patients with improved clinical control of the disease
  - In those for whom O_2 therapy has been indicated following hospital charge: reevaluate the need for O_2 therapy one month later

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] O'Driscoll et al.,[124] the Chest Foundation,[158] and the American Association for Respiratory Care.[159] LTOT: long-term home oxygen therapy.

in exercise capacity and quality of life. In addition, there was improvement in nocturnal SpO_2 and in sleep disturbances in those with exercise-induced hypoxemia and sleep disorders (sleep apneas and nocturnal hypoxemia). Although the duration of oxygen supplementation was short (up to 5 weeks), it is unknown whether the positive effects of oxygen supplementation during exercise translate to long-term benefits.[67,68] An observational study of PAH concluded that the risk of death was significantly higher among patients with severe DL_{CO} reduction (< 40% of predicted) who did not use supplemental oxygen than among those who did. However, the latter group had more PAH-specific medication use, which constitutes a selection bias.[69]

The use of LTOT in adult patients with Eisenmenger syndrome remains controversial, and there are limited data in the literature. A prospective controlled study[70] showed no impact of nocturnal oxygen use on exercise capacity, disease natural history, or survival in the 2-year follow-up period. Therefore, the use of LTOT is optional in these patients, and its prescription should be individualized.[70]

Recommendations in guidelines on the use of supplemental oxygen in PH are controversial, probably because of the absence of long-term studies.[74] Despite limited evidence, it is suggested that LTOT be prescribed for PH patients with a PaO_2 < 60 mmHg, considering symptomatic benefit and correction of exertional desaturation.[6,25]

Chart 7. Recommendations for the safe use of oxygen.[a]

- Irritation of mucous membranes and drying of secretions
  - Use humidifiers and/or saline nasal gel
- Fires and burns
  - Do not smoke or allow anyone to smoke in the home during O_2 use.
  - Keep away from sources of fire or flame, such as stoves, cigarettes, and candles.
  - Do not use emollients (because of the risk of combustion).
  - Dry hands well after using an alcohol-based hand rub.
- Leaks and explosions
  - Choose companies that follow best practices for the transport and handling of cylinders and, in particular, cylinder valves.
  - Maintenance should be performed by trained professionals only.
  - Allow easy access to and storage of cylinders in the home.
  - Keep cylinders in an upright position in well-ventilated spaces, away from the sunlight and other sources of heat (> 5 meters).
  - Close valves when O_2 is not being used.
  - Avoid hitting, tilting, and dropping the cylinders.
  - Always keep cylinders in the same place unless there is an important reason to move them.
  - Strictly follow the guidelines for handling cylinders, especially when refilling portable liquid O_2 cylinders, because of the risk of frostbite (caused by liquid O_2 at −183°C).
- CO_2 retention
  - Reduce O_2 flow rates in patients presenting with or at risk of CO_2 retention.
    - Maintain an SpO_2 of 90-92%.
    - If necessary, monitor $PaCO_2$ and pH.
- Pulmonary toxicity
  - Avoid high O_2 flow rates, especially at an FiO_2 > 50%.

[a]Based on Hardinge et al.,[6] Jacobs et al.,[20] González-Moro et al.,[25] O'Driscoll et al.,[124] the Chest Foundation,[158] and the American Association for Respiratory Care.[159]

LTOT IN PATIENTS WITH ADVANCED, CHRONIC DISEASES AND IN PALLIATIVE CARE

Promoting early interventions that not only alleviate the symptoms caused by disease progression, but also reduce emergency department visits and hospitalizations and ensure end-of-life care is essential in palliative care planning. Ideally, this requires the participation of a multidisciplinary team consisting of physicians, physiotherapists, nurses, psychologists, and social workers, with appropriate knowledge and training; however, an attending physician with a clear understanding of the patient's condition is capable of managing the disease progression, prioritizing symptom control.[72]

The use of oxygen therapy in palliative care requires the assessment of the causes that can be reversed and of objective criteria such as SpO_2, an overall assessment of the patient's needs, and an individualized treatment plan. This plan should be jointly developed by the health care team, the patient, and his or her caregivers.[73]

LTOT can relieve dyspnea if this is associated with hypoxemia, bearing in mind that dyspnea is a subjective sensation and is often independent of hypoxemia.[4] Symptom control in patients with advanced, chronic diseases is a widely discussed therapeutic resource. Current studies and recommendations demonstrate limited usefulness of oxygen therapy in some situations.[74] In practice, it is observed that the benefits of oxygen therapy are overestimated, whereas its possible risks and limitations are underestimated. An observational study including 114 patients who were near death revealed no benefit from oxygen use, with no difference between administration of oxygen and of medical air for symptom relief when PaO_2 > 55 mmHg.[75] The eventual improvement would be due to air flowing on the face, with trigeminal nerve stimulation and a reduction in dyspnea; therefore, there is no benefit from oxygen therapy in this context. The British Thoracic Society guidelines,[6] for example, recommend that oxygen use be limited to those patients with an SpO_2 < 90% on room air and that there is no role for routine SpO_2 monitoring as long as the patient is comfortable in the last days of life.[76]

The side effects of oxygen therapy include acute hypercapnia with central effects and lung injury due to oxidative stress that generally occurs at high oxygen flows.[77] The use of the oxygen therapy equipment can also lead to activity restriction, dryness of the mucous membranes, and discomfort caused by nasal cannulas

Chart 8. Protocols for the use of long-term home oxygen therapy: key points.

- Assumptions
  - LTOT is provided free of charge by municipal/state health departments via the Brazilian SUS by filling out protocols.
  - Patients and their families should be advised on the disease and the benefits of O_2 therapy, as well as on risk-reducing precautions (see Chart 7).
- Protocol for approval of LTOT

Full patient/legal guardian identification

  - Name, sex, date of birth, level of education, occupation, home address, and telephone number(s)
  - Indication for O_2 therapy, underlying disease, comorbidities, and a list of all medications used

Essential documentation

  - Arterial blood gas analysis
  - A report on the underlying disease, including a description of all relevant test results
  - Copies of the patient's (and legal guardian's) RG (ID card), CPF (individual registration number), and SUS card
  - Tests: X-ray and complete blood count
  - Proof of residence
  - A prescription for O_2 therapy
  - Source of O_2 (gaseous O_2 cylinder or O_2 concentrator via the SUS)
  - Number of L/min (at rest, during exercise, and during sleep)
  - Nasal cannula (roughly equivalent to): $FiO_2 = 21\% + (4 \times O_2$ flow rate)
  - Increase the O_2 flow rate by 0.5-1 L/min during exercise and sleep
  - O_2 delivered by catheter or mask (describe the type of O_2 delivery interface)
  - Therapeutic range for SaO_2 or SpO_2 when an oximeter is available
  - Minimum number of hours of daily use, always including the sleep period
- Periodic evaluations
  - Evaluate treatment adherence.
  - Evaluate clinical improvement and check SpO_2 with and without the use of O_2.
  - Provide clarification and correct errors in use of O_2.

Based on municipal and state protocols. LTOT: long-term home oxygen therapy; SUS: *Sistema Único de Saúde* (Unified Health System); RG: *Registro Geral*; and CPF: *Cadastro de Pessoa Física*.

or face masks.[78] The limitations caused by the use of oxygen therapy should be carefully evaluated by a multidisciplinary health care team, since some of them can have a great impact on the quality of end of life in individuals with advanced disease.[74]

The management of dyspnea in patients with advanced, chronic disease is based on the objective assessment of dyspnea, application of energy conservation techniques, optimization of treatment of the underlying disease and its complications, oxygen therapy when hypoxemia is present, cardiopulmonary rehabilitation, and use of noninvasive ventilation.[78] The use of oral opioids, notably morphine and dihydrocodeine, in doses not exceeding 30 mg/day of morphine or equivalent, has been considered beneficial in the palliation of dyspnea, with no increased risk of respiratory depression, despite adverse effects such as drowsiness, nausea, vomiting, and constipation.[79,80]

LTOT IN POST-COVID-19 PATIENTS

SARS-CoV-2 has infected and caused the death of millions of people worldwide, having a major impact on the health care system in several countries, including the lack of oxygen supply. During the pandemic, some concepts related to oxygen use, such as silent hypoxemia[81-83] and high-flow oxygen therapy,[84,85] were widely cited and discussed. Silent hypoxemia occurred most frequently in the elderly and in people with diabetes; in such patients, the hyperventilatory response to hypoxemia may be dampened. A direct action of the virus in the respiratory center, reducing the response to hyperventilation, is a hypothesis that has yet to be confirmed. A shift of the oxyhemoglobin dissociation curve to the left in infected patients could explain the fact that some patients possess greater tolerance to hypoxemia than others.[81-83]

Many patients with post-COVID-19 syndrome who developed sequelae after hospital discharge required LTOT. One study found that 13.2% of the patients who were discharged from the hospital required LTOT, and that that need decreased progressively as patients clinically recovered.[86] In another study, the risk factors associated with the need for LTOT after hospital discharge of patients with moderate to severe COVID-19 were as follows: being male; being ≥ 50 years of age; and having ≥ 3 comorbidities, especially previous lung disease.[87]

Chart 9. Oxygen therapy during air travel.[a,b]

- Assumptions
  - At sea level: BP = 760 mmHg, FiO_2 = 21%, and PaO_2 = 96-98 mmHg
  - On large aircraft flying at altitudes of up to 45,000 feet (13,716 m)
  - If aircraft cabins were not pressurized, BP and PaO_2 would be very low.
  - When pressurized, aircraft cabin conditions are equivalent to an altitude of 8,000 feet (2,438 m), where BP = 565 mmHg, FiO_2 = 15.1%, and PaO_2 = 53-75 mmHg or SpO_2 = 89-94%.
  - Aircraft cabin air is cooler and drier; many hours spent sitting immobile can cause leg edema and increase the risk of VTE.
  - Sleep and exertion can worsen hypoxemia and dyspnea.
- Absolute respiratory contraindications to air travel
  - Untreated active tuberculosis, pneumothorax < 60 days before, thoracic surgery < 15 days before, and hemoptysis
  - Need for an O_2 flow rate > 4 L/min
- Recommendations for oxygen use during air travel
  - SpO_2 < 92%
  - SpO_2 = 92-95% and ≤ 84% on a 6MWT or HAST
- Recommendations
  - Send a medical report including the ICD code(s) and the MEDIF in advance to the airlines.
  - The MEDIF must be filled in by the patient and his/her physician, being valid for 30 days.
  - Consult the list of portable O_2 concentrator brands approved for in-flight use.
  - Batteries must be enough to power a concentrator for 150% of the duration of the flight.
  - Passengers who have special needs (including auditory, visual, and ambulatory needs) and who travel frequently can fill out an FREMEC at an IATA member airline (the FREMEC is valid for one year).
  - Patients should pack their prescriptions and both their regular and exacerbation medications in their carry-on baggage.
  - Patients should request an aisle seat near a lavatory in order to reduce the need for moving around and improve humidity.
  - Patients should remain well hydrated during the flight and avoid the use of sedatives and alcoholic beverages.
  - Given that airports do not provide O_2, the airline should be informed in advance about the need for O_2 use outside the aircraft.
  - Patients must travel with a companion (see rules regarding seat discount).

BP: barometric pressure; VTE: venous thromboembolism; 6MWT: six-minute walk test; HAST: hypoxia altitude simulation test; ICD: International Classification of Diseases; MEDIF: Medical Information Form; FREMEC: Frequent Traveller's Medical Card; and IATA: International Air Transport Association. [a]Based on Ahmedzai et al.,[146] Sponholz Araújo,[151] Stoller J,[152] and the Brazilian National Civil Aviation Agency.[154] [b]See specific guidelines: Decree no. 4.794/SPO, issued on April 15, 2021 by the Brazilian National Civil Aviation Agency, and airline recommendations.

