ISSN (ON-LINE): 1806-3756

JBP
Jornal Brasileiro de **Pneumologia**

PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 47, Number 4
July | August
2021

Volume 47, Number 4 July | August 2021

HIGHLIGHT

Post-COVID-19 exercise capacity

Work-related asthma

Follow-up chest CT after surgical resection of lung câncer

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.
MP 05.2020 - Junho 2020.

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ISSN (ON-LINE): 1806-3756

Continuous and Bimonthly Publication, J Bras Pneumol. v. 47, n.4, July/August 2021

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Expediente

BRAZILIAN THORACIC SOCIETY

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E-mail: sbpt@sbpt.org.br

The Brazilian Journal of Pulmonology (ISSN 1806-3756) is published once every two months by the Brazilian Thoracic Society (BTS). The statements and opinions contained in the editorials and articles in this Journal are solely those of the authors thereof and not of the Journal's Editor-in-Chief, peer reviewers, the BTS, its officers, regents, members, or employees. Permission is granted to reproduce any figure, table, or other material published in the Journal provided that the source for any of these is credited.

ADMINISTRATIVE SECRETARIAT OF THE BRAZILIAN JOURNAL OF PULMONOLOGY
Address: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 08000 616218.
Assistant Managing Editor: Luana Maria Bernardes Campos.
E-mail: jbp@jbp.org.br | jbp@sbpt.org.br
Circulation: 4.000 copies
Distribution: Free to members of the BTS and libraries
Printed on acid-free paper

SUPPORT:
CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico
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ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 47, n.4, July/August 2021

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ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

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J Bras Pneumol. 2021;47(4):e20210213
https://dx.doi.org/10.36416/1806-3756/e20210213

Pulmonary fibrosis and follow-up of COVID-19 survivors: an urgent need for clarification

Bruno Guedes Baldi[1,2], Suzana Erico Tanni[3]

Several patients with COVID-19 present with residual interstitial lung abnormalities in the long term, and the prevalence of such sequelae will certainly increase as the pandemic is still ongoing. However, the definition of when irreversible post-COVID-19 pulmonary fibrosis is established remains poorly understood because COVID-19 survivors may present functional and tomographic improvement in the follow-up (Figure 1).[1-3] Additionally, there are a few suggestions for the best approach in the long term regarding respiratory monitoring with ancillary tests and the frequency of evaluation to assess patients with pulmonary involvement in the acute phase of COVID-19, although definitive evidence is still lacking.[1,4]

Post-COVID-19 pulmonary fibrosis may be defined as the presence of persistent fibrotic tomographic sequelae observed during follow-up, which can be associated with functional impairment.[1] However, the prevalence, pathophysiology, potential risk factors, and therapeutic approach of such a disorder are poorly known.[1]

There are various uncertainties regarding post-COVID-19 pulmonary fibrosis that need to be widely investigated as soon as possible. First, it is still unclear when tomographic features suggestive of pulmonary fibrosis are considered definitive, especially ground-glass opacities. In this scenario, recent studies have demonstrated that improvement of post-COVID-19 pulmonary abnormalities might be demonstrated in serial tomographic assessments, although very few studies assessed patients beyond six months from diagnosis.[2,3] A study in China that evaluated patients that were hospitalized with COVID-19, not requiring mechanical ventilation, demonstrated that most of the patients showed improvement in tomography, pulmonary function, and exercise-related variables, but 24% of those remained with abnormalities on CT scans one year after discharge.[2] The impact of autoimmune inflammatory activity triggered by the viral infection and the presence of genetic features and previous interstitial lung abnormalities may determine a higher risk to develop post-COVID-19 pulmonary fibrosis; however, such hypotheses need to be better clarified.[1,5] A recent study has demonstrated that shorter blood leukocyte telomere length was identified as a risk factor for the occurrence of fibrotic-like tomographic abnormalities in patients four months after COVID-19, which reinforces the hypothesis of genetic susceptibilities for the occurrence of post-COVID-19 pulmonary fibrosis.[5] Additionally, further studies evaluating histological features obtained from patients with post-COVID-19 pulmonary fibrosis are warranted for broader knowledge of this entity. Serum biomarkers such as Krebs von den Lungen-6 are promising to predict a higher risk of post-COVID-19 pulmonary fibrosis but need to be further explored in future studies.[6]

It remains uncertain when to start and which patients will benefit from the use of therapeutic modalities, including drugs and pulmonary rehabilitation, to attenuate the impairment associated with post-COVID-19 pulmonary fibrosis. The role of pirfenidone and nintedanib, which are antifibrotic drugs that can be used in several scenarios in patients with idiopathic pulmonary fibrosis, needs to be better defined in the case of those with chronic interstitial pulmonary abnormalities after COVID-19.[7,8] These antifibrotic drugs will probably be considered for those with progressive functional decline during follow-up, although randomized controlled trials are needed to respond to this hypothesis. Additionally, the role of prolonged treatment with corticosteroids in preventing post-COVID-19 pulmonary fibrosis is still uncertain, although it seems to be useful in subgroups of patients, such as those with tomographic abnormalities suggestive of organizing pneumonia.[9]

There is no robust data available to guide which tests should be performed for respiratory assessment and how often they should be routinely carried out in the follow-up of patients who had pulmonary involvement in the acute phase of COVID-19. The British Thoracic Society[4] recommended a clinical review 4-6 weeks after discharge, as well as chest X-rays and pulmonary function tests 12 weeks after discharge for patients with severe COVID-19 or multiple comorbidities. CT should be performed if there is evidence of abnormalities in chest X-rays. For patients with mild or moderate pulmonary COVID-19, they suggested a chest X-ray 12 weeks after discharge. The tests should be performed according to clinical evolution and results of the initial evaluations.[4] Although CT is the most accurate imaging method for severity assessment and follow-up of patients with pulmonary involvement secondary to COVID-19, chest X-rays may be considered for evaluation, especially in situations in which CT is not easily available.[4,10,11] Lung ultrasonography is useful for the assessment of pulmonary involvement in the acute phase of COVID-19 and is potentially valuable in the long-term follow-up of COVID-19 survivors; however, further studies are still required to confirm this applicability.[12] We consider that the best approach in the follow-up should be individualized according to the resources available, patient features, and severity of the acute phase of the

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ISSN 1806-3756

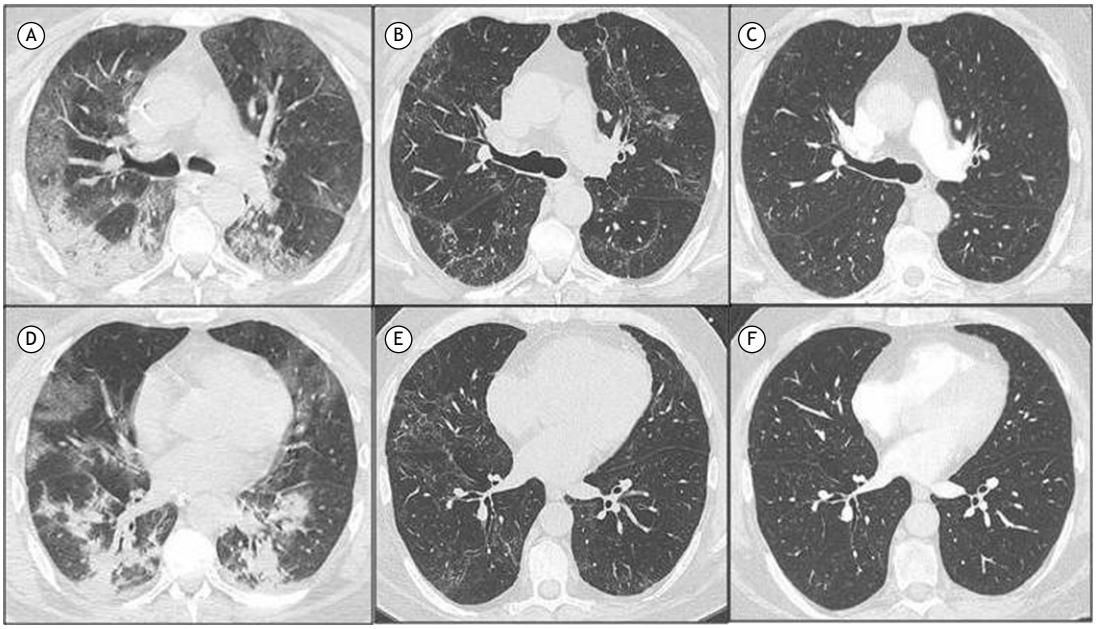

Figure 1. Chest CT scans of a 63-year-old male patient who had COVID-19 with severe pulmonary involvement and progressive improvement during the follow-up period. In A and D, CT scans in the acute phase of COVID-19, demonstrating diffuse ground-glass opacities and consolidations, predominantly in lower lung lobes. In B and E, chest CT scans obtained three months after discharge, showing a smaller extension of multifocal bilateral ground-glass and reticular opacities when compared with that in the acute phase (A and D). In C and F, chest CT scans obtained nine months after discharge, demonstrating discrete and sparse ground-glass opacities.

infection. We suggest a clinical visit and performance of an imaging test, preferably CT, at 1, 3, 6, and 12 months after discharge for those with moderate or severe pulmonary involvement in the acute phase of COVID-19 in order to assess resolution or progression of persistent interstitial lung abnormalities. Pulmonary function tests, including a six-minute walk test, should be preferably performed at 3, 6, and 12 months after discharge.

In conclusion, the various uncertainties related to pulmonary fibrosis and the optimization of respiratory follow-up after COVID-19 are expected to be clarified in the near future. Studies with longer follow-up periods are required to determine how post-COVID-19 interstitial lung disease (ILD) progresses and what the best approach for such patients in the long term is. It is essential that health care centers be organized for clinical follow-up and use of ancillary tests to care for the growing number of patients with post-COVID-19 ILD that will need to be monitored in the long term, preferably adopting a multidisciplinary approach. Additionally, various examples reinforce the potential role and expansion of telehealth in supporting the management of COVID-19 survivors, which may be helpful in such a scenario. Due to the heterogeneity of health care centers, we suggest that the implementation and standardization of care of patients with post-COVID-19 ILD should be individualized according to the resources available and the priorities established at each outpatient clinic.

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J Bras Pneumol. 2021;47(4):e20210275
https://dx.doi.org/10.36416/1806-3756/e20210275

Post-treatment lung cancer patients: residual tumor, recurrence, and second primary tumor

Dante Luiz Escuissato[1,2], Danny Warszawiak[2,3]

In an article published in the current issue of the *Jornal Brasileiro de Pneumologia*, the usefulness of routine CT follow-up for lung cancer recurrence and second primary lung cancer is questioned.[1] This question is relevant, particularly in the field of cancer imaging.

In recent years, there have been several reports of increased survival in patients with lung cancer. This is due to improved treatment options to control lung cancer and lung cancer recurrence, including surgery, radiation therapy, and systemic therapies, as well as new experimental modalities.[2]

Although the likelihood of local and distant recurrence decreases with time, the risk of second primary cancers does not, the reported incidence of second primary cancers being 8.6% in a study by Rice et al.[3] and 7.3% in a study by Fink-Neuboek et al.[4] It has also been reported that, regardless of stage and histological type, lung cancer patients are more likely to have distant metastases than local recurrence, being candidates for additional treatment.[5]

A considerable number of patients with stage I-III lung cancer will have local recurrence (22-50%) or distant recurrence (3-20%) after treatment with curative intent.[6] Because of the high risk of non-small cell lung cancer recurrence and second primary lung cancer, the National Comprehensive Cancer Network and the American Association for Thoracic Surgery recommend patient monitoring.[7] The American Society of Clinical Oncology recommends that patients undergo follow-up chest CT for recurrence every six months for two years and then annually for detection of new primary lung cancers.[8] Radiologists and nuclear medicine physicians should be able to distinguish between treatment-related findings and cancer-related findings. In comparison with CT, 18F-FDG PET/CT is associated with higher rates of detection of postsurgical recurrence, being recommended by the National Comprehensive Cancer Network to differentiate tumor recurrence from benign conditions such as atelectasis, consolidations, and radiation-induced fibrosis; however, it should be borne in mind that 18F-FDG uptake can be seen up to three months after tumor removal and up to six months after radiation therapy, particularly stereotactic body radiation therapy, and is not always indicative of tumor recurrence.[7]

According to the Union for International Cancer Control, an incomplete resection is defined by the presence of tumor in the primary site, lymph nodes, or distant sites after treatment.[9,10] This plays a major role in determining a prognosis and indicating the need for additional treatment. Because it is difficult to distinguish between recurrent and residual tumor after an apparently complete resection, surgeons have attempted to refine these definitions. In 1998, the Spanish Society of Pulmonology and Thoracic Surgery proposed the following definition of complete resection: (a) resection margins microscopically free of tumor; (b) complete mediastinal lymphadenectomy; (c) absence of extracapsular lymph node extension; and (d) the most distant lymph node stations (the highest in the superior paratracheal node and the lowest in the pulmonary ligament) must be disease free.[9] Therefore, the completeness of resection is classified as R0 (no residual tumor), R1 (microscopic residual tumor), or R2 (macroscopic residual tumor). The International Association for the Study of Lung Cancer has also proposed a definition for uncertain resection, referred to as R(un).[11] An R(un) is defined by examination of fewer than three N1 lymph nodes and three N2 lymph nodes; failure to perform lobe-specific systematic nodal dissection; the highest mediastinal lymph node removed being positive; carcinoma in situ at the bronchial margin; and positive pleural lavage cytology.[11]

According to Morellato et al.,[1] there is controversy in the literature regarding the types of tests that lung cancer patients should undergo, how often they should undergo such tests, and how long. In addition, it is not always easy to determine whether a cancer patient has a residual tumor, recurrence, or second primary tumor. Therefore, a multidisciplinary approach to diagnosis, treatment, and follow-up can minimize these uncertainties.

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J Bras Pneumol. 2021;47(4):e20210238
https://dx.doi.org/10.36416/1806-3756/e20210238

COVID-19 pandemic and the opportunity to accelerate remote monitoring of patients

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In December of 2019, a novel coronavirus, later named SARS-CoV-2, was identified as the cause of an outbreak of pneumonia in China. The disease caused by that virus was designated COVID-19 and rapidly spread throughout the world, seriously affecting Latin America.

In a different manner from the first coronavirus that caused the outbreak of SARS in 2003 and that could only replicate in the lower respiratory tract, SARS-CoV-2 begins to replicate in the upper airways and is transmissible before an infected patient develops symptoms.[1] Thus, isolation of cases and contact tracing have been shown to be a more difficult task than it was during the SARS epidemic or the H1N1 pandemic in 2009, and only few countries succeeded in doing so.[2]

Although the clinical presentation of about 80% of the patients with COVID-19 is mild, the sheer number of cases in Latin American countries has led to the collapse of the overburdened health care system in many countries, such as what happened in Guayaquil (Ecuador)[3] and Manaus (Brazil).[4] On June 10, 2021, four of the ten countries with the highest death tolls were in Latin America, namely, Brazil, Mexico, Peru, and Colombia.[5] Therefore, strategies that could actively monitor patients with mild disease and identify those who are at an increased risk of worse outcomes are of paramount importance for overburdened health care systems.

In the current number of the *Jornal Brasileiro de Pneumologia*, Simian et al.[6] present a study carried out in a large tertiary center in Santiago, Chile, which involved a cohort of 7,108 outpatients with a positive RT-PCR SARS-CoV-2 test. Of those, 1,617 patients were actively followed through online surveys during their 14-day isolation period. The authors aimed to assess whether three symptoms reported by patients during the isolation period (i.e., new-onset fever, dyspnea, and chest pain) could predict the need for hospitalization. A follow-up online survey was sent to all of the patients on days 1, 6, 10, and 14 after the positive RT-PCR test result. Response rates were above 75% for all surveys. If a patient reported one of the three red-flag symptoms, a physician or a nurse would contact the patient by phone for a detailed evaluation. A total of 76 patients (4.7%) were hospitalized during the 14-day follow-up period. New-onset fever and dyspnea (but not new-onset chest pain) were associated with an increased risk of hospitalization during the 14-day follow-up period, according to a model adjusted for age, presence of comorbidities, fever, chest pain, and dyspnea at baseline.

The study by Simian et al.[6] provides significant evidence for the adoption of active remote monitoring of red-flag symptoms in patients with COVID-19. This strategy may identify patients with a high risk of hospitalization and decrease the burden of the disease in health care systems by reducing the number of face-to-face consultations. Many other conditions could benefit from similar follow-up online surveys, including assessment of adherence to treatment.

The study[6] has two major limitations that preclude the wide adoption of the intervention. First, only 22% of all outpatients with a positive SARS-CoV-2 RT-PCR test result were included in the follow-up study. It was unclear the reason why more than 5,000 patients could not be followed. However, we can infer from the data provided that the patients who were followed had a higher burden of comorbidities. The researchers might have decided to follow a population with a higher risk of hospitalization. Second, this was a single-center study in a large tertiary center. It is possible that centers with fewer resources would not be able to implement such follow-up programs.

Although COVID-19 has caused a death toll never witnessed since the 1918 Spanish influenza pandemic, hitting Latin America even in a worse way, it has also brought a more rapid implementation of new technologies, such as telehealth for remote monitoring of patients, which can reduce the overburden in health care systems and rapidly identify patients at a higher risk of worse outcomes, and, therefore, optimize resource allocation. The study by Simian et al.[6] suggested that it is possible to remotely monitor patients with an acute illness and identify those with new-onset fever or dyspnea as having a higher risk of hospitalization so that they could be followed more closely. These programs can be implemented for the follow-up of patients with common conditions, such as acute exacerbations of COPD, asthma, and tuberculosis.

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J Bras Pneumol. 2021;47(4):e20210277
https://dx.doi.org/10.36416/1806-3756/e20210277

Importance of functional capacity assessment and physical exercise during and after hospitalization in COVID-19 patients: revisiting pulmonary rehabilitation

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We read with great interest the recent findings in the study by Zampogna et al.[1] entitled "Time course of exercise capacity in patients recovering from COVID-19-associated pneumonia." The central objective of the study was to evaluate the exercise capacity of patients four weeks after hospital discharge and after a three-month follow-up period. To that end, the authors divided the patients into two groups using the cutoff point of 75% of the predicted value for the six-minute walk distance. The main finding of that study[1] was that both groups recovered their exercise capacity and functional status after three months of follow-up. The study premise is interesting (functional assessment of patients who recovered from COVID-19) and provides the reader with important information about pulmonary rehabilitation strategies, which is one of the main challenges for COVID-19 survivors. However, some aspects of the study are subject to criticism.

Patients with COVID-19 and prolonged length of hospital stay can suffer from various functional limitations after discharge. Post-COVID symptoms include neuromusculoskeletal disorders, such as neuropathy and muscle weakness; dyspnea; severe hypoxemia; anxiety and/or depression; significant weight loss; and cardiovascular sequelae.[2,3] Therefore, these functional limitations need to be explored not only after discharge, but also during early rehabilitation in the convalescence phase.[4] In this context, a mobility team combined with interdisciplinary assistance[5] are essential to make the functionality of such patients to improve progressively, resulting in better quality of life and enabling the patients to return to their work activities.[6,7] However, it is necessary to consider some concerns related to that study.[1] There was a lack of clarity regarding the time course of the functional assessments performed, the importance and objective of the functional tests selected, and some details about the proposed rehabilitation program carried out during the follow-up. A more consistent description of the methodology should have rigorously been carried out. In this context, the study has its originality, importance, and clinical applicability jeopardized.

Considering that the mean length of ICU stay was 43 days, it is expected that the patients presented with pronounced limitations in functionality and performance of activities of daily living (ADL) and required to be followed up after discharge. The study started the evaluations approximately four weeks after discharge (4 ± 1 weeks), that is, they were extremely late, variability was high, and no details regarding the functional recovery process between discharge and beginning of follow-up were provided. In this context, it is highly recommended and desirable that rehabilitation programs that encourage functional recovery of these long-hospitalized patients should and can be started during hospitalization and need to be continued immediately after hospital discharge.[8] In addition, it is not clear in that study[1] whether the patients who were recruited after discharge had been admitted to different hospitals and, therefore, whether they had received equivalent pulmonary rehabilitation during hospitalization, which could impact their functionality after discharge.

The study has a bias in its own design, because the individuals were selected on the basis of their functional capacity and there was an imbalance in the number of individuals in each group that underwent a rehabilitation program (73% and 33% of the individuals in the <75% and ≥75% groups, respectively), evidencing a heterogeneous load of exercise training between the groups. It is highly likely that functional recovery in the <75% group was mainly due to the rehabilitation program implemented in which the patients were inserted than simply due to the time course. In addition, the study proved to be precarious since it did not present the rehabilitation structure in which the patients were submitted to from the standpoint of location (home or rehabilitation center), frequency, intensity, modality of exercise and supervision (face-to-face, telerehabilitation, unsupervised, or a combination of those).[8] In addition, heterogeneous compliance of patients in rehabilitation programs may compromise the results of the functional outcomes investigated.[9] The authors should have explored all of these aspects in more details, and, therefore, that study lacks reproducibility.[1]

Regarding functional assessments, the authors mentioned that the six-minute walk test was used in order to assess lower extremity function, but COVID-19 patients report increased dyspnea and fatigue symptoms associated with impaired performance of ADL, particularly those who survived hospitalization.[10] In this context, most of ADL require elevation of both arms, with and without support.[11] Therefore, because the assessment of ADL also requires the assessment of the functionality of the upper limbs, that would be highly recommended, since therapies aimed at improving this function can also contribute to reducing dyspnea and muscle fatigue in

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ISSN 1806-3756

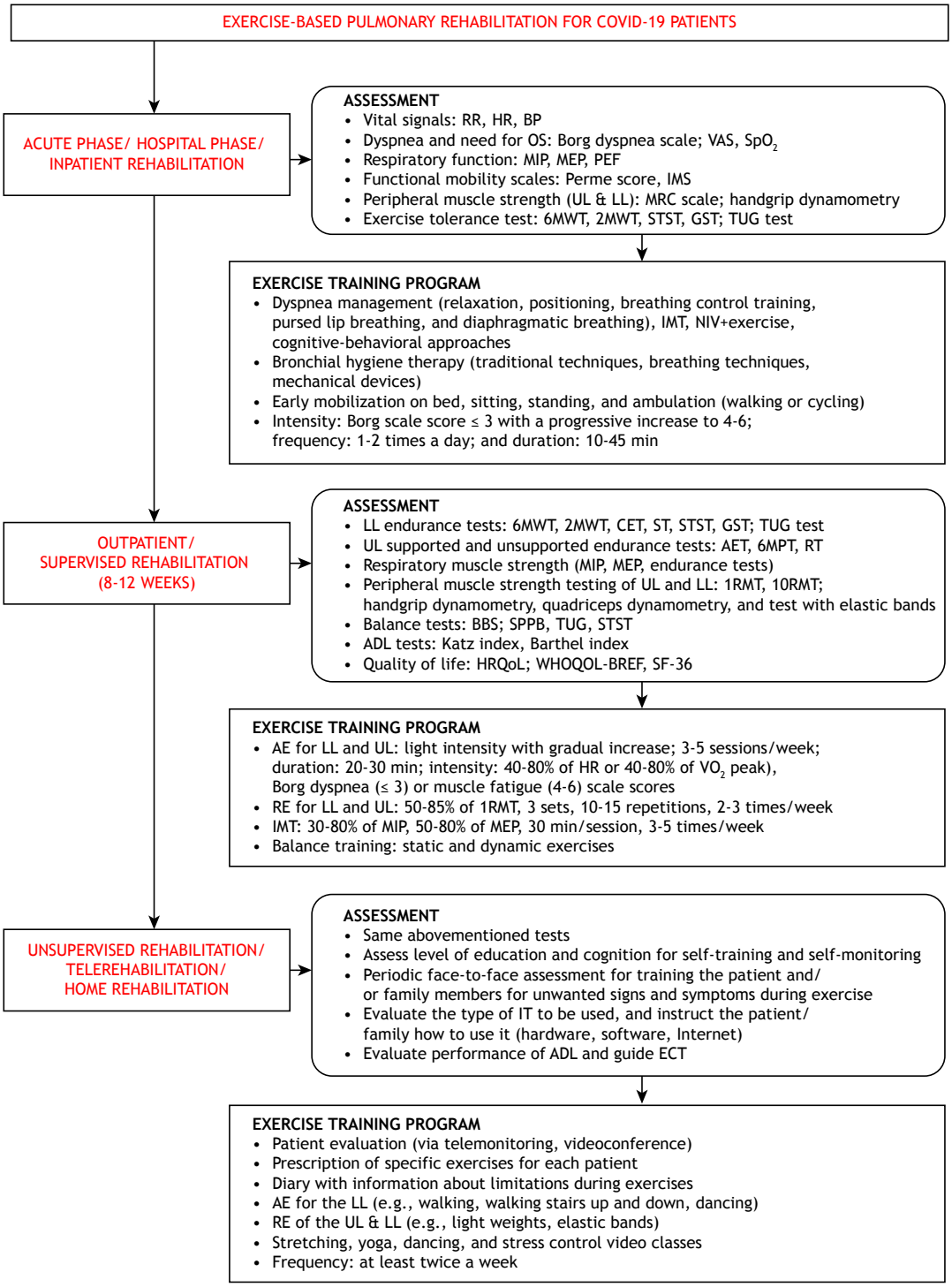

Figure 1. Recommendations for assessment and physical training during different phases of pulmonary rehabilitation in COVID-19 patients. BP: blood pressure; OS: oxygen supplementation; VAS: visual analog scale; Perme: Perme Intensive Care Unit Mobility Score; IMS: ICU mobility scale; UL: upper limbs; LL: lower limbs; MRC: Medical Research Council scale; 6MWT: six-minute walk test; 2MWT: two-minute walk test; STST: sit-to-stand test; GST: gait speed test; TUG: timed up and go; IMT: inspiratory muscle training; NIV: noninvasive ventilation; CET: cycle ergometer test; ST: step test; AET: arm ergometer test; 6MPT: six-minute pegboard test; RT: ring test; 1RMT: one-repetition maximum test; 10RMT: ten-repetition maximum test; BBS: Berg balance scale; SPPB: Short Physical Performance Battery; ADL: activities of daily living; HRQoL: health-related quality of life; WHOQOL-BREF: World Health Organization Quality of Life Instrument, brief version; SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; AE: aerobic exercise; RE: resistance exercise; IT: information technology; and ECT: energy conservation techniques.

those patients and to helping select a physical training program that can improve muscle dysfunction especially targeted for promoting functional independence for performing daily tasks in the home environment. Following this line of reasoning, it is highly recommended to assess the mechanisms of upper extremity muscle dysfunction, which can be measured and confirmed by different tests.[12]

In conclusion, despite the relevance of the study by Zampogna et al.,[1] given that the temporal evolution of functional capacity in patients affected by COVID-19 can be impacted by early and late rehabilitation, the conclusion of the study needs to be analyzed with caution. The assessment of functional capacity is important and should be directed to the phase of pulmonary rehabilitation (Figure 1). In addition, the absence of differences in the functional recovery of those individuals after a three-month period, considering that different loads of pulmonary rehabilitation were applied in both groups and no information regarding the protocol of physical exercise (intensity, duration, and number of sessions) were described, indicates that the results of that study should be evaluated with reservations. Therefore, it would be fair to assume that, above all, if the two groups were to receive equally exercise-based rehabilitation, the results would be likely to be different. Finally, we strongly recommend that a broader assessment of ADL should include activities that incorporate the upper limbs, because they are strongly associated with improvements in ADL, symptoms, and, consequently, quality of life in COVID-19 survivors.

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Ground-glass opacities with subpleural sparing

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

A 63-year-old man presented with a two-month history of progressive dyspnea and dry cough. He was undergoing outpatient investigation for arthritis. Chest CT showed ground-glass opacities at the lung bases, with subpleural parenchymal sparing (Figure 1).

Ground-glass opacity is a frequent finding on chest CT, being probably one of the most nonspecific findings, and may represent acute or chronic disorders, as well as alveolar or interstitial disorders. Sometimes, the distribution of lesions in the lung parenchyma can guide the list of diagnostic hypotheses. For instance, pulmonary edema tends to be medullary in distribution, whereas eosinophilic pneumonia tends to be located in the lung periphery. Associated CT findings, such as the presence of pulmonary cysts, nodules, pleural effusion, or enlarged lymph nodes, can aid in diagnosis.

The correlation of imaging findings with clinical and laboratory data is essential for diagnosis. Basic clinical information, such as whether the disease course is acute or chronic or whether the patient has any immunodeficiency, complains of fever, hemoptysis, or other symptoms, has preexisting diseases or extrapulmonary manifestations of the current disease, has a history of asthma, and/or is/has been in contact with antigens (mold, birds, etc.), provide a basis for narrowing diagnostic possibilities. Careful analysis of laboratory findings (abnormal blood workup, increase in inflammatory markers, presence of specific antibodies, etc.) is also important.

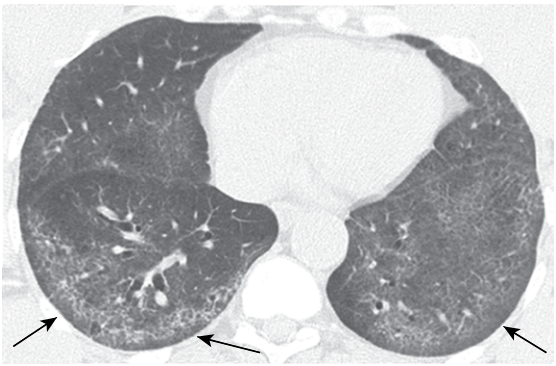

Figure 1. Axial CT of the lung bases shows peripheral ground-glass opacities containing mild reticulation, with subpleural parenchymal sparing (arrows).

Our patient presented with a very characteristic distribution of ground-glass opacities, predominating at the bilateral lung bases and sparing the subpleural parenchyma. This CT finding is highly suggestive of nonspecific interstitial pneumonia (NSIP).[1,2]

NSIP is a chronic interstitial disease characterized by inflammatory and/or fibrotic infiltration of the alveolar septa. Two forms of the disease have been described: a predominantly inflammatory cellular form and a fibrotic form. The cellular form has a better prognosis than does the fibrotic form. NSIP can be classified as idiopathic or secondary to a series of lung disorders, such as drug reactions, collagen diseases, and hypersensitivity pneumonitis. Pathological findings include homogeneous inflammatory or fibrotic infiltration of the alveolar septa, or both.[1,2] The most common clinical findings are progressive dyspnea and chronic dry cough. On CT, the major finding in the cellular form is symmetrical ground-glass opacities, whereas in the fibrotic form, there is reticulation superimposed on traction bronchiectasis/bronchiolectasis. Mild honeycombing can also occur. Lesions generally predominate in the lower and peripheral lung fields.[1,2] Subpleural sparing, as was observed in our patient, occurs in approximately half of the cases.

The clinical and laboratory evaluation of our patient led to the final diagnosis of rheumatoid arthritis, and lung biopsy confirmed suspected NSIP.

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Nonparametric statistical tests: friend or foe?

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PRACTICAL SCENARIO

The head of an ICU would like to assess if obese patients admitted for a COPD exacerbation have a longer hospital length of stay (LOS) than do non-obese patients. After recruiting 200 patients, she finds that the distribution of LOS is strongly skewed to the right (Figure 1A). If she were to perform a test of hypothesis, would it be appropriate to use a t-test to compare LOS between obese and non-obese patients with a COPD exacerbation?

PARAMETRIC VS. NONPARAMETRIC TESTS IN STATISTICS

Parametric tests assume that the distribution of data is normal or bell-shaped (Figure 1B) to test hypotheses. For example, the t-test is a parametric test that assumes that the outcome of interest has a normal distribution, that can be characterized by two parameters[1]: the mean and the standard deviation (Figure 1B).

Nonparametric tests do not require that the data fulfill this restrictive distribution assumption for the outcome variable. Therefore, they are more flexible and can be widely applied to various different distributions. Nonparametric techniques use ranks[1] instead of the actual values of the observations. For this reason, in addition to continuous data, they can be used to analyze ordinal data, for which parametric tests are usually inappropriate.[2]

What are the pitfalls? If the outcome variable is normally distributed and the assumptions for using parametric tests are met, nonparametric techniques have lower statistical power than do the comparable parametric tests. This means that nonparametric tests are less likely to detect a statistically significant result (i.e., less likely to find a p-value < 0.05 than a parametric test). Additionally, parametric tests provide parameter estimations—in the case of the t test, the mean and the standard deviation are the calculated parameters—and a confidence interval for these parameters. For example, in our practical

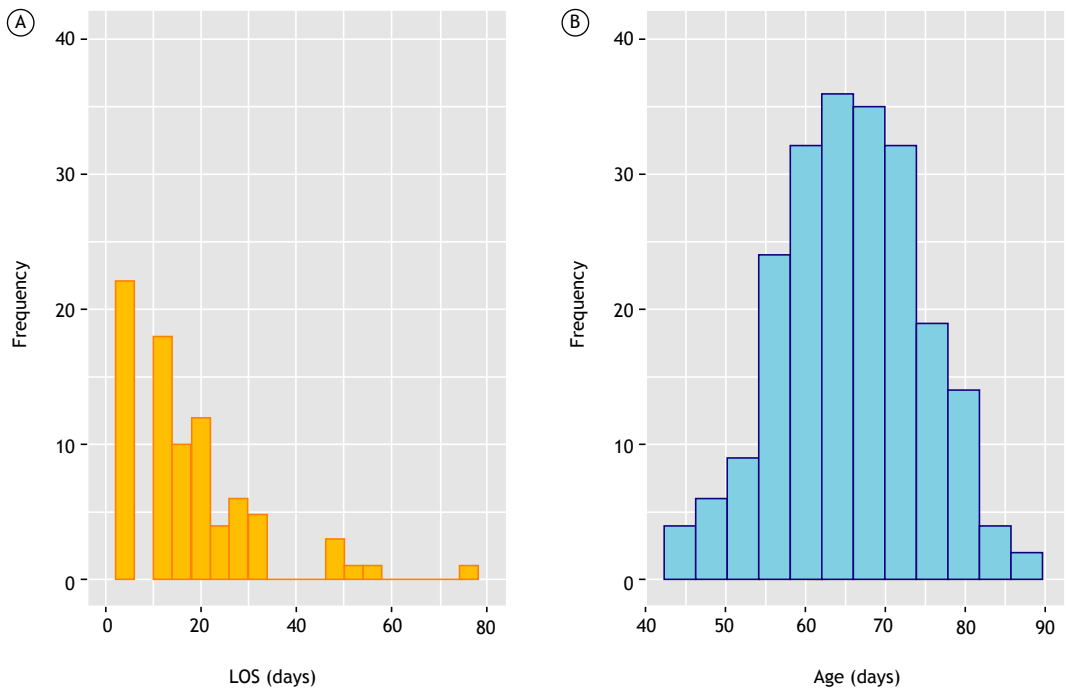

Figure 1. In A, hospital length of stay (LOS) of patients admitted for COPD exacerbations. The data clearly have a non-normal distribution and are skewed to the right. In B, age distribution of the same group of patients. The data are normally distributed (N = 200 patients).

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ISSN 1806-3756

scenario, if the difference in LOS between the groups were analyzed with a t-test, it would report a sample mean difference in LOS between the groups and the standard deviation of that difference in LOS. Finally, the 95% confidence interval of the sample mean difference could be reported to express the range of values for the mean difference in the population. Conversely, nonparametric tests do not estimate parameters such as mean, standard deviation, or confidence intervals. They only calculate a p-value.[2]

HOW TO CHOOSE BETWEEN PARAMETRIC AND NONPARAMETRIC TESTS?

When sample sizes are large, that is, greater than 100, parametric tests can usually be applied regardless of the outcome variable distribution. This is due to the central limit theorem, which states that if the sample size is large enough, the distribution of a given variable is approximately normal. The farther the distribution departs from being normal, the larger the sample size will be necessary to approximate normality.

When sample sizes are small, and outcome variable distributions are extremely non-normal, nonparametric tests are more appropriate. For example, some variables are naturally skewed, such as hospital LOS or number of asthma exacerbations per year. In these cases, extremely skewed variables should always be analyzed with nonparametric tests, even with large sample sizes.[2]

In our practical scenario, because the distribution of LOS is strongly skewed to the right, the relationship between obesity and LOS among the patients hospitalized for COPD exacerbations should be analyzed with a nonparametric test (Wilcoxon rank sum test or Mann-Whitney test) instead of a t-test.

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Extradiaphragmatic respiratory muscle perfusion during exercise in patients with COPD: impact on dyspnea

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BACKGROUND

Advances in technology, such as the use of near-infrared spectroscopy to measure local respiratory muscle blood flow,[1] make it possible to investigate whether alterations in respiratory muscle perfusion during exercise contribute to the development of respiratory muscle fatigue and to associated increases in dyspnea perception in patients with COPD.

CASE HISTORY

A 62-year-old man (BMI = 24.2 kg/m^2), former smoker, was diagnosed with COPD—FEV_1 = 56% of predicted; FEV_1/FVC = 0.37; maximum voluntary ventilation = 55 L/min (45% of predicted); static hyperinflation at rest (inspiratory capacity [IC] = 2.40 L [79% of predicted]); functional residual capacity = 6.44 L (187% of predicted); IC/TLC = 0.27; and RV/TLC = 0.47—having moderately reduced diffusion capacity (DL_{CO} = 46% of predicted), exertional dyspnea (modified Medical Research Council scale score = 2), preserved inspiratory muscle strength (MIP = 108 cmH_2O [97% of predicted]), reduced functional capacity (six-minute walk distance = 443 m [65% of predicted]), reduced peak exercise capacity (measured during a cardiopulmonary exercise test: cardiac output = 10.2 L/min; peak VO_2 = 1.26 L/min (59% of predicted), and reduced peak work rate (WR_{peak} = 100 W [54% of predicted]). The patient underwent three different exercise sessions and presented with a combination of breathlessness and leg discomfort (50% in both; Borg dyspnea and leg fatigue scores = 7), which were reported to be the main reason for interrupting exercise.

TESTING PROCEDURES

The patient performed: i) a constant-load exercise test on a cycling ergometer (CE), sustained at 80% of WR_{peak} (80 W) to the limit of tolerance (endurance cycling time = 5 min & 30 s); ii) a normocapnic hyperpnea (NH) session sustained for 5 min at similar minute ventilation (i.e., ~51 L/min) and breathing pattern as recorded during the cycling exercise test (locomotor muscles did not compete with respiratory muscles for the available blood flow; i.e., endurance stimulus); and iii) an inspiratory loaded breathing (LB) session for 5 min against an external resistance of ~50% of MIP (i.e., 55 cmH_2O; strength stimulus).[2,3]

CLINICAL OVERVIEW

During the CE test, the patient had dynamic hyperinflation (a 970 mL reduction in IC from rest) and reported very severe leg fatigue (Borg scale score = 7). Respiratory muscle work was greater during LB than during NH and CE (Figure 1A), which resulted in larger rib cage and neck muscle activation during inspiration to overcome the additional external load imposed on the respiratory system (Figure 1B). Nevertheless, the pressure-time product of inspiration accounting for the energy cost of breathing was greater during CE and NH than during LB (158 and 165 $cmH_2O \cdot s/min$, respectively, vs. 49 $cmH_2O \cdot s/min$). Cardiac output increased from rest (4.1 L/min) during all exercise sessions, and it was greater during CE than during NH and LB (9.8 L/min vs. 5.9 and 4.9 L/min, respectively). Despite a twofold increase in cardiac output during CE, scalene, intercostal and abdominal local muscle perfusion and oxygenation were lower during NH and LB (Figures 1C and 1D). It is of note that the patient reported very severe dyspnea during CE and moderate dyspnea during NH and LB (Figure 1E).

DISCUSSION AND CLINICAL MESSAGE

Collectively, this case illustrates that extradiaphragmatic respiratory muscle underperfusion occurs during high-intensity whole-body exercise. Indeed, when high-intensity endurance and strength stimuli are imposed on respiratory muscles during NH and LB, respectively and locomotor muscles do not compete with respiratory muscles for the available blood flow, cardiac output increases proportionally to the energy cost of breathing, and intercostal, scalene and abdominal local muscle perfusion increases from rest. In contrast, during CE, the patient had a decreased respiratory muscle energy supply (Figures 1E and 1F) as indicated by the decrease in extradiaphragmatic respiratory muscle perfusion and oxygenation, whilst cardiac output was twice as high as during NH and LB. Insufficient adjustment in oxygen availability to extradiaphragmatic respiratory muscles might contribute to the development of respiratory muscle fatigue and an increase in dyspnea perception, leading to premature exercise termination.[4] In support of this mechanism, improvements in oxygen delivery to extradiaphragmatic muscles by using heliox and/

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ISSN 1806-3756

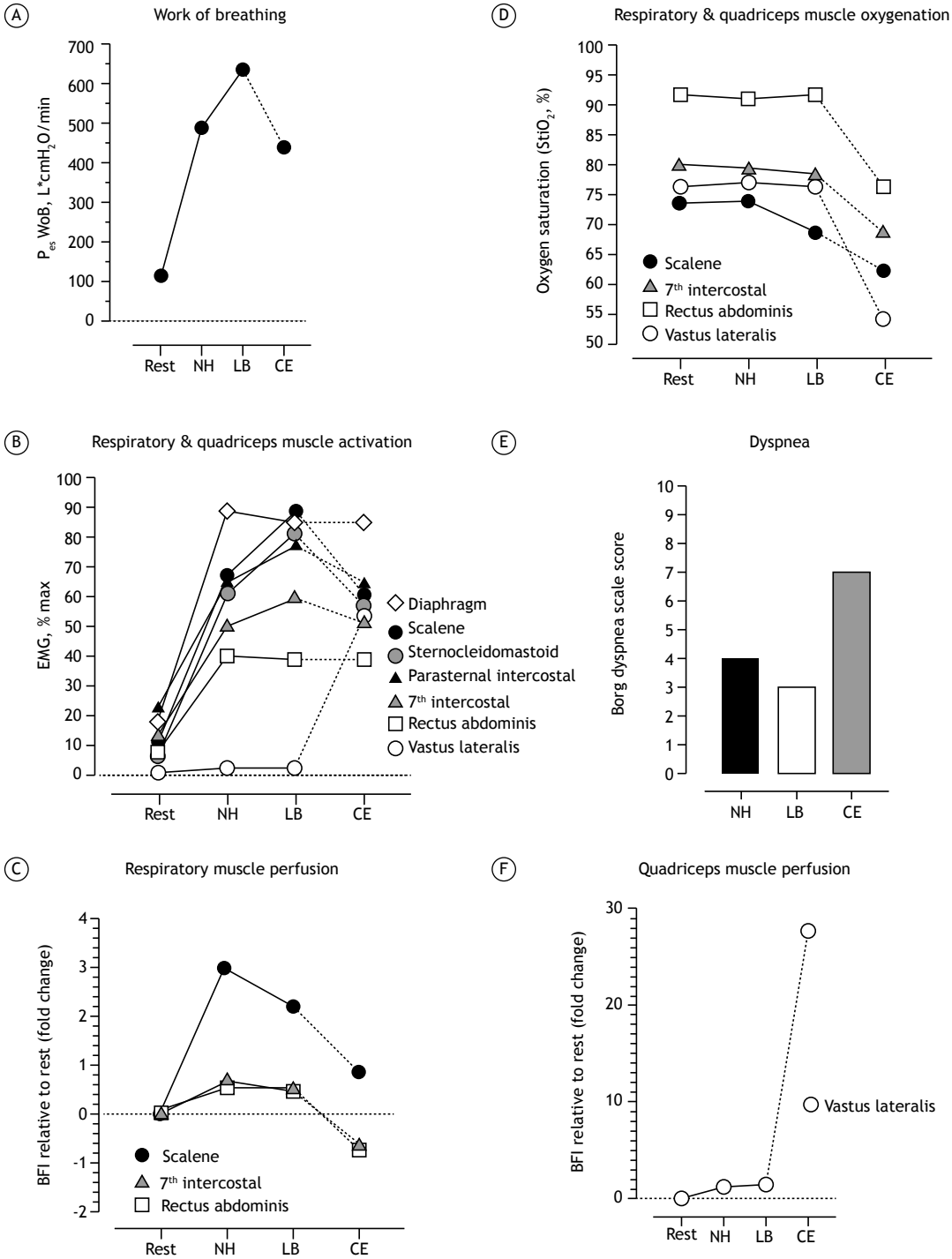

Figure 1. Respiratory muscle work (A), activation of respiratory muscles and quadriceps (B), respiratory muscle perfusion (C), oxygenation response of respiratory muscles and quadriceps (D), Borg dyspnea scale score (E), and locomotor muscle perfusion (F) in a 62-year-old man with COPD. Measurements were performed at rest; during a normocapnic hyperpnea (NH) session, representing an endurance stimulus for the respiratory muscles (i.e., locomotor muscles did not compete with respiratory muscles for the available blood flow); during a loaded breathing (LB) session, representing a strength stimulus for the respiratory muscles; and during a cycling exercise (CE) test. Pes: oesophageal pressure; WoB: work of breathing; EMG: electromyography; BFI: blood flow index; and $StiO_2$: tissue oxygen saturation.

or oxygen supplementation have been shown to be associated with less dyspnea during exercise in patients with COPD.[5] An area of specific interest for future studies is to investigate whether specific rehabilitative interventions that have been documented to increase respiratory muscle capacity (e.g., inspiratory muscle

training)[6] can also elicit improvements in availability of respiratory muscle energy and contribute to lower dyspnea perception during whole body exercise in patients with COPD.

AUTHOR CONTRIBUTIONS

ZL designed the study and drafted the manuscript. All authors read, revised and approved the final version of the manuscript.

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J Bras Pneumol. 2021;47(4):e20200557
https://dx.doi.org/10.36416/1806-3756/e20200557

Clinical outcomes of cystic fibrosis patients with hemoptysis treated with bronchial artery embolization

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Submitted: 3 November 2020.
Accepted: 22 May 2021.

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ABSTRACT

Objective: Massive hemoptysis is one of the most serious complications in patients with cystic fibrosis (CF). This study aimed to evaluate the hemoptysis-free period following bronchial and non-bronchial artery embolization (BAE/non-BAE) in CF patients and to investigate predictors of recurrent bleeding and mortality by any cause. **Methods:** This was a retrospective cohort study of CF patients ≥ 16 years of age undergoing BAE/non-BAE for hemoptysis between 2000 and 2017. **Results:** We analyzed 39 hemoptysis episodes treated with BAE/non-BAE in 17 CF patients. Hemoptysis recurrence rate was 56.4%. Of the sample as a whole, 3 (17.6%) were hemoptysis-free during the study period, 2 (11.8%) underwent lung transplantation, and 3 (17.6%) died. The median hemoptysis-free period was 17 months. The median hemoptysis-free period was longer in patients with chronic infection with *Pseudomonas aeruginosa* (31 months; 95% CI: 0.00-68.5) than in those without that type of infection (4 months; 95% CI: 1.8-6.2; p = 0.017). However, this association was considered weak, and its clinical significance was uncertain due to the small number of patients without that infection. **Conclusions:** BAE appears to be effective in the treatment of hemoptysis in patients with CF.

Keywords: Cystic fibrosis; Hemoptysis; Bronchial arteries; Embolization, therapeutic.

INTRODUCTION

Cystic fibrosis (CF) is a recessive genetic disease that mostly affects Whites and predominantly involves the lungs by impairing mucociliary clearance of airways.[1,2] This results in inflammation and chronic infection, leading to progressive obstructive lung disease, bronchiectasis, and recurrent respiratory infections.[3,4] One of the most serious complications in patients with CF is massive hemoptysis, present in approximately 4.1% of CF patients in their lifetime, with an average annual incidence of nearly 1%.[5] Bronchial artery embolization (BAE) is the current recommended treatment for patients with massive hemoptysis.[6]

The pathogenesis of hemoptysis is multifactorial.[7] Chronic inflammation and hypoxia have potential proliferative effects on bronchial circulation.[8] Arteries become tortuous, enlarged, and friable, favoring bleeding to the airways. Although there are risk factors for massive hemoptysis, such as advanced age, impairment of pulmonary function, and chronic infection with *Staphylococcus aureus*, the condition is often associated with airway infection and acute pulmonary exacerbation.[5] Therapeutic approaches depend on hemoptysis volume and patient health status. Management of hemoptysis includes conservative medical treatment and BAE/non-BAE; surgery is the final treatment option.[8]

The choice of treatment largely depends on the severity and urgency of the clinical conditions. The quantity of hemoptysis has been defined as scant (< 5 mL), mild-to-moderate (5–240 mL), and massive (> 240 mL).[6] Other authors consider that hemoptysis is massive when bleeding is > 240 mL/day or > 100 mL/day for several days.[5,9] An unequivocal indication for arterial embolization is massive hemoptysis together with clinical instability. In addition, patients who present with massive hemoptysis, become clinically stable, and no longer cough up blood should always be treated with BAE.[6] More recently, however, embolization of bronchial and non-bronchial arteries has been recommended in patients presenting with smaller hemoptysis volumes, decreased lung capacity, and difficulty to maintain airway patency.[10,11] This procedure is also recommended in patients with recurrent hemoptysis when their bronchial hygiene, respiratory physiotherapy, and lifestyles are compromised.[12,13] Bronchoscopy is not part of the routine approach prior to definitive treatment with embolization. However, chest angiotomography may be helpful in providing a thorough understanding of the anatomy and bleeding sites of bronchial arteries and non-bronchial collaterals, making embolization more effective.[14]

BAE for hemoptysis control was first described by Remy et al. in 1974.[15] Since then, several publications have

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Financial support: This study received financial support from the *Fundo de Incentivo à Pesquisa* (Research Incentive Fund) of the Porto Alegre *Hospital de Clínicas* (Protocol no. 180297-2018).

suggested different strategies for the treatment of hemoptysis with embolization, whose main purpose is to block the blood flow from the artery causing the bleeding. The success rate in controlling hemoptysis with embolization has increased in recent years due to improvements in embolic materials and catheter technology.[16,17] Arterial embolization has been particularly effective in patients with CF. In these patients, immediate control of hemoptysis has been achieved in over 90% of the cases.[12,18] However, recurrent bleeding after arterial embolization is a well-known complication, affecting 18% and 21% of the patients at 30 days and at 1 year, respectively,[17] illustrating a limitation of this technique in mid- and long-term outcomes.

The objective of the present study was to evaluate the hemoptysis-free period following BAE/non-BAE in CF patients, as well as to investigate predictors of recurrent bleeding and mortality by any cause.

METHODS

This was a retrospective cohort study including CF patients ≥ 16 years of age admitted to the Porto Alegre *Hospital de Clínicas* (HCPA), located in the city of Porto Alegre, Brazil, due to massive hemoptysis (> 240 mL/day or > 100 mL/day for 3 or more days) and submitted to BAE/non-BAE between January 1st, 2000 and December 31st, 2017. The clinical diagnosis of CF fulfilled the Cystic Fibrosis Foundation consensus criteria.[19] Data were obtained by reviewing the electronic records of the patients.

Data on the following variables were collected at the study entry date in the study: sex; ethnicity; age; presence of F508del mutation; BMI; spirometry results; six-minute walk distance; use of inhaled medications; use of azithromycin; pulmonary artery systolic pressure (estimated by Doppler echocardiography); liver transplantation; and presence of chronic respiratory bacterial infections, CF-related diabetes, pancreatic insufficiency, liver disease, previous pneumothorax, previous hemoptysis without BAE, and previous allergic bronchopulmonary aspergillosis. Spirometry records were obtained at the HCPA Pulmonary Physiology Unit, and FEV_1, FVC, and the FEV_1/FVC ratio were expressed in liters and in percentages of predicted values for sex, age, and height.[20] Prothrombin time, activated partial thromboplastin time, and platelet count were also collected at the time of bleeding. Chronic bacterial infections with *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, or *S. aureus* were defined as patients having three or more positive isolates of these bacteria during the previous 12 months.

All of the patients underwent BAE/non-BAE performed by an interventional radiologist for hemoptysis treatment. The Seldinger technique[21] was used for vascular access via femoral artery, followed by selective catheterization of bronchial arteries. In this procedure, a 2.8-F coaxial microcatheter was used for superselective catheterization, and polyvinyl alcohol particles, ranging from 300-500 μ and 500-700 μ, were used for superselective embolization. All abnormal vessels supplying the area of interest were embolized if technically possible. Non-bronchial systemic arterial collateral supply from intercostal, phrenic, internal mammary, and subclavian arteries was also approached. The total number of specific arteries that received embolization was reviewed in the electronic medical records. In addition, anomalous bronchial artery diameter (≥ 4 mm), anomalous extrabronchial circulation, and previous embolization were recorded, as were complications and adverse effects.

The present study was approved by the Research Ethics Committee of the HCPA (Protocol no. 18-0297) and *Plataforma Brasil* (Protocol no. 64430516.0.0000.5327) and was in accordance with international and national standards for clinical studies in humans (Declaration of Helsinki and Brazilian governmental regulation–*Plataforma Brasil*). Informed consent was waived by the Research Ethics Committee of the HCPA because of the retrospective nature of the study. The authors signed a commitment to privacy and personal data protection statement.

Statistical analysis

The collected data were processed using the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). A descriptive analysis was carried out for demographic characteristics and other variables of interest. The Kaplan-Meier method was used for plotting bleeding-free intervals and survival over time.

Data were analyzed from the date of patient inclusion (study entry date), that is, when the patient first underwent BAE. Outcomes were evaluated until March of 2018, which was defined as the study closing date. Patients who underwent lung transplantation or died along the study period were censored on the date of the event.

Cox proportional hazards regression was used in order to identify risk factors for repeat massive hemoptysis events and to determine the association between the baseline characteristics of the patients and outcomes. Two-tailed statistical tests were used, and significance was set at 5%. On the basis of two previous studies that reported recurrence rates of 47% and 46%,[22,23] the sample size should include approximately 41 cases within a 95% confidence interval.

RESULTS

During the study period, there were 39 hemoptysis episodes requiring BAE in 17 CF patients. General characteristics of the patients at their first hemoptysis event requiring BAE are listed in Table 1. All patients were White. The mean age was 25.0 ± 10.6 years, and 9 patients (53%) were female. Chronic bacterial infection with *P. aeruginosa* was the most prevalent (88%), followed by infection with methicillin-resistant *S. aureus* (35%), methicillin-susceptible *S. aureus*

(29%), and *B. cepacia* complex (17%). Mean values of FVC (% of predicted), FEV_1 (% of predicted), and FEV_1/FVC ratio were 56 ± 25%, 44 ± 25%, and 64.0 ± 12.5, respectively. Mean six-minute walk distance was 438 ± 123 m (Table 1).

During the study period, 9 (53%) and 8 (47%) of the patients were submitted to BAE only once and more than once, respectively (twice, in 2 patients; three times, in 2; four times, in 3; and eight times, in 1). There were no statistical differences between the patients that required one versus more than one procedure during the study regarding sex (p = 0.953), age (p = 0.139), BMI (p = 0.414), FEV_1 in % of predicted (p = 0.391), and FVC in % of predicted (p = 0.366).

Of the 39 hemoptysis episodes requiring BAE, 4 (10.3%) and 6 (15.4%) were censored due to lung transplantation and death, respectively. There was no death due to hemoptysis. The hemoptysis-free period following each procedure was determined using the Kaplan-Meier analysis (median = 17 months; mean = 46 months; Figure 1). There was no immediate recurrence (< 24 h); however, most patients (72%) developed late recurrence (after 30 days).

Results from the univariate logistic regression analysis for the risk of novel hemoptysis episodes are shown in Table 2. The only variable statistically associated with hemoptysis recurrence was chronic infection with *P. aeruginosa* (hazard ratio = 0.28; p = 0.028). Patients with chronic bacterial infection with *P. aeruginosa* had a longer hemoptysis-free period, with a median of 31 months (95% CI: 0.00-68.52) and a mean of 52 months (95% CI: 31.15-74.25) in comparison with those without that infection (median = 4 months; 95% CI: 1.8-6.2; p = 0.017).

Adverse effects following embolization occurred in 20% of the procedures. Chest discomfort, fever, and dyspnea were present after 6, 3, and 1 procedures, respectively. No dysphagia, neurological disorders, or serious complications were reported.

Flexible bronchoscopy and endobronchial irrigation with cold saline were performed in 10 hemoptysis events (8 subjects), and a balloon catheter for bronchus blocking was inserted in only 1 event prior to BAE. Chest CT scanning was performed in 4 hemoptysis events (4 subjects) prior to BAE. None of these procedures were statistically associated with the outcomes (p < 0.05).

Intravenous tranexamic acid was used as an additional therapy in 17 hemoptysis events (9 subjects). No patient was treated with nebulized epinephrine, terlipressin, or beta blockers.

Table 1. Characteristics of the patients at the first hemoptysis episode requiring bronchial artery embolization (N = 17).[a]

Variable	Patients
Sex	
Female	9 (53%)
Male	8 (47%)
Age, years	25 ± 10.6
Age at diagnosis, years	2 [18]
Ethnicity	
White	17 (100%)
BMI, kg/m^2	20.0 ± 2.2
Pancreatic Insufficiency	12 (70.6%)
CFRD	2 (11.8%)
Liver disease	4 (23%)
Liver transplantation	1 (5.9%)
Chronic respiratory infection	
Pseudomonas aeruginosa	15 (88.2%)
Burkholderia cepacia complex	3 (17.6%)
MSSA	5 (29.4%)
MRSA	6 (35.3%)
Pulmonary function	
FVC, % predicted	56 ± 25
FEV_1, % predicted	44 ± 25
FEV_1/FVC, %	64 ± 12.5
6MWD, m	438.8 ± 123.3
PASP, mmHg	22 [13]

CFRD: cystic fibrosis-related diabetes; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; 6MWD: six-minute walk distance; and PASP: pulmonary artery systolic pressure (estimated by Doppler echocardiography). [a]Qualitative data are expressed as absolute (n) and relative (%) frequencies. Quantitative data are expressed as mean ± SD or median and [IQR].

DISCUSSION

This retrospective cohort study evaluated CF patients with massive hemoptysis submitted to BAE/non-BAE in a referral hospital in southern Brazil. Of the 39 hemoptysis episodes requiring BAE/non-BAE, 22 (56.4%) evolved to novel massive hemoptysis episodes. The median hemoptysis-free period following BAE/non-BAE was 17 months. This procedure was first adopted at the HCPA in 2000. Since then, it has been playing an important role in the treatment of hemoptysis in CF patients. BAE/non-BAE was an effective treatment, with immediate hemoptysis control in all cases, since

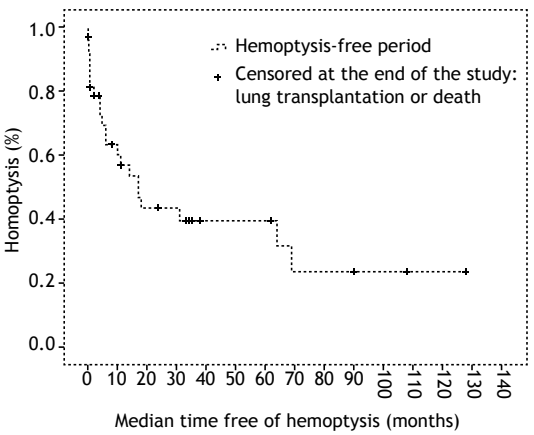

Figure 1. Kaplan-Meier analysis of hemoptysis-free period in cystic fibrosis patients undergoing bronchial artery embolization. Median survival period was 17 months (95 CI: 8.1-25.9) and mean survival period was 46.2 months (95 CI: 26.8-65.6).

Table 2. Univariate logistic regression analysis for a repeat hemoptysis episode.

Variable	β	Wald	p	HR	95% CI
Sex	0.28	0.42	0.517	1.33	0.55-3.18
Age, years	−0.06	2.65	0.103	0.94	0.87-1.01
Age at diagnosis, years	−0.05	1.65	0.199	0.94	0.86-1.03
F508del mutation	0.73	1.42	0.232	2.08	0.62-6.96
BMI, kg/m^2	−0.09	1.02	0.310	0.90	0.75-1.09
Pancreatic insufficiency	1.22	2.62	0.105	3.93	0.77-14.85
CFRD	−0.57	0.59	0.440	0.56	0.13-2.42
Previous pneumothorax	0.71	1.18	0.277	2.03	0.56-7.35
Previous hemoptysis with no BAE	0.49	0.75	0.386	1.63	0.53-5.00
ABPA	−0.55	0.55	0.458	0.57	0.13-2.48
Liver disease	0.25	0.26	0.606	1.28	0.49-3.31
Liver transplantation	−0.36	0.24	0.623	0.69	0.16-2.99
Chronic respiratory infection					
Pseudomonas aeruginosa	−1.26	4.80	0.028	0.28	0.09-0.87
Burkholderia cepacia complex	0.98	3.67	0.055	2.67	0.97-7.29
MSSA	−0.43	0.68	0.407	0.64	0.23-1.80
MRSA	0.25	0.29	0.587	1.28	0.51-3.20
Medication					
Inhaled dornase alpha	−0.56	0.80	0.368	0.56	0.16-1.94
Inhaled colistin	0.26	0.32	0.567	1.30	0.52 -3.24
Inhaled tobramycin	0.43	0.90	0.341	1.54	0.63-3.76
Azithromycin	0.60	0.66	0.414	1.83	0.42-7.89
Pulmonary function					
FVC, % predicted	−0.02	3.36	0.067	0.98	0.95-1.00
FEV_1, % predicted	−0.02	3.35	0.067	0.97	0.957-1.000
FEV_1/FVC, %	−0.02	1.77	0.183	0.97	0.94-1.01
6MWD, m	−0.00	2.80	0.094	0.99	0.99-1.00
PASP, mmHg	0.01	0.67	0.412	1.01	0.97-1.06
Platelet count	0.00	0.02	0.864	1.00	0.99-1.00
INR	1.57	1.17	0.278	4.83	0.28-83.0
Number of embolized arteries	−0.25	2.31	0.128	0.77	0.55-1.07
BAE	0.75	0.53	0.464	2.12	0.28-16.05
Non-BAE	−0.65	2.32	0.127	0.52	0.22-1.21
Anomalous bronchial artery diameter (≥ 4 mm)	0.27	0.322	0.570	1.31	0.51-3.35
Anomalous extrabronchial circulation	−0.64	0.978	0.323	0.526	0.15-1.88
Previous embolization	−0.50	1.26	0.260	0.60	0.25-1.45
Required more than one BAE procedure during the study period	−0.51	1.26	0.260	0.60	0.25-1.45

HR: hazard ratio; CFRD: cystic fibrosis-related diabetes; BAE: bronchial artery embolization; ABPA: allergic bronchopulmonary aspergillosis; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; 6MWD: six-minute walk distance; PASP: pulmonary artery systolic pressure; and INR: international normalized ratio.

no new bleeding was observed within the first 24 h. Moreover, similarly to previous studies, the long-term recurrence rate was 56%. Barben et al.[21] reported a 95% success rate in immediate bleeding control in 38 cases, whereas other studies have described long-term recurrence rates ranging from 42% to 55%.[12,17,21-24]

In a 14-year-long retrospective cohort study, Vidal et al.[25] evaluated 30 CF patients with major or persistent hemoptysis that required 42 embolization sessions. In that study, 8 patients relapsed and required a new embolization procedure. Of those, 4 and 4 patients had one and two relapses each, respectively. The mean period between the first embolization and recurrence was 27.8 months (1-49 months), and 38% relapsed within 5 years after embolization. Of the 30 patients, 8 (26.7%) died from respiratory failure and 9 (30.0%) underwent lung transplant. The failure rate in that study was comparatively higher than in our study, whose mortality and transplant rates were 17.6% and 11.8%, respectively.

In another long-term retrospective study, Barben et al.[26] investigated 52 BAE procedures in 28 CF patients. In that sample, 13 patients required more than one BAE (re-embolization rate = 46%). Of the 13 patients, 3, 1, and 2 required 3, 4, and 5 BAE procedures. The median time between the first and

second BAE procedure was 4 months. The sample in that study was younger (mean age = 15 years) than in the present study (mean age = 25 years). However, despite the age difference, those patients showed similar pulmonary function results. Advances in technology and materials used for BAE might thus justify the longer hemoptysis-free period in our study.

Pathak et al.[27] evaluated long-term outcomes following BAE to treat different lung diseases. In their study, CF was the most common cause of hemoptysis requiring BAE. The recurrence rate was 50%, similar to that in our study. The 10-year survival rate was 85% in CF patients undergoing the procedure. Neither the median nor the mean hemoptysis-free period was described.

Flight et al.[24] described 27 adult CF patients that underwent 51 BAE procedures for massive and submassive hemoptysis over a median follow-up period of 26 months. Hemoptysis recurred after 31 BAE procedures (61%). Mortality after the first BAE at 30 days and at 12 months were 3.9% and 14.8%, respectively. No significant predictors of mortality were identified.

Martin et al.[17] studied 38 BAE procedures for the treatment of hemoptysis in 28 adult patients with CF and reported 30-day, 1-year, and 3-year outcomes. Technical (freedom from repeat embolization and hemoptysis-related mortality) and clinical (freedom from repeat embolization and mortality from any cause) success rates at 30 days were 89% and 82%, respectively, whereas they were 86% and 79% at 1 year and 82% and 75% at 3 years.

When we assessed clinical features that might predict hemoptysis recurrence, we found that the presence of chronic infection with *P. aeruginosa* was the only variable that correlated with longer hemoptysis-free periods, causing a protective effect (median = 31 months). However, this association was considered weak, and its clinical significance was uncertain due to the low number of patients in the group without that type of infection (only 2 patients). Additional studies involving larger numbers of patients are needed to clarify this finding. One hypothesis that might justify this association could be the continuous use of inhaled antibiotics by patients with chronic infection with *P. aeruginosa*, reducing bacterial colonization of the airways, controlling inflammation, and improving the prognosis for hemoptysis recurrence. Respiratory bacterial infection (detected by sputum bacteriology) is often mentioned in studies regarding BAE in CF patients, because *P. aeruginosa* occurs in 56% of the cases. However, to date, there have been no studies correlating this chronic airway infection with hemoptysis recurrence.[9,28,29]

Vidal et al.[25] found that the risk of hemoptysis recurrence was higher in patients with a large number of collateral arteries. There is a lack of information regarding the risks associated with hemoptysis recurrence after BAE. In the present study no correlation was found between the prevalence of this type of arteries and recurrent bleeding.

Previous studies[17,24,30] have described severe adverse effects following BAE, including transverse myelitis, circulation stroke, and paraplegia. However, these rare complications were not identified in our study. New technologies in catheters, guidewires, and embolic agents have likely resulted in safety improvements in BAE. The prevalence of mild adverse events in the literature[17,25] ranges from 5.2% to 50.9%, and the most common symptom is chest pain. Although chest discomfort, fever, and dyspnea occurred in 20% of the cases in the present study, these adverse effects were easily controlled with medication; hence, they did not compromise the clinical outcomes.

The present study has several limitations. First, it was conducted in a single medical center with a relatively small sample size, limiting its statistical power. However, we should notice that the studies published about this subject[10,15-18,23-26] also have a small sample size. Second, the study had a retrospective design, using data obtained from a review of medical records, which are not likely to be as complete and accurate as data collected in prospective studies. Third, the BAE procedures did not follow a strict protocol in this retrospective study.

In conclusion, this retrospective cohort study showed that BAE was an effective treatment for immediate and long-term hemoptysis in CF patients. Successful control was achieved within 24 h in 100% of the cases, with a median hemoptysis-free period of 17 months. The only predictor of recurrent bleeding following BAE was the presence of chronic infection with *P. aeruginosa*, but this association was considered weak and its clinical significance was uncertain due to the small number of patients.

AUTHOR CONTRIBUTIONS

MAPS: study conception and design; data collection, analysis, and interpretation; drafting the manuscript and tables; critical review of content; and approval of the final version. PAPS and FGB: analysis and interpretation of data; drafting the manuscript; critical review of content; and approval of the final version. LAS: study conception and design; data interpretation; drafting the manuscript and figures; critical review of content; and approval of the final version. PTRD: study conception and design; data collection, analysis, and interpretation; drafting the manuscript and figures; critical review of content; and approval of the final version.

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J Bras Pneumol. 2021;47(4):e20200452
http://dx.doi.org/10.36416/1806-3756/e20200452

ORIGINAL ARTICLE

Soluble factors of mesenchimal stem cells (FS-MSC) as a potential tool to reduce inflammation in donor's lungs after hypovolemic shock

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Submitted: 23 February 2021.
Accepted: 10 April 2021.

Study carried out in the Laboratório de Pesquisa em Cirurgia Torácica, Instituto do Coracão, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP), Brasil.

ABSTRACT

Objective: The shortage of viable lungs is still a major obstacle for transplantation. Trauma victims who represent potential lung donors commonly present hypovolemic shock leading to pulmonary inflammation and deterioration and rejection after transplantation. Seeking to improve lung graft, new approaches to donor treatment have been tested. This study focuses on treatment with mesenchymal stem cells (MSCs) or soluble factors produced by MSCs (FS-MSC) using a rat model for lung donors after hemorrhagic shock. **Methods:** Forty-eight rats were divided into four groups**:** Sham (n=12), animals without induction of hypovolemic shock; Shock (n=12), animals submitted to hypovolemic shock (mean arterial pressure 40 mmHg); MSC (n=12), animals submitted to hypovolemic shock and treated with MSCs, and FS (n=12), animals submitted to hypovolemic shock and treated with FS-MSC. The animals were subjected to a 50-minute hypovolemic shock (40 mmHg) procedure. The treated animals were monitored for 115 minutes. We performed histopathology of lung tissue and quantification of inflammatory markers (TNF-α, IL-1β, IL-6, IL-10, iCAM and vCAM) in lung tissue and peripheral blood leukocytes (PBLs). **Results:** Hemorrhagic shock resulted in higher PBLs and neutrophil infiltrate in the lungs. FS animals had lower neutrophil density comparing with Shock and MSC animals ($p<0.001$). No differences in the cytokine levels in lung tissue were observed between the groups. **Conclusions:** The lungs of rats submitted to hemorrhagic shock and treated with FS-MSC showed reduced inflammation indicated in a decrease in lung neutrophil infiltrate.

Keywords: Lung transplantation; Tissue donors; Hypovolemic shock; Mesenchymal cells; Inflammation.

INTRODUCTION

Lung transplantation improves quality of life and survival in patients with end-stage lung disease.[1] Despite all developments achieved in lung transplantation, the number of recipients on waiting list has not decreased, in fact, it now exceeds the number of organs available for donation.[2] Several strategies have been proposed to increase the number of effective donors, including public pro-donor campaigns, use of donors after circulatory arrest, use of live donors, *ex vivo* lung perfusion techniques, and cell therapies.[3-5]

Acute graft rejection is common after lung transplantation and occurs in half of lung transplant recipients after transplantation[6] through mechanisms such as inflammation and pulmonary edema.

Mesenchymal stem cells (MSCs) have been studied as cell therapy for a variety of degenerative, immunological, and inflammatory disorders.[7,8] Animal studies showed that MSCs induce repair of injured organs, decrease inflammation and have an immunomodulatory action with protective effects on the cells by releasing soluble factors (FS-MSC) such as anti-inflammatory cytokines and growth factors.[9] Our hypothesis is that treating lung donors with MSCs (can potentially – can reduce or potentially reduces) reduce graft inflammation. Considering its nature as final product and immediate action, FS-MSC

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Financial support: None.

could be the alternative to contribute to an increase in the number of viable lungs for transplantation.

This study focuses on the impact of *in vivo* treatment with MSCs and FS-MSC on lung inflammation in a rat model of lung donation after hemorrhagic shock.

METHODS

This study was approved by the ethics committee [Research protocol nº 188/14]. All animals were treated according to ethical principles of the Brazilian College of Animal Experimentation and the Guide for Care and Use of Laboratory Animals, provided by the Laboratory of Animal Research Institute and published by the National Academies Press, 8th Edition, 2011.

We included forty-eight adult male Sprague Dawley rats weighing 250-350 g in this study, which were randomly attributed to the following experimental groups: Sham (n=12) – animals subjected to vascular catheterization without shock induction or treatment; Shock (n=12) – animals subjected to vascular catheterization, induction of hemorrhagic shock and treated with replacement of 25% of the blood volume previously withdrawn; MSC (n=12) – animals subjected to vascular catheterization, induction of hemorrhagic shock through blood withdrawal, and treatment with replacement of 25% of the blood volume previously withdrawn, followed by infusion of MSCs via femoral vein; FS (n=12) – animals subjected to vascular catheterization, induction of hemorrhagic shock, and treatment with replacement of 25% of the blood volume withdrawn, followed by FS-MSC infusion via femoral vein.

Experimental protocol

The animals were anesthetized with 5% isoflurane in an acrylic chamber, weighed, and immobilized on a preparation board. We performed an orotracheal intubation using a tube adequate for small animals and initiated mechanical ventilation using a ventilator, also for small animals (Harvard Apparatus, Model 683), with a tidal volume of 10 ml/kg and a frequency of 80 cycles per minute. Anesthesia was maintained by the same isoflurane.

Each anesthetized animal was placed on the operating board. After shaving the right femoral region, we made an incision followed by vessels dissection and cannulation of right femoral artery and vein using tygon indwelling catheters (Critchley, Australia) filled with saline solution and heparin. For catheters insertion into the femoral artery and vein, we used a binocular stereoscopic microscope with a magnification of 4.5X (Olympus, model SZ6145). Right femoral artery catheter was connected to a monitor (Dixtal, DX2021, Brazil) for mean blood pressure (MBP) recordings. Right femoral vein catheter was used to induce and maintain hemorrhagic shock through blood withdrawal, in addition to blood replacement and administration of MSCs and FS-MSC.

Hemorrhagic shock was induced by withdrawing blood from right femoral vein with successive aliquots until MBP reached 40 mmHg within the first 10 minutes of the experiment, as described by Nepomuceno et al.[10] Rats remained in hemorrhagic shock for 50 minutes either by withdrawing or reinfusing the blood in case of MBP change (±5 mmHg).

We monitored the Sham group throughout the experimental period. MSC, FS and Shock groups were subjected to treatment with reinfusion of 25% of the blood withdrawn after hemorrhagic shock. The MSC group received infusion of MSCs at a concentration of 1×10^7 cells in 1 ml of culture medium over a 5-minute period. The FS group received infusion of soluble factors in medium at a volume of 1 ml over a period of 5 minutes. MBP was observed during a 115-minute period (Figure 1).

Lung extraction and preservation

In the end of the experiment, we carried out pulmonary extraction through a laparotomy extended upwards with resection of the sternum and radial opening of the diaphragm. Heart was exposed and a right ventriculotomy was performed adjacent to the pulmonary artery. Inferior vena cava was severed and left ventricle was sectioned longitudinally at the tip. Antegrade pulmonary perfusion was performed with preservation solution (Perfadex®, Vitrolife Göteborg, Sweden) using a cannula introduced into the pulmonary artery through the right ventriculotomy. Preservation solution was administered by gravity from a reservoir positioned 20 cm above the heart, with spontaneous drainage of the effluent through the left ventriculotomy.

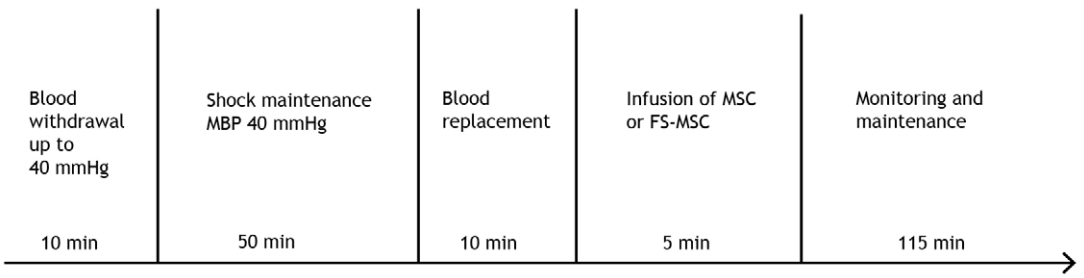

Figure 1. Timeline of the experimental procedure.

In the end of infusion, the trachea was ligated with suture below the cannula, and pulmonary extraction was performed.

Isolation and culture of mesenchymal stem cells

We performed the isolation and culture of MSCs from the adipose tissue according to protocols described in the literature by the Human Genome Group of the School of Medicine of the University of São Paulo (FMUSP).[11] The cells were stored at a concentration of $1x10^7$ cells in 1 ml of the culture medium to be applied as a single dose bolus. This concentration was determined in previous studies of the Human Genome Group of the School of Medicine of the University of São Paulo.[12] We cultured the MSCs in serum-free medium (T225 at 80% confluence) to obtain the FS-MSC . Subsequently, they were rinsed three times with 36 ml of PBS and cultured in 36 ml of DMEM/F12 culture medium without serum or antibiotics. Subsequently, we incubated the cells for eight hours followed by three rinses with 36 ml of PBS and subsequent addition of 36 ml of DMEM/F12 without serum or antibiotics. Another incubation was performed for 20 hours. Afterward, we performed the medium collection, cell count, and centrifugation at 300 × g for 5 minutes to remove debris. The supernatant was collected and the conditioned medium was stored for use. FS-MSC were stored in the medium at a volume of 1 ml to be used as a single dose bolus in each animal of the indicated group. Initial cell density, protein concentration and particle size distribution were not assessed because previous studies of the Human Genome Group of the School of Medicine of the University of São Paulo had already described these characteristics.[13]

Histology analysis

The upper right lobes of lungs were immersed in 10% buffered formalin for fixation. After 24 hours, paraffin blocks were prepared with the samples, sliced into 5 µm sections and stained with hematoxylin-eosin. Analyses were performed in duplicate by two trained researchers who were blinded for the study groups. The slides were analyzed using an Olympus CX22LED microscope with a lattice of dots and lines. For each slide, we assessed 15 fields containing greater lattice increase by counting the dots that touched the areas of pulmonary parenchyma, as well as the total neutrophil count. It was possible to estimate the parenchymal area of each animal examined through the predetermined lattice area, and the ratio of neutrophil counts to the parenchyma area provided the density of neutrophils per squared micrometer (μm^2) of pulmonary tissue. Values were then converted to squared centimeters (cm^2) to facilitate calculations.

Quantification of leukocytes in peripheral blood

Peripheral blood samples (20 µl) were collected from the tail of rats at the beginning of the protocol immediately before induction of hemorrhagic shock, as well as in the end, just before lung extraction. These samples were analyzed through total neutrophil count in Neubauer chamber.

Analysis of cytokines in lung tissue

We prepared the total protein from the animals' tissues by adding RIPA buffer (RIPA Lysis Buffer, 10x – MERK#20-188) at a ratio of 0.4 ml to each 0.1 g of tissue. A total of 10 µl of protease inhibitor cocktail (Protease Inhibitor Cocktail Set I - MERK#53131) was added to each 1 ml of the diluted RIPA buffer. The mixture was then homogenized on ice using a homogenizer (Fisherbrand™ Pellet Pestles™) and the homogenate transferred to a 2 ml Eppendorf tube. We incubated the material on ice for 10 minutes and centrifuged it at 10,000 × g at 4°C for 10 minutes. The supernatant was collected and transferred to a new Eppendorf tube. Total proteins in each sample were quantified and normalized to the value found in the assay (Kit BCA protein assay MERK #71285).

After that, we sent the material for multiplex analysis of the inflammatory cytokines TNF-α, IL-6, IL-1β, and IL-10 according to the xMap methodology (Luminex™ xMAP - Kit Cat. #RECYTMAG-65K-04 (IL-1β, IL-6, IL-10 and TNF- α), Millipore, St. Charles, MO, USA).

Statistical analysis

We performed descriptive analyses for quantitative data, means, and respective standard deviations (SD). Data without a normal distribution are presented using medians and interquartile ranges IQ (25-75%). The assumptions of the normal distribution in each group and the homogeneity of the variances between groups were assessed using the Shapiro-Wilk test and the Levene test, respectively.

For analysis of two factors (Group and Time), we applied two-way repeated measures ANOVA for a single factor (Time), while ANOVA was used to assess normally distributed variables. In case it is necessary to perform multiple comparisons of means, we used the Bonferroni test.

We applied Kruskal-Wallis test for non-normally distributed variablesand Dunn's test when multiple comparisons were required. All inferential analyses considered an α of 0.05. Descriptive and inferential statistical analyses were performed on SPSS software version 21 (SPSS 21.0 for Windows).

RESULTS

The Shock, FS and MSC groups were submitted to hemorrhagic shock from 0 to 10 minutes, showing a decrease in MBP, as predicted ($p<0.001$). During the period of hemorrhagic shock maintenance (10 to 60 minutes), these groups remained with lower MBP than the Sham group, and their means were close to that of the study design. After blood replacement (70 minutes), blood pressure of the Shock, FS and MSC groups increased. However, pressure values

remained lower comparing with those in the Sham group ($p<0.05$) and no significant differences were found ($p>0.10$) (Figure 2).

The groups subjected to hemorrhagic shock, with or without treatment, had more peripheral leukocytes in the end of the experiment in relation to the baseline data ($p<0.001$). The same increase was not found between baseline and final data in the Sham group ($p=0.805$), as observed in Figure 3a.