National and international guidelines on LTOT do not have specific guidelines for hospital discharge after SARS-CoV-2 infection. A task force of the European Respiratory Society/American Thoracic Society (ATS)[88] recommends that hospitalized patients with COVID-19 be evaluated for the need for oxygen supplementation at rest and during exercise, since progressive improvement in gas exchange is expected; however, some patients will require oxygen after hospital discharge. Another possibility is the presence of desaturation only during exercise, and therefore the need or absence of need for oxygen supplementation should be assessed.[88] The detection of decreased SpO_2 justifies the investigation of previously unknown pulmonary and cardiovascular comorbidities. Early reassessment after hospital discharge is recommended because the need for LTOT may be short-lived.[88]

LTOT IN PEDIATRIC PATIENTS

The initiation, continuation, and discontinuation of oxygen therapy in children have relevant particularities. Therefore, recommendations for adults do not apply to children. The main differences between LTOT in children and adults are as follows[89-93]:

- Physical growth and neurological development should be considered.
- The course of some diseases that cause hypoxemia in children is usually favorable; therefore, many children require LTOT only for a limited period of time.
- Most clinical conditions are peculiar to this age group, although the indications for LTOT in older children and adolescents may be similar to those in adults.
- The prescribing and monitoring of oxygen use are based on pulse oximetry rather than on arterial blood gas analysis.

Chart 10. Long-term home oxygen therapy. International guideline recommendations.[a]

Guidelines	Notes
LTOT (O_2 > 15 h/day) for COPD accompanied by a PaO_2 of ≤ 55 mmHg	
2015 BTS - Improves survival and pulmonary hemodynamics	RC - A
2020 ATS - or an SpO_2 of ≤ 88% (oximeter)	strong RC/mod QE
2020 SEPAR - Improves survival and quality of life	con RC/high QE
LTOT (O_2 > 15 h/day) for COPD accompanied by a PaO_2 = 56-59 mmHg	
2015 BTS - In case of peripheral edema, polycythemia (Ht ≥ 55%), or PH	RC - A
2020 ATS - SpO_2 = 89% + edema, Ht ≥ 55%, or cor pulmonale	strong RC/mod QE
2020 SEPAR - In case of RVF, PH, or polycythemia	con RC/mod QE
O_2 during exercise for COPD accompanied by an SpO_2 of ≤ 88% during physical activity	
2015 BTS - Do not recommend short-term O_2 therapy before or during exercise	RC - A
2020 ATS - In case of increased hypoxemia on exertion (a PaO_2 of ≤ 55 mmHg or = 56-59 mmHg + edema, Ht ≥ 55%, or cor pulmonale	cd RC/mod QE
2020 SEPAR - Can improve quality of life Can be useful during rehabilitation programs	weak RC/low QE weak RC/mod QE
O_2 during sleep in patients with COPD	
2015 BTS - Not recommended if criteria for LTOT are not met	RC - A
2020 ATS - Not evaluated	--
2020 SEPAR - If SpO_2 < 90%/≥ 30% of the total sleep time + RVF or polycythemia	con RC/high QE
O_2 for chronic diseases similar to COPD	
2015 BTS - CF, ILD, and advanced HF if PaO_2 ≤ 55 mmHg or ≤ 59 mmHg + edema, PH, or polycythemia	RC - D
2020 ATS - ILD accompanied by a PaO_2 of ≤ 55 mmHg (or an SpO_2 of ≤ 88%) or a PaO_2 = 56-59 mmHg (or an SpO_2 of ≤ 89%) + edema, Ht ≥ 55%, or cor pulmonale	strong RC/very low QE
2020 SEPAR - no comments on it	--
O_2 for palliative care	
2015 BTS - Not recommended for patients without hypoxemia or with mild hypoxemia	RC - A
2020 ATS - Not evaluated	--
2020 SEPAR - Not recommended for patients without hypoxemia[37]	--
Other issues	
2020 ATS - LTOT should not be prescribed for COPD patients with moderate hypoxemia (SpO_2 = 89-93%).	cd RC/low QE

LTOT: long-term home oxygen therapy; BTS: British Thoracic Society; ATS: American Thoracic Society; SEPAR: *Sociedad Española de Neumologia y Cirurgia Torácica*; Ht: hematocrit; PH: pulmonary hypertension; RVF: right ventricular failure; CF: cystic fibrosis; ILD: interstitial lung disease; HF: heart failure; RC: recommendation; QE: quality of evidence; con: consistent; mod: moderate; cd: conditional; D: based on consensus opinion. [a]2015 BTS: Hardinge et al.[6]; 2020 ATS: Jacobs et al.[20]; and 2020 SEPAR: González-Moro et al.[25]

- Specific equipment is required to allow for low oxygen flows.
- Many children require oxygen therapy overnight only, requiring fewer hours than those normally prescribed in adult LTOT.
- Periods such as physical activity (which includes bathing), sleep, and even feedings can lead to drops in saturation; therefore, provision of higher oxygen flow rates on these occasions should be individualized.
- All children require supervision from an adult.
- Provision of oxygen may be necessary at school for school-age children.

Conditions that most often lead to the need for LTOT in pediatric patients include bronchopulmonary dysplasia (BPD), CF, bronchiolitis obliterans, ILDs, and sickle cell disease. Because BPD is exclusive to pediatric patients and because LTOT has some peculiarities in pediatric CF patients, we chose to address these two conditions in more detail.

BPD

The most current definition of BPD is a diagnosis based on persistent radiographic changes of the lung parenchyma in preterm infants born at ≤ 32 weeks of gestational age or at 36 weeks of corrected gestational age who require ventilatory support for three or more days to maintain arterial saturation at 90-95%.[94,95]

BPD is the most common indication for LTOT in children and occurs in approximately 40% of very low birth weight newborns (< 1,000 grams).[93,96-98] Its incidence has not decreased over the years, precisely because of important advances in neonatal care, which has increasingly allowed the survival of extremely preterm infants.[94-97]

The benefits of LTOT include improvement in physical growth, neurological development, and sleep pattern, as well as a reduction in airway resistance, pulmonary artery pressure, risk of sudden death, and nocturnal awakenings. In addition, keeping the child at home

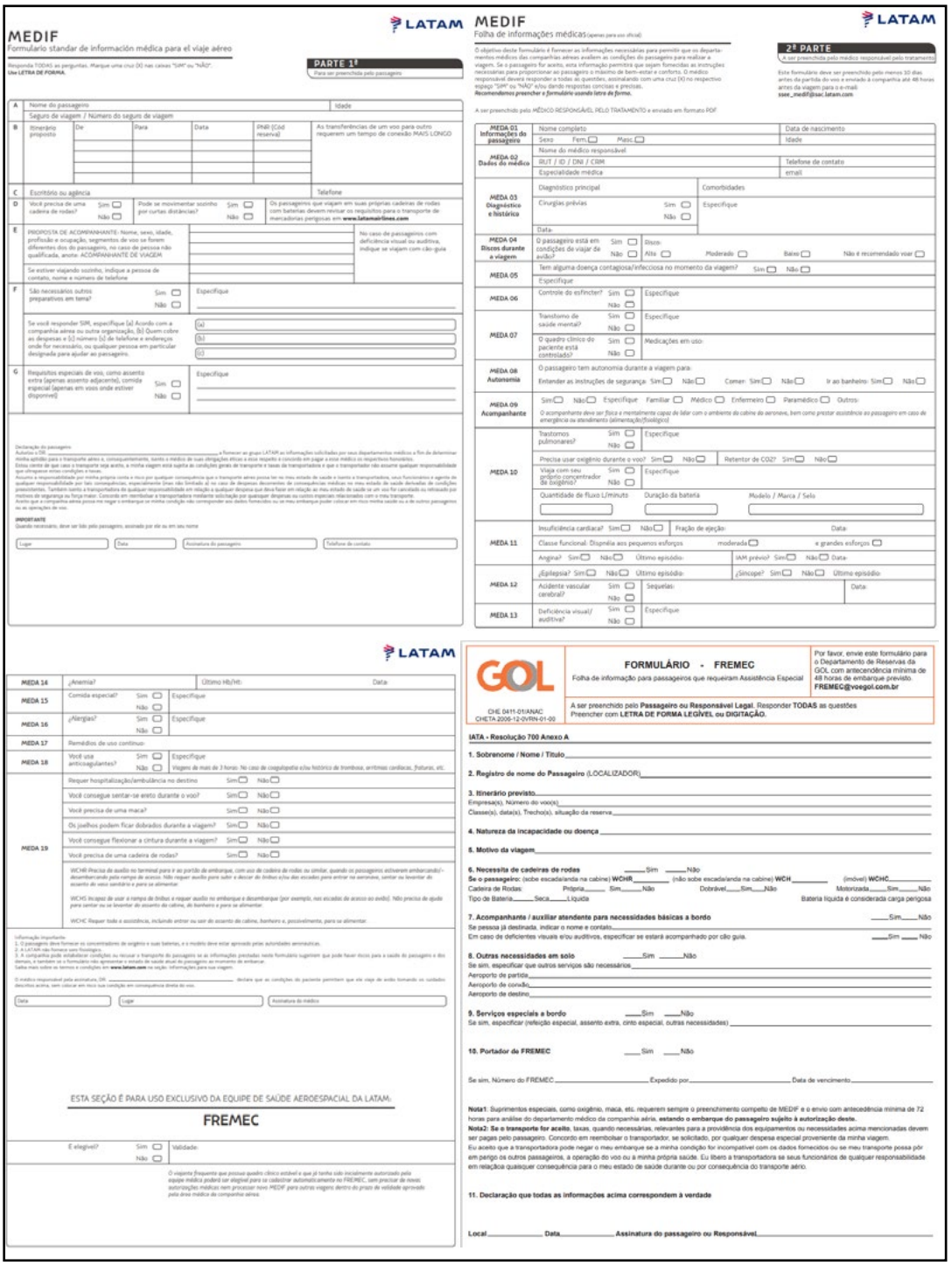


Figure 1. Examples of medical certificates requested by airlines to prove that the passenger is fit to fly: the Medical Information Form (MEDIF) and the Frequent Traveller's Medical Card (FREMEC).

with the family allows a better emotional bond and reduces the risk of nosocomial infections.[89,93]

LTOT is indicated for the patient who is clinically stable, remains oxygen dependent (SpO_2 ≤ 92% on room air), and does not have hypercapnia. Two important studies[99,100] demonstrated that maintaining SpO_2 at > 95% was related to a worse outcome, with the need to continue LTOT for a longer period. Since then, maintaining SpO_2 at > 95% has been avoided.[99,100] In contrast, another study[101] compared an SpO_2 target of 85-89% with that of 91-95% for children born before 28 weeks of gestation and demonstrated

that an SpO_2 target of < 90% was associated with an increased risk of death before discharge, resulting in the early discontinuation of the study.[101] Current recommendations are that SpO_2 should be between 90% and 95%, without frequent fluctuations during sleep or feedings.[102,103]

LTOT should be considered for patients with BPD who were born at ≥ 36 weeks of corrected gestational age, are clinically stable, and experience a weight gain of 20 grams per day.