There was no statistically significant difference in the initial leukocyte count between the distinct experimental groups and Sham group, as expected ($p=0.33$). However, significant increase in circulating leukocytes after hemorrhagic shock was found in the

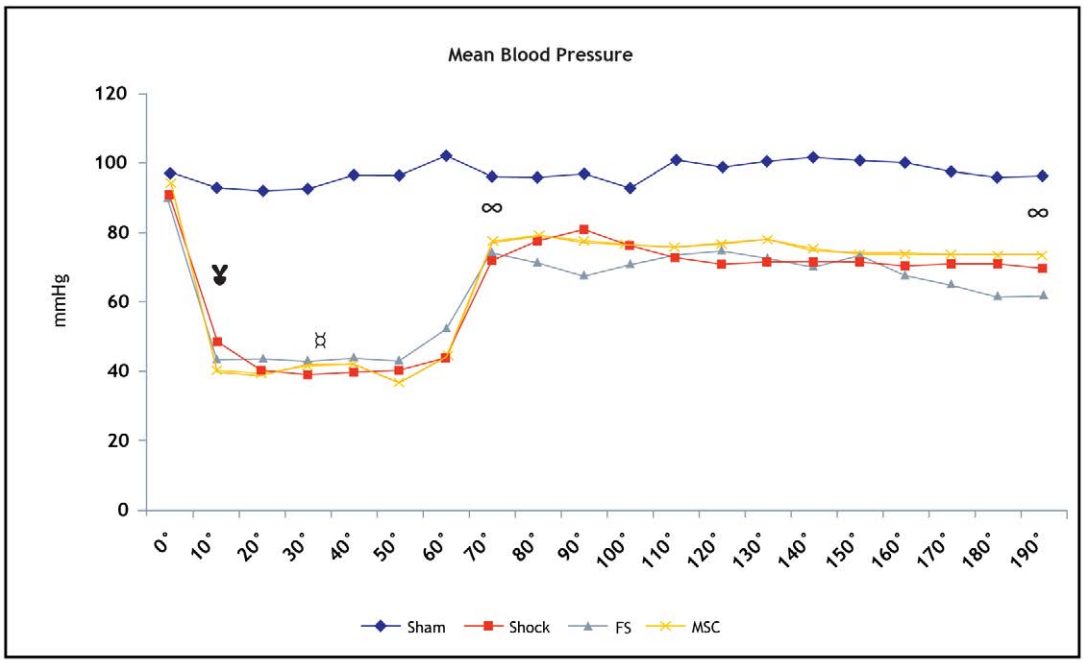

Figure 2. Mean in vivo arterial blood pressure. A statistically significant difference is found in the groups subjected to hemorrhagic shock (Shock, FS and MSC) compared to baseline (¥ $p<0.001$). During the maintenance of hemorrhagic shock, there was a significant difference between the Shock, FS and MSC groups compared to the Sham group (¤ $p<0.001$). At the end of 70 minutes and at 190 minutes, the Shock, FS and MSC groups showed a statistically significant difference compared to the Sham group (∞$p<0.05$).

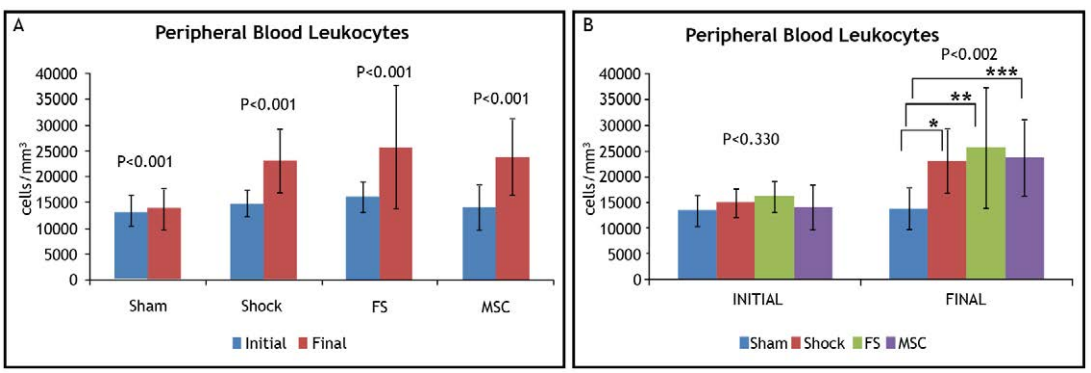

Figure 3. (a) Number of peripheral blood leukocytes collected at the bigining and at the end of the experimental protocol in each group showing a statistically significant difference between the Shock, FS and MSC groups ($p<0.001$). The Sham group showed no difference between dosages ($p=0.805$); **(b)** Figure comparing the quantification of peripheral blood leukocytes in the study groups for the initial moment and end of the experiments. There was no significant difference at baseline between groups ($p=0.33$) as opposed to the end of the experiments between the groups ($p=0.002$). A difference was found in the multiple comparisons between Sham vs Shock (*$p=0.02$), Sham vs FS (**$p=0.006$), and Sham vs MSC (***$p=0.01$).

Shock, FS and MSC groups comparing with the Sham group (p=0.002) (Figure 3b).

Lung histology showed a statistically significant difference in the neutrophil density between groups (p<0.001). MSC group had the highest neutrophil density (180.77 neutrophils/cm^2) of all groups, and the FS group had the lowest cell density (40.38 neutrophils/cm^2) (Figure 4).

By comparing the Shock and FS groups, we found a significant difference in their neutrophil densities (172.52 neutrophils/cm^2 and 40.38 neutrophils/cm^2, respectively, p<0.001); however, no significant differences appeared between the Shock and MSC groups.

Analyses of cytokines in lung tissue did not show significant difference in group comparisons in TNF-α (p=0.21), IL-6 (p=0.21), IL-1β (p=0.58).

DISCUSSION

In the scope of lung transplantation, the shortage of lung donors is one of the primary obstacles leading to a higher number of patients on waiting lists.

Because of their anti-inflammatory and antifibrotic properties, cellular therapies now represent a new therapeutic approach in this context[14,15] Preclinical studies demonstrate improvements following the administration of MSCs in various pulmonary diseases, including chronic obstructive pulmonary disease, acute respiratory distress syndrome, and idiopathic pulmonary fibrosis.[16] In this study, animals were subjected to lung injury by induction of hemorrhagic shock and treated with venous infusion of human MSCs. Lung protective effects may be related to angiogenesis and anti-inflammatory effects.[17-22]

Our study used a model of controlled hemorrhagic shock previously described in the literature.[10,23,24] Our results demonstrated the effectiveness of the reduction and maintenance of pressure levels during shock period in the Shock, MSC, and FS groups. Circulating leukocyte levels quantified prior to shock were lower than those quantified after the onset of hemorrhagic shock. In addition, this shock model showed an increase in neutrophilic infiltrate in the lung in relation to the Sham group. As expected, our results demonstrated that shock acts as a trigger of the inflammation process of. In contrast, levels of TNF-α, IL-6, IL-1β and IL-10 in lung tissue were not significantly different from those found in the Sham group.

After blood replacement and intervention in the treatment groups, we monitored the rats for 115 minutes and extracted the heart-lung block in the end of experiment. This procedure intended to mimic a clinical multiple organ-donor retrieval situation after the notification of brain death. De Oliveira et al.[25] reported a half-life of inflammatory cytokines ranging from 6 minutes to 4 hours. In a study using a hemorrhagic shock model in rats, Pati et al.[17] also collected samples to assess inflammatory cytokines within two hours. In previous studies, the authors identified that major changes in inflammatory cytokines occurred between one and four hours following shock.[26]

The concentration of MSCs used in our study was 1x10^7 cells diluted in standard medium at a single dose. The concentration of cells used in cell therapy with MSCs is still a controversial issue and not unanimous in publications on this matter. Other studies showed a positive effect for concentrations ranging from 2.5x10^5 to 9x10^7, although better results were not necessarily related to a higher concentration of cells.[27-30] Watanabe et al.[19] used a concentration of 5x10^6 cells to treat ischemia and reperfusion injury in a rat model of pulmonary transplantation. Other authors also used the same concentration of cells in respiratory therapies.[31,32] Therefore, the ideal concentration of MSCs is yet to be established.

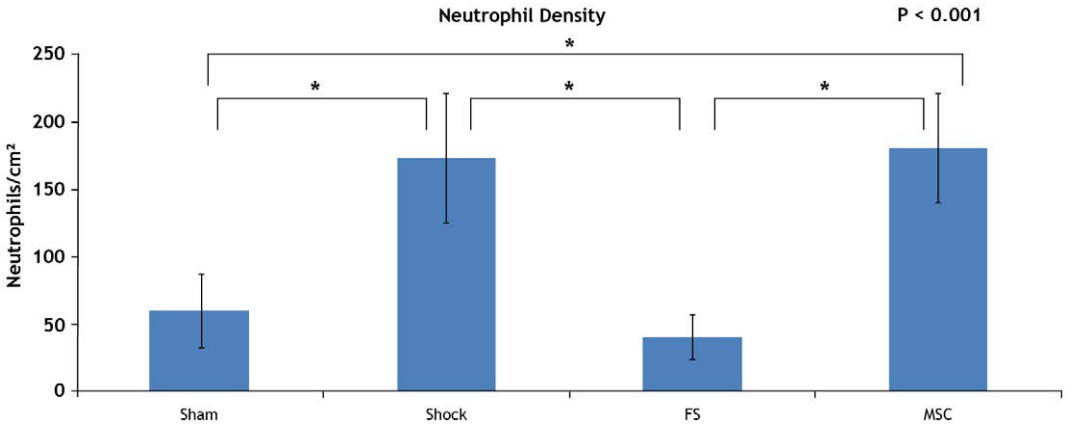

Figure 4. Comparative chart for the neutrophilic infiltrate of the groups, measured as neutrophil density. There was a significant difference between the groups (p<0.001). In the multiple comparisons, there was a significant difference in the comparisons Sham vs Shock (*p<0.001), Sham vs MSC (*p<0.001), Shock vs FS (*p<0.001), and FS vs MSC (*p<0.001).

The intravenous route of administration is well-established in literature and several studies demonstrated that lung acts as a "filter" organ responsible for the retention of most infused cells due to the small diameter of the lung network of capillaries in relation to the size of the stem cells. Such endobronchial route is also effective and may be a good option in this type of study.[33-35] A recent study compared the intravenous route to intrabronchial route and showed an advantage associated with significant retention of MSCs by the intravenous route in damaged *ex vivo* perfused lungs.[36] Other studies have also shown that infusion of MSCs is safe and well tolerated and produced no significant adverse events.[37]

Although hemorrhagic shock promotes increased neutrophilic infiltrate in the lungs, MSC treatment was not effective at inhibiting such effect. Nevertheless, we observed that the FS group had no neutrophilic lung infiltrate, which we interpreted as a result of the short observation period, which was insufficient for the mesenchymal cells to settle in the lungs and release the soluble factors.

The mechanisms of action of MSCs and their immunomodulatory actions are not fully understood. MSCs appear to exert their effects through multiple mechanisms – some are dependent on cellular interactions, while others depend on paracrine interactions, which result from either soluble secreted products or from microvesicles or cell-derived exosomes. Pati et al.[17] used a model of hemorrhagic shock similar to that in our study and treated the animals with Ringer's lactate combined with MSCs. However, the posttreatment period was much longer than ours, and the animals were evaluated 96 hours after treatment. The authors observed that MSC treatment reduced CD8+ expression, which is a specific marker for neutrophils. Chimenti et al.[38] also demonstrated the potential of pretreatment with MSCs, followed by high-volume ventilation. Pretreatment with MSCs reduced the fluid content within the lungs and improved the lung histology score. Levels of neutrophils, inflammatory protein of macrophages-2 and IL-1β were also reduced considerably. *Ex vivo* treatment of pigs with MSCs also showed no change in the level of inflammatory cytokines, such as TNF-α and IL-10.[36] Strategies to further enhancing the effectiveness of MSCs, such as overexpression of anti-inflammatory or pro-repair molecules, have also been investigated.[39]

The titration of inflammatory cytokines in the tissue used in our study were not significantly different. Pati et al.[17] obtained similar results and found no significant differences with this type of analysis.

Factors that could justify the presence of significant inflammatory infiltrate in peripheral blood and reduction in neutrophilic infiltrate in lung tissue, as found in our study, can be found in a study by Stone et al.,[40] who found that transendothelial migration of neutrophils into pulmonary endothelial cells can be effectively blocked by FS-MSC, protecting the integrity of endothelial barrier against edema.

Our study has limitations. Factors such as the absence of literature focused on the ideal amount of cells required, as well as the optimum observation time after infusion of MSCs and FS-MSC may have influenced the results. Limited time of animal monitoring and prolonged periods of maintenance of hemorrhagic shock resulted in high mortality.

Based on the neutrophil density value found in the lung, we conclude that infusion of FS-MSC can reduce levels of local inflammation in lungs of rats with hemorrhagic shock. We believe that it could be a better option than MSCs due to the immediate action provided, requiring a shorter treatment time and not allowing the inflammation process growing on.

It is essential to conduct further studies to achieve a better understanding on the action, kinetics, and dynamics of MSCs, as well as on how to use it. Time of exposure to these cells can be a determining factor in this regard. Cell therapy with MSCs and FS-MSC is a promising field in lung transplantation and may potentially contribute to improve outcomes by improving donor status and reducing post-transplant rejection.

AUTHOR CONTRIBUTIONS

VLD is the main author and participated in all phases of the project. KAOB participated in all phases of the project, contributed substantially to the manuscript, and read and approved the final version of the manuscript. NAN participated in all phases of the project and contributed substantially to the manuscript. LMR participated in all phases of the project. JDRP contributed to some phases of the project. ATC was responsible for all statistical analyses and made the Figures for the project. LCCJ was responsible for the culture and supply of the mesenchymal stem cells and their soluble factors. EG was responsible for the culture and supply of mesenchymal stem cells and their soluble factors and wrote the methodology related to the mesenchymal stem cells. MZ was responsible for the culture and supply of mesenchymal stem cells and their soluble factors and wrote the methodology related to mesenchymal stem cells. PMPF was the main advisor of the study and read and approved the final version of the manuscript.

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J Bras Pneumol. 2021;47(4):e20210076
https://dx.doi.org/10.36416/1806-3756/e20210076

Time course of exercise capacity in patients recovering from COVID-19-associated pneumonia

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Submitted: 24 February 2021.
Accepted: 2 May 2021.

Study carried out at the Istituti Clinici Scientifici Maugeri – IRCCS – Tradate, Italia.

ABSTRACT

Objective: High prevalences of muscle weakness and impaired physical performance in hospitalized patients recovering from COVID-19-associated pneumonia have been reported. Our objective was to determine whether the level of exercise capacity after discharge would affect long-term functional outcomes in these patients. **Methods:** From three to five weeks after discharge from acute care hospitals (T_0), patients underwent a six-minute walk test (6MWT) and were divided into two groups according to the distance walked in percentage of predicted values: <75% group and ≥75% group. At T_0 and three months later (T_1), patients completed the Short Physical Performance Battery and the Euro Quality of Life Visual Analogue Scale, and pulmonary function and respiratory muscle function were assessed. In addition, a repeat 6MWT was also performed at T_1. **Results:** At T_0, 6MWD values and Short Physical Performance Battery scores were lower in the <75% group than in the ≥75% group. No differences were found in the Euro Quality of Life Visual Analogue Scale scores, pulmonary function variables, respiratory muscle function variables, length of hospital stay, or previous treatment. At T_1, both groups improved their exercise capacity, but only the subjects in the <75% group showed significant improvements in dyspnea and lower extremity function. Exercise capacity and functional status values returned to predicted values in all of the patients in both groups. **Conclusions:** Four weeks after discharge, COVID-19 survivors with exercise limitation showed no significant differences in physiological or clinical characteristics or in perceived health status when compared with patients without exercise limitation. Three months later, those patients recovered their exercise capacity.

Keywords: Exercise; Health status; Rehabilitation, Respiratory muscles; Dyspnea.

INTRODUCTION

The COVID-19 pandemic has been having impressive effects worldwide, with tens of million people infected and more than one million casualties.[1] Approximately 80% of the infected individuals are asymptomatic, whereas 15% and 5% of those present with moderate/severe and critical disease, respectively.[2] Pulmonary infection can cause alveolar damages that result in hypoxemic acute respiratory failure, requiring mechanical ventilation (MV).[3,4] Muscle impairment in patients admitted to the ICU can be associated with systemic inflammation, MV, sedation, and prolonged bed rest, among other causes.[5] Long-term physical, psychological, and cognitive impairment of both survivors and caregivers needs to be investigated.[6] A high prevalence of muscle weakness and impaired physical performance was described in hospitalized patients recovering from COVID-19 who had had no previous motor limitations.[7] COVID-19 survivors complain of fatigue, muscle weakness, sleep difficulties, anxiety, and depression six months after acute infection.[8] COVID-19 survivors with functional and muscular performance impairment, dyspnea, and poor perceived health status[9] can benefit from pulmonary rehabilitation.[10]

It is unclear whether the level of exercise capacity after discharge would affect long-term functional outcomes. Therefore, the aim of the present study was to evaluate the exercise capacity of patients four weeks after discharge from an acute care facility and after a three-month follow-up.

METHODS

This was an observational prospective controlled study. The study was approved by the Central Ethics Committee of *Istituti Clinici Scientifici Maugeri* (CEC no. 2435; May 26, 2020), and the participants signed the informed consent form.

Participants

Between May 27 and September 17 of 2020, consecutive patients recovering from COVID-19-associated pneumonia

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Financial support: None.

enrolled in a follow-up program at the *Istituti Clinici Scientifici Maugeri* outpatient clinic, in the city of Tradate, Italy, were included in the study. The clinic is part of the network of referral institutions for pulmonary rehabilitation, diagnosis, and care of post-acute and post-chronic patients.[11,12] All patients had previously been admitted to an ICU, an intermediate care unit, or a respiratory unit and had been discharged home or to an inpatient multidisciplinary program in accordance with the Italian Position Paper.[10,13,14] The patients were included in the follow-up program from three to five weeks after discharge.

Measurements

The following data were collected from patients at inclusion in the follow-up program (baseline: T_0): demographics; anthropometrics; number and type of comorbidities using the Cumulative Illness Rating Scale,[15] which includes a comorbidity index and a severity index; length of hospital stay; and use of invasive or noninvasive MV. According to the distance walked on the six-minute walk test (6MWT) at T_0, that is, six-minute walk distance (6MWD) at T_0, patients were divided into two groups: those with a 6MWD < 75% of the predicted values (<75% group) and those with a 6MWD ≥ 75% of the predicted values (≥75% group).

Outcome measures were assessed, using full protective measures,[16] both at T_0 and three months after T_0 (T_1). Exercise tolerance was assessed by means of the 6MWT.[17] 6MWD was expressed in meters and in percentage of the predicted values.[18] At the beginning and at the end of the test, the perception of dyspnea and leg fatigue were assessed by means of the modified Borg scale.[19] SpO_2 and HR were monitored with a pulse oximeter (8500M; Nonin Medical, Inc., Plymouth, MN, USA) and baseline SpO_2, baseline HR, SpO_{2nadir} and HR_{peak} were recorded. Exercise-induced desaturation was defined as baseline SpO_2 – SpO_{2nadir} (ΔSpO_2) > 4% during the 6MWT.[17,20] Lower extremity function was assessed by means of the Short Physical Performance Battery (SPPB)[21] using the values predicted by Bergland et al.[22] The total SPPB score results from the sum of three components: standing balance, four-meter walk test, and moving from a sitting to a standing position (five times). The total SPPB score ranges from 0 to 12 points: 1-2, severe disability; 3-8, moderate disability; and 9-12, no disability. The minimal clinically important difference for SPPB is considered to be 1 point.[23] Arterial blood gases were measured by means of an automated analyzer in samples collected from the radial artery with the patient breathing room air or oxygen in a sitting position for at least 1 h. Motor performance was assessed by the Barthel index[24]; the total score ranges from 0 (maximum level of dependency) to 100 (complete autonomy). A score ≤ 70 corresponds to severe dependency. Dyspnea was measured by the Barthel index dyspnea.[25] Total scores range from 0 (absence of dyspnea) to 100 (extremely severe dyspnea). A reduction of 9 and 12 points is considered as the minimal clinically important difference in COPD patients without and with chronic respiratory failure, respectively.[26] Perceived health status was measured by the Euro Quality of Life Visual Analogue Scale.[27] Total scores range from 0 to 100 (higher scores represent better quality of life). Dynamic lung volumes were assessed in accordance with standards[28] using the values predicted by Quanjer,[29] whereas MIP and MEP were assessed in accordance with international guidelines[30] using the values predicted by Bruschi et al.[31]

Statistical analysis

Qualitative variables were described as absolute and relative frequencies; quantitative variables were summarized as means and standard deviations or medians and interquartile ranges, depending on their parametric or nonparametric distribution. Between-group comparisons of qualitative variables were performed with the chi-square test or Fisher's exact test. To detect any statistical difference in the comparison of parametric and nonparametric quantitative variables, respectively, the Student's t-test and the Mann-Whitney test were used. We used the Student's t-test and Wilcoxon signed-rank test to evaluate paired differences. We used Spearman's and Pearson's correlations to detect the relationships between 6MWD measured during the follow-up and clinical variables. On the basis of previously published data,[10] a baseline 6MWD of 86.7 m and a pre- and post-intervention difference of 105 m, an alpha error of 0.05, and a statistical power of 0.9 estimated a sample size = 8. A two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed with the Stata statistical software package, version 16 (StataCorp LP, College Station, TX, USA).

RESULTS

Figure 1 shows the patient selection process. During the study period, 48 individuals were referred to our clinic, 33 met the inclusion criteria, and 3 were lost to follow-up; therefore, 30 patients were included in the analysis (Figure 1). According to 6MWD at T_0, 15 and 15 patients were included in the <75% group and in the ≥75% group, respectively. Eleven patients (73%) in the <75% group and 5 patients (33%) in the ≥75% group underwent pulmonary rehabilitation ($p = 0.03$).[14]

Demographic, anthropometric, physiological, and clinical characteristics of patients at T_0 are shown in Table 1. No significant differences were found between the groups. At T_0, all of the subjects had a BMI > 23.2 kg/m^2, 11 (33.3%) of whom had a BMI ≥ 30 kg/m^2 (4 and 7 in the <75% and ≥75% groups, respectively).

Table 2 shows the exercise capacity and functional status of the patients at T_0. As expected, when compared with patients in the ≥75% group, those in the <75% group had reduced exercise capacity

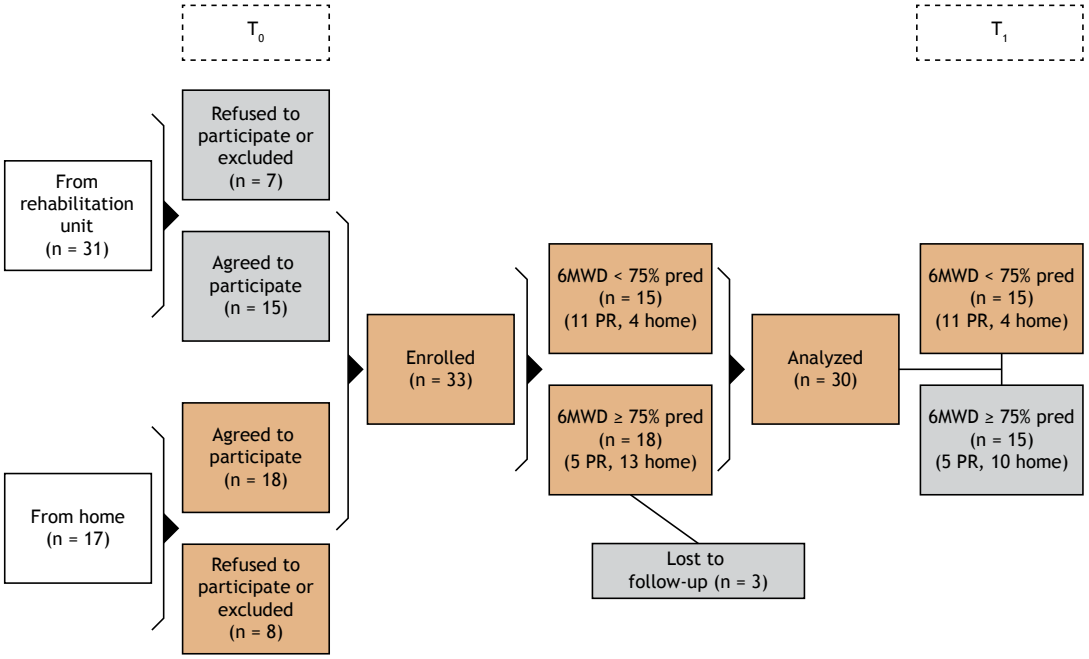

Figure 1. Flow chart of the patient selection process. T_0: enrolment visit; T_1: follow-up visit; 6MWD: six-minute walk distance; pred: of predicted; and PR: pulmonary rehabilitation.

and more severe dyspnea and had lower scores on the SPPB, but not on the Euro Quality of Life Visual Analogue Scale.

Table 3 shows the values of demographic, physiological, and functional variable results at T_1, as well as the differences ($T_1 - T_0$) regarding exercise capacity, dyspnea, and lower extremity function. No significant differences between the groups were found in anthropometric or physiological variables at T_1. However, 6MWD values and SPPB scores were higher in the ≥75% group than in the <75% group. Both groups showed improvement in exercise capacity, but only the <75% group showed significant improvements in dyspnea and in lower extremity function. As also shown in Table 3, exercise capacity and functional status results returned to predicted values in all of the patients in both groups.

Table 4 shows the correlations of demographic, physiological, and clinical characteristics at T_0 with 6MWD at T_1. Being older, having longer length of hospital stay, having comorbidities, and having needed invasive MV correlated with having lower 6MWD values at T_1. Having lower 6MWD values and lower SPPB scores at T_0 correlated with having higher 6MWD values at T_1. Because of the small sample, participating in the pulmonary rehabilitation program was not significantly correlated with exercise capacity at T_1.

DISCUSSION

The present study shows that half of the patients recovering from COVID-19-associated pneumonia may present with exercise limitation four weeks after discharge from acute care hospitals. Patients with exercise limitation and worse functional status, when compared with those without them, showed no significant differences in terms of demographic, anthropometric, physiological, or clinical characteristics, or in perceived health status. Three months after T_0, exercise capacity and functional status results returned to predicted values in both groups.

Our results confirm that COVID-19 survivors can have impaired physical functioning when they are discharged home, even after early mobilization.[32] The absence of differences at baseline highlights that the decline in physical performance cannot be attributed to lung impairment or respiratory muscle dysfunction.

As shown by the comparison with predicted values, three months after T_0, all patients recovered their exercise capacity and functional status. A large study reported that, six months after the acute infection, COVID-19 survivors complained of fatigue or muscle weakness, sleep difficulties, and anxiety or depression.[8] The length of hospital stay in acute care facilities in our sample was similar to that in the aforementioned study[8] with patients on invasive MV, noninvasive ventilation, or high flow nasal cannula (mean: 43 vs. 35 days). Exercise capacity as assessed by 6MWD three months after discharge was similar to that in the aforementioned study with patients assessed six months after discharge from acute care hospitals (mean: 94% vs. 88 % of the predicted values).[8]

The vast majority of patients (73%) with exercise limitation (<75% group) underwent pulmonary rehabilitation in accordance with the Italian Position

Table 1. Demographic, anthropometric, physiological, and clinical characteristics of patients at baseline (T_0).[a]

Characteristic	Whole sample	Group		p
		<75%	≥75%	
	(N = 30)	(n = 15)	(n = 15)	
Male gender, n (%)	21 (70.0)	11 (73.3)	10 (66.7)	1.00
Age, years	63.6 ± 12.2	65.2 ± 12.5	62.0 ± 12.0	0.48
BMI, kg/m^2	27.0 (25.3-31.0)	26.7 (23.9-30.1)	28.4 (25.5-35.2)	0.15
Current or former smoker, n (%)	12 (42.9)	9 (60.0)	3 (23.1)	0.07
Length of hospital stay, days	43.0 ± 20.1	44.1 ± 23.7	41.6 ± 15.4	0.76
Previous IMV, n (%)	6 (20.0)	4 (26.7)	2 (13.3)	0.65
Previous NIV, n (%)	13 (43.3)	9 (60.0)	4 (26.7)	0.14
Previous oxygen therapy, n (%)	23 (76.7)	11 (73.3)	12 (80.0)	1.00
COPD, n (%)	2 (6.7)	1 (6.7)	1 (6.7)	1.00
Asthma, n (%)	3 (10.0)	1 (6.7)	2 (13.3)	1.00
Pulmonary embolism, n (%)	1 (3.3)	1 (6.7)	0 (0.0)	1.00
Diabetes, n (%)	5 (17.2)	2 (13.3)	3 (21.4)	0.65
FiO_2	0.21 (0.21-0.24)	0.21 (0.21-0.28)	0.21 (0.21-0.21)	0.21
PaO_2, mmHg	83.3 ± 9.3	81.6 ± 9.5	84.7 ± 9.2	0.43
PaO_2/FiO_2	394.7 ± 45.4	388.7 ± 45.2	399.7 ± 46.8	0.57
SaO_2, %	96.5 ± 1.4	96.4 ± 1.46	96.5 ± 1.40	0.87
$PaCO_2$, mmHg	36.1 ± 2.8	36.5 ± 3.2	35.8 ± 2.4	0.56
pH	7.412 ± 0.026	7.401 ± 0.180	7.420 ± 0.280	0.06
CIRS-SI	1.5 ± 0.2	1.6 ± 0.2	1.4 ± 0.2	0.07
CIRS-CI	2.4 ± 1.5	2.6 ± 1.6	2.1 ± 1.4	0.40
MIP, cmH_2O	90.0 ± 26.3	93.3 ± 21.2	88.7 ± 29.1	0.78
MIP, % predicted	113.3 ± 40.0	96.5 ± 19.7	120.0 ± 44.8	0.34
MEP, cmH_2O	142.4 ± 48.5	147.5 ± 48.2	140.4 ± 51.1	0.82
MEP, % predicted	128.0 ± 34.5	116 ± 37.7	132.8 ± 34.0	0.43
FEV_1, L	3.0 ± 1.2	3.5 ± 1.3	2.8 ± 1.1	0.27
FEV_1, % predicted	97.1 ± 23.4	103.8 ± 38.4	94.4 ± 16.5	0.52
FVC, L	3.7 ± 1.3	4.4 ± 1.3	3.4 ± 1.3	0.20
FVC, % predicted	96.9 ± 21.3	104.5 ± 37.4	93.9 ± 12.4	0.42
FEV_1/FVC, %	77.4 (74.3-80.4)	78.6 (75.7-83.2)	76.4 (70.0-78.7)	0.37

IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; CIRS-SI: Cumulative Illness Rating Scale severity index; and CIRS-CI: Cumulative Illness Rating Scale comorbidity index. [a]Values expressed as mean ± SD or median (IQR), except where otherwise indicated.

Table 2. Exercise capacity and functional status at baseline (T_0).

Variable	Whole sample	Group		p
		<75%	≥75%	
	(N = 30)	(n = 15)	(n = 15)	
BI score	100 (100-100)	100 (95-100)	100 (100-100)	0.41
BI-d score	5 (2-16)	16 (5-12)	2 (0-5)	0.0004
SPPB total score	11 (9-12)	8.5 (6-11)	11 (10-12)	0.006
SPPB, % predicted	92.3 (76.0-101.4)	74.3 (54.5-91.7)	99.9 (92.3-102.6)	0.001
6MWD, m	406.5 (318.0-521.0)	318.0 (250.0-380.0)	510.0 (433.0-570.0)	< 0.0001
6MWD, % predicted	77.0 (64.0-98.0)	64.0 (57.0-70.0)	98.0 (85.0-109.0)	< 0.0001
SpO_{2mean}, %	93.8 ± 2.4	92.7 ± 2.9	94.6 ± 1.7	0.04
SpO_{2nadir}, %	92.0 (89.0-94.0)	89.5 (87.5-92.0)	93.0 (92.0-95.0)	0.01
ΔSpO_2 (baseline/nadir), %	−4.8 ± 3.4	−6.8 ± 3.9	−3.3 ± 1.9	0.005
Borg dyspnea scale score	2.9 ± 1.9	3.4 ± 1.9	2.6 ± 1.9	0.29
Borg leg fatigue scale score	2 (0.5-3.0)	2.0 (0.5-3.5)	3.0 (1.0-3.0)	0.69
EuroQoL-VAS score	80.3 ± 12.7	79.1 ± 15.0	81.5 ± 10.2	0.61

BI: Barthel index; BI-d: Barthel index dyspnea; SPPB: Short Physical Performance Battery; 6MWD: six-minute walk distance; and EuroQoL-VAS: Euro Quality of Life Visual Analogue Scale. [a]Values expressed as mean ± SD or median (IQR).

Table 3. Anthropometric, physiological, and functional variables at T_1 and p-values of the differences between T_1 and T_0 within the groups[a] and between the groups.[b,c]

Variable	<75% group	p[a]	≥75% group	p[a]	p[b]
BMI, kg/m²	28.0 (24.0-30.0)	0.87	27.8 (25.2-35.0)	0.68	0.32
PaO_2, mmHg	84.3 ± 8.1	0.22	83.4 ± 6.4	0.29	0.76
$PaCO_2$, mmHg	36.8 ± 2.9	0.46	37.6 ± 2.9	0.17	0.49
pH	7.421 ± 0.03	0.005	7.417 ± 0.03	0.85	0.69
SaO_2, %	96.8 ± 1.1	0.29	96.8 ± 0.8	0.55	0.95
PaO_2/FiO_2	401.7 ± 38.8	0.22	397.2 ± 30.6	0.29	0.76
MIP, cmH_2O	84.5 ± 25.6	0.91	93.5 ± 21.8	0.01	0.31
MIP, % predicted	103.7 ± 28.1	0.87	121.6 ± 40.3	0.02	0.17
MEP, cmH_2O	133.3 ± 46.5	0.03	144.7 ± 47.3	0.29	0.51
MEP, % predicted	119.9 ± 28.9	0.03	134.3 ± 35.7	0.35	0.24
FEV_1, L	2.8 ± 0.8	0.66	3.0 ± 1.0	0.01	0.63
FEV_1, % predicted	101.3 ± 21.9	0.72	103.5 ± 18.4	0.04	0.77
FVC, L	3.3 (2.7-4.7)	0.12	3.6 (2.7-5.0)	0.02	1.00
FVC, % predicted	106 (77-123)	0.48	96 (88.127)	0.02	1.00
FEV_1/FVC	75.0 ± 9.1	0.13	78.1 ± 6.7	0.56	0.30
BI-d score	2 (0-5)	0.0007	0 (0-2)	0.20	0.09
ΔBI-d score	−10.9 ± 9.5	-	−1.0 ± 4.6	-	0.002
SPPB total score	10 (10-12)	0.003	12 (12-12)	0.06	0.007
ΔSPPB total score	+2.3 ± 2.4	-	+0.7 ± 1.3	-	0.03
SPPB, % predicted	94.4 (90.8-102.2)	0.002	101.9 (100.1-102.6)	0.06	0.02
6MWD, m	479.4 ± 65.9	0.0001	545.2 ± 95.2	0.004	0.04
Δ6MWD, m	+158 (100-200)	-	+43 (5-97)	-	0.0001
6MWD, % predicted	94.1 ± 12.2	0.0005	109.5 ± 10.8	0.003	0.001
Δ6MWD, % predicted	+28.0 (19.0-44.0)	-	+9.0 (3.0-19.0)	-	0.0005
SpO_{2mean}, %	93.8 (90.0-95.1)	0.94	95.2 (94.5-96.1)	0.90	0.05
SpO_{2nadir}, %	92 (88-93)	0.23	94 (93-96)	0.52	0.04
ΔSpO_2 baseline/nadir, %	−4 (−8.3 to −2.6)	0.15	−3 (−4.3 to −0.5)	0.97	0.15
EuroQoL-VAS score	78.7 ± 14.2	0.91	85.7 ± 11.5	0.06	0.15

BI-d: Barthel index dyspnea; SPPB: Short Physical Performance Battery; 6MWD: six-minute walk distance; and EuroQoL-VAS: Euro Quality of Life Visual Analogue Scale. [a]Values expressed as mean ± SD or median (IQR).

Table 4. Correlations of demographic, physiological, and clinical characteristics at T_0 with the six-minute walk distance at T_1.

Characteristic	rho	p
IMV	-0.39	0.03
NIV	-0.36	0.05
Oxygen therapy	-0.27	0.14
Exposure to rehabilitation	-0.30	0.11
Age	-0.62	0.0002
Previous LoS in acute phase	-0.58	0.002
BMI, kg/m²	-0.10	0.61
CIRS-SI	-0.61	0.0004
CIRS-CI	-0.52	0.003
BI-d	-0.45	0.01
SPPB total score	0.65	0.0001
6MWD at T_0	0.75	< 0.0001
VC, %	-0.28	0.37

IMV: invasive mechanical ventilation; NIV: noninvasive ventilation; LoS: Length of hospital stay; CIRS-SI: Cumulative Illness Rating Scale severity index; CIRS-CI: Cumulative Illness Rating Scale comorbidity index; BI-d: Barthel index dyspnea; SPPB: Short Physical Performance Battery; and 6MWD: six-minute walk distance.

Paper,[14] in comparison with 33% of the patients in the ≥75% group. The small sample size impedes a reliable comparison between patients who did and did not undergo pulmonary rehabilitation. However, our results confirm those of another study[10] that showed that a pulmonary rehabilitation program could improve but not fully recover exercise capacity. Furthermore, in our study, due to the small sample size, participation in a pulmonary rehabilitation program was not associated with exercise capacity at T_1.

There was no difference in perceived health status between patients with or without exercise limitation. In other words, at least in this sample of patients, there was a dissociation between exercise capacity and health status. This observation has been also reported in other studies about other diseases[33] and probably reflects the fact that health status does not depend on exercise capacity only. This underlines the importance of evaluating this parameter specifically.

The present study has limitations. Standard respiratory muscle or lung function tests, including assessment of diffusing capacity at discharge from acute care hospitals, could not be performed for safety reasons. The small sample size impedes a reliable

comparison between patients who did and did not undergo pulmonary rehabilitation.

In conclusion, patients recovering from COVID-19-associated pneumonia may present with exercise limitation four weeks after discharge from acute care hospitals. No significant differences were found in any demographic, anthropometric, physiological, or clinical characteristics or in perceived health status between patients with or without exercise limitation. However, three months later, the measurements of exercise capacity and functional status returned to the predicted values in both groups. Despite the small sample size and the possible lack of external validity, our findings may guide clinicians who treat COVID-19 survivors to design suitable rehabilitation programs.

ACKNOWLEDGMENTS

The authors would like to thank Dr. Denise Rossato Silva (Federal University of Rio Grande do Sul, Porto Alegre, Brazil) for her useful comments about the manuscript.

AUTHOR CONTRIBUTIONS

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

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J Bras Pneumol. 2021;47(4):e20210131
https://dx.doi.org/10.36416/1806-3756/e20210131

Clinical characteristics and predictors of hospitalization among 7,108 ambulatory patients with positive RT-PCR for SARS-CoV-2 during the acute pandemic period

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Submitted: 2 April 2021.
Accepted: 25 May 2021.

Study carried out at the Clínica Las Condes, Santiago, Chile

ABSTRACT

Objective: To describe baseline characteristics of outpatients with a positive RT-PCR for SARS-CoV-2 and to define whether "red flags" (new-onset fever, dyspnea, and chest pain) can predict clinical worsening during the isolation period. **Methods:** This was an epidemiological, observational, descriptive study. Between March and September of 2020, all outpatients who tested positive for SARS-CoV-2 at a tertiary medical center located in Santiago de Chile were included. Demographic variables, comorbidities, red flags, and other symptoms were compiled using follow-up surveys at specific time points. The risk of clinical worsening (hospitalization) and adjusted hazard ratios (HRs) were calculated. **Results:** A total of 7,108 patients were included. The median age was 38 years (range, 0-101), and 52% were men. At baseline, 77% of the patients reported having characteristic symptoms of SARS-CoV-2 infection. The most prevalent onset symptoms were headache (53%), myalgia (47%), and fever (33%). According to the follow-up surveys, the incidence of symptoms decreased during the isolation period; however, 28% of the patients still presented with symptoms on day 14. The risk of hospitalization for patients with new-onset fever and dyspnea during the follow-up period was HR = 7.43 (95% CI, 3.85-14.3, p<0.01) and HR = 5.27 (95% CI, 1.52-18.30; p < 0.01 for both), respectively. New-onset chest pain showed no association with clinical worsening. **Conclusions:** In this sample of outpatients with a recent diagnosis of SARS-CoV-2 infection, a survey-based monitoring of symptoms was useful to identify those at risk of clinical worsening. New-onset fever and dyspnea during the isolation period were considered as red flags associated with clinical worsening and warrants prompt medical evaluation.