The initial oxygen flow rate is 1-2 L/min, maintaining SpO_2 between 92% and 95%. A decrease in oxygen flow may be considered after 4 weeks if the patient is stable and continue experiencing adequate weight gain. The oxygen flow rate should be reduced by 0.25-0.1 L/min, initially while the child is awake, as long as SpO_2 remains at ≥ 92%.[97]

CF

The prescribing of LTOT in CF patients should be individualized, and, in general, children and adolescents should receive it via a nasal cannula, with pertinent adaptations, as in the case of patients with a tracheostomy.[104] Oxygen therapy will reduce dyspnea and delay the onset of *cor pulmonale*. School children and adolescents with a PaO_2 ≤ 55 mmHg or an SpO_2 ≤ 88% should receive oxygen at the lowest flow rate possible to maintain SpO_2 at > 90%.[90,104] Recent publications by the ATS recommend considering the prescription of LTOT for pediatric CF patients who maintain saturation at 90-93% but have exertional dyspnea.[89,90] The prescription of LTOT for infants and preschool children is indicated to maintain SpO_2 at ≥ 93%, in a manner similar to that in patients with BPD.[92]

Weaning from LTOT in pediatric patients

Weaning from LTOT may occur with lung growth and maturation, and possible improvement of the lung disease. The physician should clinically evaluate the patient and make sure, on the basis of SpO_2 measurements, that weaning is feasible.[89,90] Weaning will be adjusted weekly by gradually reducing oxygen flow or by discontinuing LTOT for increasingly longer periods of the day, maintaining weekly to monthly medical visits to ensure safe weaning.[89] Infants receiving flows of up to 0.1 L/min, preschool children receiving flows of 0.1 to 0.25 L/min, and older children receiving flows of 0.25 to 0.5 L/min may be able to discontinue LTOT. After oxygen is discontinued, it is strongly suggested that nocturnal oximetry with an appropriate pediatric device be performed.[89,90] The LTOT equipment must remain in the patient's home for as long as necessary to ensure his or her safety[89]; the national recommendation suggests a period of at least 3 months after LTOT discontinuation.[92] Then, monitoring by oximetry should be performed on two occasions one month apart, and, if oximetry values remain adequate, the LTOT equipment can be removed from the patient's home.[92]

LTOT IN PATIENTS WITH SLEEP-DISORDERED BREATHING

Sleep-disordered breathing is characterized by repetitive sleep-related respiratory events, causing intermittent hypoxemia and sleep fragmentation, and includes OSA, central sleep apnea (CSA), and sleep-related hypoventilation; OSA is the most prevalent form of sleep-disordered breathing.[105]

The intensity and frequency of intermittent hypoxemia during recurrent episodes of apnea/hypopnea during sleep commonly lead to cardiovascular, metabolic, and neurocognitive consequences, impacting morbidity and mortality.[106]

Positive airway pressure (PAP) is the standard therapy for maintaining upper airway patency and correcting intermittent hypoxemia.[105,107] However, although PAP is an extremely effective treatment, PAP adherence is limited.[105,107,108]

OSA

A systematic review and meta-analysis of RCTs showed the superiority of CPAP over nocturnal oxygen use in reducing the apnea-hypopnea index (AHI) in individuals with OSA.[109] However, previous studies have documented an increase in the duration of obstructive respiratory events during nocturnal oxygen use.[38,110] In a recent meta-analysis, supplemental oxygen therapy, when compared with CPAP, was less efficient in reducing the AHI, the duration of SpO_2 < 90%, and systemic blood pressure, as well as in improving sleep quality.[111] Oxygen can be used in conjunction with PAP therapy when SpO_2 remains at ≤ 88% for at least 5 min despite adequate titration and complete control of obstructive events (initiate oxygen at 1 L/min and titrate to maintain SpO_2 at 88-94%).[112]

CSA

Previous studies have reported the beneficial effect of oxygen supplementation on CSA associated with Cheyne-Stokes respiration in individuals with congestive heart failure (CHF).[113,114] Two meta-analyses compared the effect of CPAP, adaptive servo-ventilation (ASV), and oxygen supplementation on the AHI and on left ventricular ejection fraction (LVEF) in CHF patients with CSA associated with Cheyne-Stokes respiration.[115,116] The first meta-analysis,[115] which included 919 patients, showed that ASV was most likely to reduce the AHI, followed by oxygen supplementation and CPAP. In the second meta-analysis,[116] which included 951 patients, CPAP and ASV, in contrast to nocturnal oxygen, were found to be equally efficient in improving LVEF. Although ASV can improve the AHI and LVEF, one study observed increased mortality in CHF patients with CSA and an LVEF ≤ 45%.[117] Nocturnal oxygen therapy may not eliminate obstructive events that often coexist with central events in patients with CHF.[118] In patients with CSA, nocturnal oxygen effectively reduces the AHI secondary to CSA and improves SpO_2, and may serve as an alternative to PAP therapy.[108,119]

However, long-term studies assessing the impact of LTOT on CSA are lacking.

COPD-OSA overlap syndrome

The COPD-OSA overlap syndrome causes more severe nocturnal hypoxemia than either COPD or OSA alone, leading to a poor prognosis.[120,121] Nocturnal oxygen therapy may be indicated in COPD patients when nocturnal hypoxemia persists despite appropriate treatment.[38,108,110] However, because oxygen suppresses the hypoxic respiratory drive, it may contribute to prolonging apnea duration, leading to hypercapnia and acidosis in patients with OSA, especially those with COPD-OSA overlap syndrome or hypoventilation.[38,108,110] Current treatment of patients with COPD-OSA overlap syndrome includes regular CPAP therapy, noting that CPAP is indicated in severe or moderate OSA when there are associated symptoms or significant nocturnal hypoxemia. There is no indication for CPAP in mild OSA.[120]

In observational studies, patients with COPD-OSA overlap syndrome who were treated with CPAP had survival rates comparable to those of patients with COPD alone, whereas those with this overlap syndrome who were not treated with CPAP had higher mortality.[121]

Obesity hypoventilation syndrome

The obesity hypoventilation syndrome (OHS) comprises the triad of obesity, gas exchange abnormalities (hypercapnia), and absence of alternative explanations for hypoventilation. The most recent publications by the ATS and the European Respiratory Society recommend that CPAP, rather that BiPAP, be used as first-line treatment for outpatients with OHS and severe OSA, an association that is present in more than 70% of patients with OHS.[122,123] However, noninvasive ventilation is preferred in a minority of the patients with OHS who do not have OSA or have milder forms of OSA (approximately < 30%). Oxygen therapy alone in OHS should be avoided because of its detrimental effect on ventilation and the risk of it precipitating hypercapnic respiratory failure.[123]

OXYGEN THERAPY DURING EXERCISE AND PULMONARY REHABILITATION

Tissue oxygenation depends on factors including the transfer of oxygen from the atmosphere to the lungs; adequate oxygen delivery to peripheral tissues through hemoglobin transport and adequate blood flow; oxygen delivery to the mitochondria for aerobic ATP synthesis; and muscle oxygen utilization.[124]

The main effects that oxygen therapy during exercise has on COPD and ILD are as follows: a central effect, preventing reduced cerebral oxygenation; a ventilatory effect, with decreased respiratory drive resulting from reduced carotid chemoreceptor stimulation and reduced dynamic hyperinflation; a cardiovascular effect, achieved through pulmonary vasodilation, increased cardiac output, and decreased pulmonary artery pressure; and a muscle effect, with reduced muscle dysfunction, reduced lactic acid production, and reduced activity of muscle metaboreceptors, reducing respiratory drive.[125-127] Modulation of these mechanisms can improve symptoms such as dyspnea and fatigue, as well as improving quality of life and exercise capacity, particularly during rehabilitation. However, controversy remains in the literature regarding oxygen therapy, especially for normoxemic patients with or without exercise-induced hypoxemia.

COPD

Exercise-induced hypoxemia is common in patients with COPD, being found in almost half of patients referred for pulmonary rehabilitation (PR). In general, these patients do not tolerate high-intensity exercise, and a reduction in training intensity is required in many cases; this, however, could limit the efficacy of PR.[128] In a study evaluating acute oxygen therapy, 124 patients with moderate to severe COPD were divided into three groups: normoxemic patients, patients with resting hypoxemia, and patients with exercise-induced hypoxemia; they underwent a six-minute walk test (6MWT) while receiving oxygen or compressed air.[129] The two groups of patients with hypoxemia benefited from oxygen therapy delivered by nasal cannula (NC), with increased exercise capacity, although the difference was not clinically significant (> 30 m).[129] In a study comparing the effects of oxygen and compressed air delivered during exercise training in normoxemic patients without exercise-induced hypoxemia (n = 29), oxygen therapy resulted in increased training intensity and exercise capacity (cycle ergometer endurance: 14.5 min vs. 10.5 min; $p < 0.05$) during a PR program.[130] It is of note that oxygen responders present with higher oxygen desaturation[131] and lower exercise capacity[132] at baseline or a > 10% increase in the distance covered at baseline.[132]

In a multicenter study involving 111 patients with moderate to severe COPD and exercise-induced hypoxemia (an SpO_2 of < 90% during the 6MWT), oxygen therapy did not result in an increase in exercise capacity or quality of life when compared with supplemental compressed air. It is of note that both groups benefitted from exercise training, with significant increases in exercise capacity and quality of life.[133] However, the question remains whether the proposed level of training intensity was actually achieved.[134] In another study, patients with severe to very severe COPD and resting hypoxemia (n = 50) received oxygen therapy (constant oxygen flow rates vs. automated oxygen titration).[135] Automated oxygen titration resulted in improvements in oxygenation, walking endurance time, SpO_2, PaO_2, and dyspnea, with no impact on $PaCO_2$. In comparison with nonresponders, those who responded to automated oxygen titration tended to have lower lactate values, less leg fatigue at the end of the endurance test, and less dyspnea.[135] In a study comparing oxygen therapy delivered via a Venturi mask and high-flow nasal cannula (HFNC)

oxygen therapy during exercise training, both groups of patients benefitted from the exercise training program, with significant improvements in exercise capacity, symptoms, and quality of life.[136]

In a recent systematic review and meta-analysis of 7 studies evaluating oxygen therapy and PR, it was shown that oxygen therapy delivered during PR did not improve exercise capacity, dyspnea scores, or quality of life, although the level of evidence was weak, primarily because of the heterogeneous interventions across studies.[137]

Despite the conflicting results across studies, international guidelines state that patients receiving LTOT should receive oxygen therapy during exercise training and increase the flow as the demand for oxygen increases during exercise.[6,20,25] In some cases, there might be a need for a formal assessment demonstrating improvement in exercise tolerance with the addition of acute oxygen therapy.[6,20,25]

ILD

Patients with ILD have reduced exercise tolerance (as assessed by the 6MWT), maximal oxygen uptake, and endurance time. Reduced exercise capacity is associated with poor survival. In a study comparing acute oxygen therapy and supplemental compressed air in patients with mild to moderate ILD (n = 72) and exercise-induced hypoxemia, oxygen was found to increase endurance time, reduce desaturation, and reduce the number of symptoms.[138] Respondents were those who achieved a lower nadir SpO_2 on the 6MWT performed when receiving compressed air at baseline[138]; a similar result was found when an FiO_2 = 50% was compared with supplemental compressed air.[139]

It is known that patients with ILD can have significant desaturation (e.g., an SpO_2 of < 80% on exertion), and it is not always possible to maintain an SpO_2 > 90% with the use of oxygen therapy delivered by NC. In a study comparing oxygen therapy delivered by a conventional NC and oxygen therapy delivered by a pendant NC with an incorporated reservoir (Oxymizer; Drive DeVilbiss Healthcare, Port Washington, NY, USA) in patients receiving ambulatory oxygen therapy (n = 21), there was improvement in exercise tolerance, but no impact on dyspnea.[140] Although oxygenation improved, the improvement was not sustained during exercise, even with the use of the Oxymizer.[140] In a study of patients with severe ILD (n = 25) tested on room air, receiving oxygen therapy via NC at 4 L/min, or receiving HFNC oxygen therapy with an FiO_2 of 50% at 30-50 L/min (heated to 34°C and humidified), those who received HFNC oxygen therapy showed higher endurance time than did those in the other two groups, with HFNC oxygen therapy being associated with delayed oxygen desaturation kinetics, impaired chronotropic response, reduced perception of dyspnea, and reduced ratings of perceived leg fatigue.[141] In comparison with an FiO_2 of 21%, hyperoxia (an FiO_2 of 30-60%) resulted in increased endurance time, decreased ventilation, reduced perception of dyspnea,[142] and significantly improved muscle oxygenation as assessed by fatigability, with reduced leg discomfort during exercise.[127]

Although oxygen therapy has been found to increase exercise capacity, a systematic review showed that oxygen therapy has no impact on dyspnea during exercise in patients with ILD.[57] Because patients with ILD require high oxygen flow rates in many cases, it is important to select the most appropriate oxygen delivery interface (an NC or a simple face mask, for example), and when a higher oxygen concentration is required, other devices should be evaluated, including nonrebreather masks and HFNC, the latter being selected and used in accordance with institutional protocols.