Keywords: Ambulatory care; COVID-19; Follow-up studies; Hospitalization; Outpatients.

INTRODUCTION

The first confirmed case of COVID-19 in Latin America was reported in Brazil on February 26, 2020.[1] In Chile, the first patient was diagnosed on March 3, 2020, and the infection rate rapidly increased in the following months.

In most cases, the clinical presentation of COVID-19 is mild (81%), the symptoms are generally self-limiting, and recovery usually occurs within 14 days (mean = 11.5 days).[2,3]

Active monitoring of outpatient cases (and close contacts) is essential as a measure to contain the pandemic. Knowing the evolution of symptoms and the characteristics of patients who worsen during the isolation period may improve monitoring planning and optimize health resources. Of the few studies that have evaluated the symptomatology and evolution of these patients, two have reported that up to 30% of patients continue having symptoms at 14-21 days after infection.[4,5] Additionally, prompt recognition of patients with an increased risk of hospitalization is strongly needed.

The objective of the present study was to describe the characteristics of outpatients who tested positive for SARS-CoV-2 at a tertiary health care center in Chile and to define whether "red flags" (new-onset fever, dyspnea, and chest pain) can predict clinical worsening.

METHODS

This study followed the current recommendation from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Table S1).[6] This was an epidemiological, observational, analytical study of a prospective cohort of outpatients with a positive SARS-CoV-2 RT-PCR test at the *Clínica Las Condes*, a private center located in the urban area of Santiago de Chile, between March 26 and September 30 of 2020. Both adult and pediatric patients who tested positive for SARS-CoV-2 by RT-PCR performed on an outpatient basis

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Financial support: None.

ISSN 1806-3756

were included regardless of the indication for the exam. Hospitalized patients who underwent RT-PCR testing and those who were hospitalized upon performing the test were excluded. Data were obtained from the institutional COVID-19 Research Registry approved by the institutional research ethics committee (April 6, 2020), as was the study. Management and analysis of the anonymized data were performed in accordance with the Declaration of Helsinki.

Baseline demographic and clinical information

A baseline online survey using the institutional Research Electronic Data Capture (REDCap) platform was conducted at the time of the examination and was completed by the patients, which included demographic (age and sex) and clinical variables (onset symptoms related to COVID-19, comorbidities, smoking status, and pregnancy). A summary of the survey is shown in Table S2.

Follow-up surveys

As of June 17, 2020, four follow-up surveys were included in the information collection protocol during the isolation period (14 days since the SARS-CoV-2 RT-PCR test was performed): at 24 h after the positive result and on days 6, 10, and 14 after the test being performed. Participants were consulted regarding their current condition (isolation at home or hospitalized) and the evolution of symptoms related to COVID-19. If a patient reported fever, dyspnea, or chest pain in any of the follow-up surveys conducted during the isolation period, an alert was generated (a red flag for hospitalization), and the patient was contacted by phone by a doctor or nurse from the COVID-19 Surveillance Team. Symptom identification was performed according to the COVID-19 Task Force from the *Clínica Las Condes* based on expert opinions due to the lack of literature on COVID-19. Finally, when the follow-up isolation period was finished (day 17 after the test was performed), a survey was sent by e-mail to each patient to determine perceived compliance with isolation during the period (a scale from 0 to 100, in which 0 corresponded to "I did not comply with the isolation recommendations at all" and 100 corresponded to "I strictly complied with the isolation recommendations, remaining isolated in a room at home"). In addition, people who continued to self-isolate were asked about symptoms related to COVID-19 as well as whether they had been retested (RT-PCR) and, if so, the result.

Statistical analysis

An initial descriptive analysis of all patients during the study period was performed, and the following variables were analyzed: demographic variables, comorbidities, onset symptoms, and information obtained from isolation compliance and contact tracing surveys. In a second analysis, the evolution of the patients surveyed during the isolation period was described, detailing symptoms related to COVID-19 and the symptom alerts that were generated.

Categorical variables are presented as absolute and relative frequencies. Continuous variables are expressed as medians and ranges when the data presented non-normal distribution and as means and standard deviations when the data presented normal distribution. Continuous variables were compared using the Mann-Whitney test, and the chi-square test was used for categorical variables.

Predictors associated with hospitalization risk

We determined the associations between the proposed red flags (new-onset fever, new-onset dyspnea, or new-onset chest pain) at any point during the follow-up period and incident hospitalization during the first 14 days after RT-PCR. The Kaplan-Meier survival analysis was used, along with the log-rank test (Mantel-Cox) and calculation of the Cox proportional hazard ratio (HR). We included the following covariables on the basis of clinical relevance: age, sex, diabetes, hypertension, obesity, asthma, cardiovascular disease, smoking history, and number of comorbidities, as well as fever, chest pain, and dyspnea at baseline (https://academic.oup.com/aje/article/177/4/292/147738).

Statistical significance was set at $p < 0.05$. Statistical analyses were performed using the R Commander software (https://cran.r-project.org/) and the IBM SPSS Statistics software package, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Between March 26 and September 30, 2020, a total of 35,327 SARS-CoV-2 RT-PCR tests were performed at the *Clínica Las Condes*, and 7,683 patients tested positive (21.7%). Of those, 575 (7.4%) were hospitalized and, therefore, excluded from the analysis. In the first descriptive analysis, 7,108 patients were included. For the second analysis, a subgroup of 1,617 patients (22.7%) who completed all of the online surveys during the isolation period (14 days) was included. Figure 1 shows a flow chart of the patients included in the study.

The number of outpatients with a positive SARS-CoV-2 RT-PCR test result by sampling date during the study period is shown in Figure S1, which peaked at 338 daily cases on May 25, 2020.

General characteristics and onset symptoms of the patients

Table 1 shows the general characteristics of the overall sample. In summary, 52.2% of the patients were male; the median age was 38 years (range, 0-101 years); 6.3% of the patients were under 18 years of age; and 10.6% were over 60 years of age. The most prevalent comorbidities were hypertension (10.3%), diabetes (4.2%), and obesity (4.2%). At baseline, 77% of the patients had symptoms at the time of the SARS-CoV-2 RT-PCR test. The most prevalent symptoms were headache (53%), myalgia (47%), fever (33%), and

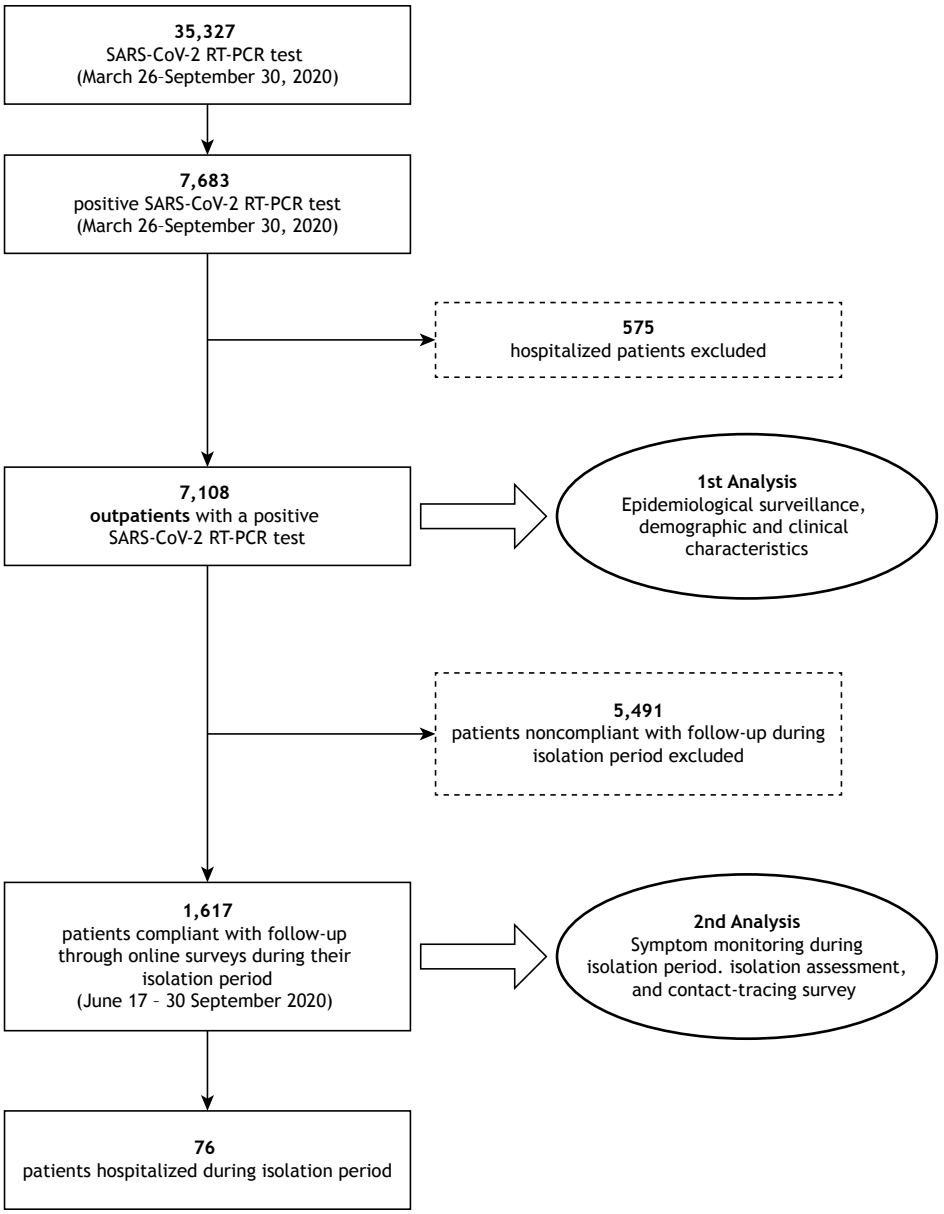

Figure 1. Flow chart of the patients included in the study.

cough (33%). In Table 2, onset symptoms are compared by sex and age. A higher proportion of symptoms was noted in females than in males (80% vs. 74%; $p < 0.001$). Regarding the frequency of onset symptoms, statistically significant differences were found for all symptoms when compared by sex. In men, the most common symptoms were headache (50%), myalgia (46%), and fever (39%), and, in women, headache and myalgia were more prevalent (57% and 47%, respectively), followed by cough (34%). When compared by age group, patients between 19 and 59 years of age had the highest proportion of symptoms (78%). Regarding onset symptoms, patients under 18 years of age most commonly presented with fever (49%), headache (39%), and cough (24%). In contrast, for the 19-to-59-year-old group, the most common onset symptoms were headache (56%), myalgia (49%), and cough (33%); the onset symptoms for the group older than 60 years of age were similar, but the frequencies of headache and myalgia were lower (42% and 39%, respectively), and the frequency of cough was higher (40%).

Symptom monitoring

Most of the patients completed the follow-up survey at 24 h after the positive test result (82%), as well as at day 6 (79%), day 10 (75%), and day 14 (75%). When comparing the completion rate of the follow-up surveys by age, a significantly lower percentage of responses was noted in the ≥ 60-year-old group than in the ≤ 18-year and 19-to-59-year groups (66% vs. 78% vs. 80%; $p < 0.0001$).

Table 1. General characteristics of the patients with a positive SARS-CoV-2 RT-PCR test result.[a]

Characteristic	Group			p
	Total sample (N = 7,108)	No follow-up (n = 5,491)	Follow-up (n = 1,617)	
Age, years	38 [0-101]	38 [0-101]	37 [0-100]	0.04
Sex				
Male	3,713 (52.2)	2,827 (51.5)	841 (52.0)	0.71
Female	3,395 (47.8)	2,619 (48.7)	776 (48.0)	0.83
Comorbidities				
Hypertension	729 (10.3)	517 (9.4)	212 (13.1)	< 0.01
Diabetes	299 (4.2)	219 (4.0)	80 (4.9)	0.09
Obesity	298 (4.2)	188 (3.4)	110 (6.8)	< 0.01
Asthma	264 (3.7)	196 (3.6)	68 (4.2)	0.23
Cardiovascular disease	54 (0.8)	40 (0.7)	14 (0.9)	0.57
Immunosuppression	50 (0.7)	28 (0.5)	22 (1.4)	< 0.01
Chronic neurologic disease	34 (0.5)	21 (0.4)	13 (0.8)	0.03
Chronic kidney disease	27 (0.4)	14 (0.3)	13 (0.8)	< 0.01
Chronic lung disease	20 (0.3)	13 (0.2)	7 (0.4)	0.19
Chronic hepatic disease	8 (0.1)	3 (0.1)	5 (0.3)	< 0.01
Without comorbidities	5,194 (73.1)	4,282 (78.0)	1,100 (68.0)	< 0.01
Current smoking habit	501 (7.0)	307 (5.6)	194 (12.0)	< 0.01
Pregnancy	46 (1.4)	33 (0.6)	13 (0.8)	0.37

[a]Values expressed as median [range] or n (%).

Table 2. Presence/absence of symptoms at SARS-CoV-2 RT-PCR testing and onset symptoms by sex and age.[a]

Characteristic	Total sample	Sex		p	Age bracket, years			p
	(N = 7,108)	Male (n = 3,713)	Female (n = 3,395)		≤ 18 (n = 447)	19-59 (n = 5,903)	> 60 (n = 758)	
Asymptomatic	1,645 (23)	957 (26)	688 (20)	< 0.001	134 (30)	1,270 (22)	241 (32)	< 0.001
Symptomatic	5,463 (77)	2,756 (74)	2,707 (80)		313 (70)	4,633 (78)	517 (68)	
Onset symptoms								
Headache	2,918 (53)	1,380 (50)	1,538 (57)	< 0.001	121 (39)	2,578 (56)	219 (42)	< 0.001
Myalgia	2,546 (47)	1,270 (46)	1,276 (47)	0.0029	65 (21)	2,277 (49)	204 (39)	< 0.001
Fever	1,786 (33)	1,069 (39)	717 (26)	< 0.001	153 (49)	1,458 (31)	175 (34)	< 0.001
Cough	1,807 (33)	877 (32)	930 (34)	< 0.001	74 (24)	1,525 (33)	208 (40)	< 0.001
Sore throat	1,313 (24)	574 (21)	739 (27)	< 0.001	64 (20)	1,163 (25)	86 (17)	< 0.001
Anosmia	1,271 (23)	589 (21)	682 (25)	< 0.001	32 (10)	1,175 (25)	64 (12)	< 0.001
Congestion	1,038 (19)	471 (17)	567 (21)	< 0.001	50 (16)	922 (20)	66 (13)	< 0.001
Dysgeusia	962 (18)	428 (16)	534 (20)	< 0.001	26 (8)	890 (19)	46 (9)	< 0.001
Weakening	925 (17)	441 (16)	484 (18)	0.0029	43 (14)	753 (16)	129 (25)	< 0.001
Dyspnea	389 (7)	170 (6)	219 (8)	< 0.001	14 (4)	332 (7)	43 (8)	0.0798
Diarrhea	609 (11)	282 (10)	327 (12)	0.0021	45 (14)	511 (11)	53 (10)	0.1537
Fatigue	540 (10)	239 (9)	301 (11)	< 0.001	19 (6)	461 (10)	60 (12)	0.0221
Chest pain	439 (8)	178 (6)	261 (10)	< 0.001	12 (4)	391 (8)	36 (7)	< 0.001
Nauseas/vomiting	346 (6)	109 (4)	237 (9)	< 0.001	38 (12)	279 (6)	29 (6)	< 0.001
Anorexia	341 (6)	152 (6)	189 (7)	0.0036	25 (8)	256 (6)	60 (12)	< 0.001
Conjunctivitis	218 (4)	96 (3)	122 (5)	0.0130	6 (2)	199 (4)	13 (3)	0.0041

[a]Values expressed as n (%).

The presence of symptoms decreased during the isolation period. At 24 h after the result, 88% of the patients reported symptoms attributable to COVID-19, whereas 76%, 62%, and 28% reported such symptoms at days 6, 10, and 14, respectively. The most prevalent symptoms at 14 days of self-isolation were anosmia (47%), headache (40%), and cough (38%). Figure 2 shows the symptomatology evolution in relation to the total number of patients with positive SARS-CoV-2 tests. Details of the symptoms for the total number of symptomatic patients are provided in Table S3.

No significant differences regarding sex, age, or comorbidities were found between symptomatic and asymptomatic patients during the isolation period (Table S4). Of the asymptomatic patients who underwent SARS-CoV-2 RT-PCR tests (n = 436), 243 (55.7%) developed symptoms during the follow-up period on different days; 195 (45.0%) developed symptoms in the first 24 h; 36 (15.0%), at day 6; 10 (5.0%), at day 10; and 2 (1.0%), at the end of the isolation period. The most common symptoms at 24 h after the result were headache (36%), nasal congestion (29%), and cough (26%).

Hospitalization and symptom alerts

During the follow-up period, 5% of the patients reported having been hospitalized during the isolation period. The median age of hospitalized patients was

54 years (range, 0-88 years), and most were male (64%). Table 3 shows the baseline characteristics of the patients who were and were not hospitalized during the isolation period.

A total of 698 symptom alerts were generated for 235 patients during the follow-up period. A total of 47% of the alerts was reported during the first 24 h of follow-up, followed by 29% on day 6, 17% on day 10, and 7% on day 14. The most common warning symptom was chest pain throughout the follow-up period. Table S5 provides the data for hospitalization reports and symptom alerts.

Predictors associated with hospitalization risk

We found an increased risk of hospitalization in patients with new-onset fever and dyspnea, respectively (HR = 7.43 [95% CI, 3.85-14.30]; and HR = 5.27 [95% CI, 1.52-18.30], p < 0.01 for both), during follow-up (Figure 3). A summary of non-adjusted and adjusted HRs of the red flags is shown in Table 4.

Survey at the end of isolation period

Of the total number of outpatients, 64% completed the survey at the end of the isolation period. During this period, 9% of patients reported having visited an emergency service. On average, 87% of the patients surveyed reported that they had complied with self-isolation. The patients were isolated at home with households (median of 3 people [IQR, 2-4]); 52% of household contacts presented with symptoms attributable to COVID-19 after being infected.

DISCUSSION

Prompt identification of patients with a worse prognosis is important to reduce the rate of complications and, therefore, reduce the number of severe cases of COVID-19 in the ambulatory setting. In the present study,

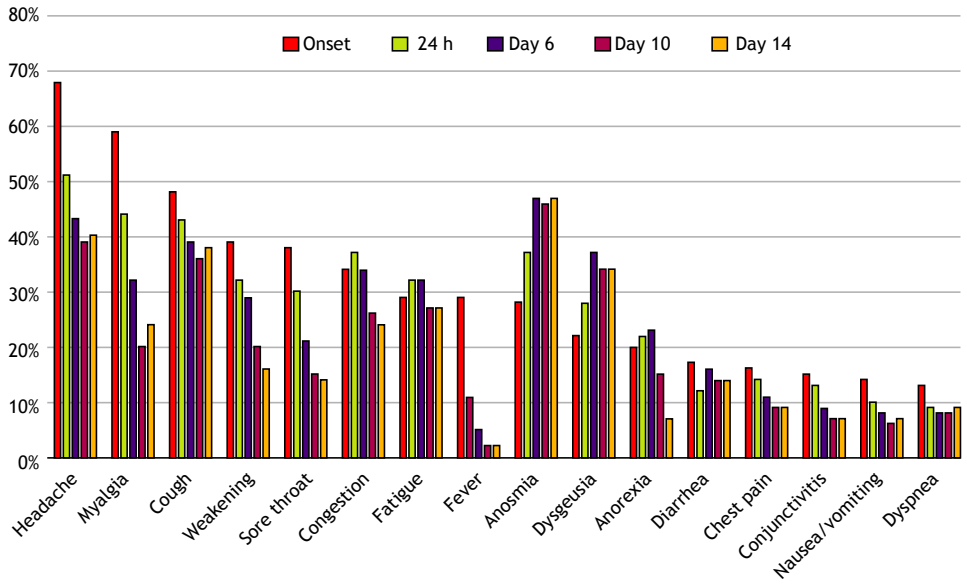

Figure 2. Symptom monitoring during the isolation period in symptomatic outpatients with a positive SARS-CoV-2 RT-PCR test result.

Table 3. Baseline characteristics of hospitalized and non-hospitalized patients during the isolation period.[a]

Characteristic	Group		p
	Hospitalized (n = 76)	Non-hospitalized (n = 1,541)	
Age, years	54 [0-88]	38 [0-100]	< 0.01
Sex			
Male	49 (64.5)	792 (51.4)	0.02
Comorbidities			
Hypertension	19 (25.0)	193 (12.5)	< 0.01
Diabetes	8 (10.5)	72 (4.7)	0.21
Obesity	5 (6.6)	105 (6.8)	0.93
Asthma	7 (9.2)	61 (4.0)	0.25
Cardiovascular disease	1 (1.3)	13 (0.8)	0.49
Current smokers	8 (10.5)	299 (19.4)	0.05
Onset symptoms	67 (88.2)	1114 (72.3)	< 0.01

[a]Values expressed as median [range] or n (%).

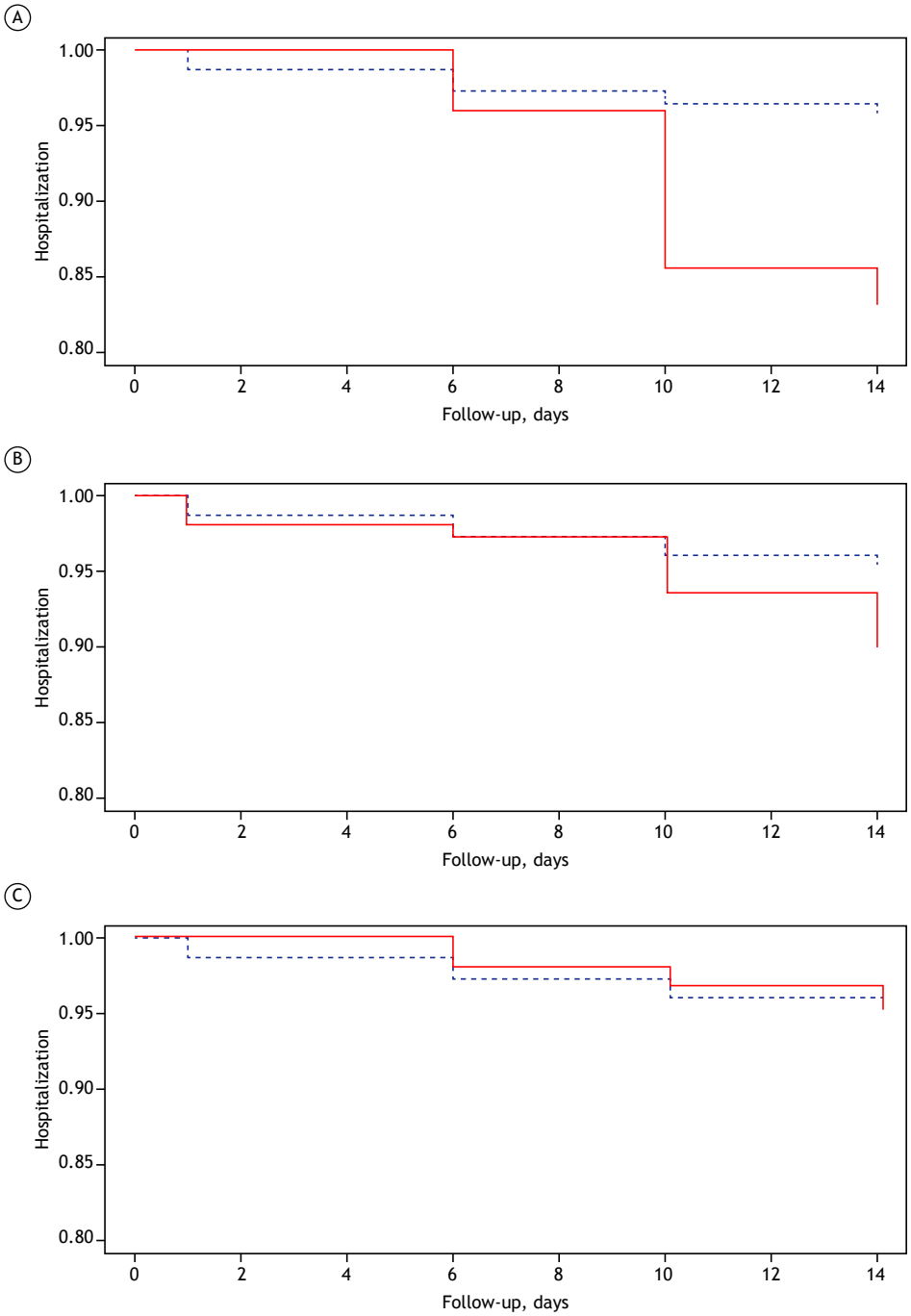

Figure 3. Survival analysis of the associations of new-onset fever (3A), new-onset dyspnea (3B), and new-onset chest pain (3C) with hospitalization.

Table 4. Summary of the association between red flags during follow-up and risk of hospitalization.

Variable	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)	p*
New-onset fever	4.18 (2.30-7.60)	< 0.01	7.43 (3.58-14.31)	< 0.01
New-onset dyspnea	2.33 (1.23-4.41)	< 0.01	5.27 (1.52-18.30)	< 0.01
New-onset chest pain	0.94 (0.43-2.06)	0.89	1.01 (0.46-2.21)	0.98

HR: hazard ratio. *Cox proportional hazard model adjusted by age, gender, diabetes, hypertension, obesity, asthma, cardiovascular disease, smoking history, number of comorbidities, fever, chest pain, and dyspnea at baseline.

we developed a survey-based follow-up intervention for 2 weeks including 7,108 outpatients infected with SARS-CoV-2 in Chile during the first 6 months of the pandemic. The main contribution of the present study

was the evaluation of three different "red flags" during the follow-up period and their associations with the risk of hospitalization. Although we found unadjusted associations between the three red flags and incident hospitalization, our adjusted analysis identified new-onset fever as the major risk factor. We found these results valuable, and further research, including a machine learning approach with training and validation datasets, is necessary.

Clinical characteristics, onset symptoms, and evolution of the patients during the isolation period have been described, thus contributing to knowledge regarding the natural history of this disease in its mild form to improve prevention measures and early detection of complications. In the overall sample, 7.6% of the patients were hospitalized at the time of testing, which is consistent with the results by Lechien et al.[3] that reported that 8% of the patients required hospitalization in a European cohort. Others have reported higher percentages (close to 20%), which were influenced by the smaller numbers of subjects studied.[7,8] In our study, the clinical characteristics were similar to those in previous studies.[7,9-12] The median age was 38 years (< 18 years of age = 6.3%), which is similar to a Chilean study including 1,125 outpatients (median age = 36 years [IQR, 28-50 years])[13] and other studies in Europe and North America.[3,8]

Regarding the onset symptoms attributable to COVID-19, the proportion of asymptomatic outpatients was higher than was that reported in other cohorts,[9] which may be explained by the massive testing performed in Chile regardless of symptomology, where only a medical order is required for the test. The most prevalent symptoms in outpatients were headache, myalgia, fever, and cough, which is consistent with other studies.[4,10]

The symptoms reported by the outpatients decreased as the isolation period progressed; however, on day 14, 28% of the patients still had symptoms attributable to COVID-19, which was also observed by Tenforde et al.,[8] who reported that 36% of the patients were symptomatic at 14-21 days after a positive SARS-CoV-2 test. Conversely, Bi et al.[5] estimated that the median recovery time from symptom onset was 20.8 days, which may imply that the isolation period should be increased, consequently resulting in further absences from work. This group of patients must be evaluated over a longer period to determine the impact of persistent symptoms and the long-term health repercussions for recovered patients.[14] Moreover, 56% of the asymptomatic patients who underwent testing developed symptoms during the isolation period, the vast majority of whom presenting symptoms between 1 and 6 days after testing.

During the isolation period, 5% of the patients reported having been hospitalized, most of whom were male, confirming reports from other studies that stated that the hospitalization rate for males was twice or three times higher than that for women.[15,16] In a retrospective multicenter study in the USA in which patients with a positive SARS-CoV-2 test result were contacted by telephone between 14 and 21 days after diagnosis, 8% of the patients reported requiring hospitalization during their isolation period.[8] Our smaller proportion of hospitalization cases during the period of isolation may be due to the greater number of asymptomatic patients (23% vs. 4% in that study[8]).

Virtual patient monitoring and counseling were possible in our center, which proved to be effective for investigating warning symptoms in 15% of the patients during the follow-up period. In the first stage, follow-up was conducted by phone; however, with the increase in the number of cases, telephone contact could not be maintained with all patients. Therefore, follow-up was continued via email. Surprisingly, this change decreased the patient response rate by only 9% (from 92% to 83%). This result shows that the follow-up of patients treated on an outpatient basis via email using an automated platform is possible, including continuous support from a health team that responds to the needs of patients, resolves concerns, and ensures timely referrals if warning symptoms emerge.[5] Special attention should be directed towards patients older than 60 years of age because the response rate in this age group was significantly lower (66% vs. 80% in those < 60 years) and because this age group has higher risks of complications and need for hospitalization.[10]

Our study has limitations. First, all the information in relation to symptoms and comorbidities was self-reported by the patients, which may result in information bias. Information about clinical outcomes during the isolation period (ICU admission and mortality) was not considered in the study protocol. Second, the results reflect the experience of a single center at the national level, which were acquired by analyzing 2% of RT-PCR-confirmed SARS-CoV-2 cases reported in Chile in the same period. Third, the proportion of patients lost to follow-up after a positive RT-PCR result was high, and this group of patients reported different characteristics when compared with those included in the cohort analysis, decreasing the applicability of the results. Further studies, including big data analyses, are necessary to validate our results. Despite the abovementioned limitations, a large cohort of outpatients was described and incorporated into an innovative virtual health monitoring system (REDCap platform), with a response rate close to 80%.

Knowing the demographic and clinical characteristics of patients in different populations is essential to address this pandemic. Email contact with outpatients with SARS-CoV-2 infection during self-isolation is possible and effective. This strategy allows continuous contact with patients and facilitates evaluations of risk symptoms in a timely manner, thus optimizing human resources in hospitals during a period of high health care demand. New-onset fever or dyspnea during the isolation period warrants a prompt medical evaluation.

AUTHOR CONTRIBUTIONS

DS, MM, MC, and MR: study design and execution. DS, MM, MR, JD and GL: data extraction and analysis. DS, MM, JD and GL: drafting the manuscript. DS, MM, MC, MR, JD and GL: critical revision and final approval of the manuscript.

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J Bras Pneumol. 2021;47(4):e20210092
https://dx.doi.org/10.36416/1806-3756/e20210092

ORIGINAL ARTICLE

Lung ultrasound as a predictor of mortality of patients with COVID-19

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Submitted: 10 March 2021.
Accepted: 04 June 2021.

Study carried out in the intensive care unit of Hospital Alemán (German Hospital), Buenos Aires, Argentina.

ABSTRACT

Objective: To evaluate the performance of lung ultrasound to determine short-term outcomes of patients with COVID-19 admitted to the intensive care unit. **Methods:** This is a Prospective, observational study. Between July and November 2020, 59 patients were included and underwent at least two LUS assessments using LUS score (range 0-42) on day of admission, day 5th, and 10th of admission. **Results:** Age was 66.5±15 years, APACHE II was 8.3±3.9, 12 (20%) patients had malignancy, 46 (78%) patients had a non-invasive ventilation/high-flow nasal cannula and 38 (64%) patients required mechanical ventilation. The median stay in ICU was 12 days (IQR 8.5-20.5 days). ICU or hospital mortality was 54%. On admission, the LUS score was 20.8±6.1; on day 5th and day 10th of admission, scores were 27.6±5.5 and 29.4±5.3, respectively (P=0.007). As clinical condition deteriorated the LUS score increased, with a positive correlation of 0.52, P <0.001. Patients with worse LUS on day 5th versus better score had a mortality of 76% versus 33% (OR 6.29, 95%CI 2.01-19.65, p. 0.003); a similar difference was observed on day 10. LUS score of 5th day of admission had an area under the curve of 0.80, best cut-point of 27, sensitivity and specificity of 0.75 and 0.78 respectively. **Conclusion:** These findings position LUS as a simple and reproducible method to predict the course of COVID-19 patients.

Keywords: Lund diseases; COVID-19; Ultrasonography.

INTRODUCTION

The new coronavirus disease (COVID-19) can result in severe and even fatal respiratory diseases such as acute respiratory distress syndrome (ARDS).[1] Non-invasive diagnostic methods have gained ground in clinical practice, especially in critical and emergency medicine as rapid, reliable, and reproducible information at the patient's bedside has contributed to the more accurate etiological diagnosis of acute pathology and a more targeted treatment.[2,3] In the context of the COVID-19 pandemic, ultrasound has become a useful tool in intensive care, with a POCUS (Point of Care Ultrasound) approach.[4]

Lung ultrasound (LUS) is available in countries with different levels of development of their healthcare systems and offers advantages compared to computed tomography (CT), which requires transferring patients outside intensive care units or chest radiography, which has shown limitations for the diagnosis and monitoring of pulmonary pathology in critical patients.[5] Several studies have shown that LUS can detect interstitial disease, subpleural consolidations, and respiratory distress of any aetiology, with sensitivity and specificity superior to chest radiography and comparable to CT.[6-8] Indeed, LUS has already been recommended in past viral pandemics[9] and growing evidence demonstrates its effectiveness in patients with COVID-19,[10] which allows identifying the degree of lung involvement, its course, and the possible association between the initial lung involvement and its prognosis.[11-15]

Our objective was to evaluate the performance of LUS through the lung ultrasound score (LUS score) to determine the severity of pneumonia and the short-term outcomes of patients with COVID-19 admitted to the intensive care unit. We hypothesize that the Lung Ultrasound Score (LUS) correlates with clinical evolution and predicts mortality in critically ill COVID-19 pneumonia patients.

METHODS

This is an observational, analytical, prospective, single-centre study performed at the Intensive Care Unit (ICU) of the Hospital Alemán in Buenos Aires, Argentina; a teaching hospital with a 30-bed ICU, 15 of these were purposed to COVID-19 care. The study was approved by the independent ethics committee of

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Financial support: None.

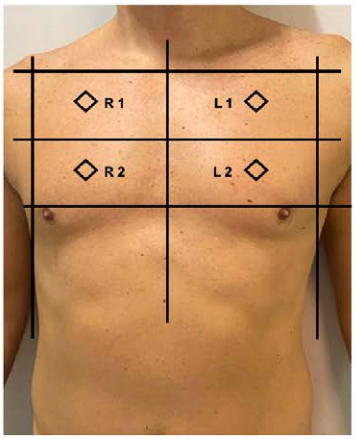
ISSN 1806-3713

Hospital Alemán. The informed consent of the patients or their representatives was obtained. The study was performed in compliance with Act 25.326/Habeas Data. We preserved the identity of the participants according to local and international standards and legislation.

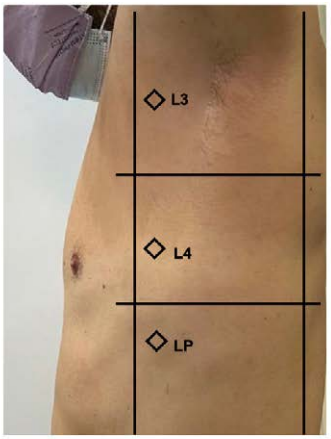
We included all patients with a confirmed diagnosis of COVID-19 by polymerase chain reaction (PCR) techniques, admitted to the ICU with respiratory failure, between July 1, 2020, and October 31, 2020, and who had at least two LUS. LUS was performed at baseline (time of admission to ICU), on day fifth and day 10th of admission to ICU. We excluded patients under 18 years old, those whose reason for admission to the ICU was not respiratory failure despite a confirmed diagnosis of COVID-19, and those with advance directives and do not resuscitate orders. Patients with low supplemental oxygen requirements were admitted to the ICU they showed a rapid radiological progression, deterioration with tachypnoea, and/or poor ventilatory mechanics.

After obtaining informed consent and within 48 hours after admission to ICU, the first evaluation was performed using a Philips ultrasound machine, model CX 50, low-frequency convex transducer (2-6 MHz), with lung software (Philips Medical Systems, Bothell, WA, USA), at a pre-established depth of 11 to 14 cm. The LUS score was calculated according to methods described by Soldati et al. with a modification.[16] Instead of dividing the posterior areas into three regions, these were divided into two regions (upper and lower regions), and PLAPS point was added to lateral regions as pulmonary consolidation was observed. For this purpose, each hemithorax was divided into seven regions, right anterior between the clavicle upwards and the tenth intercostal space downwards, laterally between the right edge of the sternum and the anterior axillary line, and divided into upper and lower areas; right lateral between the axillary gap upwards and a line that continues from the tenth intercostal space downwards, between the anterior axillary lines and the posterior axillary line and divided into upper and lower; the posterior region was also divided into upper and lower, with lateral limits between the posterior axillary line and the spine and the superior region; and classified as follows: R1 (upper right anterior region) R2 (lower right anterior region), R3 (right axillary region), R4 (lower right lateral region), R5 (upper right posterior region), R6 (lower right posterior region), and R7 - PLAPS (posterior and/or lateral alveolar and/or pleural syndrome) (region between the union of the posterior axillary line and the intersection of the imaginary line that continues through the tenth intercostal space, requiring the visualization of the diaphragm for the correct exploration of the pleural fundus). In the same way and with equal limits, the left hemithorax was taken, naming each of the zones as L1 (upper left anterior region), L2 (lower left anterior region), L3 (left lateral region), L4 (lower left lateral region), L5 (upper left posterior region), L6 (lower left posterior region), and L7 – PLAPS. Figure 1 shows LUS regions.

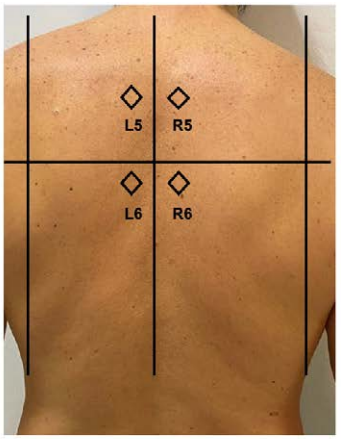
Each area was assigned a value according to the following assessment from 0 to 3 points. A-lines: normal pleural line, normal reverberation artifacts of the pleural line accompanied by lung sliding, corresponding to normal lung aeration = 0 points. B-lines: hyperechoic lines vertical to the pleural line rising from it and reaching the end of the screen, erasing the A-lines or in concert with them in the case of pulmonary pathology associated with COVID-19, representing reverberant artifacts of interlobar or oedematous alveolar septa, were divided into B1 separate B-lines corresponding to moderate loss of lung aeration = 1 point. Three or more lines define B1. B2 coalescent B-lines corresponding to a severe loss of pulmonary



R1 (Upper right anterior region), R2 (Lower right anterior region), L1 (Upper left anterior region), L2 (Lower left anterior region)



L3 (Left axillar region), L4 (lower left lateral region), LP (Left PLAPS)



L5 (upper left posterior region), L6 (lower left posterior region), R5 (upper right posterior region), R6 (lower right posterior region)

Figure 1. Caption. Lung Ultrasound Score regions.

aeration, which was = 2 points, and pulmonary consolidation which was = 3 points.[17] Thus, the LUS score could have a normal value of 0 and the worst value of 42. This evaluation was performed by three intensive care physicians trained in performing LUS, at the bedside of the patient with confirmed COVID-19 using an ultrasound machine exclusively dedicated to these patients. Personal protective equipment was used for all studies and measurements were taken offline to reduce exposure time. The interobserver variability for LUS score measurement was determined by an independent expert operator who was blinded to the study.

At each assessment, we recorded the clinical condition measured by the level of ventilatory support: "mild" when the patient required a nasal O_2 cannula; "moderate" when the patient required non-invasive ventilation/high-flow nasal cannula; "severe" when the patient required mechanical ventilation. In addition, the following parameters were measured: leukocytes, C-reactive protein, platelets, LDH, troponin-t, ferritin, and D-dimer. This evaluation was repeated on days fifth and 10th of ICU admission. Also, we recorded the number of days of ICU and hospital admission, ICU and hospital mortality, the total days of mechanical ventilation, and destination after hospital discharge (Home - Home Admission - 3rd level health centre).

For statistical analysis, continuous data were expressed as mean and standard deviation (SD), or as median and interquartile range [IQR 25-75], as appropriate. Normality analysis was performed using the Shapiro-Wilk test. Categorical data were expressed as absolute values and/or percentages. Student's t-test or Mann Whitney's U-test was used to comparing parametric and non-parametric continuous variables, respectively; and the Chi-square test and Fisher's exact tests were used to compare categorical variables. The relationship between the variables was initially determined through univariate analysis. For the multiple regression analysis, we selected the variables that we considered relevant (principle of parsimony) and/or those that in the univariate analysis resulted in a value $p<0.1$. Those patients with missing data on the variables of importance were excluded from the analysis. The statistical analyses were performed with the software R version 3.3.3.

RESULTS

During the four months of the study, 249 patients were admitted to ICU, of which 78 (31%) patients were diagnosed with COVID-19. A total of 19 patients were excluded for the following reasons: eight lacked ultrasound evaluations, five were admitted because of non-respiratory causes, five had a long hospital stay before the diagnosis of COVID-19 and one patient had a do-not-resuscitate/do-not intubate order. Finally, 59 patients were included in the final analysis. The mean age was 66.5±15 years and 43 (73%) of 59 patients were male. Severity at admission measured by APACHE II averaged 8.3±3.9 and Charlson's comorbidity score showed a mean of 3.2±2. Twelve (20%) patients had malignancy and 9 (15%) patients were fragile (Clinical Frailty Scale >4). In 46 (78%) patients, a non-invasive ventilation/high-flow nasal cannula was used, during a median of 3.5 days (IQR 2-6 days), and in 38 (64%) patients, mechanical ventilation was required, during a median of 12 days (IQR 9.25-19.75 days). The median stay in ICU was 12 days (IQR 8.5-20.5 days) and the median stay in hospital was 20 days (IQR 13.5-28.5 days). Mortality in ICU and hospital was 54%. The demographic characteristics of the patients are summarized in Table 1.

The median time from the diagnosis of COVID-19 to the first LUS was 5 days (IQR 3.5-9 days). The total median LUS score at admission was 20.8±6.1; at day 5, it was 27.6±5.5 and at day 10, 29.4±5.3 ($p=0.007$). As clinical condition deteriorated (according to the requirement for mechanical ventilation support), the LUS score increased, with a positive correlation of 0.52, $p<0.001$. On day 10 (n=41), LUS scores were 19.1±3.4, 23.3±4.5, 30.8±5.3 in the mild, moderate, and severe groups, respectively. When analysing the biochemical markers at the time of the first LUS evaluation, none of them showed a statistically significant association with the clinical condition, unlike the LUS score. The group of patients whose LUS score at day 5 was worse than baseline had a 76% mortality versus a 33% mortality in the group of patients whose LUS scores improved during the same period (OR 6.29, 95%CI 2.01-19.65, $p=0.003$). Table 2 shows ICU mortality according to changes observed with the LUS score.

This difference was also observed on day 10 of admission to ICU. In multivariate analysis, adjusted by age, APACHE II, and Charlson, the LUS score was an independent predictor of mortality (OR 1.32, 95%CI 1.14 -1.60, $p=0.001$). In another regression model in which sex and body mass index were adjusted, the LUS score was also an independent predictor of mortality (OR 1.30, 95%CI 1.14-1.54, $p<0.001$). The sensitivity and specificity of the LUS score to predict patient mortality were evaluated. The LUS score at ICU admission showed an area under the curve (AUC) of 0.64, with 25 as the best cut-point, sensitivity of 0.63, and a specificity of 0.59. And on the fifth day after admission, the LUS score presented an AUC of 0.80, with the best cut-point of 27, sensitivity and specificity of 0.75 and 0.78, respectively (Table 3 and Figure 2). Figure 3 shows examples of LUS images of patients included in the study.

DISCUSSION

Our findings show that lung ultrasound score is a feasible and easy method to predict the clinical course of critically ill patients with COVID-19. When patients' clinical condition deteriorated, the score significantly increased. Indeed, the LUS score was an independent predictor of mortality and when assessed on day 5 of

admission to ICU, the score presented an acceptable area under the curve.

The histopathologic features of COVID-19 pneumonia are characterized by alveolar damage, including alveolar oedema, while the inflammatory component is mild and patchy. Reparative processes with hyperplasia of pneumocytes and interstitial thickening may then occur; in advanced phases, there appear gravity-dependent consolidations similar to those of respiratory distress, as well as haemorrhagic necrosis, alveolar congestion, oedema, desquamation, and fibrosis.[18] Therefore, tools that can reliably assess lung involvement can also predict clinical deterioration. Our study suggests that the LUS score was useful to evaluate patients with COVID-19 and that, early after admission, could predict a higher risk of mortality.

The LUS score could define alterations that affect the relationship between tissue and air on the lung surface;[19] indeed, the higher score, the greater was the loss of pulmonary aeration. The median time between the diagnosis of COVID-19 and the first LUS evaluation was five days, and this may explain the difference between the first and the second LUS evaluation performance to predict unfavourable outcomes. In fact, the second evaluation was performed on average 10 days after diagnosis, when COVID-19 presents an inflammatory peak, mainly due to the increase of proinflammatory cytokines.[20,21] It has been shown that patients with respiratory distress from COVID-19 can retain near-normal lung compliance at the initial stages of the disease despite good oxygenation to later deteriorate or improve.[22,23]

Table 1. Demographic and clinical characteristics.

Characteristics	Value in total patients (n = 59)
Age, mean±SD	66.5 ±15.0
Male, n (%)	43 (73)
APACHE II. mean±SD	8.3±3.9
Charlson Score. mean±SD	3.2±2.0
Cancer, n (%)	12 (20)
Fragile patients (CFS >4). n (%)	9 (15)
BMI, mean±SD	27.6±4.5
Support	
Non-invasive ventilation/high-flow nasal cannula, n (%)	46 (78)
Days of the cannula, median (IQR)	3.5 (2-6)
Mechanical ventilation, n (%)	38 (64)
Days of MV. median (IQR)	12 (9.25-19.75)
ECMO, n (%)	1 (2)
Haemodialysis, n (%)	9 (15)
Neuromuscular blocking agents, n (%)	35 (59)
Days of neuromuscular blocking agents, median (IQR)	8 (5-10)
Days from diagnosis to LUS, median (IQR)	5 (3.5-9)
Length of ICU stay, days, median (IQR)	12 (8.5-20.5)
Length of hospital stay, days, median (IQR)	20 (13.5-28.5)
ICU mortality, n (%)	32 (54)
Hospital mortality, n (%)	32 (54)

Abbreviations: CFS = Clinical Frailty Scale; BMI = body mass index; APACHE = Acute Physiology and Chronic Health Evaluation; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; SD = standard deviation; IQR = interquartile range.

Table 2. ICU mortality according to LUS score changes.

LUS score change	n (%)	ICU mortality (%)	OR (CI 95%)	P-value
LUS on 5th day of admission				0.003
Improved score	30 (51)	33		
Deteriorated score	29 (49)	76	6.29 (2.01-19.65)	
LUS on the 10th day of admission				0.023
Improved score	18 (44)	33		
Deteriorated score	23 (56)	74	5.67 (1.47-21.89)	

Improved or deteriorated compared to the previous assessment. LUS = Lung ultrasound score; ICU = intensive care unit; OR = odds ratio; CI = confidence interval.

Table 3. Multivariate regression; mortality predicted by LUS.

Model	OR (95%CI)	p-value
Model 1 (adjusted by age, APACHE, Charlson)	1.32 (1.14-1.60)	0.001
Model 2 (adjusted by sex and BMI)	1.30 (1.14-1.54)	< 0.001

	ROC AUC	Sensitivity	Specificity	PPV	NPV
LUS at admission					
LUS > 25	0.64	0.63	0.59	0.65	0.57
LUS on 5th day of admission					
LUS > 27	0.80	0.75	0.78	0.80	0.72

AUC = area under the curve; ROC = receiver operating characteristic curve; PPV = positive predictive value; NPV = negative predictive value; LUS = Lung ultrasound score.

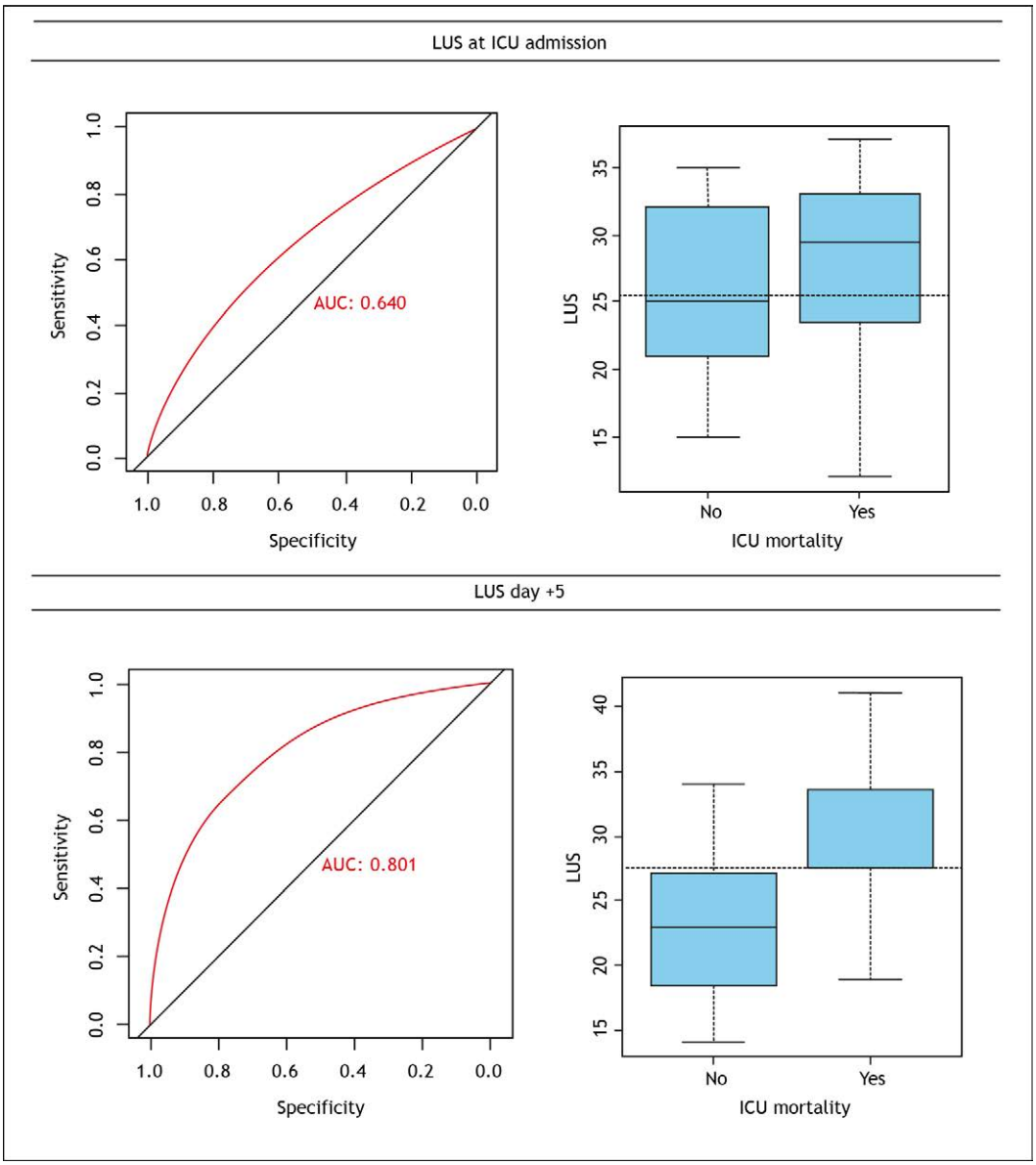


Figure 2. Sensitivity and specificity of the LUS score to predict patient mortality at the intensive care unit.

The LUS score showed an association to the clinical severity of patients with COVID-19 at the baseline assessment on the day of admission to ICU; however, it was on the fifth day of hospitalization that the score reached its best AUC to predict mortality. In a comparable study, this difference in the score was

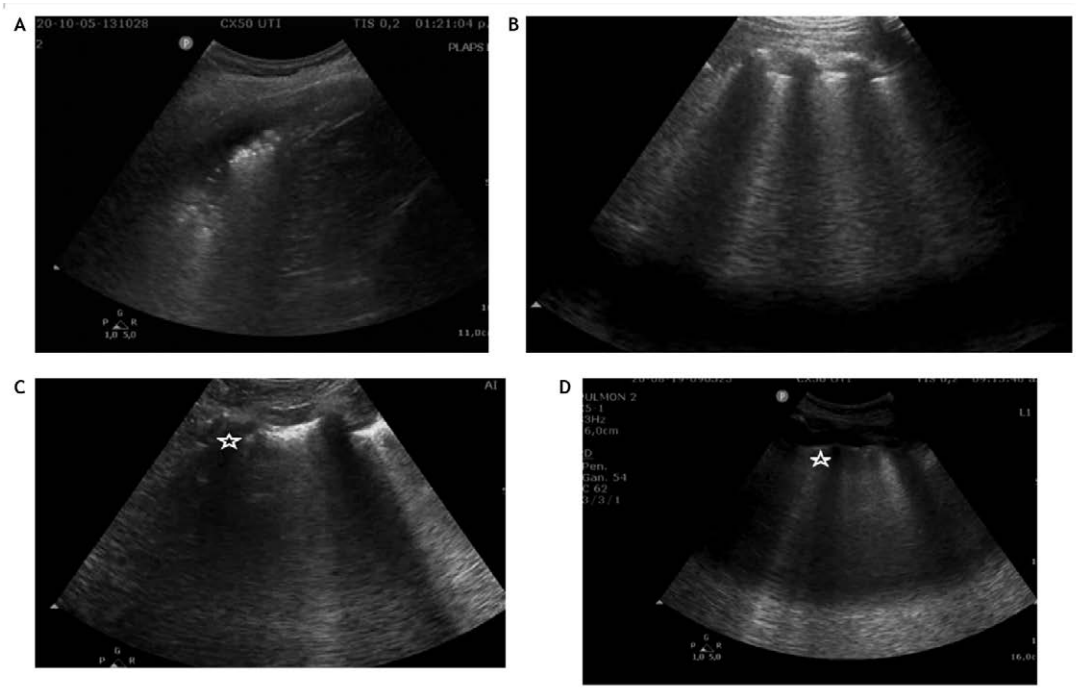


Figure 3. LUS images of patients included in the study.

already significant in the first LUS assessment.[24] Lichter et al.also showed that the LUS score could identify the appearance of pleural thickening and effusion, predicting clinical deterioration which translated to the need for mechanical ventilation and mortality.[24] In their study, an LUS score higher than 18 indicated a significantly lower survival.[24]

Our study was directed to the most critical group of patients with COVID-19 at our hospital; those patients who required hospitalization in ICU because of acute respiratory failure. As a result, our LUS score values were higher than those in previous publications, which included patients being admitted to emergency departments or general wards, in their initial stages of the disease.[13] In addition, we decided to include the lung lateral region to the axilla and to the PLAPS points, where pleural effusion and larger consolidations are usually observed. The pleura is not described in detail because although it was found to be altered (pleural disruption, pleural thickening), the transducer was intended for the assessment of type A, type B lung patterns, and subpleural consolidations and in the PLAPS points. bilateral pathological characteristics were found in 100% of our population, in concordance with other LUS studies in patients with COVID-19[18,20] and the most common findings were B lines and subpleural consolidations in posterior segments.

Our study has several limitations that should be taken into consideration when interpreting our results. It was performed in a single centre, with a small number of patients; some of them had been first admitted into the general ward before being transferred to ICU, overestimating the score cut point to predict poor clinical evolution and mortality. The use of a low-frequency, high-penetrance transducer could have missed a more accurate assessment of pleural line characteristics. Other limitations were that the onset of symptoms was not recorded, other infections were not assessed, and that not all potential confounders and effect modifiers were measured, such as lung oedema, as a result of limited resources during the pandemic.

Our findings must be interpreted with caution. Apart from the limitations listed above, it is critical that the implementation of lung ultrasound must be supervised by trained personnel. Our study contributes to the literature supporting the use of ultrasound lung evaluation as a simple method to predict the course of COVID-19 patients, their need for mechanical ventilation, and death. LUS is an easily available tool that could help clinicians plan the management of patients with COVID-19.

AUTHOR CONTRIBUTIONS

FAS and AM: conceptualization. FAS, AM, SS, DI, ALD, BTO, CC and CB: data collection. FAS, AM and JO: data analysis. FAS, AM, JO and JR: investigation. AM and JR: draft writing. AM and JR: visualisation. All authors: revision.

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J Bras Pneumol. 2021;47(4):e20210039
https://dx.doi.org/10.36416/1806-3756/e20210039

Association between cardiovascular mortality and STOP-Bang questionnaire scores in a cohort of hospitalized patients: a prospective study

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Submitted: 2 February 2021.
Accepted: 9 June 2021.

Study carried out at the IRB Servicio de Salud Bio-Bio, Los Ángeles, Chile.

ABSTRACT

Objective: Obstructive sleep apnea (OSA) is associated with an increased risk of mortality and cardiometabolic diseases. The STOP-Bang questionnaire is a tool to screen populations at risk of OSA and prioritize complementary studies. Our objective was to evaluate the clinical utility of this questionnaire in identifying patients at an increased risk of mortality after discharge in a cohort of hospitalized patients. **Methods:** This was a prospective cohort study involving consecutive patients admitted to an internal medicine unit between May and June of 2017 who were reevaluated three years after discharge. At baseline, we collected data on comorbidities (hypertension, obesity, diabetes, and fasting lipid profile) and calculated STOP-Bang scores, defining the risk of OSA (0-2 score, no risk; ≥ 3 score, risk of OSA; and ≥ 5 score, risk of moderate-to-severe OSA), which determined the study groups. We also recorded data regarding all-cause and cardiovascular mortality at the end of the follow-up period. **Results:** The sample comprised 435 patients. Of those, 352 (80.9%) and 182 (41.8%) had STOP-Bang scores ≥ 3 and ≥ 5, respectively. When compared with the group with STOP-Bang scores of 0-2, the two groups showed higher prevalences of obesity, hypertension, diabetes, and dyslipidemia. Multivariate analysis showed an independent association between cardiovascular mortality and STOP-Bang score ≥ 5 (adjusted hazard ratio = 3.12 [95% CI, 1.39-7.03]; p = 0.01). Additionally, previous coronary heart disease was also associated with cardiovascular mortality. **Conclusions:** In this cohort of hospitalized patients, STOP-Bang scores ≥ 5 were able to identify patients at an increased risk of cardiovascular mortality three years after discharge.

Keywords: Sleep Apnea, Obstructive; Risk assessment; Surveys and questionnaires; Cardiovascular diseases/mortality.

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent condition, with an increased risk of cardiovascular complications. This condition is prevalent and underdiagnosed in some countries, mainly due to a lack of sleep study testing. Previous studies report that 1 billion people are at risk of OSA worldwide.[1,2] In Chile, the population at risk of OSA is 22%, and the risk of moderate-to-severe OSA is about 9%.[3] According to the American Academy of Sleep Medicine, OSA can be diagnosed through polysomnography or type III channel. The diagnosis requires the presence of an abnormal apnea-hypopnea index (AHI ≥ 5 events/h), and the presence of at least one of the following symptoms: sleepiness/fatigue, sleep disturbed by gasping or choking, snoring or apnea witnessed by a third party, or comorbidities such as hypertension, coronary artery disease/stroke, heart failure, diabetes, and mood changes. The diagnosis can be directly made with an AHI ≥ 15 events/h. Severity ranges from mild OSA (AHI between 5-15 events/h), moderate OSA (AHI between 15-29 events/h), and severe OSA (AHI ≥ 30 events/h).[4,5] Discrimination between mild OSA and moderate-to-severe OSA is relevant to clinical practice. Moderate-to-severe OSA is associated with an increased risk of hypertension, diabetes mellitus (DM), dyslipidemia, obesity, and major cardiovascular events—acute myocardial infarction (AMI), coronary heart disease (CHD), stroke, atrial fibrillation (AF), and cardiovascular mortality.[6]

Although sleep studies are scant in some countries, different clinical questionnaires are available to identify populations at risk of OSA. This approach is also useful to define populations with an increased risk of cardiovascular comorbidities, such as hospitalized patients. Moreover, by means of these clinical predictor rules, clinicians can also identify populations with a high pre-test probability of OSA and, therefore, define the best cost-benefit diagnostic study after discharge.

The STOP-Bang questionnaire is a useful clinical screening tool for patients at risk of OSA (threshold score, ≥ 3),

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Financial support: None.

and of moderate-to-severe OSA (threshold score, ≥ 5). The sensitivity and specificity of this questionnaire are 90% and 49%, respectively, using a cut-off score ≥ 3 to identify the risk of OSA. However, using a cut-off score of ≥ 5, the sensitivity and specificity to identify the risk of moderate-to-severe OSA are 96% and 25%, respectively. Given the excellent sensitivity, the STOP-Bang questionnaire has been proposed as a screening tool in different epidemiological studies.[7,8]

The combination of OSA and other significant cardiovascular comorbidities included in the STOP-Bang questionnaire suggests that it could help identify the population with an increased risk of mortality in the medium term, especially in hospitalized patients. The objective of the present study was to evaluate the association between the risk of OSA measured by the STOP-Bang questionnaire and the risk of all-cause and cardiovascular mortality in hospitalized patients.

METHODS

This was an observational, prospective cohort study following current recommendations from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[9] Between May and June of 2017, we consecutively included patients admitted to the internal medicine unit in one single university health care center located in the city of Los Ángeles, Chile.

The included cohort was prospectively followed up by June of 2020. Patients admitted for any medical reason were screened for potential inclusion. We included patients > 18 years of age who gave a written informed consent. We excluded patients who were unable to complete the questionnaire, those submitted to any type of surgery during hospitalization, transferred to an ICU, considered to be at the end of life due to any medical comorbidity, or lost to follow-up. The study protocol was approved by the Ethics Research Committee of the *IRB Servicio de Salud Bio-Bio* (Protocol #25, August of 2017). The study was conducted in accordance with the guidelines set forth in the Declaration of Helsinki and good clinical practice.

Demographic data (gender, age [being elderly was defined as being ≥ 65 years of age]), as well as smoking history, alcohol consumption, comorbidities at baseline (arterial hypertension, DM, CHD, and stroke), and current medications (lipid-lowering, antidiabetic, antihypertensive, and anticoagulant medications), were collected. Data about comorbidities and reason for admission were retrieved by both self-report and medical records.

Exposure was defined as the risk of OSA measured by the STOP-Bang score at admission. The questionnaire was evaluated according to a prior validation in the population in Chile.[7,8] Sleep-related symptoms (snoring, tiredness, and observed apnea) were recorded by either self-report or partner response. Blood pressure was measured with a standard mercury sphygmomanometer on the left arm after 10 min of rest in accordance with the current guidelines of the American Heart Association.[10] Weight and height were measured after an overnight fast with patients wearing only underwear. BMI was calculated as weight (kg)/height^2(m^2), and neck circumference was measured using a plastic tape meter at the cricoid level (Adam's apple).

A venous blood sample was collected from all of the patients within the first 48 h after admission. The sample was obtained in the morning after an overnight fast. We included a fasting lipid profile. Patients with an abnormal lipid profile were classified according to the type of dyslipidemia: LDL dyslipidemia; hypertriglyceridemia; mixed dyslipidemia; and HDL dyslipidemia, in accordance with current recommendations.[10] Using the clinical and laboratory data, we calculated the cardiovascular risk using the American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease (ASCVD) risk score[10] at baseline in the population between 34 to 79 years of age.

The primary outcome of the present study was the risk of all-cause mortality after discharge in patients with a STOP-Bang score ≥ 3 and in those with a score ≥ 5. As a reference, both groups were compared with patients with a STOP-Bang score between 0-2 after follow-up. The secondary outcome was the risk of cardiovascular mortality in the same groups. Mortality data was obtained by the *Servicio de Registro Civil e Identificación* (www.registrocivil.cl) and categorized as either all-cause mortality or cardiovascular mortality in accordance with the International Classification of Diseases, version 9 (ICD-9). Details regarding cardiovascular mortality as defined in the present study are available in Chart S1.

Individual data were included in a case report form and transferred to an Excel spreadsheet. Continuous data were reported as means and standard deviations; categorical data were reported as frequencies. Intergroup differences were evaluated using the Student's t-test for continuous data and using the chi-square test or Fisher's exact test for categorical data. Odds ratio and respective 95% CIs were also reported.

The association between the groups and the primary outcome was evaluated using Kaplan-Meier survival analysis and the log-rank test (Mantel-Cox test). The incidence ratio of mortality was evaluated using an adjusted hazard ratio (HR) with Cox proportional hazards regression. As covariables, we included confounder variables related to an increased risk of cardiovascular mortality not included in the STOP-Bang questionnaire (dyslipidemia, smoking history, alcohol consumption, previous CHD, ASCVD risk score, and use of lipid-lowering, antidiabetic, antihypertensive, and anticoagulant medications at baseline). The level of significance was set at $p < 0.05$. Statistical analysis was performed with the SPSS Statistics software package, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A flow chart of the patient selection process is shown in Figure 1. A total of 510 patients were screened, and

435 were included in the study for further analysis. The mean age of the cohort was 60.98 ± 17.10 years, 199 (45.7%) of the patients were considered elderly, 233 (53.6%) were male, 352 (80.9%) had a STOP-Bang score ≥ 3, and 192 (44.1%) had a STOP-Bang score ≥ 5. The ASCVD risk scores regarding patients with a STOP-Bang score of 0-2, ≥ 3, and ≥ 5, respectively, were 10.1 ± 11.2%, 22.6 ± 16.3%, and 24.6 ± 15.8%. A summary of baseline characteristics and reasons for admission is shown in Table S1.

A summary of clinical characteristics and differences among the groups are shown in Table 1. The mean age in the group with a STOP-Bang score ≥ 3 (n = 352) was 62.0 ± 16.5 years, 196 (55.7%) were male, and the mean BMI was 33.9 ± 6.5 kg/m^2. The prevalences of hypertension, DM, and dyslipidemia were 73.3%, 43.8%, and 59.4%, respectively. Of the 209 patients with dyslipidemia, 71 (34.0%) had hypertriglyceridemia, 60 (28.7%) had LDL dyslipidemia, and 78 (37.3%) had mixed dyslipidemia. Cardiovascular reasons for admission were heart failure, new-onset AF, unstable angina, and AMI.

The mean age in the group with a STOP-Bang score ≥ 5 (n = 182) was 62.55 ± 15.00, and the mean BMI was 35.78 ± 6.9 kg/m^2. Of the 182 patients in this group, the prevalence of hypertension, DM, and dyslipidemia were 84.0%, 50.0%, and 59.3%, respectively. Of the 108 patients with dyslipidemia, 37 (34.3%) had hypertriglyceridemia, 26 (24.1%) had LDL dyslipidemia, and 45 (41.7%) had mixed dyslipidemia. The reasons for hospitalization in this group were heart failure, in 10.9%; new-onset AF, in 1.1%; unstable angina, in 13.7%; and AMI, in 37.9%.

In comparison with the control group (STOP-Bang score of 0-2), those with a score of ≥ 3 and ≥ 5 presented with a similar clinical profile, with no statistically significant differences. A greater number of patients in both study groups were elderly (p = 0.09) and male (p = 0.01). In addition, the two study groups showed greater prevalences of comorbidities (BMI ≥ 35 kg/m^2, hypertension, DM, and dyslipidemia; p < 0.01 for all). Although no differences were found regarding cardiovascular events at admission between the control and the study groups (Table 1), there was a significant increased risk of both all-cause and cardiovascular mortality (p = 0.04 and p = 0.01, respectively) in the group with a STOP-Bang score ≥ 5 (Table 2).

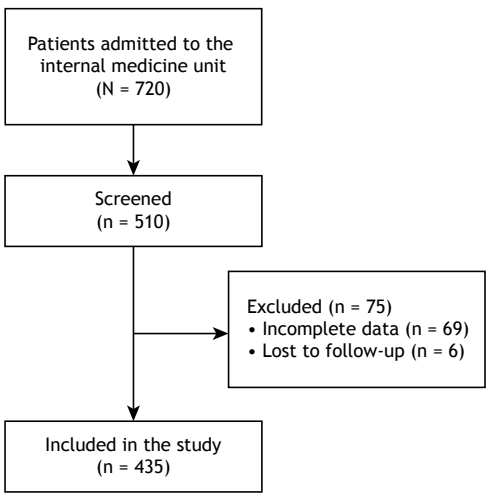

Figure 1. Flow chart of the patient selection process during the study period.

After 36 months of follow-up, 95 patients died, cardiovascular events being the reason in 34. The clinical characteristics of those who died or survived are shown in Tables 3 and 4. In the unadjusted analysis, a STOP-Bang score ≥ 3 showed no significant associations with all-cause mortality (HR = 1.36 [95% CI, 0.77-2.36]; p = 0.28) or cardiovascular mortality (HR = 2.94 [95% CI, 0.88-9.78]; p = 0.07). However, the adjusted analysis showed a significant association with cardiovascular mortality (HR = 4.67 [95% CI, 1.27-17.08]; p = 0.02).

In the unadjusted analysis, a STOP-Bang score ≥ 5 had no association with all-cause mortality (HR = 1.45 [95% CI, 0.96-2.20]; p = 0.17). However, the adjusted analysis showed a significant association (HR = 1.58 [95% CI, 1.01-2.48]; p = 0.04). Regarding cardiovascular mortality, both unadjusted and adjusted analyses showed significant associations with a STOP-Bang score ≥ 5: HR = 2.31 (95% CI, 1.13-4.70); p = 0.02; and HR = 3.12 (95% CI, 1.39-7.03); p = 0.01, respectively (Table 2 and Figure 2). The summary of the unadjusted and adjusted analyses is shown in Table 2. In addition, previous CHD at baseline was also associated with cardiovascular mortality in the group with a STOP-Bang score ≥ 5 (HR = 2.34 [95% CI, 1.04-5.26]; p = 0.04).

DISCUSSION

The main findings of the present study were that the STOP-Bang questionnaire was able to identify cardiovascular risk in hospitalized patients up to 36 months of follow-up; that, after adjusted analyses, the independent variables associated with a higher risk of cardiovascular mortality were a STOP-Bang score ≥ 3 and CHD at baseline; and that a STOP-Bang score ≥ 5 was associated with a higher risk of all-cause and cardiovascular mortality.

Hospitalized patients present with different levels of risk than does the general population. In our study, we hypothesized that the STOP-Bang questionnaire could identify populations with an increased risk of cardiovascular mortality to prioritize additional sleep studies. Moreover, we found an increased prevalence of patients at risk of OSA when we compared results from previous hospital-based studies.[11-13] Sharma et al.[11] reported a prevalence of OSA in 84% of hospitalized obese patients (BMI ≥ 30 kg/m^2). Goring & Collop[12] reported a prevalence of OSA diagnosed by polysomnography of 77% in hospitalized patients. Identifying hospitalized patients at risk of OSA is an important issue, because they have response

Table 1. Clinical characteristics of the patients included in the study according to STOP-Bang scores (N = 435).[a]

Characteristic	STOP-Bang score			p*
	0-2 (n = 83)	≥ 3 (n = 352)	≥ 5 (n = 182)	
Age, years	56.61 ± 18.74	62.01 ± 16.57	62.55 ± 15.04	0.01
Age ≥ 65 years	38.5%	47.4%	65.1%	0.12
Male	44.57%	55.68%	60.43%	0.01
BMI, kg/m^2	30.72 ± 5.73	33.93 ± 6.58	35.78 ± 6.96	< 0.01
BMI ≥ 35 kg/m^2	9.4%	12.5%	14.1%	< 0.01
ASCVD, %	10.1 ± 11.2	22.6 ± 16.3	24.6 ± 15.8	< 0.01
Former/current smoking	38.4%	52.3%	59.1%	< 0.01
Hypertension	19.2%	73.2%	84.0%	< 0.01
Diabetes mellitus	14.4%	43.7%	50.0%	< 0.01
Dyslipidemia	37.3%	59.3%	59.3%	0.01
Hypertriglyceridemia	41.9%	33.9%	34.3%	
High LDL	38.7%	28.7%	24.0%	
Mixed dyslipidemia	19.3%	37.3%	41.6%	
Medication				
Lipid-lowering	31.6%	48.3%	43.5%	< 0.01
Antidiabetic	9.2%	39.4%	48.1%	< 0.01
Anticoagulant	16.2%	52.0%	71.5%	< 0.01
Antihypertensive	15.2%	68.7%	75.4%	< 0.01
Reason for admission				
Decompensated HF	12.0%	13.0%	10.9%	0.47
AF	4.6%	34.0%	1.0%	0.17
CHD	15.6%	15.9%	13.7%	0.40
AMI	1.2%	2.5%	37.9%	0.29

ASCVD: American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease risk score; HF: heart failure; AF: atrial fibrillation; CHD: coronary heart disease; and AMI: acute myocardial infarction; [a]Values expressed as mean ± SD, except where otherwise indicated. *In comparison with the STOP-Bang score 0-2 group.

Table 2. Summary of the associations of STOP-Bang scores with all-cause and cardiovascular mortality.

	Unadjusted HR (95% CI)	p	Adjusted HR* (95% CI)	p
All-cause mortality				
STOP-Bang ≥ 3	1.36 (0.77-2.36)	0.28	1.52 (0.83-2.79)	0.17
STOP-Bang ≥ 5	1.45 (0.96-2.20)	0.07	1.58 (1.01-2.48)	0.04
Cardiovascular mortality				
STOP-Bang ≥ 3	2.94 (0.88-9.78)	0.07	4.67 (1.27-17.08)	0.02
STOP-Bang ≥ 5	2.31 (1.13-4.70)	0.04	3.12 (1.39-7.03)	0.01

HR: hazard ratio. *Cox proportional hazards model adjusted by dyslipidemia, former or current smoking, alcohol consumption, previous cardiovascular heart disease, and American College of Cardiology/American Heart Association Atherosclerotic Cardiovascular Disease risk score, as well as lipid-lowering, antidiabetic, antihypertensive, and anticoagulant medications at baseline.

events more rapidly. Therefore, the use of validated questionnaires that indicate a higher risk of OSA is a useful intervention to reduce complications.[13] The present study found an increased risk for OSA (80%) in our sample, and 40% of patients had a STOP-Bang score ≥ 5. This high prevalence is due to older age, obesity, and hypertension, which are common in hospitalized patients. Moreover, after a three-year follow-up period, this increased prevalence was associated with an increased risk of cardiovascular mortality.

The STOP-Bang questionnaire was initially developed by researchers in the field of anesthesiology.[14] Previous studies evaluated its accuracy in different clinical practices, such as in sleep study centers or in perioperative settings.[15,16] This questionnaire is an easy tool to screen populations at risk of OSA. Additionally, the STOP-Bang questionnaire has been shown to be a good screening tool to identify individuals with hypertension or DM at risk of OSA.[17-19]

Data regarding the use of the STOP-Bang questionnaire in hospitalized patients are scarce, and the clinical utility of this questionnaire in this population is unclear. Previously, we analyzed the cross-sectional relationships of STOP-Bang questionnaire scores with cardiovascular events (composite outcomes included major adverse cardiovascular events, cardiovascular mortality, acute coronary syndrome, and decompensated heart failure) during the first 30 days of hospitalization and with cardiovascular risk using the ASCVD risk score calculator. According to the ASCVD risk score,

Table 3. Comparison between all-cause mortality and survival groups after follow-up.[a]

Baseline characteristic	Group		p
	All-cause mortality (n = 95)	Survival (n = 340)	
Age, years	68.1 ± 14.3	59.3 ± 17.3	< 0.01
Age ≥ 65 years	61.7	42.0	0.01
Male	61.7	51.6	0.06
STOP-Bang score	4.2 ± 1.4	3.9 ± 1.8	0.19
≥ 3	87.6	79.3	0.05
≥ 5	48.1	40.3	0.12
Hypertension	77.7	59.6	0.01
Diabetes mellitus	44.4	36.7	0.12
Dyslipidemia	54.3	55.3	0.48
BMI ≥ 35 kg/m^2	9.8	10.7	0.50
Reason for admission			
Decompensated HF	13.5	12.7	0.47
Unstable angina	49.3	18.3	0.01
AMI	1.2	25.4	0.41
AF	3.7	33.8	0.55

HF: heart failure; AMI: acute myocardial infarction; and AF: atrial fibrillation. [a]Values expressed as mean ± SD or %.

Table 4. Comparison between cardiovascular mortality and survival groups after follow-up.[a]

Baseline characteristic	Group		p
	CV mortality (n = 34)	Survival (n = 340)	
Age, years	73.8 ± 11.8	60.4 ± 17.1	0.02
Age ≥ 65 years	75.0	43.7	0.01
Male	67.8	52.5	0.08
STOP-Bang score	4.6 ± 1.1	3.9 ± 1.7	0.04
≥ 3	86.4	79.8	0.06
≥ 5	67.1	40.7	0.01
Hypertension	67.8	62.6	0.36
Diabetes mellitus	50.0	37.3	0.12
Dyslipidemia	46.4	55.7	0.08
BMI ≥ 35 kg/m^2	13.5	11.0	0.48
Reason for admission			
Decompensated HF	25.0	12.0	0.05
Unstable angina	10.7	16.2	0.32
AMI	3.5	2.2	0.49
AF	10.7	2.9	0.06

HF: heart failure; AMI: acute myocardial infarction; and AF: atrial fibrillation. [a]Values expressed as mean ± SD or %.

we found that the cardiovascular risk in patients with a STOP-Bang score ≥ 3 was 24.3%, whereas that in those with a STOP-Bang score of 0-2 was 10.9%.[20]

In the present study, we included a single cohort of an understudied population (hospitalized individuals admitted to an internal medicine unit) followed for 36 months to determine the clinical utility of the STOP-Bang questionnaire in the identification of the risk for all-cause and cardiovascular mortality. We hypothesized that populations at risk of OSA would have an increased risk of cardiovascular mortality, mainly due to cardiovascular events defined in the ICD-9. We predefined to include hospitalized patients with mild-to-moderate disease in order to rule out those with severe acute disease, who might present with an increased risk of morbidity and sequelae. Our results provide new data about hospitalized patients. We studied the clinical utility of the STOP-Bang questionnaire in a specific population at risk of general or moderate-to-severe OSA. Our results demonstrated clinical differences between patients at risk of OSA and those without that risk. Additionally, after confounder analysis, previous CHD at baseline was also associated with cardiovascular mortality.

We also found an increased prevalence of cardiometabolic disease in patients at risk of OSA. First, the prevalence of hypertension ranged between 73% and 84%, which is higher than the prevalence reported in other studies.[21] However, most of those studies were performed in sleep study centers, not with

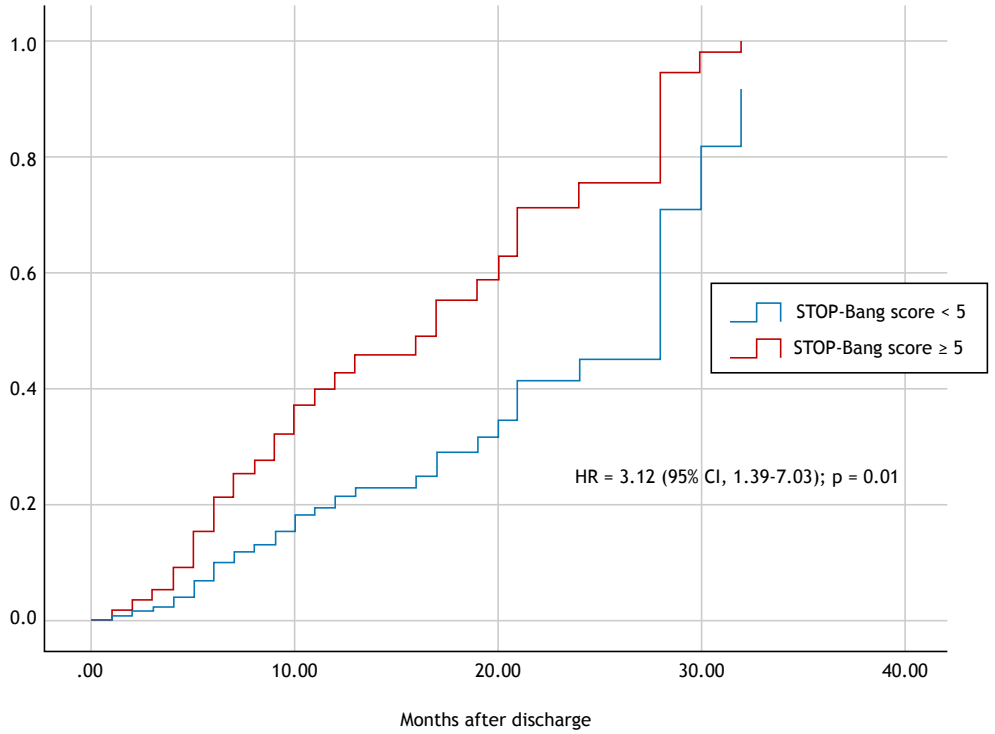

Figure 2. Cumulative incidence of cardiovascular mortality in the groups of patients with a STOP-Bang score < 5 (blue line) and ≥ 5 (red line). HR: hazard ratio.

hospitalized patients. Second, the prevalence of DM ranged between 44% and 50%. Pataka et al.[17] reported a prevalence of DM of 57% in patients with severe OSA; the sensitivity of the STOP-Bang questionnaire in the patients with DM was 81% for mild OSA and 95% for severe OSA. In that study,[17] the prevalence of dyslipidemia was 14%, whereas that was 59% in our study. An increased risk of dyslipidemia was previously reported by Chou et al.[22] in patients with OSA (61.1%). In another study,[23] the prevalence of dyslipidemia was 26% in the general population. In accordance with data from the European Sleep Apnea Database,[24] the prevalence of hyperlipidemia was 26% and 15% in patients with and without OSA, respectively, and this increase was independent after confounder analysis. However, those studies were performed in outpatient scenarios, either as population-based studies or at sleep study centers. Finally, regarding cardiovascular reasons for admission, the discharge of patients with heart failure and OSA was independently associated with an increased risk of mortality after 6-12 months of follow-up (RR = 1.53).[25]

The strengths of the present study are its prospective design, including consecutive Latin American patients admitted for any medical reason to an internal medicine service and the fact that the completion of the STOP-Bang questionnaire and the initial evaluation were performed within the first 48 h after admission.