PH

The benefits and safety of PR in patients with PH have been reported, particularly in the last 15 years. In the guidelines for PR in patients with PH,[143] based on published protocols, oxygen was delivered as needed, and desaturation was considered an adverse event in 16 (2.4%) of the 674 patients included in the study. In an evaluation of 519 patients included in different studies, exercise training was generally based on ~60% of the maximum HR (which should not exceed 120 bpm) and an SpO_2 > 85-90%. An oxygen desaturation of < 85-90% or an HR > 120 bpm were used as criteria to adjust training intensity, resulting in early exercise termination or a reduction in training intensity.[144,145]

OXYGEN DURING AIR TRAVEL

Commercial aircraft flights can reach altitudes of up to 45,000 feet (13,716 m), resulting in major reductions in barometric pressure and PaO_2.[146] Aircraft cabins are pressurized to an altitude of 8,000 feet (2,438 m), and, at this altitude, FiO_2 inside the aircraft is 15.1%; in a healthy individual, depending on his/her age and minute ventilation, PaO_2 and SaO_2 decrease to 60-75 mmHg and 89-94%, respectively.[146-148]

In situations of hypobaric hypoxia, an adequate PaO_2 is maintained through an increase in minute ventilation, HR, and cardiac output, as well as pulmonary vasoconstriction with redistribution of blood flow to apical regions, affecting V/Q. Although most individuals tolerate these changes well, some can experience dyspnea, sleepiness, cognitive changes, fainting, and chest pain.

Patients with chronic lung disease, especially those on LTOT or with borderline SpO_2 levels, as well as patients with other diseases that are accompanied by hypoxemia, will experience worsening hypoxemia and can present with clinical manifestations during flights.[147-150] Therefore, patients at risk of hypoxemia during air travel should be evaluated for the need for oxygen therapy. The use of LTOT, the presence of comorbidities, and reports of respiratory symptoms

such as dyspnea, cough, and chest pain during previous flights should be investigated. Patients should only travel when they are in a stable phase of their disease.[148] In addition, during flights, passengers remain immobile for long periods of time and are exposed to low temperatures and dry air, all of which are factors that increase the risk of exacerbations and other complications, such as venous thromboembolism, thus reinforcing the importance of maintaining an adequate SpO_2 during air travel.[151]

Patients with an SpO_2 > 95% on room air can fly without supplemental oxygen; however, those with an SpO_2 of ≤ 92% should receive supplemental oxygen during air travel. Patients with an SpO_2 between 92% and 95% should undergo a 6MWT or a hypoxia altitude simulation test, the latter being rarely available in Brazil. Patients in whom SpO_2 remains ≤ 84% during either of the aforementioned tests will also require supplemental oxygen during air travel.[149,150] A hypoxia altitude simulation test simulates an aircraft cabin with decreased barometric pressure and FiO_2. Ideally, the test should be performed in a hypobaric chamber; however, hypobaric chambers are scarcely available, and test results are unreliable when the test is performed in a normobaric chamber.[149,150]

Patients who require an oxygen flow rate > 4 L/min in order to correct hypoxemia should be discouraged from flying, and, if they do fly, they should use aeromedical transport.[151] It is of note that these recommendations are primarily based on studies of patients with COPD and are extrapolated to other respiratory diseases.[152,153]

After performing an evaluation, the attending physician must fill out a Medical Information Form, which is provided by airlines and which, in addition to including other relevant information, states that the patient is fit to fly provided that he/she receives the required oxygen flow rate. The form should be filled out at least 72 h before the flight so that there is enough time to submit it to the airline. Patients should plan their trips in advance because time for approval varies across companies.[151-153]

On the aircraft, oxygen therapy can be delivered via oxygen supplied by the airline (an oxygen cylinder or concentrator) or via the patient's own portable oxygen concentrator, provided that it has been approved for in-flight use. While staying at airports, patients must use their own portable oxygen concentrators. The Brazilian *Agência Nacional de Aviação Civil* (National Civil Aviation Agency) has recently published supplementary guidelines on the use of portable oxygen concentrators on commercial aircraft.[154] The most important points are as follows: only brands approved for in-flight use are allowed; neither concentrators nor batteries can be checked at the airline counter; and batteries must be enough to power a concentrator for at least 150% of the duration of the flight. Unfortunately, commercial airlines do not have homogeneous rules regarding how the aforementioned form should be or the supply of oxygen. Attending physicians must seek information on company policies and procedures in order to provide appropriate patient guidance (Chart 9 and Figure 1).

PRECAUTIONS WHEN PRESCRIBING LTOT

Some precautions should be taken when prescribing LTOT. Patients should receive continuing education and training in oxygen device use, safety, and self-management. Physicians prescribing LTOT should be prepared to do the following: a) determine the objective of and need for LTOT by means of arterial blood gas analysis; b) fill out reports correctly and adhere to municipal or state protocols; c) select a qualified supplier of durable medical equipment; d) titrate oxygen on different occasions (e.g., at rest, during activities of daily living, during sleep, on exertion/during exercise, during trips, and during exacerbations) in order to determine the oxygen flow rate required to maintain an SpO_2 > 90%; e) test the flowmeter, because the oxygen flow rate being displayed might be different from that which is actually being supplied; f) prescribe the most appropriate oxygen flow rate for each specific situation, the minimum duration of use, a variety of sources of oxygen supply, and necessary accessories; g) reassess periodically the need for LTOT for prescription renewal/change; and h) educate patients and their families on the correct use of LTOT, focusing on the importance of treatment adherence. The recommendations are summarized in Charts 1-7 (on practical aspects of prescribing oxygen) and Chart 8 (on the protocol for prescribing oxygen), as well as in Chart 9 and Figure 1 (on air travel).

FINAL CONSIDERATIONS

The use of LTOT became widespread beginning in the 1980s. Despite the scarcity of studies and the number of unanswered questions, the benefits of LTOT were quickly disseminated, and several pulmonology societies around the world began to recommend the use of LTOT. The recommendations herein reflect an integration of current and previously established evidence—with LTOT being prescribed for patients with severe resting hypoxemia in order to improve survival and quality of life—supported by studies of patients with COPD. Existing evidence suggests that LTOT should not be prescribed for COPD patients with moderate resting hypoxemia. Oxygen prescription for ILD patients with severe resting hypoxemia is strongly recommended. Evidence is still lacking on the role of LTOT in other lung diseases, such as PH, and on the use of LTOT during sleep and during physical activity. Future studies should evaluate the safety of the shared decision between patients and their physicians regarding LTOT and the best approach to discontinuing LTOT in patients without severe resting hypoxemia.

It should be noted that LTOT programs have high costs and that it is important to prescribe LTOT

correctly so that patients can really benefit from it, achieving the expected results in the medical, social, work, and family realms.[6,19,20,25] We analyzed in detail the recommendations in the three most recent international guidelines on LTOT,[6,20,25] and they are summarized in Chart 10. Although we agree with the recommendations, we emphasize the need for further studies, particularly those focusing on chronic diseases other than COPD.

AUTHOR CONTRIBUTIONS

All authors participated in all stages of the study (including the planning of the study and the writing, reviewing, and revising of the manuscript) and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Pulmonary complications after hematopoietic stem cell transplantation in children: a functional and tomographic evaluation

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TO THE EDITOR,

Hematopoietic stem cell transplantation (HSCT) is the treatment of choice for neoplastic and non-neoplastic diseases in children,[1,2] and despite advanced supportive care and specific treatments, pulmonary complications still occur in a large proportion of all hematopoietic stem cell recipients, accounting for considerable morbidity and mortality.[1,2,4]

Etiologically, these complications can be organized according to the time elapsed since transplantation. In the pre-engraftment phase (first 30 days after the procedure), non-infectious complications and fungal pneumonia are more common. In the early stage (first 100 days), viral infections are frequent, especially cytomegalovirus, although non-infectious complications, such as pulmonary edema and idiopathic pneumonia syndrome, can also be observed. In the late stage (after the first 100 days), the main complications are associated with chronic graft-versus-host diseases (GVHD), such as bronchiolitis obliterans (BO) and BO with organizing pneumonia.[1-4]

Pulmonary function tests (PFTs) can help identify the level of deterioration in the post-HSCT period.[7] Although computerized tomography (CT) scanning is the method of choice for detecting pulmonary abnormalities, CT scan findings are generally nonspecific and require clinical and temporal correlations based on the patient's immunological status.[5,6,8]

A retrospective review was performed on all the under 14-year-old patients who received HSCT at a referral center from 2013 to 2017, regardless of the underlying diseases that prompted the indication for transplantation. The study was approved by the Ethics Committee for Research Involving Human Beings of CHC-UFPR, under protocol number CAAE: 87629118.3.0000.00.

One hundred and sixty-one patients were transplanted in the analyzed period and had their medical records scrutinized. According to Table 1, one hundred and six patients (65.8%) were male, and the mean age was 7.9 ± 4 years old. Additionally, 143 (88.8%) received a single transplant, 14 (8.7%) received two transplants, and 4 (2.5%) received three transplants. Among the 143 single transplant patients, 92 (57.1%) had non-related donors.

After HSCT, 44 (27.3%) patients sustained 69 events of pulmonary complication. Of these, 26 patients (59.1%) had one pulmonary complication, 13 (29.5%) had two, 3 (6.8%) had three, and 2 (4.5%) had four.

Post-transplant PFT was conducted in 79 (49.1%) children, 35 (44.3%) of whom had functional changes identified at clinical follow-up. Nonspecific ventilatory defects were found in 52 (65.7%) patients, while 20 (25.7%) had mild obstructive ventilatory disorder, 2.9% had severe obstructive ventilatory defects, and 5.7% confirmed restrictive ventilatory defects.

Chest CT was performed in 75 (46.6%) patients in the post-transplant follow-up, 61 (81.3%) of which presented abnormalities. The findings and frequencies were nodules in 52.5% of the cases; atelectasis in 34.4%; ground-glass opacification in 34.3%; mosaic attenuation patterns in 27.9%; ground-glass halo nodules in 23%; bronchial thickening and consolidation, both in 16.4%; lymph node/lymphadenomegaly in 14.8%; tree-in-bud patterns in 11.5%, and other findings (pleural effusion, interlobular septal thickening, and bronchiectasis) in 50.8%.

Chronic pulmonary disease was observed in six (3.7%) patients, three with diagnoses of pulmonary veno-occlusive disease and three with bronchiolitis obliterans (BO).

Death as an outcome occurred in 31 (19.3%) cases. The cause was predominantly pulmonary in nine (29%) of the deaths, which included invasive aspergillosis in three (33.3%), cytomegalovirus pneumonitis in three (33.3%), herpetic pneumonia in one (11.1%), both aspergillus and cytomegalovirus pneumonitis in one (11.1%), and undefined respiratory failure in one (11.1%).

There were no significant differences concerning age, sex, or donor type among patients who had developed pulmonary complications after HSCT. A significant association regarding the presence of pulmonary complications was observed in those undergoing more than one transplant (p=0.009).

No significant associations were found between the occurrence of chronic pulmonary disease (pulmonary veno-occlusive disease or BO) and the variables analyzed (age, sex, type of donor, and number of transplants).

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Table 1. General characteristics of transplanted pediatric patients from 2013 to 2017.

Variables (N = 161)	n (%)
Sex	
Male	106 (65.8)
Female	55 (34.2)
Hematopoietic stem cell transplant	
Single	143 (88.8)
> 1 transplant	18 (11.2)
Underlying disease	
Fanconi anemia	54 (33.5)
Severe aplastic anemia	27 (16.8)
Leukemias / lymphomas	27 (16.8)
Wiskott-Aldrich Syndrome	19 (11.8)
Other inborn errors of immunity*	17 (10.6)
Congenital Dyskeratosis	7 (4.3)
Type of Transplantation	
Autologous	0
Allogeneic	161 (100)
Donor	
Exclusively matched unrelated	92 (57.1)
Exclusively matched related	60 (37.3)
Unrelated and related	9 (5.6)
Chest CT scan**	
Normal	14 (18.7)
Pulmonary changes	44 (58.6)
PFTs***	
Normal	44 (55.7)
Altered	35 (44.3)
Pulmonary complications	
Yes†	44 (27.3)
No	117 (72.7)
Chronic pulmonary diagnosis	6 (3.7)
Death	31 (19.3)
Total	161

*Mucopolysaccharidosis, X-linked adrenoleukodystrophy.**Percentage calculated on the total number of patients who performed chest CT (n=75). ***Percentage calculated on the total number of patients who performed pulmonary function tests (n=79). †Pulmonary complications: Viral infection (26%), Fungal infection (20.2%), Small airway disease (14.4%), Pulmonary edema (11.5%), Pulmonary hypertension (7.2%), Pulmonary veno-occlusive disease (4.3%), Bacterial infection (2.8%), Idiopathic pneumonia (2.8%), Pulmonary hemorrhage (2.8%), Atypical infection (2.8%), Diffuse alveolar damage (2.8%), Drug reactions (1.4%).

This study aimed to describe the leading post-transplant pulmonary complications in children by analyzing the patients' characteristics and the possible factors associated with the occurrence of such complications.

Viral and fungal infections were the most prevalent causative agents, contradicting other studies[2-4,9] in which bacterial infections were the most common. Such divergence may be related to the large number of autologous transplants in other studies; our study included only allogeneic transplants, where opportunistic infections are more common due to prolonged immunosuppressive therapy.

As for non-infectious post-HSCT complications, non-cardiogenic pulmonary edema was also prevalent. Usually, this condition can be related to pulmonary toxicity induced by drugs, sepsis, aspiration, hemoderivative transfusion, acute GVHD, or heart disease after total body irradiation.[1,2,4]

Changes in pulmonary function were seen in approximately half of the patients submitted to spirometry, and nonspecific ventilatory defect (NVD) was the main finding. Spirometry findings vary in transplanted children. Srinivasan et al. (2017) found that obstructive defect was the primary finding (43%), followed by restrictive (25%), mixed (5%), and normal lung function (27%) in children with a median of 5 years post-HSCT.[10] Jung et al. (2021) showed that changes in FEV1 in the first 3 months after BO diagnosis impacted outcomes such as death and lung transplantation, indicating the need for earlier monitoring and interventions to change survival indicators.[7]

The chest CT abnormalities found in the present study were highlighted in previous reviews, particularly airspace consolidation, ground-glass attenuation, and nodules.[8,9] These findings are important markers for the differential diagnoses of lung conditions, some of which are typical of specific clinical scenarios.[8,9]

Pulmonary veno-occlusive disease and BO were diagnosed in 1.8% of the patients in this study. Characterized by an impairment of the small airways, BO is described as a primary late non-infectious pulmonary

syndrome after allogeneic HSCT that usually presents after the first 100 days after HSCT.[1-3] It is most frequently described after conventional myeloablative regimens and busulfan-based preparative regimens.[1-4,9] One limitation of our study was the lack of pre-HSTC data collection; such information would likely explain the results. Other known BO risk factors include a lower baseline FEV1/FVC ratio, non-Caucasian ethnicity, lower circulating immunoglobulin G levels, conditioning with busulfan, non-related donors, and female donors.[1,2,4,9]

This review illustrates the size of the problem, in which pulmonary complications occurred in 27.3% of the patients and death in 19.3% of the cases in children transplanted at the referral center.

Pulmonary complications after HSCT in children are relevant causes of morbidity and mortality in this group of patients. Knowing the main events, the patient's profile and the factors involved comprise the first step in designing strategies for the prevention and management of these complications.

AUTHOR CONTRIBUTIONS

DCC: conceptualization (Lead), data curation (Lead), formal analysis (Lead), investigation (Lead), methodology (Lead), project administration (Lead), supervision (Lead), writing-original draft (Lead), writing-review & editing (Lead). PMS: data curation (Lead), formal analysis (Lead), investigation (Lead), methodology (Lead), project administration (Lead), writing-original draft (Lead). TAPJ: data curation (Supporting), methodology (Supporting). SN: formal analysis (Supporting), methodology (Supporting). GL: formal analysis (Supporting), methodology (Supporting). CAR: data curation (Supporting), formal analysis (Supporting), methodology (Supporting), writing-review & editing (Lead). HJCN: data curation (Supporting), formal analysis (Supporting), methodology (Supporting), writing-review & editing (Lead). CMSB: Data curation (Supporting), Methodology (Supporting), Project administration (Supporting), Writing-review & editing (Lead). NARF: data curation (Lead), formal analysis (Lead), methodology (Lead), supervision (Lead), writing-review & editing (Lead).

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Lung cancer surgery in Brazil during the COVID-19 pandemic: How many were left behind?

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TO THE EDITOR,

Lung cancer is the leading cause of oncological mortality in Brazil, being responsible for approximately 30,000 deaths in 2019.[1] To date, surgical treatment is the best therapeutic option for patients with non-small cell lung cancer and is the mainstay approach for early-stage disease (stages I and II). Delays in treatment are thought to be major contributors to suboptimal outcomes, and efforts have been made to reduce the time between the diagnosis and initiation of treatment, with Brazilian laws requiring that such interval must not exceed 60 days, following international guidelines and recommendations.[2,3]

The COVID-19 pandemic and its hazardous consequences have brought major difficulties to the diagnosis and management of lung cancer in Brazil.[4] Outpatient consultations, as well as surgical and diagnostic procedures, were halted across the country, leading to significant challenges to both diagnosing and treating malignancies following the regular pre-pandemic oncological guideline protocols. Patt et al. (2020) demonstrated that lung cancer screening rates have declined by up to 75% in the U.S. motivated by the pandemic. The decision to reschedule or completely forego screenings by both patients and healthcare providers has led to fewer cancer diagnoses,[5] with similar findings being reported in Europe.[6] Moreover, a recent systematic review and meta-analysis suggested that extended delay to surgery is associated with decreased overall survival in lung cancer.[7] In this context, the impact of the COVID-19 pandemic on the surgical treatment of lung cancer patients in Brazil remains unknown.

Here, we aimed to analyze the impact of the COVID-19 pandemic on the surgical treatment of lung cancer patients in Brazil through a retrospective analysis with a time-series of lung cancer surgeries, from May 2018 to May 2021, collected from the oncology panel[8] of the Department of Informatics of the Brazilian National Health System (DATASUS). Of note, the information provided by the oncology panel is registered on the first day of treatment. Data were retrieved following the 10th revision of the International Classification of Diseases (ICD-10), codes C33 and C34, for lung and tracheal cancer surgeries, as well as for chemotherapy and radiotherapy. We defined the beginning of the COVID-19 pandemic in Brazil as April 2020. Data on COVID-19 cases in the country were obtained from the Brazilian Department of Health website.[9] All statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) software, version 18 (IBM Corp., Armonk, NY, USA). Time-series forecasting was performed using the SPSS time-series modeler/expert modeler.[10]

A total of 38,945 patients with lung cancer were treated (including all treatment modalities) in the Brazilian public healthcare system (SUS) from May 2018 to May 2021. When comparing the periods before and after April 2020, we found a median of 1,079 *vs*. 986 lung cancer patients treated per month, respectively. The median frequency of surgeries for lung cancer registered in Brazil before April 2020 was 164 per month (P25-P75, 155-178). Based on the previous 23 months, a trend for the April 2020 - May 2021 interval was calculated (r^2=0.89). In comparison with the predicted trend, there was an actual decrease (mean difference -41.24, 95% CI [-26.63; -55.85]) in the number of lung cancer surgeries registered per month (Figure 1). There was also a negative correlation (R=-0.54, p=0.03) between the number of lung cancer surgeries and the number of new COVID-19 cases per month since the first confirmed case in February 2020.

Based on the time-series analysis, our study suggests that up to 781 lung cancer patients did not receive appropriate surgical treatment as a consequence of the COVID-19 pandemic in the Brazilian public healthcare system between April 2020 and May 2021 (Figure 1).

Some explanations might account for the different surgery patterns regarding new COVID-19 cases depicted in Figure 1. The first spike in COVID-19 cases initiated in April 2020 and peaked in August of that year. It was significantly associated with fewer surgeries compared to the same interval in 2019 (monthly averages, 142.8 *vs*. 175.8 surgeries, respectively). Despite relatively few new COVID-19 cases, this stage was marked by lockdown policies and, more importantly, concern among the population, including lung cancer patients who may have preferred to stay home rather than seek appropriate care in hospitals. Meanwhile, the second spike initiated in November 2020 and peaked in April 2021. In this stage, the expected seasonal recovery in lung cancer surgeries following the end and the first few months of the year observed from November 2018 to April 2019 was not reproduced (monthly averages, 152.8 *vs*. 131.8 surgeries, respectively). We suspect this

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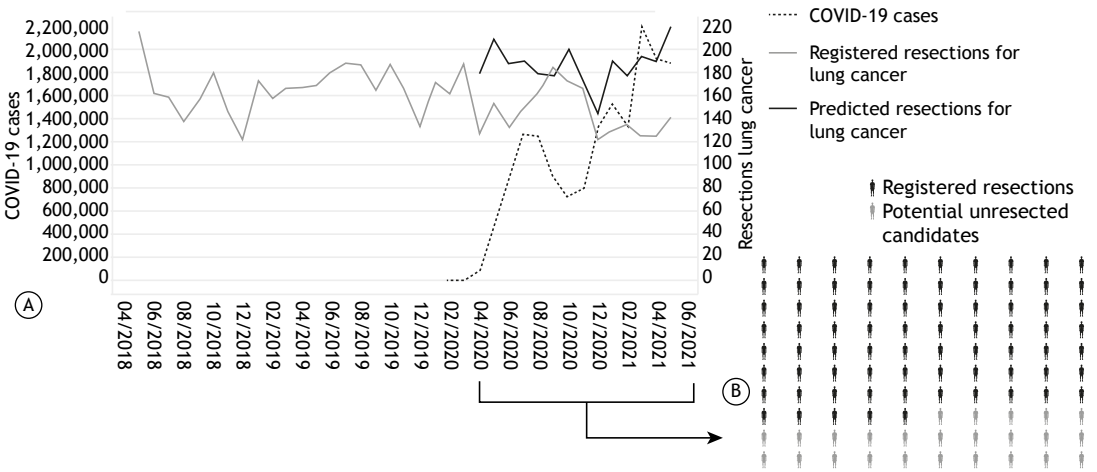

Figure 1. a) COVID-19 cases in Brazil and the number of registered and predicted resections for lung cancer. COVID-19 cases and resections for lung cancer can be visualized in this figure using different scales. b) Proportion of potential unresected lung cancer surgical candidates: 2,340 resections were registered during the pandemic in the analyzed period, with up to 781 potential candidates for surgical resection being withheld from appropriate treatment.

finding may be part of a reflection of the pandemic's worst scenario in Brazil. In summary, the variation in the number of surgeries showed a modest correlation with the number of new COVID-19 cases; thus, we hypothesize that variables other than raw pandemic patterns may come into play.

The data presented herein has some limitations. First, we recognize that time-series analyses may be prone to errors caused by corrupt or missing data. It is known that DATASUS might have a delay of up to 6 months for procedure registration. The authors regularly checked for updates while writing this manuscript, with stable numbers of procedures in this period. Additionally, unexpected data discrepancies were not observed in the interval used for time-series construction. Second, we evaluated aggregate ecological data, which were not intentionally designed to serve as cancer registries; therefore, the data may be prone to bias. However, DATASUS, the best-known national database available, is based on billing information, being audited by competent authorities. Third, the oncology panel only accounts for patients that effectively started treatment by the Brazilian public health system, so data on the number of lung cancer patients is probably underestimated in our study. Finally, the number of lung cancer patients managed by the private sector was not included in our analysis. Notwithstanding, SUS is the world's largest public health system with 100% of population coverage, while the private sector provides additional coverage to approximately 25% of the population. From this perspective, we suspect the magnitude of the impact of the COVID-19 pandemic on lung cancer patients might be even greater than that verified herein.