The study also has limitations. The patients included were not submitted to sleep studies to confirm or rule out OSA. However, this study was designed to evaluate the risk of mortality using the STOP-Bang questionnaire, and these data can be used to improve the identification of hospitalized patients with an increased risk of OSA and, therefore, of worse outcomes, which might allow the incorporation of various interventions to reduce that risk.

In conclusion, in this cohort of hospitalized patients in an internal medicine unit, the STOP-Bang questionnaire was able to identify those with an increased risk of mortality. A STOP-Bang score ≥ 5 is an easy and useful tool to identify patients at risk of all-cause and cardiovascular mortality within a three-year follow-up period.

AUTHOR CONTRIBUTIONS

GL: study design and guarantor of the study. JC, AS, BS, FR, and GV: data extraction. AS, GL, and GV: data analysis. GL, JC, GV, FR, AO, and CN: interpretation of results. GL, GV, JC, AO, and CN: manuscript drafting. GL, FR, AS, BS, AO, and CN: manuscript revision and editing. All authors approved the final version of the manuscript.

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J Bras Pneumol. 2021;47(4):e20200584
https://dx.doi.org/10.36416/1806-3756/e20200584

ORIGINAL ARTICLE

Prospective evaluation of EBUS-TBNA specimens for programmed death-ligand 1 expression in non-small cell lung cancer patients: a pilot study

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Submitted: 30 November 2020.
Accepted: 6 April 2021.

Study carried out at the European Institute of Oncology, Milan, Italy.

ABSTRACT

Objective: EBUS-TBNA cytological sampling is routinely performed for pathological diagnosis, mediastinal staging, and molecular testing in lung cancer patients. EBUS-TBNA samples are not formally accepted for testing programmed death-ligand 1 (PD-L1) expression. The objective of the study was to compare the feasibility, reproducibility, and accuracy of PD-L1 expression assessment in cytological specimens and histological samples. **Methods:** We prospectively collected histological (transbronchial forceps biopsy) and cytological (EBUS-TBNA) samples from peribronchial neoplastic lesions during an endoscopic procedure at the same target lesion for the pathological diagnosis and molecular assessment of stage IV non-small cell lung cancer (NSCLC). **Results:** Fifteen patients underwent the procedure. Adequate cytological samples (at least 100 neoplastic cells) were obtained in 12 cases (92.3%). Assessment of PD-L1 expression was similar between histological and cytological samples (agreement rate = 92%). Sensitivity and diagnostic accuracy of EBUS-TBNA cytological specimens were 88.9% and 100%, respectively. **Conclusions:** The evaluation of PD-L1 expression in EBUS-TBNA cytological specimens is feasible and presents good reproducibility when compared with routine histological samples. EBUS-TBNA cytological samples could be used for the assessment of PD-L1 expression in patients with NSCLC as a minimally invasive approach in stage IV NSCLC cancer patients.

Keywords: Ultrasonography; Biopsy, needle; Lung neoplasms; Molecular targeted therapy.

INTRODUCTION

Despite the advances in diagnostic modalities and imaging methods, lung cancer remains a leading cause of death worldwide.[1] Up to 80% of patients present with advanced disease at the time of diagnosis, and systemic therapy may represent the only treatment option.[2,3]

Novel therapeutic strategies using molecular targeted drugs focused on genetic alterations have demonstrated to be the best treatment option in various clinical scenarios.[4] Molecular targeted therapies improve survival in metastatic adenocarcinoma with genetic mutations such as epidermal growth factor receptor (EGFR), ALK, ROS proto-oncogene 1 tyrosine kinase (ROS1), and v-Raf murine sarcoma viral oncogene homolog B (BRAF) rearrangement.[5]

More recently, immunotherapy with monoclonal antibodies blocking the programmed death-ligand 1 (PD-L1) has shown to be a promising treatment option in patients with advanced non-small cell lung cancer (NSCLC) in terms of overall survival when compared with standard chemotherapy regimens.[6] Thus, the evaluation of PD-L1 protein expression is essential in identifying patients that may benefit from immunotherapy the most.[7,8]

In the last several years, minimally invasive procedures have become the standard of care for the diagnosis and staging of NSCLC patients. Procedures such as EBUS-TBNA often provide all the necessary information, from tissue sampling to molecular evaluation, and cause few complications.[9-12] Cytological specimens by EBUS-TBNA have successfully been used for the assessment of various molecular targets, such as EGFR, ALK, and ROS-1,[8] and have proven to be adequate and comparable to histological samples for the evaluation of target markers.[13]

Diagnostic immunohistochemical assays to evaluate PD-L1 expression in tumor cells were officially developed to test tumor tissue samples.[14] However, their use for cytological evaluation of cell-block specimens is not accepted "worldwide," especially for patients included in clinical studies. Therefore, the objective of this pilot study was to evaluate and compare the feasibility and

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Financial support: None.

ISSN 1806-3756

reproducibility of PD-L1 expression assessment in EBUS-TBNA specimens and in histological specimens.

METHODS

The study was approved by the research ethics committee of the institution, and all participants gave written informed consent.

Patients with suspected advanced (stage IV) NSCLC underwent bronchoscopy for pathological definition, and molecular assessment of pulmonary lesions was carried out. Patients were selected on the basis of the identification of lesions on CT that showed a high probability to be sampled by both EBUS-TBNA and transbronchial biopsy. During the procedure, both histological (transbronchial biopsy) and cytological (EBUS-TBNA) samples were collected from the same peribronchial neoplastic lesion. A flow chart of the procedure is shown in Figure 1.

Fifteen consecutive patients who underwent bronchoscopy for the pathological diagnosis and evaluation of molecular PD-L1 expression were included in the analysis. Specimens were considered adequate if a minimum of 100 viable tumor cells were present. Samples with fewer than 100 viable tumor cells were considered inadequate and were excluded from the analysis.[15]

EBUS-TBNA samples

EBUS-TBNA samples were collected from peribronchial lesions adjacent to the airways. The procedure was performed under local anesthesia (1% lidocaine) and moderate sedation provided by an anesthesiologist. Ventilation was spontaneous. All procedures were performed by the same team of interventional pulmonologists using a convex probe (EBUS Convex Probe BF-UC180F; Olympus Europa SE & Co. KG, Hamburg, Germany) and a dedicated ultrasound processor (EU-ME2; Olympus). EBUS-TBNA specimens were collected with a 22G dedicated needle (Vizishot NA-201SX-4022; Olympus).

A very small amount of the aspirated material was pushed out by the internal stylet and smeared onto glass slides, air dried, and stained with modified May-Grünwald-Giemsa (Diff-Quik) stain for rapid on-site evaluation (ROSE). The remaining aspirate and other needle passes—minimum of 3 needle passes, ranging from 3 to 5 according to the percentage of tumor cells present on the smear (ROSE)—were placed in saline solution for cell-block processing and further cytological evaluation.[10]

Histological samples

A transbronchial biopsy was performed inserting a large (2.8 mm) endoscopic forceps into the pulmonary lesion. Neoplastic pulmonary lesions were previously confirmed with radial EBUS probe and fluoroscopy, and a guide sheath kit (SG-201-C; Olympus) was used in order to maintain the correct position of the forceps. No endobronchial visible lesions were biopsied.

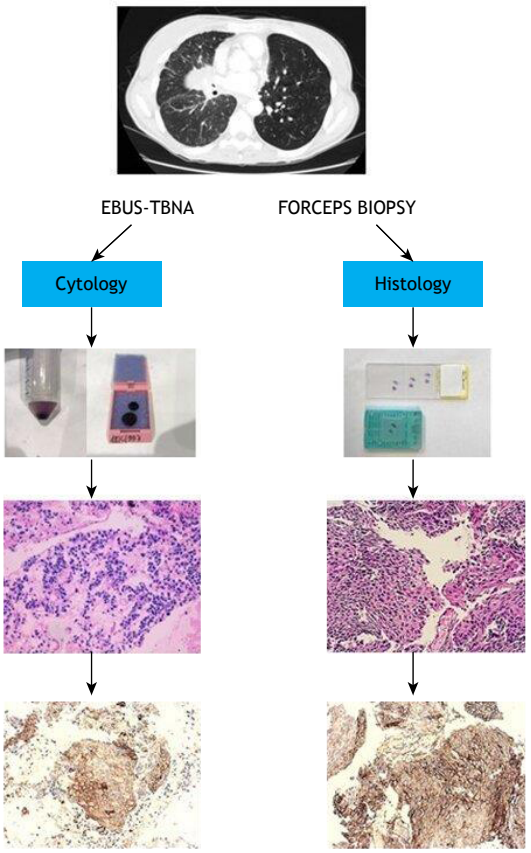

Figure 1. Flow chart of collection and analysis of cytological and histological specimens. The same peribronchial lesion was biopsied by forceps biopsy (right side) and EBUS-TBNA (left side).

The first biopsy sample obtained was rolled onto a glass slide for "biopsy imprinting" and immediate cytological evaluation (ROSE) for the adequacy of the specimen. Once adequacy was confirmed, further biopsies were performed and immediately fixed in formalin for histological evaluation, as previously described.[16]

PD-L1 and immunohistochemistry technical aspects

Cell blocks from EBUS-TBNA specimens were prepared with no methanol-based fixative. The cytological material was centrifuged, stained with H&E, coated with fluid agarose to form a firm cell block, and finally processed in accordance with standard histopathological methods used for formalin-fixed paraffin-embedded samples.[17]

Ten consecutive 2-to-3-mm thick sections were obtained from each cell block; the first and the last sections were stained with H&E to make sure that diagnostic tumor cells were present in all of the slides. In selected cases, in order to differentiate between adenocarcinoma and squamous cell carcinoma, we performed immunocytochemical stains for thyroid transcription factor-1 and p40 (an antibody that recognizes ΔNp63, a p63 isoform suggested to be highly specific for squamous/basal cells).[18]

PD-L1 expression was evaluated with the PD-L1 IHC 22C3 pharmDx kit (Agilent Technologies, Santa Clara, CA, USA), a qualitative immunohistochemical assay that uses monoclonal mouse anti-PD-L1 antibody, clone 22C3, using the EnVision FLEX visualization system on Autostainer Link 48 (Agilent).[15]

Specimens were considered adequate if a minimum of 100 viable tumor cells were present. In each case, a tumor proportion score (TPS) was calculated. TPS is the proportion of viable tumor cells showing partial or complete membrane staining. TPS was considered negative if the proportion of stained cells was < 1%; weakly positive, if it ranged from 1% to 49%; and strongly positive, if it was ≥ 50%.

Two experienced pathologists independently examined all samples. Disagreements were discussed and resolved by consensus. Forceps biopsy samples were processed in accordance with standard histopathological methods.

Statistical analysis

Continuous data were reported as means and standard deviations. Categorical and numerical data were presented as absolute and relative frequencies. Inadequate samples (adequate biopsy samples presenting > 100 viable cells but inadequate EBUS-TBNA samples) were excluded from the accuracy analysis because the objective of the study was to show concordance between samples. To test the correlation between risk classes, Spearman's rank correlation test was used. A ROC curve was generated to determine the best threshold. Significance was set at $p < 0.05$. Statistical analysis was performed using RStudio, version 3.6.1 "Action of the Toes" (RStudio Inc., Boston, MA, USA), with the packages standard, *rcmdr*, and *irr*.[19,20]

RESULTS

Fifteen patients were included in the study. Adequate samples (at least 100 viable neoplastic cells) were obtained from both cytological and histological specimens in 12 patients (80%). Demographic characteristics of patients were the following: 13 male patients (83.3%); and median age = 66 years (range: 54-78 years). Regarding tumor cell types, adenocarcinoma and squamous cell carcinoma were identified in 11 and 4 patients, respectively. Histological and cytological PD-L1 expression results are shown in Table 1.

Three patients with inadequate samples were included in the aggregate analysis but excluded from the accuracy analysis. In 11 patients, there was complete agreement between cytological and histological PD-L1 expression results regardless of the subtypes: adenocarcinoma, in 9 patients (Figure 2); and squamous cell carcinoma, in 2 (Figure 3). In one case (adenocarcinoma), there were discordant results (negative cytology and weakly positive histology). The results of PD-L1 expression in EBUS-TBNA cytological samples showed an area under the ROC curve of 0.79 (Figure 4A). Sensitivity, diagnostic accuracy, and negative predictive value were 88.9%, 91.7%, and 75.0%, respectively. PD-L1 staining showed a negative reaction, a weakly positive reaction, and a strongly positive reaction in 16.7%, 16.7%, and 66.7% of the histological samples, respectively, and in 25.0%, 8.3%, and 66.7% of the cytological samples.

Considering the different cutoffs for PD-L1 expression, the agreements between histological and cytological specimens considered negative, weakly positive, and strongly positive were 80%, 67%, and 100%, respectively. The Spearman's rank correlation test showed a highly significant correlation between the TPS of histological and cytological samples (rho = 0.836; $p = 0.0060$; Figure 4B).

DISCUSSION

Nowadays, EBUS-TBNA is part of the daily routine clinical practice in various thoracic diseases.[10] Due to its low invasiveness and the possibility of

Table 1. Histological subtypes and programmed death-ligand 1 (PD-L1) expression results.

Patient	Histological subtype	PD-L1 histology (TPS%)	PD-L1 cytology (TPS%)
1	Adenocarcinoma	5	2
2	Adenocarcinoma	2	< 1
3	Adenocarcinoma	90	90
4	Squamous cell carcinoma	60	60
5	Adenocarcinoma	< 1	< 1
6	Adenocarcinoma	60	55
7	Adenocarcinoma	80	75
8	Adenocarcinoma	80	80
9	Adenocarcinoma	80	70
10	Adenocarcinoma	70	70
11	Squamous cell carcinoma	< 1	< 1
12	Adenocarcinoma	70	80
13	Squamous cell carcinoma	80	-
14	Adenocarcinoma	2	-
15	Squamous cell carcinoma	2	-

TPS%: tumor proportion score in %.

obtaining repeated samples, EBUS-TBNA is often the procedure of choice for the pathological diagnosis and molecular assessment in patients with advanced stage NSCLC.[21] Up to 80% of NSCLC patients present with advanced disease at the time of diagnosis and could be potential candidates for targeted drug therapy.[2] In our experience, up to 98.5% of the patients are diagnosed with a minimally invasive procedure that provides cytological and cell-block specimens.[10]

The modern oncological approach associates minimally invasive procedures with less invasive oncological treatments for better survival and lower complication rates. The development of an optimal modality that enables the acquisition of sufficient amounts of high-quality tissue without surgery is essential in the molecular targeted therapy era. Molecular testing is crucial in the management of patients with NSCLC lung cancer, especially in directing targeted therapy with EGFR tyrosine kinase inhibitors and other molecular markers.[8] Molecular targetable mutations such as *EGFR* were initially evaluated in histological specimens until it was demonstrated that they could also be assessed in EBUS-TBNA specimens with equivalent sensitivity.[13]

In the last years, immunotherapy for the treatment of lung cancer with immunotherapeutic agents targeting the immune checkpoint pathways, such as PD-L1, has shown promising results, with prolonged clinical responses and tolerable toxicity.[6]

Selection of patients that could benefit from immunotherapy is mandatory in advanced NSCLC,[22] and PD-L1 is the only biomarker validated and approved as a companion diagnostic tool prior to immunotherapy in clinical practice. PD-L1, together with EGFR, BRAF, ALK, and ROS-1, represents a mandatory biomarker to be evaluated in samples used for the pathological diagnosis of NSCLC so that the best treatment strategy can be offered. Other markers, such as HER2, KRAS, RET, and *MET* 14 exon skipping mutation, are also recommended.[23]

To date, the gold standard for the assessment of PD-L1 expression is immunohistochemistry performed in formalin-fixed paraffin-embedded histological specimens,[24] and there is limited evidence that PD-L1 expression could be reliably assessed in EBUS-TBNA cytological specimens in daily clinical practice. A previous study[25] reported the feasibility of cytological evaluation of PD-L1 in a variety of 30 cytological preparations from samples of patients with NSCLC. The authors concluded that cell-block preparations could replace histological tissue for determining PD-L1 status in NSCLC patients. However, that study evaluated different types of cytological specimens involving different types of tumors, different collection sites, and different analytical laboratory processes, causing several biases.[25]

Another study[26] reported a comparison between cytological and histological samples. That study presented with a considerable bias related to the lack of standardization of cytological and histological samples. Cytological samples were obtained from different sites

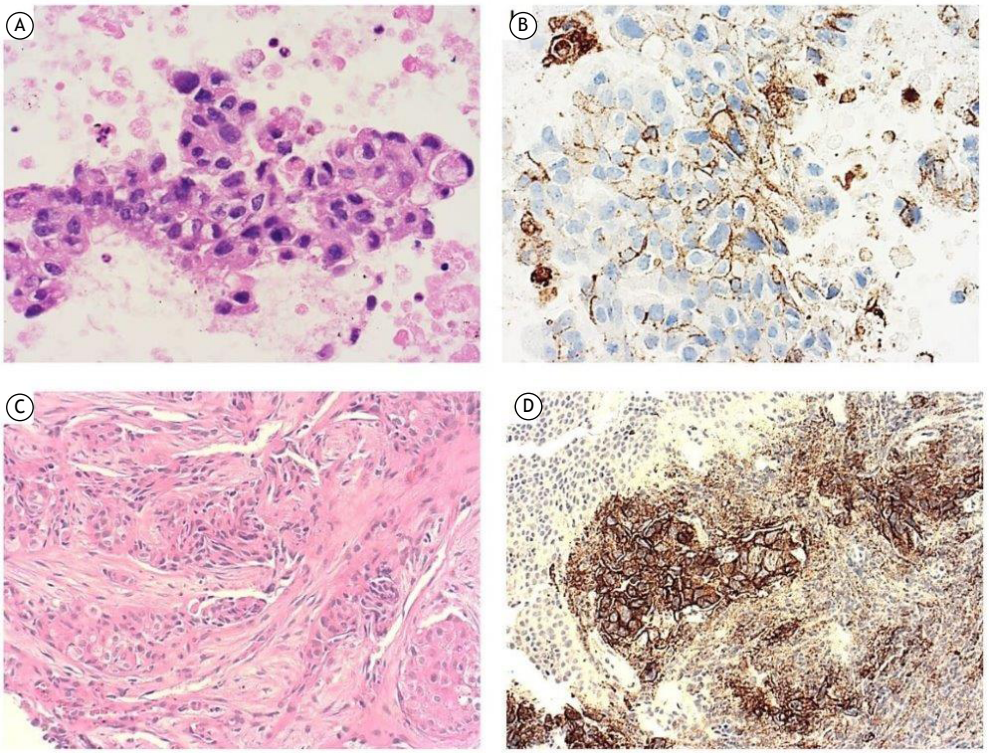

Figure 2. Photomicrographs of EBUS-TBNA (A and B; formalin-fixed paraffin-embedded cell-block sections) and forceps biopsy samples (C and D) of a patient diagnosed with adenocarcinoma (solid type), using H&E (A and C) and PD-L1 staining (B and D). The percentage of PD-L1 positive cells is higher than 50% in both samples.

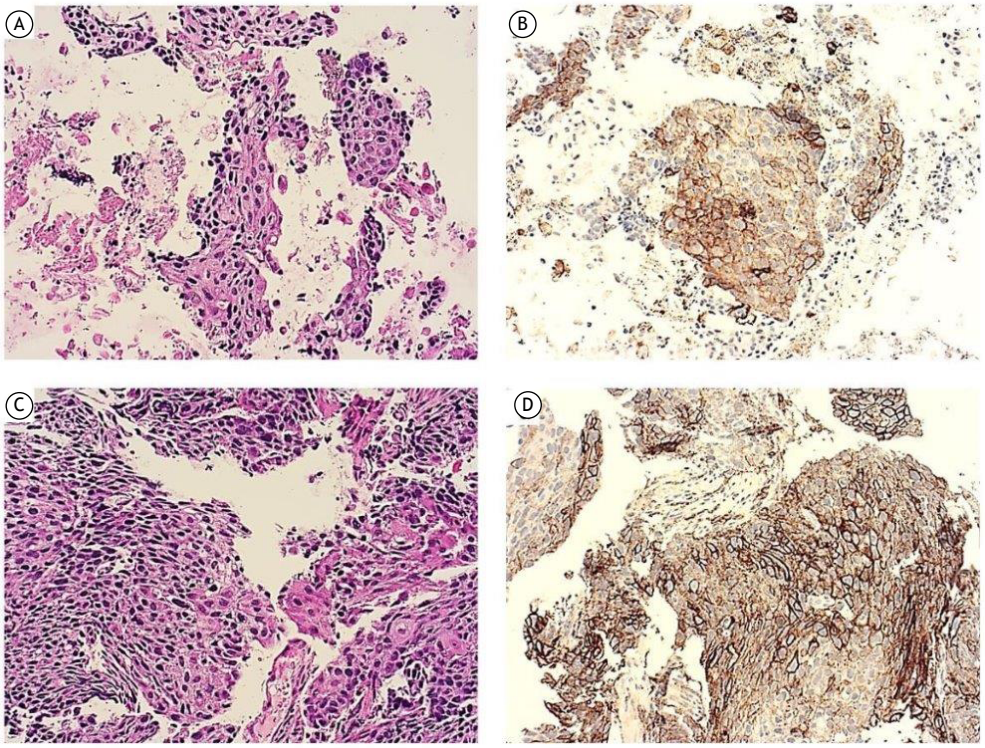

Figure 3. Photomicrographs of EBUS-TBNA (A and B; formalin-fixed paraffin-embedded cell-block sections) and forceps biopsy samples (C and D) of a patient diagnosed with nonkeratinizing squamous cell carcinoma, using H&E (A and C) and PD-L1 staining (B and D). The percentage of PD-L1 positive cells is higher than 50% in both samples.

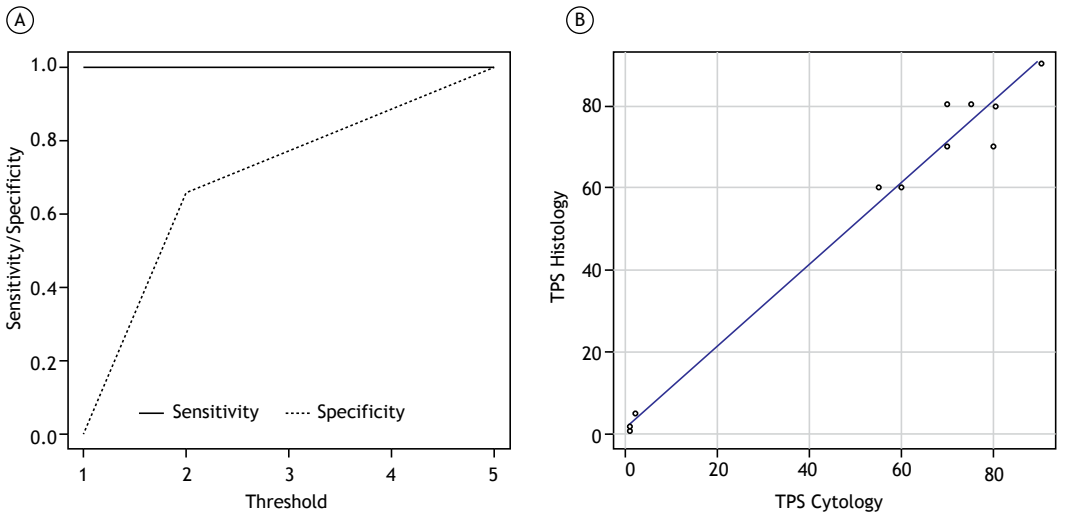

Figure 4. In A, ROC curve of programmed death-ligand 1 expression results (AUC = 0.79; sensitivity = 88.9%; and specificity = 91.7%). In B, scatter plot of tumor proportion score (TPS) for cytology and histology (rho = 0.836; p = 0.006).

with different needle types, and histological samples were obtained from many different sites, including needle biopsies. In addition, cytological and histological samples were not collected at the same time. Different pathological subtypes, including malignant mesothelioma and metastasis other than lung cancer, were included in the analysis. As it is known, PD-L1 expression in tumors is dynamic and can change over time and according to different tumor sites; therefore, collecting samples at different times can generate a bias in the analysis of PD-L1 expression itself.[7] In the present study, we prospectively evaluated the feasibility of PD-L1 expression in EBUS-TBNA samples comparing them with histological specimens of the same lesion

that were collected at the same time, thereby avoiding any collection or selection bias that could change the PD-L1 expression profile.

Our results showed an excellent agreement between cytological and histological specimens in the evaluation of PD-L1 expression in NSCLC specimens. The agreement between histological and cytological specimens regarding PD-L1 expression was 80%, 67%, and 100%, respectively, for negative, weakly positive, and strongly positive results. In one case, there were discordant results: negative cytology (< 1%) and focal, weakly positive histology (2%). We excluded inadequate samples (adequate biopsy presenting > 100 viable tumor cells but EBUS-TBNA samples < 100 viable cells). Inadequate samples were related to the presence of blood in excess or necrosis in the cell block.

This pilot study has limitations. The major limitation was the small number of patients included in the analysis. Selecting patients with peribronchial lesions that are able to be biopsied with a forceps and EBUS-TBNA is quite infrequent, but it was mandatory to exclude any possible sample bias. Another limitation of the study is related to the reproducibility of PD-L1 expression results in EBUS-TBNA lymph node specimens. Although PD-L1 expression may be different between the primary tumor and lymph node metastasis, a good concordance (70-90%) has been reported at clinically relevant cutoffs.[24]

In the present study, despite the limited sample size, the feasibility and reproducibility of PD-L1 expression results in EBUS-TBNA specimens have demonstrated that it is possible to obtain sufficient tissue sample from one single procedure for pathological diagnosis, staging, and complete molecular assessment, underpinning the personalized therapy era that combines minimally invasive procedures with biological agents for the best oncological results. The good concordance between histological and cytological samples shows promising results for the evaluation of PD-L1 expression in EBUS-TBNA specimens. Further studies are needed to confirm this evidence.

ACKNOWLEDGEMENTS

We would like to thank the professional English translator Ms. Susan Jane West for reviewing the manuscript.

AUTHOR CONTRIBUTIONS

JG and LS: study conception and design; and materials or referral of patients. LS: study conception and design. FDM and SMD: materials or referral of patients. EGR, CDT, and MB: data collection/assembly. LB and MC: data analysis and interpretation. GS: administrative support. All authors: drafting and revision of the manuscript; and approval of the final version.

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J Bras Pneumol. 2021;47(4):e20210025
https://dx.doi.org/10.36416/1806-3756/e20210025

Routine follow-up after surgical treatment of lung cancer: is chest CT useful?

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Submitted: 4 February 2021.
Accepted: 15 May 2021.

Study carried out at the A.C. Camargo Cancer Center, São Paulo (SP) Brasil.

ABSTRACT

Objective: To report the experience of a routine follow-up program based on medical visits and chest CT. **Methods:** This was a retrospective study involving patients followed after complete surgical resection of non-small cell lung cancer between April of 2007 and December of 2015. The follow-up program consisted of clinical examination and chest CT. Each follow-up visit was classified as a routine or non-routine consultation, and patients were considered symptomatic or asymptomatic. The outcomes of the follow-up program were no evidence of cancer, recurrence, or second primary lung cancer. **Results:** The sample comprised 148 patients. The median time of follow-up was 40.1 months, and 74.3% of the patients underwent fewer chest CTs than those recommended in our follow-up program. Recurrence and second primary lung cancer were found in 17.6% and 11.5% of the patients, respectively. Recurrence was diagnosed in a routine medical consultation in 69.2% of the cases, 57.7% of the patients being asymptomatic. Second primary lung cancer was diagnosed in a routine medical appointment in 94.1% of the cases, 88.2% of the patients being asymptomatic. Of the 53 patients who presented with abnormalities on chest CT, 41 (77.3%) were diagnosed with cancer. **Conclusion:** Most of the cases of recurrence, especially those of second primary lung cancer, were confirmed by chest CT in asymptomatic patients, indicating the importance of a strict follow-up program that includes chest CTs after surgical resection of lung cancer.

Keywords: Lung neoplasms/surgery; Neoplasm recurrence, local; Neoplasms, second primary.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide. In Brazil, lung cancer is the fourth most incident type, with an estimated 30,200 new cases in 2020.[1] Only 20% of the new cases present with localized disease amenable to surgical resection, and half of the patients will recur even after complete surgical resection.[2] Another concern is the risk of second primary lung cancer in lung cancer survivors; previous studies reported a rate of 1-3% per patient-year.[3] Diagnosis of recurrence and second primary lung cancer justify the organization of a follow-up program. Some authors reported that 60-75% of recurrence cases were found on routine chest CT scans in asymptomatic patients.[4] Unfortunately, most recurrences occur at a distant site where curative treatment is impossible, and even the majority of the local recurrences are not resectable and have dismal prognosis.[5] However, early diagnosis of lung cancer during a screening program has led to a 20% reduction in cancer-specific mortality.[6] The high risk of a second primary lung cancer justifies the inclusion of such patients in a screening program based on annual low-dose CT. Other reasons that justify follow-up are identifying and treating early and late effects of oncologic treatment; caring for other primary cancers that are amenable to primary and secondary prevention; and managing patient anxiety and fear of recurrence.[7]

Although the risks of recurrence and second primary lung cancer are well known, an optimal follow-up strategy has yet to be well defined and remains controversial in different guidelines.[8-10] There is no consensus regarding the modality, examinations, frequency, and follow-up period. Various studies have recommended chest CT as the imaging test for follow-up.[9,10] However, it has no influence on overall survival apparently. Moreover, little is known about the optimal time intervals for evaluating patients in a follow-up program.[11-15]

The aim of the present study was to report the experience of a routine follow-up program based on chest CT.

METHODS

This was a retrospective review of non-small cell lung cancer patients who were submitted to complete surgical resection between April of 2007 and December of 2015 at the A.C. Camargo Cancer Center, located in the city of São Paulo, Brazil. This study was approved by the local institutional review board (Reference no. 1980/14).

The inclusion criteria were undergoing complete surgical resection of non-small cell lung cancer and participating

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Financial support: None.

in the follow-up program at our institution. Age was considered at the date of surgical treatment. Histological types were classified according to pathological reports. Clinical and pathological stages were defined in accordance with the American Joint Committee on Cancer staging manual.[16] All patients underwent PET/CT and brain MRI for staging.

Surgical treatment included parenchymal resection (segmentectomy, lobectomy, or pneumonectomy) and mediastinal lymphadenectomy. Adjuvant treatments were indicated at the discretion of the clinical oncologist and/or radiotherapist. We defined the end of treatment as the date of surgical resection or the date of the end of adjuvant treatment.

Follow-up

The institutional routine was based on medical consultations and chest CTs in all cases, and ancillary tests were ordered according to initial assessment. The intervals between follow-up evaluations were as follows: every three months in the first and second year in the program; every six months between the third and fifth years; and every year after five years. Routine follow-up evaluation was defined as a visit scheduled according to our routine evaluation. Non-routine follow-up evaluation was defined as a medical appointment scheduled on a different date motivated by some clinical manifestation at the outpatient clinic or ER.

According to the information recorded in the medical charts, patients were classified as symptomatic or asymptomatic. Symptomatic patients reported any symptoms (spontaneously or stimulated by direct medical questioning) or presented with any findings on physical examination. Patients classified as asymptomatic had neither symptoms nor abnormal findings on physical examination.

The endpoint of each follow-up visit was classified into four categories: 1. no evidence of cancer; 2. recurrence of previous lung cancer; 3. second primary lung cancer; and 4. second primary extrapulmonary cancer. Recurrence was defined preferentially by biopsy. In cases in which biopsy was judged to be unnecessary or difficult to perform, recurrence was determined by clinical and radiological evaluations according to the characteristics of imaging examinations (CT, MRI, or PET/CT) and evolution in sequential assessments. Local recurrence was defined as a tumor occurring at the resection margins, regional recurrence was defined as a tumor in mediastinal lymph nodes, and distant recurrence was defined as a tumor in other organs outside the ipsilateral hemithorax. Recurrence in the ipsilateral pleura and in multiple nodules in the ipsilateral lung was also classified as distant recurrence. However, differentiation between systemic recurrence and second primary lung cancer was very controversial in the cases of a single nodule in the ipsilateral remnant lung. A new pulmonary neoplasm identified during a follow-up evaluation was classified as second primary lung cancer when the histological type was different from the primary one. In patients presenting with the same histological type, second primary lung cancer was defined in accordance with the criteria defined by Martini and Melamed[13]: a) different localization from the primary tumor, preferentially in the contralateral lung; b) disease-free interval greater than two years; and c) absence of involvement of a common lymph node chain between the former and the current primary tumor. Second primary extrapulmonary cancer was defined by anatomopathological examination and classified according to the anatomic site.

Statistical analysis

Continuous variables were expressed as medians and minimum-maximum variations, and categorical variables were expressed as absolute and relative frequencies. Time to recurrence and time to the diagnosis of second primary lung cancer were calculated from the date of cancer treatment completion to the date of confirmation of recurrence or second primary lung cancer by biopsy or clinical diagnosis. Correlations were determined by the chi-square test or Fisher's exact test. The level of significance was set at $p < 0.05$.

RESULTS

Between 2007 and 2015, 148 lung cancer patients were included in the study. The median age was 67 years (range, 25-86 years). The characteristics of the patients are described in Table 1.

Pulmonary lobectomy was the most common type of surgical resection (67.6%), and most of the patients (53.4%) were classified as pathological stage IA (Table 2). In this sample, 41 patients (27.7%) received adjuvant treatment: chemotherapy, in 31 (21.1%); radiotherapy, in 2 (1.3%); and chemoradiation, in 8 (5.4%).

The median time of follow-up was 40.1 months (range, 0.6-123.2 months). The median number of consultations per patient was 9 (range, 1-22), and the median number of chest CTs per patient was 7 (range, 0-18). In the first year of follow-up, the median number of chest CTs was 3 (range, 0-5), whereas this was only 1.5 (range, 0-4) in the second year of follow-up.

We assessed patients according to their adherence to the routine follow-up program of our institution. Regarding the number of chest CTs during the follow-up program, only 21 patients (14.2%) completed it properly, whereas 110 (74.3%) and 17 (11.5%), respectively, underwent fewer and more chest CTs than it was recommended.

In our sample, 95 (64.2%) of the patients were classified as showing no evidence of cancer in the last follow-up visit. Recurrence was identified in 26 patients (17.6%): locoregional recurrence, in 13 (8.8%), and distant recurrence, in 13 (8.8%). Recurrence was confirmed by biopsy and based on imaging assessment in 16 and 10 patients, respectively. The median time to recurrence was 15.1 months (range, 1.2-59.3 months).

Seventeen patients (11.5%) had the diagnosis of second primary lung cancer: confirmed by biopsy, in 16, and by imaging assessment, in 1. The median time to recurrence was 33.3 months (range, 1.2-75.1 months). Second primary lung cancer was contralateral in 14 (82.4%) of the patients. Adenocarcinoma was the most common histological type, in 10 patients (58.8%), followed by squamous cell carcinoma, in 3 (17.6%); large cell carcinoma, in 2 (11.8%); and unspecific non-small cell lung cancer, in 2 (11.8%). Distribution according to clinical stage was as follows: I (n = 8; 47%); II (n = 1; 5.9%); IIIA (n = 4; 23.5%); IIIB (n = 1; 5.9%), and IVA (n = 2; 11.8%). Figure 1 depicts that most recurrence cases were identified in the first 20 months of follow-up, whereas second primary lung cancer was more commonly identified after 30 months of follow-up.

Second malignant extrapulmonary neoplasms were diagnosed in 10 patients (6.7%) in the following primary sites: pancreas, in 3; breast, in 2; colon, in 1; prostate, in 1; soft tissue sarcoma, in 1; kidney, in 1, and brain, in 1.

Table 1. Clinical characteristics of the patients included in the study (N = 148).

Characteristic	n	%
Gender		
Male	83	56.1
Female	65	43.9
Tobacco use		
Yes	91	61.5
No	57	38.5
Histology		
Adenocarcinoma	99	69.9
Squamous cell carcinoma	34	23.0
Other	15	10.1
Laterality		
Right	92	61.4
Left	58	38.6
Primary tumor site		
Upper lobe	79	53.3
Middle lobe	11	7.3
Lower lobe	44	30.0
More than one lobe	14	9.3

Table 2. Type of pulmonary resection and pathological stage.

Characteristic	n	%
Type of surgical resection		
Lobectomy	100	67.6
Sublobar resection	29	19.6
Pneumonectomy	10	6.8
Bilobectomy	9	6.1
Pathological stage		
IA	79	53.4
IB	20	13.5
IIA	15	10.1
IIB	10	6.8
IIIA	20	13.5
IIIB	3	2.0
IVA	1	0.7

Recurrence was diagnosed in a routine medical consultation in 18 of the 26 patients (69.2%), 15 of whom (57.7%) were asymptomatic, and abnormalities were identified on a routine chest CT: nodule, in 7; mediastinal lymph nodes, in 3; pleural nodule, in 2; tracheal tumor, in 1; mediastinal tumor, in 1; and pancreatic nodule, in 1. Symptoms related to recurrence were observed in 11 (42.3%) of the patients: pain, in 6; dyspnea, in 2; hemoptysis, in 1; dizziness, in 1; and hoarseness, in 1.

Second primary lung cancer was diagnosed in a routine medical appointment in 16 (94.1%) of the patients, and most of them (88.2%) were asymptomatic. Only 2 patients (11.8%) presented with symptoms of dyspnea (in 1) and hemoptysis (in 1). Of the 15 asymptomatic patients, the most frequent finding on chest CT was pulmonary nodule, in 13 patients, followed by mediastinal lymph node, in 1; and ground glass opacity, in 1.

Table 3 shows that chest CT findings in asymptomatic patients diagnosed second primary lung cancers (88.2%) more frequently than recurrence (57.7%; p = 0.04).

Abnormalities on chest CT were found in 53 patients (35.8%). Figure 2 shows the findings, ancillary examinations performed, presence of symptoms, and endpoints. PET/CT was performed in 34 patients (64.1%). Of the 53 patients, 12 (22.7%) had no cancer despite abnormal CT results. Among these patients, PET/CT and bronchoscopy were performed in 5 and in 1, respectively.

DISCUSSION

There is controversy in the literature about modality, frequency, and duration of follow-up, as well as type of examinations to be performed, after surgical resection of lung cancer.[14] We analyzed the follow-up program at our institution, with a special focus on the role of chest CT. In the present study, the median follow-up period was 40.1 months. The median number of chest CTs per patient was 3 in the first year of follow-up, but it dropped to 1.5 in the second year. Only 14.2% of the patients underwent the exact number of chest CTs recommended by the current institutional protocol, whereas most of the patients (74.3%) were submitted to fewer chest

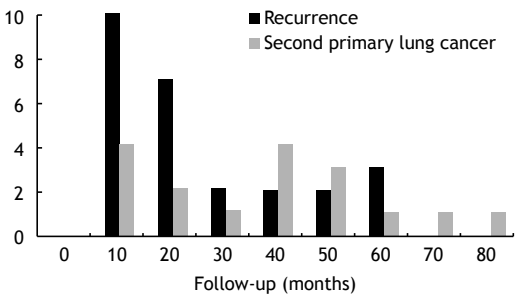

Figure 1. Number of patients diagnosed with recurrence or second primary lung cancer during the follow-up period.

CTs than what our protocol recommended. Recurrence was observed in 17.6% of the sample (median time to recurrence = 15.1 months). Most recurrence cases were detected in routine consultations (69.2%) and on routine chest CT with abnormal findings in asymptomatic patients (57.7%). Second primary lung cancer was found in 11.5% of the patients, most of them being asymptomatic (88.2%) and having abnormal chest CT findings. We observed that abnormal chest CT findings in asymptomatic patients diagnosed second primary lung cancers (88.2%) more frequently than recurrence (57.7%; p = 0.04).