To our knowledge, this is the first study to evaluate the impact of the COVID-19 pandemic on lung cancer surgical treatment using nationwide data. Even though the presented data is descriptive, it may serve as a call for action for health authorities to develop strategies to appropriately manage an upcoming considerable amount of lung cancer patients who were not operated on when necessary as an impact of the ongoing COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

GMH, WKS, DCM, LFLA, and MGS contributed to the conception and planning of the study, the interpretation of data, writing and reviewing the preliminary and definitive versions, and the approval of the final version of the manuscript.

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Inflammatory myofibroblastic tumor of the lung - an explosive metastatic case

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TO THE EDITOR,

The term inflammatory myofibroblastic tumor (IMT) refers to a tumor with chronic inflammatory infiltrate, aggressive behavior, and evidence of chromosomal rearrangement, especially anaplastic lymphoma kinase (ALK) translocation.[1]

Here, we report a rare case of a myofibroblastic lung tumor with ALK translocation in a 50-year-old man, a former smoker, who complained of myalgias, sudoresis, fever, and weight loss for the past two months.

Initial thoracic computed tomography (CT) revealed a solid mass measuring 3.3 cm x 3 cm in the left pulmonary apex, and a positron emission tomography (PET) scan detected hypermetabolic uptake (SUV-26) in the pulmonary lesion, as well as diffuse exuberant osteomedullary hypermetabolism. Bronchioalveolar lavage was negative for mycobacteria and other microorganisms, and two transbronchial and one transthoracic biopsy only evidenced a chronic inflammatory infiltrate. A myelogram suggested a monoclonal gammopathy of undetermined significance.

Following failed attempts at diagnosis, the patient exhibited refractory fever, pleuritic pain, and productive cough. A follow-up CT detected the growth of the left pulmonary mass; thus, lobectomy was proposed (Figure 1A).

The intraoperative descriptions indicated a liquefied purulent mass. After surgery, the patient developed marked epigastralgia, and an abdominal CT revealed a hepatic lesion with a necrotic center (Figure 1B). Hepatic biopsy evidenced a necrotic liquefied and purulent content. Also, because of a transitory loss of consciousness, cranial CT was performed, with the identification of an intra-axial lesion suggestive of secondary deposit.

The histopathology of the lung specimen and cytology of the hepatic punction revealed an epithelioid variant of IMT in the lung, with ALK rearrangement. The patient started Crizotinib, with no time to establish an eventual response as he died 5 days later.

The biological behavior of IMTs is highly unpredictable and has a wide spectrum of severity. For years, there has been controversy regarding whether it should be categorized as a reactive lesion to an infection or local trauma with an aggressive local inflammatory response or an actual neoplastic lesion. The term "inflammatory myofibroblastic tumors" emerged in the past years according to the recent WHO classification of soft tissue tumors.[2] The expression of ALK-1 documented in approximately 50% of IMTs has contributed to distinguishing these tumors from other nonspecific inflammations, pointing also to a better prognosis of IMTs with ALK rearrangement. Distant metastases, although rare, may occur, primarily in ALK-negative IMTs.[1]

These tumors are most frequent in children and young adults, accounting for around 50% of all pulmonary neoplasms in infants and less than 1% of lung tumors in adults.[3] Due to the broad spectrum of radiological manifestations and nonspecific clinical behavior, these tumors are difficult to diagnose. Surgical resection is usually performed in solitary lesions in order to establish the diagnosis and provide adequate treatment. Complete surgical resection with clear margins is associated with a favorable prognosis.[4] Radiation may also be applied in recurrent cases or situations of local organ invasion.[5]

Despite the scarce evidence regarding the treatment of these tumors in adults, Crizotinib is widely used and effective in patients with ALK-positive non-small-cell lung cancer. Discussing the rationale for genomic target therapy, several case reports in which ALK inhibitors were used, namely Crizotinib, in ALK-positive IMTs, reported

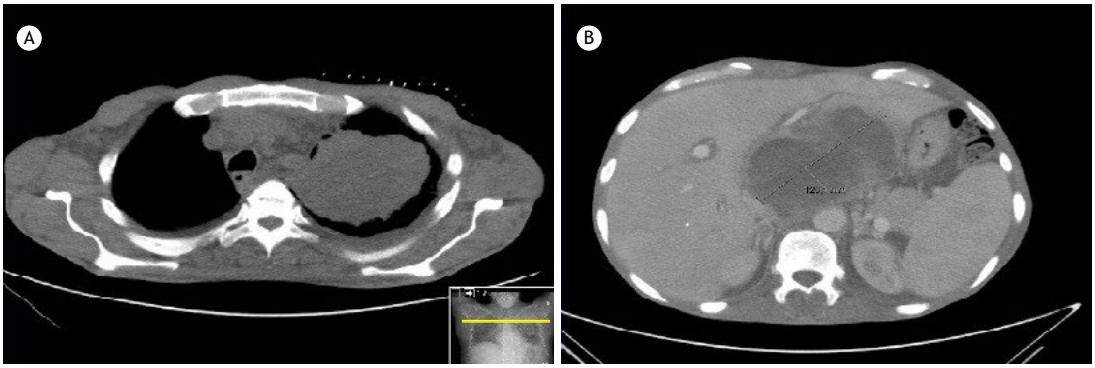

Figure 1. Computed tomography (CT) images. A – Left pulmonary apex with necrotic and abcessed tissue. B – Hepatic abcessed/nodular lesion with necrotic component.

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variable degrees of success.[5-7] A prospective study involving 20 patients with advanced, inoperable IMTs with ALK translocation stated that Crizotinib was an active treatment associated with objective responses in 50% of patients, with long-lasting progression-free survival in most of them.[8]

In this case, the explosive local and metastatic growth conjectured the worsening of the prognosis, and Crizotinib was used as an unsuccessful lifesaving attempt. The highly variable reported outcomes, in addition to the lack of experience in most cancer centers in adult IMT, make the treatment still a matter of debate.

AUTHOR CONTRIBUTIONS

WV: diagnosis of the patient. LR, RP, and FF: scientific revision of the manuscript. All authors revised the final version of the manuscript and agreed upon its submission.

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Bone metastasis after stage IIIA non-small cell lung cancer: risks and prognosis

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TO THE EDITOR

Lung cancer (LC) is one of the most common cancers with high morbidity and mortality rates. Stage IIIA Non-Small Cell Lung Cancer (NSCLC) is considered a heterogeneous disease due to the distinct outcomes in individuals with the same staging and the diversity of subsets in the TNM System. Approximately 54% of NSCLC with stages between II and IIIA present recurrence or metastasis.[1,2]

Bone metastases (BMs) are observed in approximately 30% of patients with advanced NSCLC. Skeletal involvement may be a source of serious complications, also known as skeletal-related events (SREs). These include pathological fractures, radiotherapy for bone pain, malignant hypercalcemia, and spinal cord compression.[3,4]

Information on the risk factors and clinical course of BMs is important to define strategies for their early detection and to predict their impact on the lives of patients with NSCLC. Therefore, the purpose of this study was to investigate risk factors for BM and survival in patients with stage IIIA NSCLC.

We conducted a retrospective cohort study including patients diagnosed with stage IIIA NSCLC between 2000 and 2014 at the Brazilian National Cancer Institute (INCA). Clinical and sociodemographic data were extracted from physical and electronic medical records. The analyzed data included age, sex, ethnicity, smoking status, performance status (PS), histology including adenocarcinoma, squamous cell carcinoma, and large cell carcinoma subtypes; tumor size and affected regional lymph nodes; metastasis, BM, SREs, and treatments performed.

BM was confirmed by at least one of the following tests: computed tomography, magnetic resonance imaging, bone scintigraphy, pet scan, or biopsy, according to the hospital's routine. All patients were followed up for at least 60 months after the diagnosis of NSCLC, until death, or until the last visit to the hospital (loss of follow-up).

Descriptive statistics were used to analyze all variables. Survival analysis was performed using the Kaplan-Meier method. In order to calculate the risk of developing BM, univariate analysis was performed using binary logistic regression. In all analyses, p-values <0.05 were considered statistically significant. The data were analyzed using the SPSS (Statistical Package for the Social Sciences for Windows, São Paulo, Brazil) software, version 21.0.

The present study was approved by the Research Ethics Committee of the Brazilian National Cancer Institute (Protocol No. 233.245).

A total of 403 patients diagnosed with stage IIIA NSCLC were included. The patients were predominantly elderly (64.3%), male (66.3%), white (69.2%), and had a smoking history (93.3%). The majority were PS 0-1 (54.6%), had squamous cell carcinoma (49.2%), and underwent non-surgical treatment (82.9%). As for tumor size, the most frequent were T2 and T3 (36.7% and 48.4%, respectively), which exhibited dissemination to regional lymph nodes (N1=11.7% and N2=78.2%).

BM was detected in 50 patients (12.4%). The median time between the diagnosis of NSCLC and the development of BMs was 7.78 months (95% CI, 3.27 - 12.30). The most affected sites were the spine (50.0%), ribs (46.0%), and pelvis (11.0%).

The univariate analysis of the clinical and sociodemographic factors associated with the development of BM is shown in Table 1. After adjusting for potential confounding factors, the multivariate model showed a 4% reduction in the risk of developing BM, with a higher risk among younger individuals (adjusted OR 0.96, 95% CI, 0.93-0.99, p=0.023). Those with lower PS (0 and 1) at the time of NSCLC diagnosis had a 2.92-fold greater risk of developing BM (adjusted OR 2.92; 95% CI, 1.11-7.70; p=0.030).

The median survival time was 13.07 months (95% CI, 11.10-15.04) for patients who did not develop BM and 16.26 months (95% CI, 13.73-18.79) for those who did (p=0.940). After the diagnosis of BM, the median survival time was 5.84 months (95% CI, 4.39-7.30).

Among the 50 patients who developed BMs, 38.0% presented with at least one SRE. The most common SREs were radiotherapy for bone pain (22%), spinal cord compression (12%), pathological fractures (10%), and malignant hypercalcemia (8%).

After BM, the mean number of hospitalizations for patients who developed SREs was 1.63 (±1.49), and the mean number of hospitalizations for patients who did not develop SREs was 1.06 (±1.45); however, this difference was not significant (p=0.139).

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Table 1. Factors associated with the development of bone metastases (univariate analysis).

Characteristics	BM		OR (95% CI)	p-value
	Yes (N = 50)	No (N = 353)		
Age (years, mean ± SD)	59.8±9.1	64.3±10.2	0.95 (0.93-0.98)	0.004
Sex				
Women	15 (30.0)	121 (34.3)	Reference	0.550
Men	35 (70.0)	232 (65.7)	1.21 (0.63-2.31)	
Ethnicity / Skin color				
Brown / Black	10 (20.8)	109 (31.1)	Reference	0.147
White	38 (79.2)	241 (68.9)	1.71 (0.82-3.57)	
Marital Status				
Living with a partner	31 (62.0)	216 (62.1)	Reference	0.993
Living without a partner	19 (38.0)	132 (37.9)	1.00 (0.54 -1.84)	
Years of education				
≤ 8 years	33 (66.0)	257 (73.6)	Reference	0.259
> 8 years	17 (34.0)	92 (26.4)	1.43 (0.76 -2.70)	
Smoking				
No	2 (4.0)	23 (6.6)	Reference	0.490
Yes	48 (96.0)	328 (93.4)	1.68 (0.38-7.36)	
Histology				
Non-adenocarcinoma	25 (50.0)	200 (56.7)	Reference	0.376
Adenocarcinoma	25 (50.0)	153 (43.3)	1.30 (0.72-2.36)	
Tumor				
T3 and T4	28 (59.6)	206 (60.1)	Reference	0.949
T1 and T2	19 (40.4)	137 (39.9)	1.02 (0.54-1.89)	
Lymph node involvement				
N1 and N2	42 (89.4)	320 (93.8)	Reference	0.256
N0	5 (10.6)	21 (6.2)	1.81 (0.65-5.06)	
Performance Status*				
≥ 2	5 (10.0)	98 (28.1)	Reference	0.010
0-1	45 (90.0)	251 (71.9)	3.51(1.35 -9.11)	
Metastases prior to BM				
Yes	8 (16.0)	73 (20.7)	Reference	0.441
No	42 (84.0)	280 (79.3)	1.36 (0.61-3.04)	
NSCLC treatment				
Surgery	7(14.0)	62 (17.6)	Reference	0.532
Other treatments	43 (86.0)	291 (82.4)	1.30 (0.56 -3.04)	

NSCLC= Non-small cell lung cancer; BM= Bone metastasis; OR= Odds Ratio; CI= Confidence Interval. p-values in bold were statistically significant. *At the time of stage IIIA NSCLC diagnosis.