The rate of second primary lung cancer has been reported as high as 1-3% per patient-year in previous studies.[3] Lou et al.[4] reported 7% of cases of second primary lung cancer in a follow-up program. Similarly to our findings, Kent et al.[17] reported a second primary lung cancer rate of 11%. Interestingly, the risk of developing an extrapulmonary primary malignancy in this scenario has been poorly studied. Few authors reported the incidence of additional extrapulmonary malignancy, ranging from 1% to 26%.[18-20] Similarly to our results, Son et al. reported a 4.7% rate of second primary non-pulmonary malignancy during the follow-up of patients submitted to lung cancer resection.[20] The follow-up period is an excellent opportunity for preventing different primary and secondary neoplasms. These aspects should be considered in a comprehensive survivorship program after curative treatment of lung cancer.

Although most guidelines have recommended the use of chest CT in follow-up programs after curative surgical resection of lung cancer, there is no consensus about its usefulness in this scenario.[21] Lou et al.[4] reported their vast experience about the role of chest CT in the follow-up of surgically treated lung cancer patients. Similarly to our experience, they found that recurrence and second primary lung cancer

Table 3. Association of the method of diagnosis (symptoms or chest CT in asymptomatic patients) with recurrence or second primary lung malignancy.

	Symptoms	Chest CT	Total	p
Recurrence	11 (42.3%)	15 (57.7%)	26 (100%)	0.04
Second lung cancer	02 (11.8%)	15 (88.2%)	17 (100%)	

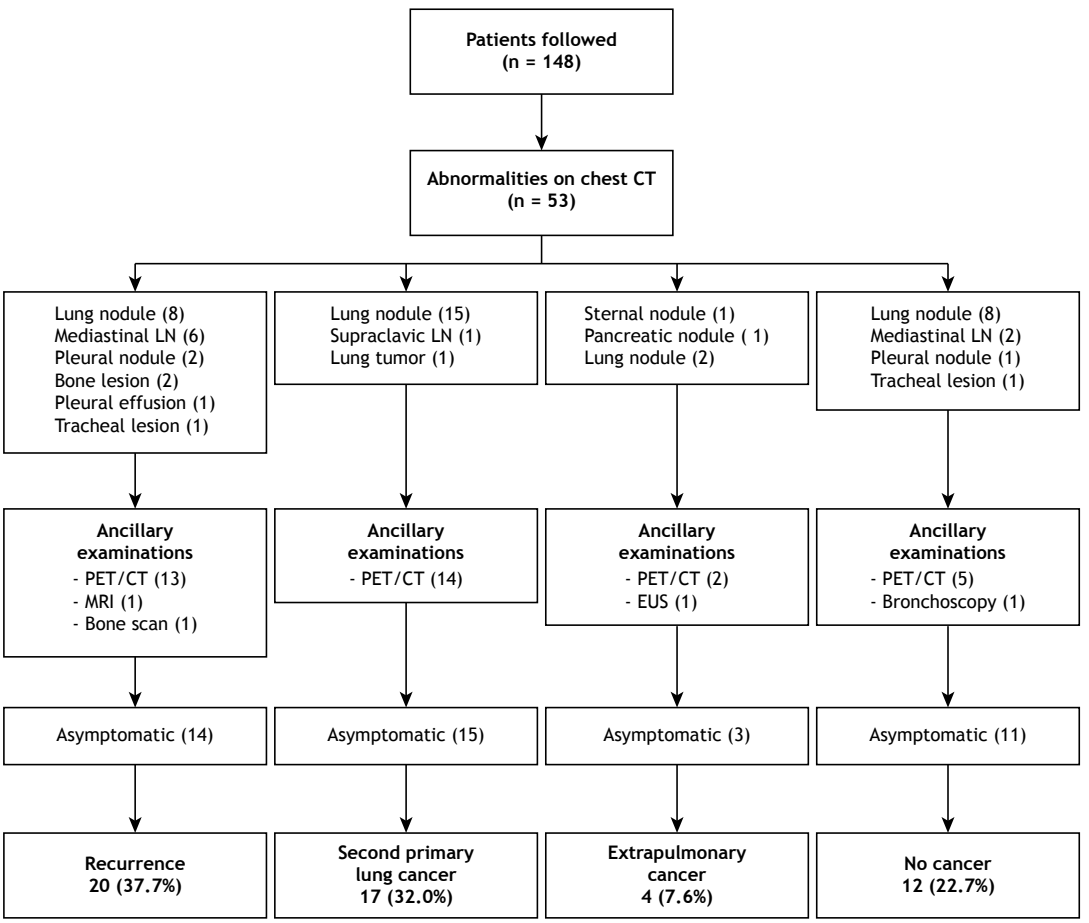

Figure 2. Types of abnormal findings on chest CT, ancillary examinations performed, and endpoints (n = 53). LN: lymph node; and EUS: endoscopic ultrasound.

were diagnosed in 61% and 93% of asymptomatic patients, respectively, by chest CT and during a routine consultation. Recently published screening studies have affirmed the importance of early diagnosis of lung cancer.[6,17] Therefore, we can extrapolate these results to the early diagnosis of second primary lung cancer during a follow-up program. However, we cannot assume that the early diagnosis of recurrence might impact on overall survival or quality of life. A systematic review and meta-analysis found a trend toward better survival in an intensive follow-up program, and the identification of recurrence in asymptomatic patients was associated with significantly increased survival.[22] Crabtree et al.[23] reported that chest CT resulted in earlier diagnosis of successive malignancy, although no difference in survival was demonstrated when chest CT and chest X-ray were compared. In our experience, chest CT significantly identified more cases of second primary lung cancer than those of recurrence, and time to recurrence was shorter than time to diagnosis of second primary lung cancer.

The optimal interval between surveillance screenings is not well defined, although most of the guidelines recommend surveillance every six months in the first two years, and then annually.[10,11] On the basis of our previous experience, we have recommended a stricter follow-up program than those in most guidelines.[15] However, the present study showed that most of the patients had been submitted to fewer chest CTs than suggested in our guideline. The low adherence rate to our follow-up protocol can be explained by its short time interval, especially in the first two years of follow-up. We also found that most of recurrence cases occurred in the first two years of follow-up, whereas cases of second primary lung cancer occurred more commonly after the third year of follow-up. This suggests that surveillance should be stricter in the first two years of follow-up in order to detect recurrence and should be maintained annually over time. In analogy to screening guidelines,[6,17] conventional chest CT could be replaced by low-dose chest CT after the second year of follow-up. Currently, for initial stages (I and II), we recommend the use of chest CT every six months in the first two years of follow-up, followed by annual exams after the third year.

In our follow-up program, abnormalities on chest CT were found in all cases of recurrence or second primary lung cancer. Korst et al.[24] studied 92 patients with abnormal chest CT findings in a follow-up program and reported that pulmonary nodules and pleural effusion were associated with recurrence. Interestingly, the abnormalities considered as false positives were very similar to those observed in patients who had recurrence or second primary lung cancer. False positive results might lead to unintended consequences, such as performing additional examinations (including risky invasive procedures or greater radiation exposure even if the procedures are noninvasive), decreasing cost-effectiveness, and increasing patient anxiety and fear. Similarly to our results, Lou et al.[4] reported 25% of false-positive findings on chest CT, and additional invasive procedures were performed in only 5% of the cases.

The most important limitation of the present study was its retrospective design. Although our cohort had a long follow-up period, the study reflects the experience of a single institution specializing in cancer care and might not be generalized. The classification of abnormal or suspicious findings on chest CT was determined by clinicians and might have decreased the rate of false-positive results. However, we believe that this is not a problem, because, in practice, the interpretation of the exam is made by the clinician and not by the report of the imaging examination alone. In some cases, it might be difficult to distinguish between pulmonary recurrence and second primary lung cancer, especially in retrospective studies. The impact on overall survival should be the major endpoint to evaluate the efficacy of a follow-up strategy after surgical resection of lung cancer. Due to the small number of patients and the lack of a control group (patients not enrolled in the follow-up program), we were unable to evaluate overall survival in the present study.

In conclusion, we found that most cases of recurrence, and especially most of the cases of second primary lung cancer, were detected on the basis of abnormal chest CT findings in asymptomatic patients, which suggests the importance of a strict follow-up program that includes chest CT after surgical resection of lung cancer.

AUTHOR CONTRIBUTIONS

JBFM and JLG: study conception and design; data collection, analysis, and interpretation; writing and critical revision of the manuscript; and approval of the final version. MDG: study conception and design; data analysis and interpretation; critical revision of the manuscript; and approval of the final version. MLLM and HAC: data collection, analysis, and interpretation; critical revision of the manuscript; and approval of the final version. ADO: data analysis and interpretation; critical revision of the manuscript; and approval of the final version. JPOM and MVBB: study design; critical revision of the manuscript; and approval of the final version.

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J Bras Pneumol. 2021;47(4):e20210018
https://dx.doi.org/10.36416/1806-3756/e20210018

The impact of the stratification by degree of clinical severity and abandonment risk of tuberculosis treatment

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Submitted: 1 February 2021.
Accepted: 30 March 2021.

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

ABSTRACT

Objective: Evaluate the impact of the instrument of the "Stratification by Degree of Clinical Severity and Abandonment Risk of Tuberculosis Treatment" (SRTB) on the tuberculosis outcome. **Methods:** This study was a pragmatic clinical trial involving patients with a confirmed diagnosis of tuberculosis treated at one of the 152 primary health care units in the city of Belo Horizonte, Brazil, between May of 2016 and April of 2017. Cluster areas for tuberculosis were identified, and the units and their respective patients were divided into intervention (use of SRTB) and nonintervention groups. **Results:** The total sample comprised 432 participants, 223 and 209 of whom being allocated to the nonintervention and intervention groups, respectively. The risk of treatment abandonment in the nonintervention group was significantly higher than was that in the intervention group (OR = 15.010; $p < 0.001$), regardless of the number of risk factors identified. Kaplan-Meier curves showed a hazard ratio of 0.0753 ($p < 0.001$). **Conclusions:** The SRTB instrument was effective in reducing abandonment of tuberculosis treatment, regardless of the number of risk factors for that. This instrument is rapid and easy to use, and can be adapted to different realities. Its application showed characteristics predisposing to a non-adherence to the treatment and established bases to mitigate its impact.

Keywords: Tuberculosis; Patient compliance; Risk factors; Treatment adherence.

INTRODUCTION

In recent years, the number of tuberculosis cases has decreased globally. However, this reduction has been insufficient to reach the goals of the WHO End TB Strategy worldwide.[1] These goals will only be achieved if diagnosis, treatment, and prevention are focused on the patient and in their needs in a context of universal health care coverage.[1,2]

Tuberculosis remains one of the major 10 causes of death in the world, affecting 1.3 million people; there were approximately 10 million patients with tuberculosis in 2018.[2] Treatment success rates remain low, reinforcing the need for health care models that facilitate the adequate monitoring of people with tuberculosis.[1,2]

Brazil is one of the 20 countries with the highest burden of tuberculosis, with an estimated 91,000 cases and 7,000 annual deaths.[2] Belo Horizonte (BH) is the capital of the second most populous state in the country, with cure rates (72.5%) and treatment abandonment (11.8%) outside the recommended international parameters of at least 85% and at most 5%, respectively.[3]

Despite the high effectiveness of the recommended therapeutic procedures for the treatment and prevention of tuberculosis,[4,5] low adherence to the treatment is considered the main challenge for the global control of the disease.[6-9] The inadequate treatment interruption can cause consequences individual and collectively, such as death, sequelae, appearance of drug-resistant *Mycobacterium tuberculosis*, increased costs for health systems, in addition providing a place for the permanence of the source of infection in the community.[4,5,7,9-11]

International agencies have been advocating for the Directly Observed Treatment (DOT) since 1994 to strengthen treatment adherence. Its premise is to guarantee the visualization of the medication taken by the patient and to strengthen their bond with the health care team.[2,4-6] Various studies have shown that DOT alone does not provide greater treatment adherence and have pointed out the need for other measures.[5,7,8,10,12-14]

Strengthening adherence interventions can have a greater impact on the health of the population, when compared with any other improvements in

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Financial support: This study received financial support from the Brazilian National Ministry of Health by means of transfer of resources to the Belo Horizonte City Hall (Ordinance no. 3.110 GM/MS from December 17, 2013). It also received financial support from the *Fundação de Amparo à Pesquisa de Minas Gerais* (FAPEMIG, Foundation for the Support of Research in the State of Minas Gerais; APQ 03266-13/APQ 00094-12) and the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Grants 446796/2014 and 310174/2017-7).

medical treatment.[15,16] Low adherence is a primary determinant of treatment effectiveness, because it reduces the expected clinical benefits. It is believed that its magnitude and effect are even greater, especially in developing countries, given the scarcity of resources and the inequalities in access to the health care system.[6,7] The ideal care organization requires coordination of patient needs and the identification of possible barriers to treatment.[9-11,17,18]

Health systems such as Primary Health Care (PHC) consider this level of care to be the preferred access to the care network. PHC uses technologies of high complexity and low technological density that should solve health problems of greater frequency and relevance in its territory,[19] including tuberculosis.[4-7,9,10,20]

Proper management of chronic health conditions imposes the need to stratify cases so that patients receive differentiated care, which is an attribute of a rational and resolving health care system. The population stratification process is central to health care models because it allows the identification of people and groups with similar health needs that must be cared by specific technologies and resources, based on different approach of people and groups that present similar risks.[21,22] Usually, without risk stratification, the services supply follows demand criteria, generating unnecessary interventions, depriving differentiated attention according to people's needs.[16-18]

Tuberculosis is considered a chronic disease, and it is extremely important to recognize the social determinants involved in the process. Patients need an individualized approach, as the frequency of associated diseases is high, as well as other vulnerabilities. Many factors are associated with adherence to the TB treatment, including patient characteristics, the relationship between the health care provider and the patient, the prolonged treatment regime and the organization of health systems.[4-10]

This study aims to assess the impact of the instrument of the "Stratification by Degree of Clinical Severity and Abandonment Risk of Tuberculosis Treatment" (SRTB) on the tuberculosis outcome.

METHODS

This was a pragmatic clinical trial involving patients with a confirmed diagnosis of tuberculosis who were treated at one of the 152 PHC units in the city of Belo Horizonte, Brazil, between May of 2016 and April of 2017. All of the PHC units in the city were divided into two groups, taking into consideration the administrative organization of the health care network, the presence of cluster areas for tuberculosis in the territory, and social vulnerability indexes, in order to avoid selection bias in the sample.

We used a georeferencing software (https://www.mapdevelopers.com/batch_geocode_tool.php) and the addresses of the participants with the objective of determining the geographic location of 70-90% of the cases between 2012 and 2015 in order to define the existence of possible clusters. Maps were created for each of those years, as was one for the four years as a whole, using the TerraView software (www.dpi.inpe.br/terraview). In order to assess the presence of clusters we used the SaTScan software (https://www.satscan.org/download_satscan.html), which was adopted to search for high rates with the purely spatial discrete Poisson scan model.

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (Protocol no. 43320015.4.0000.5149), and all participants agreed to participate and signed a free an informed consent form.

The SRTB instrument (Chart 1) was developed considering international guidelines for the management of tuberculosis.[4,5,10,15,20,23] The instrument is structured into two parts: the degree of clinical risk (low/medium/high/very high), according to disease presentation, presence of comorbidities, bacterial resistance and clinical complications, with the premise of referring the patient to the ideal level of health care (PHC, Secondary Reference - medical specialties, Tertiary Reference – emergency hospitals/health units); and the risk degree of abandoning the treatment - low/high - in order to strengthen compliance measures linking it to the PHC unit).

All of the patients diagnosed with tuberculosis who were 18 years or older and agreed to participate in the study were interviewed by trained researchers and had their home address linked to the respective PHC unit. The PHC units were divided into two groups: nonintervention and intervention. In both, a questionnaire was applied, validated for research, which contains sociodemographic characteristics (sex, race/color self declaration, education, marital status and income), individual characteristics (homeless person, freedom deprivation), clinical characteristics (signs/symptoms, comorbidities: people living with the Human Immunodeficiency Virus (HIV/AIDS), alcoholism, smoking and use of illicit drugs), characteristics of treatment (history of previous treatment for TB, adverse reaction to drugs, DOT, report of symptoms improvement after the second month of treatment) and operational characteristics of the health system (epidemiological surveillance and case monitoring). The SRTB instrument was used only in the intervention group, and the patients in this group were monitored regarding the implementation of the recommendations in the instrument. Treatment outcomes were as follows: cure (considering clinical, radiological, and/or bacteriological results), treatment abandonment (i.e., not taking the medication for a period longer than 30 consecutive days), and death.

Descriptive analyses were performed with the Stata statistical software package, version 14 (StataCorp LP, College Station, TX, USA), according to the selected characteristics stratified by group, by means of frequency of distribution and measures of central tendency and dispersion for the characteristics studied.

Chart 1. Stratification by degree of clinical severity and abandonment risk of tuberculosis treatment.

STRATIFICATION BY DEGREE OF CLINICAL SEVERITY AND ABANDONMENT RISK OF TUBERCULOSIS TREATMENT			
1st STEP RISK OF ABANDONMENT OF TREATMENT	I	**LOW RISK** TB without identified risk of abandonment	**DOT** (preferably at the health unit or other place to be agreed). **Guidance regarding the disease and drug treatment.** **Involvement of the multidisciplinary team.**
	II	**HIGH RISK** TB with identified risk of abandonment; (1) Social vulnerability; (2) Abusive / harmful use of alcohol and other drugs; (3) History of previous TB treatment abandonment; (4) Homeless situation; (5) HIV infection; (6) Freedom deprivation.	**DOT** (preferably at the health unit or other place to be agreed). **Guidance regarding the disease and drug treatment.** **Involvement of the multidisciplinary team.** (1) Social service; (2) Mental Health Services; (3) Identification and intervention in previous abandonment factors; (4) Social Work and Mental Health; (5) Teams from the Secondary Reference Centers for HIV / AIDS; (6) Immediately report to the epidemiological surveillance service, informing the probable prison unit.
2nd STEP CLINICAL RISK	A	**LOW RISK** - Pulmonary, ganglionic and/or pleural TB	**Primary Health Care:** - Basic health unit
	B	**MEDIUM RISK** - Confirmed extrapulmonary TB (except, ganglion and pleural); - TB with severe comorbidities; - TB with clinical complications and/or major adverse effects to treatment; - Treatment failure; - TB resistant to a medication.	**Secondary Reference Clinic:** - Children: Reference center for pediatric TB; - Adults: Reference center in TB in adults; - HIV / AIDS: Reference center in TB-HIV - infectious diseases.
	C	**HIGH RISK** - TB + clinical/surgical criteria for hospitalization - MDR or XDR - Confirmed tuberculous meningoencephalitis	**Tertiary Reference Clinic or hospitalization:** - Children: Reference hospital for pediatric TB; - Adults: Reference hospital for TB in adults; - HIV / AIDS: Reference hospital in TB-HIV - infectious diseases
	D	**VERY HIGH RISK** - Suspected tuberculous meningitis; - TB with signs of severity: respiratory failure (hypoxemia or tachydyspnea), circulatory failure (oliguria or hypotension) and severe change in mental status; - TB with complications that require immediate assistance intervention	**Emergency Health Unit**

DOT: directly observed treatment; TB: tuberculosis; MDR: multidrug resistant; and XDR: extensively drug resistant.

The magnitude of the association between the explanatory variables and the "treatment abandonment" event was estimated using odds ratio and its corresponding 95% CI for each variable, obtained by logistic regression. In the univariate analysis, variables with $p \leq 0.20$ in the Wald test were manually selected for the multivariate analysis. The level of significance required for inclusion in the final model was $p < 0.05$. The likelihood ratio test was used in order to compare the models. The goodness of fit of the final models was assessed by the Hosmer-Lemeshow test. Survival analysis was performed, according to Cox's semi parametric model, to estimate the occurrence of treatment abandonment between groups.

RESULTS

During the study period, 623 tuberculosis patients were identified, of whom 476 were interviewed. Of those, 44 patients were excluded from the study: a change in the diagnosis (n = 16), place of residence other than Belo Horizonte (n = 6); and a lack of follow up at the PHC unit (n = 22). Therefore, the study sample comprised 432 participants, who were divided into the nonintervention (n = 223) and intervention (n = 209) groups.

After the similarity test between the groups and the univariate logistic regression, no significant differences were found, unless for income, presence

of comorbidities and adverse reaction, demonstrating the homogeneity of the sample.

The descriptive analysis (Table 1) revealed a predominance of male individuals, and approximately half of the total sample had a low level of education (≤ 8 years of schooling). In addition, 319 patients (73.8%) had comorbidities, 123 (28.5%) were alcoholics, 170 (39.4%) were current smokers, 69 (16.0%) made use of illicit drugs, and 203 (47.0%) presented with adverse reactions to medications in the second month of treatment (Table 1).

In the nonintervention group, in the univariate analysis, several characteristics were associated with treatment abandonment: non-white color, single marital status, low income (criteria used by the Brazilian Federal Government which considers families that have a monthly income per capita of up to half a minimum wage or a total family income up to three minimum wages), homeless person, presence of comorbidities, alcoholism, smoking, use of illicit drugs, retreatment by re-entry after abandonment, presence of one or more risk factors identified (low income, homeless person, retreatment for re-entry after abandonment, alcoholism and/or use of illicit drugs). In the intervention group, none of these characteristics were associated with treatment abandonment.

The variables sex, education, DOT performance, presence of adverse reaction to medications and improvement of symptoms, assessed in the second month of treatment, as well as HIV/AIDS co-infection, did not show an association in both groups.

In the multivariate analysis, we adjusted the variables related to treatment abandonment, producing two models (Table 2): one taking into consideration the number of risk factors identified; and one using the following variables: low income, retreatment, use of illicit drugs and/or alcohol, and homeless people. In both models, adherence to DOT and the use of the SRTB instrument reduced the risk of treatment abandonment.

The impact of income on tuberculosis treatment was evident (Figure 1). Low income was associated with a greater chance of dropping out. The abandonment risk decreases when the income increases, showing an inverse relation. The income effect under the risk of abandonment practically disappears for people with an income above R$ 5,000 per month.

Treatment abandonment was more likely to occur in the nonintervention group, when compared with the intervention group (OR = 15.010; p < 0.001). The application of the SRTB instrument reduced the impact of all characteristics associated with treatment abandonment.

The number of risk factors directly increased the "abandonment" outcome in the nonintervention group. However, this outcome was not significant in the intervention group, regardless of the number of risk factors identified (Figure 2).

The Kaplan-Meier curves followed by the log-rank test (Figure 3) were statistically different (p < 0.001), showing that the intervention was effective in reducing treatment abandonment in the intervention group. The Cox proportional hazards model showed an association between the exposure factor, whether or not it was part of the intervention group (hazard ratio = 0.0753).

DISCUSSION

Treatment success for patients with tuberculosis at a high risk of abandonment is exceptionally difficult, requiring intense commitment and innovative approaches. The use of the SRTB instrument significantly reduced the risk of treatment abandonment (OR = 15.010; p < 0.001), even in the presence of one or more risk factors (OR:4.376 p=0.001 to 12.240 p<0.001). Studies that promoted a set of treatment adherence interventions reported lower treatment abandonment rates.[6-12,14,15] The greater adherence of patients to drug treatment can be achieved by combining interventions aimed at the identified risk factors. Even considering that these measures have a cost, it is still less than the consequences of the abandonment.[2,6,7,14,24] Due to the set of interventions performed, a reduction in abandonment was observed in intervention group (with SRTB it was 92.5% more slow at any time of follow-up - HR:0.0753) when compared to nonintervention group, showing a strong association between the occurrence of abandonment and the proposed strategy by SRTB.

Abandonment among non-white patients may be associated with social issues evidenced in the present study, because low income is more common in that population in Brazil.[19] Therefore, poverty is one of the main reasons for patients not to understand the benefit of clinical treatment. Other studies[2,20,25-27] corroborate the connection between social capital and health: as the family income increased, treatment abandonment significantly decreased. Poor people generally have less access to health care services or have access to health care facilities with fewer resources. In addition, that population is exposed to social determinants of tuberculosis, which indicates the need for further government actions in order to promote equity.[2,20,25-27]

The present study showed that DOT reduced the risk of treatment abandonment when associated with other measures, but only in the intervention group. The effectiveness of DOT, a globally recommended strategy to strengthen treatment adherence, is questioned in some studies,[26,27] being especially directed at vulnerable groups.[28,29] Other authors have demonstrated that DOT reduced dropout, especially when other support measures are involved, such as educational and psychological support programs.[14,30]

It is evident that good health care services are necessary to ensure that patients benefit from the treatment, but this alone is insufficient; the autonomy

Table 1. Characteristics of the sample of patients diagnosed with tuberculosis in the nonintervention and intervention groups, Belo Horizonte, Brazil (N = 432).[a]

Characteristic	Group		p*
	Nonintervention (n = 223)	Intervention (n = 209)	
Sociodemographic			
Sex			
Male	162 (72.65)	141 (67.46)	0.240
Female	61 (27.35)	68 (32.54)	
Self-reported race/skin color			
White	47 (21.08)	39 (18.66)	0.530
Non-White	176 (78.92)	170 (81.34)	
Level of education			
> 8 years of schooling	96 (43.05)	92 (44.02)	0.847
≤ 8 years of schooling	127 (56.95)	117 (55.98)	
Marital status			
Not single	109 (48.88)	120 (57.42)	0.076
Single	114 (51.12)	89 (42.58)	
Income[b]			
Not low	110 (49.33)	125 (59.81)	0.033
Low	113 (50.67)	84 (40.19)	
Clinical			
Comorbidities			
No	71 (31.84)	42 (20.10)	0.006
Yes	152 (68.16)	167 (79.90)	
HIV			
No	206 (92.38)	190 (90.91)	0.581
Yes	17 (07.62)	19 (09.09)	
Alcoholism			
No	155 (69.51)	154 (73.68)	0.336
Yes	68 (30.49)	55 (26.32)	
Smoking status			
Never smoker	100 (44.84)	95 (45.45)	0.318
Former smoker	40 (17.94)	27 (12.92)	
Smoker	83 (37.22)	87 (41.63)	
Illicit drug use			
No	188 (84.68)	173 (83.17)	0.670
Yes	34 (15.32)	35 (16.83)	
Monitoring			
Why did you seek a health care unit?			
Physician or family referral	87 (39.01)	96 (45.93)	0.146
Self-referral	136 (60.99)	113 (54.07)	
Adverse reactions to medications in the 2nd month			
No	151 (69.59)	71 (34.13)	< 0.001
Yes	66 (30.41)	137 (65.87)	
Treatment outcome			
Cure	183 (82.06)	206 (98.56)	> 0.001
Abandonment	40 (17.94)	3 (1.44)	

[a]Values expressed as n (%). [b]In accordance with the Brazilian Federal Government criteria, families that have a monthly income per capita of up to half the minimum wage or a total family income up to three minimum wages are considered as having low income (minimum wage: R$1,045 [US$209 on 2020/01/07]). *Qui-square test.

of patients, who choose whether they will take their medication or not, should be considered. This point of view emphasizes that a health care system should be targeted to the needs of patients and not only to mechanisms for monitoring behavior, such as DOT; usually, patients with chronic diseases have difficulty in adhering to the recommended protocols.[19,21]

Other characteristics showed a strong association with treatment abandonment in the nonintervention group: people on the street,[17,27] presence of comorbidities,[4,20]

alcohol abuse and/or illicit drugs use,[14,17] smoking,[14,26] and re-entry into treatment.[20,26] Thus, the identification of these characteristics provides more precise strategies for reducing initial risks with the use of the SRTB instrument.

The interaction between people on the street and abusive use of alcohol and/or illicit drugs was evidenced, revealing a ten times greater chance of abandoning treatment (OR:10.769 p=0.002); being five times greater than the presence of only the variable abuse of alcohol and/or illicit drugs. Homeless people are recognized as one of the groups with the highest prediction of abandonment, especially when the use of associated licit and/or illicit drugs are identified.[27,31] The SRTB mitigated the impact of all these interactions by targeting strategic interventions and organized in order to promote greater adherence to treatment, such as social support and care with a multidisciplinary team.

Several other factors are associated with non-adherence to TB treatment, such as ignorance about the disease and its treatment, stigma, absence of a psychosocial approach; interventions are recommended to address these determinants in the routine of services.[4,5,14,27] Another predisposing cause of treatment abandonment is the improvement of

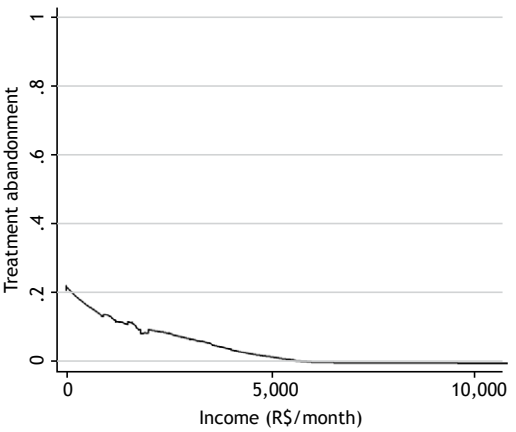

Figure 1. Impact of income on the abandonment of tuberculosis treatment. Reference: R$1.00 was equivalent to US$0.20 on Jan 7, 2020.

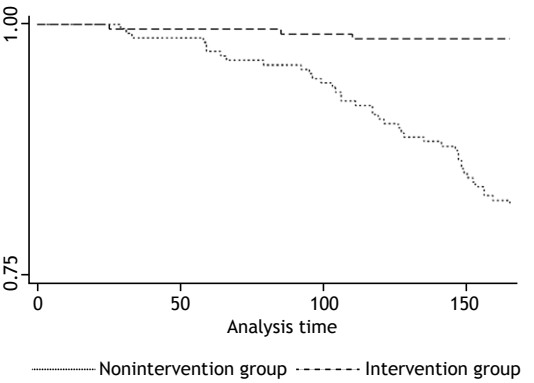

Figure 3. Kaplan-Meier curves comparing treatment abandonment between the nonintervention and intervention groups.

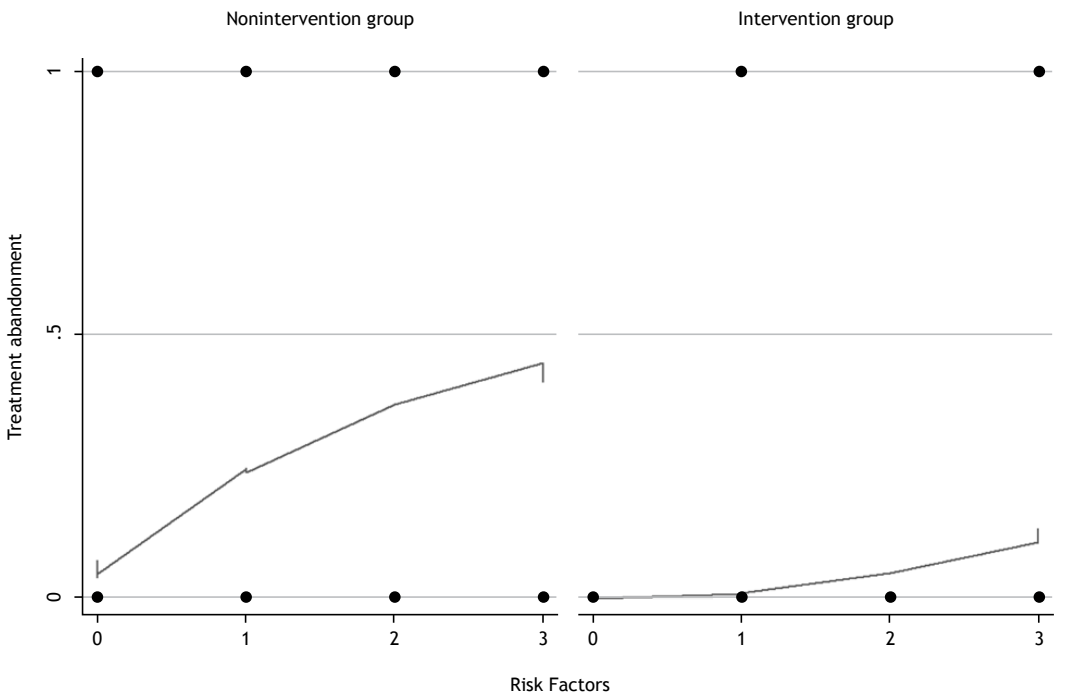

Figure 2. Risk of treatment abandonment in the nonintervention and intervention groups, by number of risk factors for treatment abandonment.

Table 2. Multiple analysis of the characteristics related to the treatment dropout among the groups studied, Belo Horizonte, Minas Gerais, Brazil.[§]

Description	Number of risk factors		According to risk factors	
	P-value	OR (95% CI)	P-value	OR (95% CI)
Group				
A (non-intervention)		1 (reference)		1 (reference)
B (intervention)	< 0,001	0,07 (0,02 - 0,23)	< 0,001	0,07 (0,90 - 0,22)
Self-reported race / skin color				
White		1 (reference)		1 (reference)
Not white	0,016	6,52 (1,41 - 30,13)	0,068	4,07 (0,90 - 19,40)
Directly Observed Treatment				
Not		1 (reference)		1 (reference)
Yes	0,025	0,42 (0,20 - 0,90)	0,009	0,34 (0,15 - 0,77)
Number of risk factors				
None		1 (reference)		---
1 (one)	0,001	4,38 (1,78 - 10,75)		---
2 (two)	< 0,001	11,80 (3,80 - 36,79)		---
≥ 3 (three or more)	< 0,001	12,24 (3,84 - 39,02)		---
According to risk factors				
Interaction: use of illicit drugs and/or alcohol and homeless				
does not use illicit drugs and/or alcohol and is not homeless		---		1 (reference)
does not use illicit drugs and/or alcohol and is homeless		---		***
uses illicit drugs and/or alcohol and is not homeless		---	0,015	2,71 (1,22 - 6,05)
uses illicit drugs and/or alcohol and is homeless		---	0,002	10,77 (2,32 - 50,04)
Income				
Not low		---		1 (reference)
Low		---	0,020	0,99 (0,98 - 0,99)
Retreatment for re-entry after abandonment				
Not		---		1 (reference)
Yes		---	0,018	3,08 (1,21 - 7,80)

(§) Two final models have been proposed. (***) In the study, none of the patients were on the street without using illicit drugs and/or alcohol, which is why it is not possible to estimate the OR of this class.

symptoms in the second month of treatment,[31] but this factor showed no associations with treatment abandonment in the present study, corroborating the findings of other authors.[32] In addition, no associations were found related to adverse reactions to medications, sex, or level of education.[17,33,34]

Care models that integrate the different attention levels are recommended to achieve better results in the treatment of TB.[2,19-21] This disease is managed on an outpatient basis, except for cases that require greater propaedeutic support and therapeutic.[4,5,11,14,20,35] Patients monitored at other levels of care have lower adherence to treatment,[32,35] in addition to the poor-quality health care services that enhance abandonment.[14,27,34]

The limitations of the present study were the impossibility of interviewing patients with severe tuberculosis who died prior to the interview and the impossibility of interviewing those coinfected with HIV/AIDS, whose follow-up was carried out in secondary/tertiary referral centers.

In conclusion, the SRTB instrument was effective in reducing abandonment of tuberculosis treatment, even in the presence of one or more risk factors. The implementation of the SRTB instrument and the monitoring of the process of the explained recommendations and its application not only showed characteristics predisposing to non-adherence to treatment, but also established bases to mitigate its impact. The SRTB instrument organizes the levels of care by stratifying the cases, as well as demonstrating the need for a set of person-centered interventions to achieve greater treatment success. It is an instrument of easy and quick applicability that can be adapted to different realities, considering the potential of the local health network and available resources

ACKNOWLEDGMENTS

The authors would like to thank the members of the Group of Research on Mycobacterial Diseases at the *Universidade Federal de Minas Gerais*. The authors are also grateful to the Graduate Program in Infectious Diseases and Tropical Medicine of University of Minas Gerais School of Medicine and to the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development).

AUTHOR CONTRIBUTIONS

PDN: main author, study design and execution; analysis of results; scientific writing of the manuscript; and approval of the final version. JPAH: statistical analysis; scientific review of the article; and approval of the final version. JVCR: study execution; analysis of results; scientific writing of the manuscript; and approval of the final version. CHLS: study execution; scientific review of the article; and approval of the final version. INA: study execution; analysis of results; scientific review of the article; and approval of the final version. WSC: supervision; manuscript correction; scientific review of the article; and approval of the final version. SSM: study design; coordination; manuscript correction; scientific review of the article; and approval of the final version.

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https://dx.doi.org/10.36416/1806-3756/e20210089

REVIEW ARTICLE

Inspiratory muscle training in interstitial lung disease: a systematic scoping review

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Submitted: 18 April 2021.
Accepted: 28 April 2021.

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ABSTRACT

Inspiratory muscle training (IMT) has been described as one of the components of the treatment of chronic lung conditions such as obstructive and restrictive lung diseases. Although the number of studies showing results of IMT in patients with interstitial lung disease (ILD) is scarce when compared with studies in patients with COPD, evidence points to benefits of IMT in this population. This scoping review aimed to explore the role and the rationale of IMT in patients with ILD and to gather recent evidence on the effects of IMT in this population. The studies included in this review showed improvements in respiratory muscle function, quality of life, exercise capacity and dyspnea after ILD patients participated in programs that included stand-alone IMT or combined with pulmonary rehabilitation. There is still a gap in the literature to allow a clear conclusion on the indications of IMT as part of ILD treatment because of poor research design and small numbers of participants. Therefore, although IMT seems to have a positive effect in patients with ILD, current evidence prevents us from drawing a definite conclusion. Further studies need to be conducted using better research methodology to demonstrate and confirm the positive effects of IMT.

Keywords: Respiratory muscles; Lung diseases, interstitial; Rehabilitation.

BACKGROUND

Respiratory muscles are responsible for creating air flow to the lungs by elevating the ribs and increasing the chest wall dimensions, as well as decreasing airway resistance and intrathoracic pressure.[1] During breathing, the activation of respiratory muscles can be very different from the activation of other skeletal muscles. However, the capability of adaptation to different conditions and functional demands is comparable between those two muscle groups, hence having a similar response to training stimulus.[1,2] A literature review conducted by Powers & Criswell[3] described an increase in the number of fibres and mitochondrial activity in respiratory muscles after specific endurance respiratory training. That study showed positive effects of training, with the reduction of oxidative stress and a delay in respiratory muscle fatigue.[3] Three different fibre types can be found in respiratory muscles and are the same encountered in peripheral skeletal muscles: type I, type IIA and type IIB. However, the proportion and distribution of these fibres across the diaphragm muscle, for example, are different from those across other peripheral muscles, such as the quadriceps. The diaphragm presents 80% of oxidative fibres (types I and IIA), that is, fatigue resistant fibres, whereas the quadriceps shows only 35-45% of oxidative fibres.[4]

The role of inspiratory muscles has been poorly investigated in patients with interstitial lung disease (ILD). Nevertheless, the mechanisms of inspiratory muscle training (IMT) have been extensively studied and its effects could possibly be extended to people with lung parenchymal disorders.

A recent brief review by Jensen et al.[5] investigated the physiological mechanisms of exertional breathlessness in patients with ILD and suggested that it is related to increased neural respiratory drive. In patients with ILD, the ability to answer to an increased ventilatory demand is mainly impaired because of reduced lung compliance. In this case, the respiratory system is forced to work in a non-ideal pressure-volume relationship, contributing to weakness of the inspiratory muscles. Consequently, the breathing frequency increases to abnormal levels as a result of a constrained expansion of V_T, leading to increased respiratory muscle effort and breathlessness rating.[5]

A literature review published in 2013[6] explored the connection between weakness of inspiratory muscles and poor exercise tolerance in people with sarcoidosis. Evidence of decreased MIP and inspiratory muscle endurance in that population was shown and was related to decreased exercise tolerance and respiratory muscle failure.[6]

Currently, several studies have described the use of IMT as part of the treatment of patients with lung conditions such as COPD, asthma and ILD. The American Thoracic Society (ATS) and the European Respiratory Society (ERS)[7] have recommended that IMT be an additional intervention to pulmonary rehabilitation (PR) programs as part of the treatment of patients with chronic lung

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Financial support: None.

ISSN 1806-3756

diseases, especially in the presence of inspiratory muscle weakness.