The issues addressed herein are relevant since BM has a negative impact on quality of life and promotes the increased use of healthcare resources.[4,5]

The data obtained in the present study showed that with every one year of increasing age, patients had 4% less risk of developing BM, corroborating other studies.[6] A Swedish study that addressed patients with LC showed that BM was more common in younger patients (OR 0.76, 95% CI, 0.69-0.85). The authors argue that angiogenesis may be impaired in the elderly, a fact that would compromise tumor growth and metastasis vascularization.[6]

In this study, after adjusted analysis, patients with a PS of 0 or 1 at the time of NSCLC diagnosis had a greater risk of developing BM. A recent Chinese study, which evaluated 5,051 patients with NSCLC, showed that younger patients had a higher proportion of EGFR/ALK mutations, as well as longer survival. This better prognosis can lead to more time for the development of complications of the disease, such as the development of BM.[7]

The median survival time of patients with stage IIIA NSCLC after diagnosis of BM in the current study was 5.84 months. Other studies have shown similar results.[8-10] Zhang et al. (2019) analyzed data from 125,652 patients and found a median survival rate after BM of 4 months.[8] Meanwhile, after analyzing a total of 34,584 patients, Wang et al. (2019) reported a 6-month survival rate for patients diagnosed with BM.[9]

There were some limitations in our study. Being a retrospective study with a long period of inclusion, temporal and selection bias may have been inevitable. However, this study presented advantages. The size of the analyzed population was relatively large, and patients with stage IIIA NSCLC were specifically included. Data on this group of patients are scarce in the specialized literature.

In conclusion, the present study revealed that younger patients with lower PS had a higher risk of developing BM after stage IIIA NSCLC. After BM, these patients have a poor prognosis.

AUTHOR CONTRIBUTIONS

GTS, CMB, and LMS participated in the design and planning of the study, in obtaining, analyzing, and/or interpreting data, in writing and/or critically reviewing, and in the final approval of the published version; MMZ and GJC participated in the analysis and/or interpretation of the data, as well as in the writing and/or critical review and final approval of the published version; AB and LCST participated in the writing and/or critical review and final approval of the published version.

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No controversy: e-cigarettes are not a treatment for tobacco/nicotine cessation

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Electronic nicotine delivery systems (ENDS) or electronic cigarettes (ECs) were developed by Hon Lik, a Chinese pharmacist, and patented in 2003.[1] In 2014, a review article in the *Jornal Brasileiro de Pneumologia*[1] stated that ENDS were "controversial" and that few studies had evaluated "the effects of ECs on smoking reduction and cessation over a 6-to 24-month period."

On August 19th, 2015, the UK Government issued a press release with the headline "E-cigarettes around 95% less harmful than tobacco estimates landmark review," publicizing a new report[2] commissioned by Public Health England (PHE) and led by Professor Ann McNeill and Professor Peter Hajek, worshipping the use of ECs as a harm reduction strategy and minimizing their associated risks. The claim of safety attracted huge media interest worldwide.

PHE reported that ENDS were "95% less harmful than tobacco" based on a single publication that was biased in several ways.[3] In July of 2013, PHE gave a two-day workshop in London that included an international expert panel[3] in order to review the context of perceived types of harm from nicotine-containing products, the range of the products (obviously including ENDS), and the criteria of such harms. During the workshop, the products were scored according to the types of harm, and weights were applied to the results. There was no formal criterion for the recruitment of the experts (some of whom were not even from the health field), as well as a lack of hard evidence of the type of harm caused by most of the products in the majority of the criteria and plenty of conflicts of interest of several of the participants, as highlighted in publications by the British Medical Journal in September[4] and November[5] of 2015, but not fully disclosed in the study.[3] The study was basically a biased opinion of a group "in the pay of manufacturers", as stated in the title of an article published by the Daily Mail newspaper.[6]

In 2018, PHE reiterated its claim that vaping "is at least 95% safer than smoking" and reinforced its use for "smoking cessation," even recommending it for pregnant women.[7] In the same year, The Royal College of Psychiatrists[8] published a position statement endorsing the use of varenicline and ECs to reduce the prevalence of smoking among people with mental health problems.

The ENDS industry (the so-called "Big Vape") is owned by major tobacco companies (known as "Big Tobacco"). In 2018 alone in the USA, the top 25 EC manufacturers brought in more than $2.5 billion in sales: 96% of these sales were from brands owned in whole or part by the Big Tobacco.[9] In 2018, the EC market revenue in the United Kingdom was $2,498.07 million, according to the webpage statista.com.[10]

Tobacco harm reduction rationale involves providing tobacco users who are "unwilling or unable to quit" less harmful nicotine-containing products for continued use.[11] The skepticism toward harm reduction is based on the history of low-yield tar/nicotine cigarettes that are promoted and marketed as having lower health risks.[11] Only later scientists learned that the so-called "healthier cigarettes" were a deceptive way to mitigate consumers' health concerns and to keep them in pre-contemplation stages: a strategy to undermine cessation. ENDS have been aggressively marketed using similar tactics.

A randomized controlled trial compared the effectiveness of ENDS with nicotine replacement therapy (NRT) for "smoking cessation."[12] It was one of the top ten most read articles between January and July in 2019 (year of publication). The study has multiple and important biases: researchers did not ensure that each group used only one of the medications (3% of ENDS users also used NRT, and 20% of those using NRT also used ENDS), there was no objective method to assess adherence, behavioral support officers knew the groups to which the patients had been allocated, and intention-to-treat analysis was not carried out. The 1-year abstinence rate was 18.0% and 9.9% in the EC and NRT groups, respectively. The abstinence rate in the NRT group was half the rates that are typically found in NRT trials: Rosen et al.[13] selected three systematic reviews published by the Cochrane Collaboration involving 61 randomized clinical trials involving first-line smoking cessation medications and investigated smoking cessation within 6 and 12 months of follow-up. The meta-analysis showed that 19.8% of the participants who used NRT remained abstinent at 12 months.[8]

There are nearly 2,000 chemicals that are inhaled with the use of ENDS, most of which are ignored.[14] ENDS aerosol is not harmless "water vapor": it contains heavy metals, ultrafine particulates, and cancer-causing agents. ECs are cigarettes! Therefore, they share the same adverse health effects of combustible cigarettes and also have their own specific risks, such as the so-called *e-cigarette or vaping use-associated lung injury*.[15] The consequences of long-term use of these devices remain unknown.[15]

Health care professionals must adhere to the Hippocratic principle *primum non nocere* (do no harm). ECs are not a smoking cessation treatment. Using ENDS causes diseases, replicates behavioral and social characteristics of smoking, perpetuates nicotine addiction, and renormalizes smoking.

CONFLICTS OF INTEREST

None declared.

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Mortality rates and epidemiological changes in critically ill Coronavirus Disease 2019 patients after a vaccination program in Brazil

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TO THE EDITOR,

The Coronavirus Disease 2019 (COVID-19) emerged as a serious public health problem worldwide.[1] To date, more than 31 million cases and almost 669,000 deaths due to COVID-19 have been confirmed in Brazil. The highest costs and mortality rates have been attributed to critically ill elderly patients with comorbidities who underwent invasive mechanical ventilation (IMV).[2] Multiple treatments and preventive measures, such as the use of face masks, social distancing, rigorous hand hygiene, medicines, and vaccines against severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), have been used, but which of them was the best at reducing the number of cases and mortality rates?

After vaccination programs were implemented in December in Israel[3] and England,[4] there was a significant reduction in the number of symptomatic and asymptomatic cases, hospitalizations, severe disease, and deaths due to COVID-19. In Brazil, the SARS-CoV-2 vaccination program was initiated on January 17th, 2021, prioritizing health professionals and the elderly population with comorbidities. Until June 26th, 2021, 11.92% of the Brazilian population was completely vaccinated, and 33.21% received only one dose; this period was the worst in terms of the number of cases and lethality in 2021, mainly in younger age groups.[5] Thus, in the present letter, we aimed to compare the changes in the mortality rates and epidemiology of critically ill COVID-19 patients before and after the first 6 months following the vaccination program against SARS-CoV-2 in Brazil.

This retrospective study analyzed the data of adult patients with COVID-19 admitted to intensive care units (ICUs) in Brazil. Patients were included when SARS-CoV-2 infection was confirmed by real-time polymerase chain reaction (RT-PCR) testing. Ethics committee approval was not required since the data were obtained from a national registry of the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe), which is available online at https://covid.saude.gov.br.

The critically ill COVID-19 patients were divided into two groups according to hospitalization date. Those admitted between March 1–December 31, 2020, were included in the pre-vaccination period group, while those hospitalized between January 1–June 26, 2021, were included in the post-vaccination period group. The monthly evaluated variables were mean age, the frequency of patients without comorbidities, and mortality rate.

Data were analyzed using the SPSS software, version 27.0. A descriptive analysis of the study population was performed using mean and standard deviation measures as continuous variables and absolute and relative frequency distribution as categorical variables. The t-test was used to compare continuous variables, while the chi-square test was performed to compare categorical variables. Differences were considered significant when the *p*-value was < 0.05.

This study evaluated a total of 116,640 patients admitted to the ICU in the pre-vaccination period and 124,153 patients hospitalized in the post-vaccination period, of whom 68,052 (58.3%) and 82,402 (66.4%) died, respectively. After the vaccination program against SARS-CoV-2, the critically ill COVID-19 patients were compared with those from the pre-vaccination period. The frequency of infection among patients < 60 years of age increased, and the mean age of the patients decreased, especially after the vaccination period when compared to the pre-vaccination period group (Figures 1A and 1B). However, there were temporal trends of increase in the ICU mortality rate, the frequency of patients without comorbidities, and the need for IMV (Figures 2A, 2B, and 2C).

The present study identified consistent changes in the age group profiles in confirmed, critically ill COVID-19 patients after the vaccination program against SARS-CoV-2 in Brazil. Patients younger than 60 years of age became the group that was more frequently admitted to the ICU, with increased ICU mortality rates and the need for IMV. This outcome strongly suggests that the SARS-CoV-2 vaccines protect the Brazilian population and should be widely offered to all age groups, including children and adolescents.

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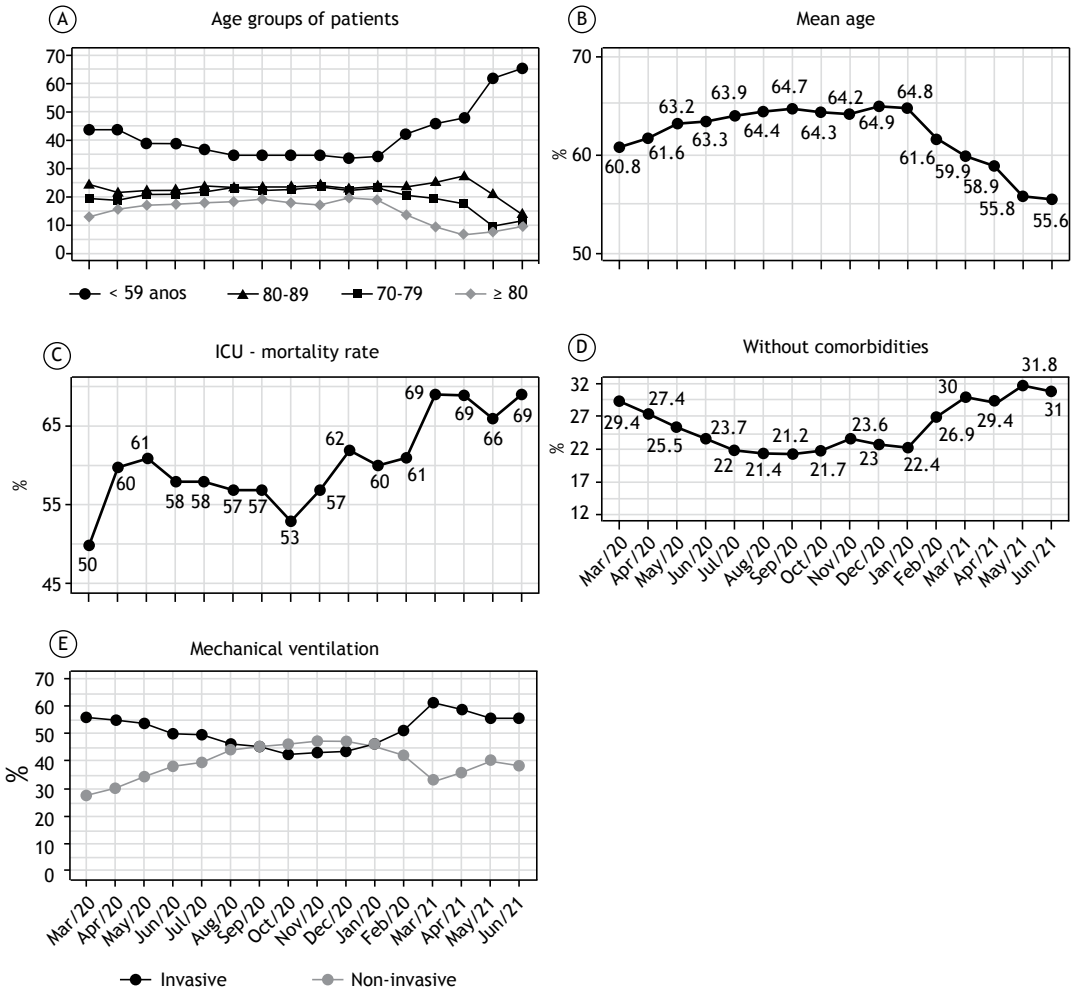

Figure 1. Temporal distribuition of COVID-19 patients admitted to the ICU: (A) Frequency of patients by age group; (B) Mean age of the COVID-19 patients. (C) ICU mortality rate; (D) Frequency of patients without comorbidities; (E) Frequency of patients under different kinds of mechanical ventilation.

Some drugs have shown beneficial effects in the treatment of critically ill COVID-19 patients. Dexamethasone presented a rate ratio of 0.83 (95% CI, 0.75–0.93) for all hospitalized patients and 0.64 (0.51–0.81), especially for patients undergoing invasive ventilation.[6] Interleukin-6 receptor blockers (tocilizumab, sarilumab) also promoted decreased mortality,[7] although their high costs hampered the availability for treating patients mainly in the public health system. Furthermore, more knowledge on COVID-19, particularly the use of non-invasive and invasive ventilation, could improve the quality of health assistance.[8]

The World Health Organization (WHO) and all the medical societies have suggested that everyone be vaccinated as soon as possible. Different vaccines against SARS-CoV-2 have been considered efficacious and safe.[3,4,9] The most important endpoints related to the effectiveness of a vaccine are the ability to reduce hospital or critical care admission and/or death.[10] Our study identified changes in the frequency of the age groups of critically ill COVID-19 patients after the vaccination program, specifically in older vaccinated adults, who exhibited a reduction in ICU admission frequency. Thus, it can be inferred that the vaccination program against SARS-CoV-2 was the most important measure to control the COVID-19 pandemic.

The COVID-19 frequency and mortality rates were much more uncontrolled until the 1st semester of 2021 in Brazil. The SARS-CoV-2 Gamma variant was predominant in this period and related to higher severity and mortality, mainly in younger age groups when compared to variants B.1.1.28 and B.1.1.33, which were the most prevalent in 2020 in Brazil.[5] Our study showed that patients below 60 years of age increased ICU mortality rates, due to the fact that elderly people were a priority for vaccination. This finding is of concern since the younger population is economically active and probably responsible for the financial obligations of their families and labor companies. Therefore, we can infer that the Gamma variant had a higher capacity to spread than the other variants. However, it occurred especially among younger people since they had not yet been vaccinated.

In conclusion, this study identified an important change in the age group frequency of critically ill COVID-19 patients, decreasing in the older population after the vaccination program against SARS-CoV-2 in Brazil. Although these findings suggest that vaccine distribution prevented new critical care admissions, especially in priority groups that underwent vaccination, there was a concern regarding increased ICU mortality rates and/or the need for IMV, which affected mainly younger patients because they had not yet been vaccinated. Investing in vaccines against SARS-CoV-2 was the quickest and most appropriate way to control this terrible COVID-19 pandemic, which, unfortunately, is still underway.

ACKNOWLEDGMENTS

We would like to express our gratitude and respect for all the Brazilian families who lost relatives throughout the COVID-19 pandemic. We also want to congratulate all health professionals who have worked relentlessly for the recovery of all COVID-19 patients. Finally, we thank the team of the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe) for making the utilized database available online and in the public domain; this study would not have been possible without this organization and the data collected from them.

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Takayasu's arteritis with pulmonary artery involvement

Marina de Moraes Carvalho da Silva[1], Rosana Souza Rodrigues[1,2], Edson Marchiori[1]

A 26-year-old man was hospitalized with a history of dyspnea and chest pain. Physical examination revealed systemic arterial hypertension and reduced arterial pulses in the upper limbs. Pulmonary computed tomography (CT) angiography showed dilation of the right pulmonary artery and the lower lobe branches (Figure 1A), stenosis of the left pulmonary artery tree (Fig. 1B), aneurismatic dilation of the pulmonary artery trunk (Fig. 1C and 1D), and diffuse and irregular aneurysm of the descending thoracic aorta (Fig. 1E). Carotid artery magnetic resonance angiography revealed left carotid artery narrowing with focal stenosis points (Fig. 1F). These angiographic findings and the clinical history led to the diagnosis of Takayasu's arteritis (TA).

TA is a chronic autoimmune disease characterized by inflammation of the aorta and its branches. This process leads to arterial wall thickening, with consequent stenosis and occlusion, along with lumen dilation, aneurysms, and dissection. The clinical presentation of the disease is related to tissue ischemia and organ failure. The detection of vascular alterations by angiography is mandatory for TA diagnosis. Other criteria include pulse deficit or claudication, blood pressure discrepancy, bruits, hypertension, and acute phase reactants. Pulmonary artery involvement is a rare complication that is usually seen in later stages of TA and is associated with pulmonary hypertension, leading to right ventricular failure and worsening of the patient's prognosis.[1,2]

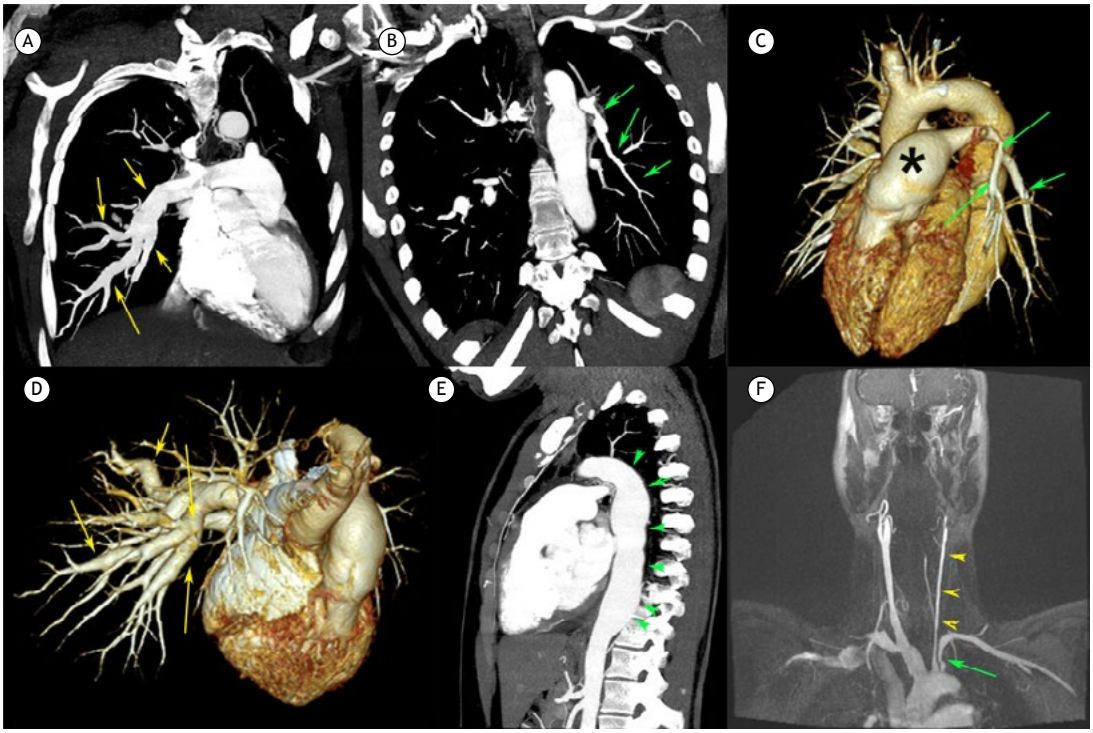

Figure 1. Pulmonary CT angiography images with maximum intensity projection (MIP; A and B), three-dimensional volume-rendered (C and D), and sagittal MIP (E) reconstruction showing dilation of the pulmonary artery trunk (asterisk in C) and the right pulmonary artery and its lower lobe branches (yellow arrows in A and D), substantial stenosis of the left pulmonary artery tree (green arrows in B and C), and diffuse and irregular aneurysm of the descending thoracic aorta (green arrowheads in E). Coronal MIP reconstruction of a post-contrast T1-weighted fat-saturated carotid magnetic resonance angiography sequence (F) showing diffuse narrowing of the left carotid artery (yellow arrowheads). Note also stenosis in the emergence of the left subclavian artery (green arrow).

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Tables and Figures: All tables and figures should be in black and white, on separate pages, with legends and captions appearing at the foot of each. All tables and figures should be submitted as files in their original format. Tables should be submitted as Microsoft Word files, whereas figures should be submitted as Microsoft Excel, TIFF or JPG files. Photographs depicting surgical procedures, as well as those showing the results of exams or biopsies, in which staining and special techniques were used will be considered for publication in color, at no additional cost to the authors. Dimensions, units and symbols should be based on the corresponding guidelines set forth by the Associação Brasileira de Normas Técnicas (ABNT, Brazilian Association for the Establishment of Technical Norms), available at: http://www.abnt.org.br.

Legends: Legends should accompany the respective figures (graphs, photographs and illustrations) and tables. Each legend should be numbered with an Arabic numeral corresponding to its citation in the text. In addition, all abbreviations, acronyms, and symbols should be defined below each table or figure in which they appear.

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Examples: Journal Articles

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

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

Other situations:

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

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CONHEÇA O NOVO APLICATIVO DA BAYER!

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

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

Baixar na App Store

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

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

Referências:

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

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

Chegou: EGURINEL® (pirfenidona)

O primeiro similar de pirfenidona do Brasil!

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

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

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

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