The rationale behind the recommendation of IMT to patients with chronic lung diseases can be related to a very common symptom to most of the patients: dyspnea. Diaphragm work increases during exercise, and patients with chronic lung diseases use a larger proportion of their MIP than do healthy subjects. Because of this different breathing pattern, there is an increase in dyspnea during exercise, leading to fatigue of the respiratory muscles and restriction of exercise capacity.[8,9] In addition, when there is an increase in respiratory work, a competition between peripheral muscles and respiratory muscles can take place. In patients with COPD, a consumption of blood supply from the respiratory muscles during exercise can go up to 35%, whereas that consumption is 15% in healthy subjects.[10]

IMT is also associated with structural changes in muscle fibre types and fibre distribution in inspiratory muscles. After five weeks of IMT, patients with COPD showed an increase in the number of type I fibres, as well as an increase in fibre II size in external intercostal muscle.[11] IMT was able to improve inspiratory muscle work capacity by decreasing the relative work (percentage of maximal muscle work capacity). After IMT, there is a decrease in the amount of cardiac output consumed by the inspiratory muscles; consequently, a bigger portion of cardiac output can be redirected to peripheral muscles and increase exercise capacity.[12]

In a systematic review, Gosselink at al.[13] reported that IMT used as a stand-alone intervention is able to increase inspiratory muscle strength and endurance significantly as well as improving exercise capacity and quality of life and decreasing dyspnea in patients with COPD. Studies included in that review showed that patients presenting with inspiratory muscle weakness are better responders to IMT when compared with patients without it.[13] IMT has also been shown to improve inspiratory muscle strength and exercise capacity in patients with ILDs such as idiopathic pulmonary fibrosis (IPF), although there is less evidence in the literature.[14,15]

ILDs are a group of heterogeneous disorders that affect the lung parenchyma and are mostly associated with poor morbidity and high mortality rates. Most of ILDs involve common features and symptoms, such as dyspnea, cough, gas exchange deficiency, hypoxemia and decreased lung volumes that could lead to respiratory failure. ILDs can also be defined as diffuse parenchymal lung diseases, which could be classified by the presence of a known cause, as idiopathic interstitial pneumonia, as granulomatous pneumonia, or others.[16,17] Chart 1 shows the classification of ILDs in accordance with the ATS/ERS.[18]

Diagnosis and treatment of ILDs require a multidisciplinary approach and a comprehensive evaluation through history combined with physical examination and tests. The use of additional testing is quite often needed, and HRCT is a valuable tool to reach a specific diagnosis with confidence. Most of the times HRCT is enough for a definitive diagnosis, avoiding further invasive testing such as bronchoscopy or surgical lung biopsy.[19] In 2014, Meyer[19] published an interesting diagnostic approach to ILDs (Figure 1).

Once a definitive diagnosis is reached, there are essential elements to be considered for the treatment of ILDs, such as pharmacological agents, lung transplantation, supportive therapies, symptom relief management and treatment of comorbidities.

Corticosteroids, immunosuppressive agents and anti-inflammatory agents are medications that are most frequently prescribed for ILDs; more recently, anti-fibrotic medications have also been recommended for the treatment of patients with not only IPF, but also with other fibrotic ILD, such as rheumatoid arthritis-associated ILD, systemic sclerosis-associated ILD, connective tissue disease-associated ILD, hypersensitivity pneumonitis and unclassifiable idiopathic pneumonitis. Anti-fibrotic medications have been shown to decrease disease progression (decrease in FVC) with a similar magnitude of effects for the overall population of ILD patients.[20-23]

It is important to consider measurements of disease progression and symptom relief in patients with ILDs. Dyspnea measurements and lung function tests evaluating FVC and DL_{CO} are routinely performed to monitor the disease. The six-minute walk test is also part of the routine evaluation of disease progression and provides valuable information regarding functional capacity.[19]

PR is one of the non-pharmacological therapies that should be considered in the management of ILDs. Some studies[24,25] have been conducted in order to evaluate the effects of PR in patients with ILD, such as functional capacity, breathlessness and quality of life. The ATS/ERS have defined PR as an intervention to reduce symptoms and improve functional status and performance of activities of daily living, contributing to reduce healthcare costs.[7]

A Cochrane systematic review published in 2008[24] evaluated the safety of physical training for patients with ILD. Randomised and quasi-randomised studies were searched in the literature, and five studies were included in the analysis; a subanalysis was performed for IPF. Physical training was shown to be safe and improve functional exercise capacity, dyspnea and quality of life in patients with ILD, including those with IPF, although long-term effects of physical training could not be demonstrated.[24]

In 2013, Holland et al.[25] described ways to adapt PR programs for patients with IPF. In summary, the PR program for patients with fibrotic ILD should include the same components as does that for those with other severe lung conditions, such as aerobic and strength exercising as well as an educational component addressing depression and anxiety, which are usually present in this population. The PR

Chart 1. Classification of interstitial lung diseases.[18]

Diffuse parenchymal lung disease with a known cause, such as collagen vascular disease, environmental ILD or drug-induced ILD
Idiopathic interstitial pneumonias
IPF
Idiopathic interstitial pneumonias other than IPF
Desquamative interstitial pneumonia
Acute interstitial pneumonia
Nonspecific interstitial pneumonia
Respiratory bronchiolitis ILD
Cryptogenic organising pneumonia
Lymphocytic interstitial pneumonia
Granulomatous diffuse parenchymal lung disease: sarcoidosis
Other forms of diffuse parenchymal lung disease: lymphangioleiomyomatosis, Langerhans cell histiocytosis/ histiocytosis and eosinophilic pneumonia

ILD: interstitial lung disease; and IPF: idiopathic pulmonary fibrosis.

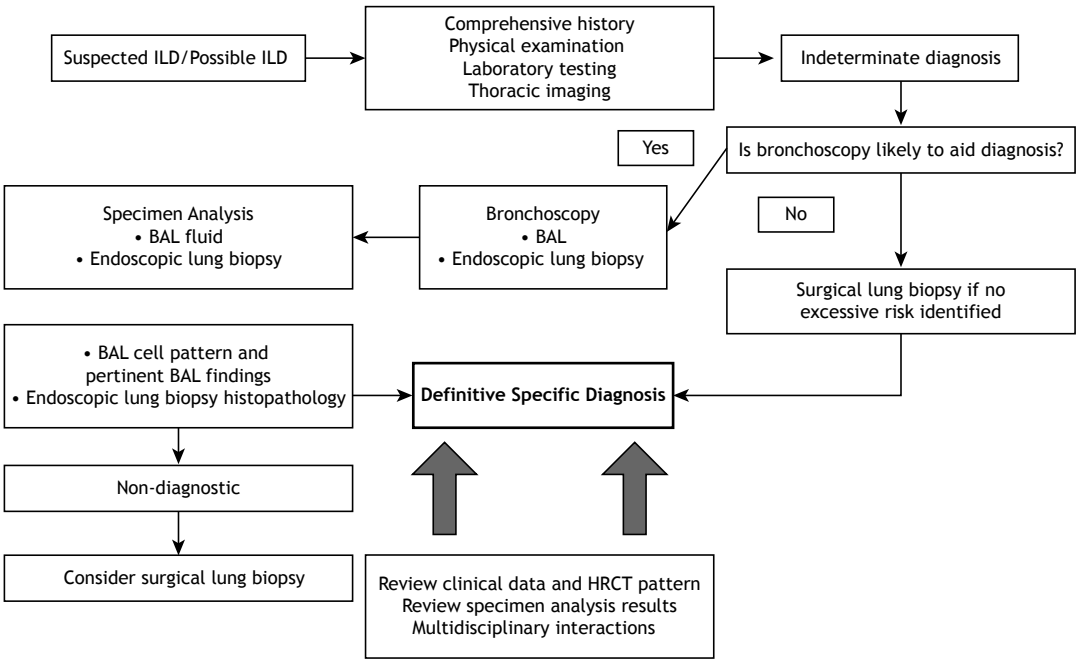

Figure 1. Schematic representation of the diagnosis process for interstitial lung disease. Adapted from Meyer.[19] ILD: interstitial lung disease.

program, however, should consider that the incidence of pulmonary hypertension in ILD patients is greater and that decreased exercise tolerance and disabling dyspnea might be present. Different exercise protocols or exercise modalities such as interval training, water exercise and neuromuscular stimulation should be considered, because these patients are prone to presenting with more severe limitations.[25]

IMT is one of the components of PR and has been extensively described in the literature in patients with COPD and asthma. One of the first studies to investigate IMT was described by Leith & Bradley in 1976.[26] That was the first study to demonstrate that inspiratory muscles could be trained, strength and endurance being increased. The first IMT protocol described in the literature used non-linear resistance devices and showed inconsistent results.[27] Then, a linear resistance device combined with a pressure threshold breathing device (Threshold-IMT; Respironics, Andover, MA, USA) was introduced,[28] and, in 1988, the effects of IMT in patients with COPD who used such devices for two months were evaluated.[29] The pressure threshold breathing device provides a resistance from −7 cmH_2O to −41 cmH_2O. Larson et al.[30] compared the differences between IMT using a resistance from 15% to 30% of MIP for training and two different protocols. Their results showed better improvements in inspiratory muscle strength, endurance and exercise tolerance evaluated with the 12-minute walk test in patients who trained using higher resistance.[30]

There are many different protocols varying in number of weeks and resistance during training. In 2006, Hill et al.[31] innovated by proposing a high-intensity interval IMT for patients with COPD. The study compared high-intensity interval training resistance (≥ 60% of MIP) with constant training resistance at 10% of MIP.

The protocol consisted of eight weeks of IMT, three times per week, for 21 min (Figure 2).[31] The study showed that high-resistance interval training allowed participants to achieve higher training resistance with a significant increase in strength, endurance and quality of life, as well as a significant decrease in dyspnea during activities of daily living when compared with low-intensity constant training.[31]

The role of IMT as an additional therapy to PR or as a stand-alone intervention in patients with ILD has yet to be established, and the number of studies in the literature is scarce.

SCOPE OF THE SYSTEMATIC SEARCH

As described by Arksey & O'Malley,[32] a scoping review aims to explore a research area and to provide coverage of the literature available on a specific topic. This scoping review aimed to explore the effects of IMT in patients with ILD.

A systematic search using the Ovid MEDLINE platform and PubMed was performed to identify interventional studies in English including the terms "interstitial lung disease" and "inspiratory muscle training" and their variations. Additional hand searching was performed following reference lists from included articles and grey literature (Figure 3).

Sixty-three studies were identified, and only four studies have reported the effects of IMT alone or combined with PR in patients with ILD. Figure 3 shows the flow chart of the literature search.

EFFECTS OF IMT ALONE OR IN COMBINATION WITH PR

Jastrzebski et al.[33] evaluated the effects of PR in patients with pulmonary fibrosis. The six-week PR program included cycling for 15 min, general exercise and IMT performed using a threshold device (six cycles of five breaths twice a week). The results of that study showed improvement in dyspnea (Borg scale) and quality of life (Medical Outcomes Study 36-item Short-Form Health Survey and Saint George's Respiratory Questionnaire).

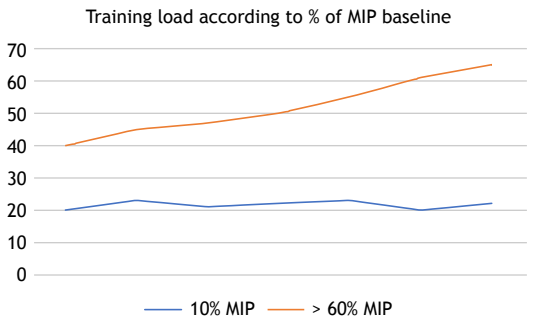

Figure 2. Schematic representation of progression of training load used in the inspiratory muscle training protocol described by Hill et al.[28]

In 2019, Kaushal et al.[34] also evaluated the effects of respiratory muscle training and PR in patients with ILD. The PR program included exercise training for 60 min—endurance training (cycle ergometry), flexibility training, strength training and respiratory muscle training (threshold IMT)—three days a week for eight weeks. All the sessions were supervised, and the participants also attended educational sessions on breathing exercises, lung health, medication and stress management. Outcome measurements—six-minute walk distance (6MWD), respiratory muscle pressure, severity of dyspnea and lung function parameters—were taken at baseline, at the end of the PR program and at a follow-up visit six months after the end of the program. After eight weeks of PR, the participants with ILD (IPF and non-IPF) showed statistically significant improvement in functional capacity (increase in 6MWD), which decreased at the end of the follow-up period. Dyspnea changed from severe to mild according to the modified Medical Research Council (mMRC) scale after PR. Inspiratory muscle pressure significantly increased after exercise training and was negatively correlated with Borg scale scores for dyspnea, which indicates that increased muscle strength could have led to improvements in dyspnea. However, those effects were not sustained after completion of the PR program and reversed after six months of follow-up.[34]

An interventional study[32] investigated the effects of an IMT program on patients with advanced lung disease. The sample included 22 participants with ILD (IPF or hypersensitivity pneumonitis). Although there were patients with restrictive and/or obstructive disease and no control group, the results showed the benefits of IMT regarding dyspnea during activities of daily living and quality of life, as well as improvements in respiratory muscle strength and endurance. In that study,[32] IMT was defined as a high-intensity interval training program performed during eight weeks using a tapered flow resistive loading device, proving to be more feasible and leading to better adherence to training.[35,36] In 2018, the same group used the same program to evaluate the effects of IMT based on the perception of the patients with advanced lung disease.[37] The authors interviewed the patients, including two participants with IPF, after the completion of high-intensity IMT for eight weeks. The patients reported that there was an improvement in mobility and breathlessness after IMT, leading to better performance on activities of daily living and communication.[37]

Three case reports about PR in sarcoidosis, combined pulmonary fibrosis and emphysema, and IPF were included in the present review. Herrera-Olivares et al.[38] reported the case of a female patient with sarcoidosis who performed an exercise program, including high-intensity interval training, high-load resistance training and IMT using a mechanical threshold loading device for 4.5 years. The results showed improvements in cardiorespiratory fitness and functional capacity.[38] De Simone et al.[39] also reported the effects of a PR program that included interval training, high-load resistance

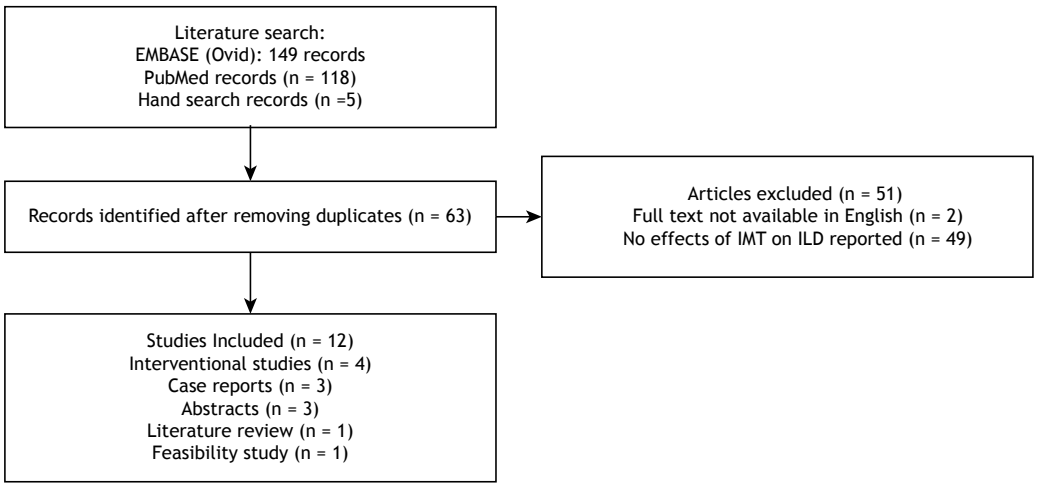

Figure 3. Flowchart of literature search. IMT: inspiratory muscle training; and ILD: interstitial lung disease.

training and IMT using a mechanical threshold loading device in a 65-year-old male patient with combined pulmonary fibrosis and emphysema syndrome. There were improvements in exercise capacity (6MWD), depression levels, health-related quality of life (Saint George's Respiratory Questionnaire) and dyspnea.[39] Another case report demonstrated that long-term combined interval aerobic training, resistance training and IMT helped maintain functional independence, walking capacity, and tolerance to resistance training in a 56-year old man before he experienced a decline in functional capacity due to IPF.[40]

Three abstracts that reported the effects of IMT on ILD were included in this scoping review. Kerti et al.[41] aimed to investigate the effects of IMT in association with PR on functional parameters and quality of life in patients with ILD. No control group seemed to be used; however, the results showed improvements in functional capacity (6MWD), quality of life, dyspnea (mMRC) and inspiratory muscle strength. Nykvist et al.,[42] using the same idea, evaluated the effects of IMT in combination with physical exercising on patients with IPF. Improvements in 6MWD, inspiratory muscle strength, dyspnea (mMRC), fatigue and quality of life (chronic respiratory disease questionnaire) were reported in the group that performed IMT and exercising when compared with the group only performing IMT.[42] Koulopoulou et al.[43] showed the results of a pilot study investigating the effects of high-intensity IMT on exercise capacity, dyspnea, inspiratory muscle function and health-related quality of life. The study included 17 patients with ILD who performed a high-intensity IMT program (n = 9) or a low-intensity IMT program (n = 8) for eight weeks. Quality of life, dyspnea and inspiratory muscle strength were evaluated. The results revealed a significant increase in inspiratory muscle strength in the intervention group, but no differences were found between the intervention and control groups regarding quality of life, dyspnea or exercise capacity.[43]

The results of this scoping review show that the role of inspiratory muscles and IMT has been poorly investigated in patients with ILD. Studies vary in methodology and lack control groups to prove the benefits of IMT on top of recommended PR. Nevertheless, the mechanisms of IMT have been extensively studied, and their effects could possibly be extended to patients with pulmonary parenchymal disorders. A recent review by Álvarez-Herms et al.[44] investigated the role of IMT in hypoxia and showed that IMT is an effective therapy to enhance strength and endurance of the respiratory muscles in healthy athletes, contributing to improved ventilatory function. The authors concluded that IMT would possibly have effects on factors that limit the respiratory system under stress, including premature fatigue, delay of respiratory muscle metaboreflex, perception of dyspnea, increased peripheral oxygen saturation and positive blood redistribution to locomotor muscles.[44] These results could potentially explain how IMT could benefit patients with ILD when acting towards a decrease in exercise fatigue, dyspnea and delay of metaboreflex.

A recent study by O'Connor et al.[45] evaluated the feasibility of IMT as an acceptable treatment option for patients with COPD who declined PR. The study showed that there was a lack of motivation, lack of information regarding the benefits of PR programs and barriers for attendance, such as transportation to the PR centre. It is likely that the same barriers would be faced by patients with ILD, and further studies are needed in this area. In that study,[45] IMT proved to be acceptable and feasible to be performed and the investigated participants showed good adherence to the therapy, thus becoming a possible option in the management of patients with ILD who decline participation in PR.

FINAL CONSIDERATIONS

Inclusion of IMT in the treatment of patients with ILD needs to be better explored, because there is a limited number of articles in the literature that confirm

its benefits to this population. There is an evident gap in the literature regarding the effects of IMT on patients with ILD, although published studies tend to demonstrate benefits in terms of improvement in quality of life, activities of daily living and exercise capacity. Evidence of effects of IMT on ILD is poor, and studies exploring this therapy included a small number of subjects or had a poor research methodology. Consequently, it is not possible to draw definitive conclusions regarding the potential benefits of IMT to this population. Further well-designed studies should be conducted for the evaluation of the effects of IMT on patients with ILD and the possibility of inclusion of IMT as part of ILD patient management, as a component of PR programs or even as an additional option for patients who refuse PR.

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J Bras Pneumol. 2021;47(4):e20200577
https://dx.doi.org/10.36416/1806-3756/e20200577

REVIEW ARTICLE

Work-related asthma

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Submitted: 12 November 2020.
Accepted: 5 April 2021.

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ABSTRACT

Work-related asthma (WRA) is highly prevalent in the adult population. WRA includes occupational asthma (OA), which is asthma caused by workplace exposures, and work-exacerbated asthma (WEA), also known as work-aggravated asthma, which is preexisting or concurrent asthma worsened by workplace conditions. In adults, the estimated prevalence of OA is 16.0%, whereas that of WEA is 21.5%. An increasing number of chemicals used in industrial production, households, and services are associated with the incidence of adult-onset asthma attributable to exposure to chemicals. This review article summarizes the different types of WRA and describes diagnostic procedures, treatment, prevention, and approaches to patient management. It is not always easy to distinguish between OA and WEA. It is important to establish a diagnosis (of sensitizer-/irritant-induced OA or WEA) in order to prevent worsening of symptoms, as well as to prevent other workers from being exposed, by providing early treatment and counseling on social security and work-related issues.

Keywords: Asthma, occupational/diagnosis; Asthma, occupational/prevention & control; Asthma, occupational/therapy; Allergens; Bronchial provocation tests.

INTRODUCTION

Asthma ranks second among the most prevalent chronic respiratory diseases worldwide.[1] In 2017, the prevalence of asthma was estimated at 273 million cases (3.6% of the world population) and the incidence of asthma was estimated at 43 million cases.[1,2] Asthma is the second leading cause of death from a chronic respiratory disease worldwide, with an estimated 500,000 deaths in 2017[3] and a mortality rate of 6.48/100,000 population.[1] Of the aforementioned deaths, approximately 7% were work-related.[4]

Work-related asthma (WRA) is asthma that is caused by exposures at work (occupational asthma [OA]) or that is exacerbated by exposures at work (work-exacerbated asthma [WEA], also known as work-aggravated asthma). OA is defined as asthma symptoms accompanied by reversible airflow obstruction or bronchial hyperresponsiveness caused by conditions attributable to the occupational environment rather than to stimuli encountered outside the workplace.[5,6] OA can be caused by sensitizers or irritants.[6] Sensitizer-induced OA is more common than irritant-induced OA, accounting for approximately 90% of cases.[7] Sensitizer-induced OA is characterized by the onset of symptoms after a latency period (i.e., symptoms occurring months or years after exposure). An earlier onset is associated with a higher level of exposure, as well as with the sensitizing agent and individual characteristics.[8] Sensitizing agents can be of high molecular weight (> 5 kDa),[9,10] mostly proteins, with an IgE-mediated immune mechanism, or low molecular weight, with a mechanism that has yet to be elucidated in most cases.[6] OA without latency (also known as nonimmunologic asthma) is asthma induced by irritants[6] and accounts for 5-18% of cases, its prevalence varying across studies and environments.[7] Irritant-induced asthma occurs after a single exposure or multiple exposures to high concentrations of an irritant.[11] However, it has been suggested that chronic exposure to irritants at low concentrations is also associated with the development of irritant-induced asthma.[12-14] Reactive airway dysfunction syndrome is the first and best known description of irritant-induced asthma, the onset of which is less than 24 h after exposure to high levels of an irritant, with symptoms, functional changes, or both lasting three months or more.[11,12] WEA is defined as preexisting or concurrent asthma that is worsened by workplace conditions, the former being asthma with onset before entering the worksite of interest and the latter being asthma with onset while employed in the worksite of interest but not due to exposures in that worksite. In this case, the workplace

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Financial support: None.

is related to worsening or exacerbation of previously controlled asthma.[15]

WRA is a common and preventable occupational disease that causes limitations in work and activities of daily living, has unfavorable socioeconomic outcomes, and affects working-age individuals, requiring attention from physicians, researchers, and health care providers. When WRA goes unrecognized and untreated, it can progress to severe asthma, difficult-to-control asthma, or both.[14] In a multicenter retrospective study conducted in Europe, 16.2% of OA patients met criteria for severe asthma,[16] whereas, in non-WRA patients, the reported prevalence of severe asthma was approximately 5%.[17] Factors associated with severe OA include persistent exposure to the causative agent at work, a longer duration of disease, a lower level of education, a diagnosis of childhood asthma, and expectoration.[16]

The studies included in the present review article were retrieved from the MEDLINE (PubMed) database by the following search terms (and Boolean operators): (work-related asthma) OR (occupational asthma) OR (work-aggravated asthma) OR (work-exacerbated asthma) OR (irritant-induced asthma). The search included peer-reviewed articles published between January 1, 2000 and October 31, 2020 and written in English, Portuguese, Spanish, French, or Italian. Article inclusion was determined by the authors of the present study, and the articles were not systematically reviewed. We included original articles, review articles, consensus statements, and articles published before the year 2000 and addressing the topics discussed herein.

OCCUPATIONS AND EXPOSURES ASSOCIATED WITH WRA

Given that millions of people are exposed to sensitizers and irritants at work and at home, public health surveillance is required in order to identify and prevent such exposures, as well as for the diagnosis and early treatment of those who develop asthma. Approximately 600 agents have been related to OA, 400 of which involve sensitizing mechanisms.[18] Asthma symptoms can be worsened by defined agents (any substance that acts through known or unknown immune-mediated mechanisms or as an airway irritant) and environmental conditions such as low temperatures and air pollution in the workplace. In 2016, 24.0% of men and 13.4% of women worldwide were estimated to be exposed to asthma-causing agents in the workplace.[19]

Sensitizers

In a recent multicenter study conducted in Europe and involving a cohort of 635 workers,[20] a total of 8 high- or low-molecular-weight agents were found to account for more than 70% of all OA cases: flour, isocyanates, persulfates, metals, latex, wood, quaternary ammonium compounds, and acrylates. Chart 1 shows the most prevalent sensitizers, by molecular weight (high or low), as well as commonly associated occupations/workplaces and exposures.[20-24] High-molecular-weight agents consist of proteins of animal or vegetable origin. Low-molecular-weight agents include organic and inorganic compounds that act as haptens, some of which have IgE-mediated immune mechanisms, including platinum salts (industrial catalysts), trimellitic and phthalic anhydrides (found in paints and sealants), persulfates (henna hair dye), reactive dyes, and, more rarely, diisocyanates. Low-molecular-weight sensitizers without an IgE-mediated mechanism include diisocyanates (found in paints and varnishes, as well as in polyurethane production), acrylates (glues and adhesives), wood compounds, such as plicatic acid (red cedar), metals (chromium, nickel, and cobalt), and glutaraldehyde.

Irritants

Causative agents of irritant-induced OA include ammonia, cement dust, chloride, cleaning products, diesel exhaust, tobacco smoke, isocyanates, fire smoke, sulfur dioxide, mixed agents in swine confinement facilities, and welding fumes (Chart 2).[12,13,24-26]

Exposure to dust, environmental tobacco smoke, air pollution, stressful activities, temperature variations, and physical exertion are also associated with WEA.[15] Occupations and exposures associated with WRA vary across studies. In a study conducted in Canada[27] and involving workers claiming compensation for asthma, 39% had WEA; of those, most (67%) had irritant-induced asthma, and the most common irritants were paints, solvents, calcium oxide, acids, ammonia, cigarette smoke, glutaraldehyde, and welding fumes.

In recent decades, several studies conducted in industrialized countries have shown an increased risk of developing asthma in cleaners.[28,29] Among cleaners in northern Europe, a significant relationship was found between the number of years worked as a cleaner and the risk of developing asthma.[30] In a study analyzing 3,634 cases of WRA in the state of Michigan, USA, exposure to cleaning products was found to have increased from 5% to 20%, cleaning products having become the agents most commonly associated with asthma in the last 30 years.[31] In a study involving 394 patients diagnosed with OA in the city of São Paulo, Brazil, women were found to be most commonly exposed to cleaning products (38.5%) and fumes released in the manufacture of plastics (18.5%), whereas men were found to be most commonly exposed to isocyanates (24.8%) and metal fumes (18.9%).[32] Among the most widely used cleaning products, the most common sensitizers are quaternary ammonium compounds, amines, and flavoring agents, whereas the most common irritants are sodium hypochlorite, hydrochloric acid, and alkaline agents (ammonia and caustic soda).[28,29]

In summary, the occupations/workplaces/exposures most commonly associated with WRA are painting, cleaning, carpentry, beauty salons, health services,

Chart 1. Most common sensitizers, by molecular weight (high or low), as well as commonly associated occupations/workplaces and exposures.

Sensitizer	Occupation/Workplace/Exposure
High molecular weight (≥ 5 kDa)	
Flours and grains	bakers, food industry
Latex	health care workers; producers and frequent users of latex products
Enzymes	manufacture and use of detergents; pharmaceutical and food industries
Plant-derived products	agricultural workers
Animals and animal-derived products	laboratories, veterinaries, agricultural workers
Fungi	offices, schools, cleaners
Low molecular weight (< 5 kDa)	
Diisocyanates	polyurethane production; foam production; automotive paint and polyurethane varnish; plastics industry
Persulfates	hairdressers
Metals (chrome, nickel, cobalt, zinc, platinum salts)	metal coatings (galvanization), welders, pharmaceutical industry, and refineries
Quaternary ammonium compounds	cleaners
Acrylates	dentists, adhesive resins, synthetic fabrics, printer inks, plastics industry, manicurists
Wood dust	carpenters
Cleaning products: chloride, ammonia, glutaraldehyde	cleaners and health care workers
Drugs (e.g., antibiotics)	pharmaceutical industry
Phthalic and trimellitic anhydrides	epoxy resin manufacture, spray paint workers

Chart 2. Occupations/workplaces and agents/mixed agents associated with irritant-induced occupational asthma.

Occupation/workplace	Agents/mixed agents
Cleaners and health care workers	chloride, ammonia, disinfectants, hydrochloric acid, organic solvents
Aluminum smelting	fluorides, sulfur dioxide, aluminum oxide
Pulp and paper mills	sulfur dioxide
Swine and dairy production	aerosols from endotoxins and organic dusts; manure gases
Dark-room environment	acetic acid
Welding	nitrogen oxides, fluorides, ozone, metals
Biocides	ethylene oxide, formalin, insecticides (organophosphates, organochlorines, and carbamates)
Construction work	spray paints, cement dust, calcium oxide (lime), floor sealant (aromatic hydrocarbons)
Firefighters, first responders, security agents	smoke (fires), fumes released by chemical spills
Mechanics, highway workers, and railroad workers	diesel exhaust, organic solvents

and the food industry (exposure to flours, animal proteins, and condiments). However, it should be noted that it is no longer enough to know the occupation of affected individuals in order to understand exposures and work environments; there is a need to know the workplaces and agents that can induce or exacerbate asthma symptoms.

EPIDEMIOLOGY AND RISK FACTORS

In an analysis of epidemiological studies, the reported prevalence of adult-onset asthma attributable to occupational exposures was 16%.[33] The prevalence of WEA varies across studies depending on the definition of WEA and the diagnostic criteria. It is estimated that 21.5% of adults with asthma experience exacerbation or worsening of symptoms because of exposures in the workplace.[15] The overall number of deaths from OA in 2017 was approximately 34,000. The number of disability-adjusted life years for OA in 2017 was 1.910 million,[4] disability-adjusted life years being the sum of the years of life lost to premature death and years lived with disability.

Factors associated with an increased risk of developing asthma include the type of exposure (the risk of developing asthma ranging from 5% for exposure to isocyanates to 50% for exposure to platinum salts), the level of exposure (a higher level of exposure translating to a higher risk of developing asthma), smoking (the risk of developing asthma being well defined for exposures such as platinum salts and anhydrides), a history of bronchial hyperresponsiveness, and presence of rhinitis/

atopy (the risk of developing asthma being well defined for exposure to high-molecular-weight agents).[6,7,33,34]

DIAGNOSIS

A diagnosis of WRA should be considered in adults who develop asthma or experience exacerbation of preexisting asthma.[5] Several definitions of and diagnostic criteria for WRA have been proposed.[5,10,15] The proposed diagnostic criteria are summarized in Figure 1 and include the following: A) a diagnosis of asthma; B) onset or worsening/exacerbation of symptoms after entering the worksite of interest; and C) an association between asthma symptoms and work. Additional criteria include the following: 1) workplace exposure to an agent known to cause asthma; 2) workplace exposure to an agent or conditions known to cause asthma exacerbation; 3) worsening of FEV_1, PEF, or a combination of the two, or hyperresponsiveness after nonspecific bronchial challenge testing during periods of work in comparison with periods away from work; 4) positive response to specific bronchial challenge testing; and 5) onset of asthma symptoms after exposure to irritants.

A diagnosis of OA is made if A+B+C are met, together with 3, 4, or 5. A diagnosis of probable OA is made if A+B+C are met, together with 1. A diagnosis of WEA is made if A+B+C are met, together with a diagnosis of preexisting asthma or concurrent asthma (i.e., asthma with onset after entering the worksite of interest) and 2+3 or more frequent/more severe asthma attacks, need for medication use, or a combination of the two, with a diagnosis of OA being excluded. According to the European Academy of Allergy and Clinical Immunology,[12] irritant-induced OA is diagnosed in the absence of a history of asthma, being classified as follows: (i) acute (i.e., definite irritant-induced OA)—asthma that develops within a few hours after a single exposure to very high levels of irritants; (ii) subacute (i.e., probable irritant-induced OA)—asthma that develops within a few days or weeks after multiple high-level exposures to irritants; and (iii) chronic (i.e., possible irritant-induced OA)—asthma resulting from chronic exposure to moderate levels of irritants (i.e., with a latency period).

Given that each year new chemicals are produced and made available for use, the possibility of new exposures should always be considered.

DIAGNOSTIC PROCEDURES

Occupational history and evaluation of the causative agent

In the early stages of WRA, patients report experiencing asthma symptoms or worsening of asthma symptoms at work, the symptoms resolving or improving when patients are away from work (on weekends/vacation). The symptoms tend to worsen with continued exposure, and it takes longer for any noticeable improvement to occur when patients are away from work. Late asthmatic reactions to the allergen, leading to worsening of symptoms at the end of the day or after work hours, can make it difficult to evaluate WRA, whereas exposure to irritants and sensitizers in the home can worsen asthma outside the workplace.[7] The clinical history is more reliable to exclude than to confirm OA. In a study of asthma patients, clinical history had a negative predicted value of 83%, whereas a history suggestive of OA had a positive predictive value of 63%.[35] Therefore, medication use, emergency department visits, and hospitalizations are useful objective parameters to quantify the course of the disease.[5] Identification of the causative agent also supports a diagnosis of WRA and makes it possible to minimize future exposures and prevent new cases among exposed workers, as well as to identify new agents.[36,37] If the clinical history, the occupational history, and the presence of a causative agent in the workplace are suggestive of WRA, timely further investigation is needed, preferably while the patient is still employed and exposed to the causative agent, for an objective assessment of asthma to establish its relationship with the work environment and adopt measures to protect workers.[5]

Objective measurements

Serial PEF measurements

Serial measurements of PEF (Figure 2) have a good level of evidence for the diagnosis of WRA. Good-quality measurements can be obtained with appropriate training and patient instructions. Although false or inaccurate measurements cannot be ruled out, serial PEF measurements provide the simplest and least expensive method to assess patient response to inhaled agents or work environment conditions, being recommended worldwide.[5,10] Serial PEF measurements should be obtained at least four times a day, no more than 2-3 h apart, during the course of two weeks at work and two weeks away from work. Patients perform three maximal inspiratory maneuvers followed by a maximal forced expiratory maneuver. The best of triplicate recordings made at each time point is used for comparative analysis.[5,10] Serial PEF measurements are highly sensitive and specific for the diagnosis of OA.[5] Although visual interpretation of measurements is the most commonly used method of analysis, statistical methods can be used, such as comparison of daily means between periods at work and away from work.[37,38] In addition, PEF records can be interpreted by Oasys-2 freeware (Occupational Asthma System; Oasys Research Group, UK), developed to aid in the diagnosis of WRA through analysis of PEF records. The developers of Oasys-2 recommend that PEF records be analyzed for periods of work-rest-work (two periods of days at work, separated by a period of days away from work) and rest-work-rest (two periods of days away from work, separated by a period of days at work), with measurements obtained at least four times a day.[39,40]

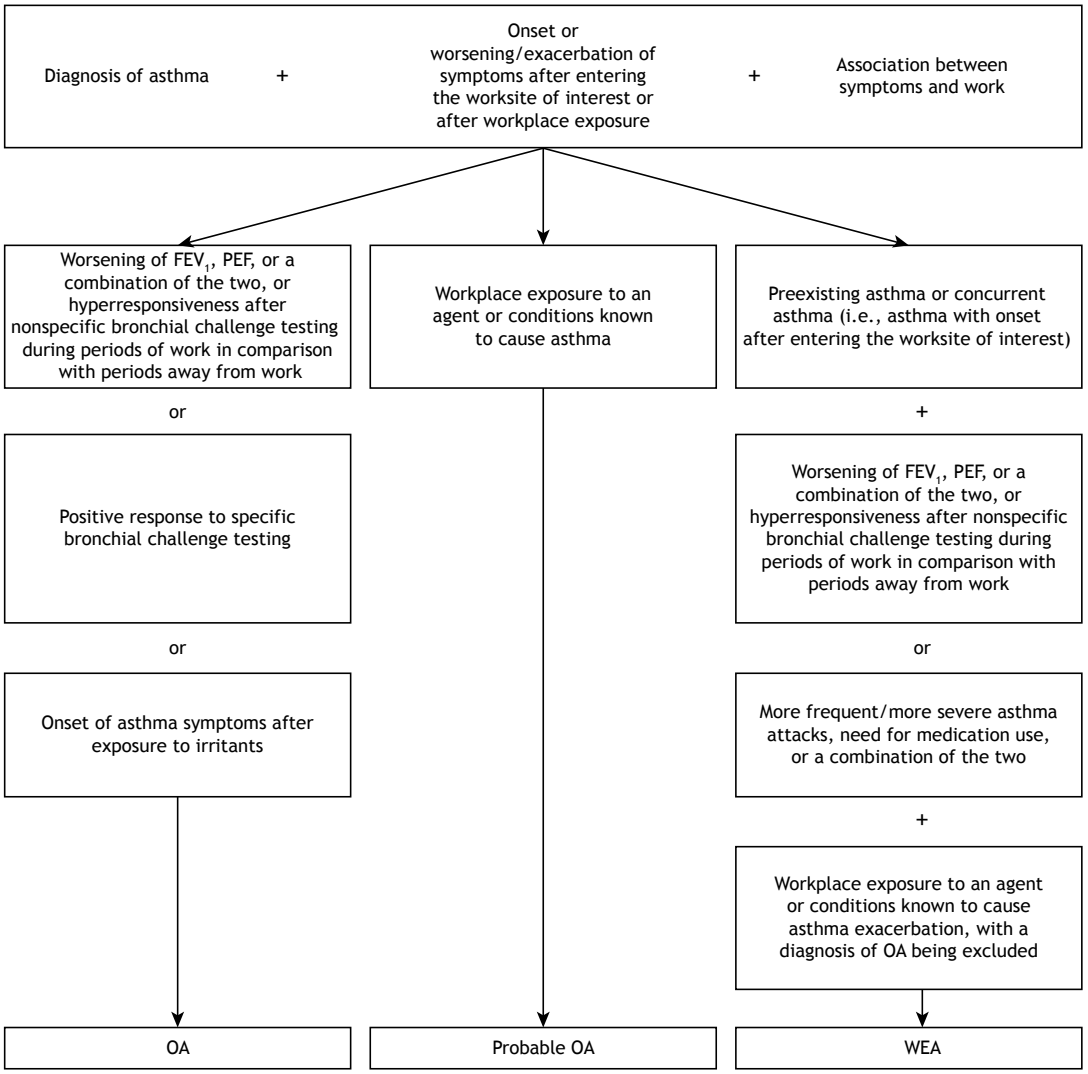

Figure 1. Algorithm for the diagnosis of work-related asthma. OA: occupational asthma; and WEA: work-exacerbated asthma.

Spirometry and nonspecific bronchial challenge testing

Spirometry and nonspecific bronchial challenge testing play an essential role in the diagnosis of asthma and can aid in confirming the impact of work exposures on lung function. Although it is possible to compare FEV_1 measurements before and after a work shift, they are less accurate and more difficult to perform than PEF measurements. In contrast, serial measurements of bronchial hyperresponsiveness to methacholine or histamine are useful diagnostic tools for the investigation of WRA when performed during periods of work and periods away from work.[5] These measurements are based on the hypothesis that hyperresponsiveness is greater when workers are exposed to the causative or exacerbating agent than when they are not (for at least two weeks).[5,10,41] The result is considered significant when more than twice the concentration of the inhaled agent is needed to cause a drop of 20% or more in FEV_1 during a period away from work in comparison with a period of work.[34] Serial measurements of bronchial hyperresponsiveness are moderately sensitive and specific for the diagnosis of OA (48-67% and 54-78%, respectively) and can aid in the diagnosis when PEF measurements are inconclusive or when patients are unable to perform the maneuvers/recordings correctly.[37,38] Normal results in workers away from exposure are not sufficient to exclude the diagnosis.[42] In symptomatic workers exposed to the suspected causative agent, a negative result practically rules out the diagnosis of WRA, although the seasonal use of products in work environments should be investigated.[41] Exacerbating factors such as cold air and exercise are less sensitive to nonspecific bronchial challenge testing, exercise testing and exposure to temperature variations therefore being more appropriate, although the latter is more feasible in the workplace than in health care facilities.[43]

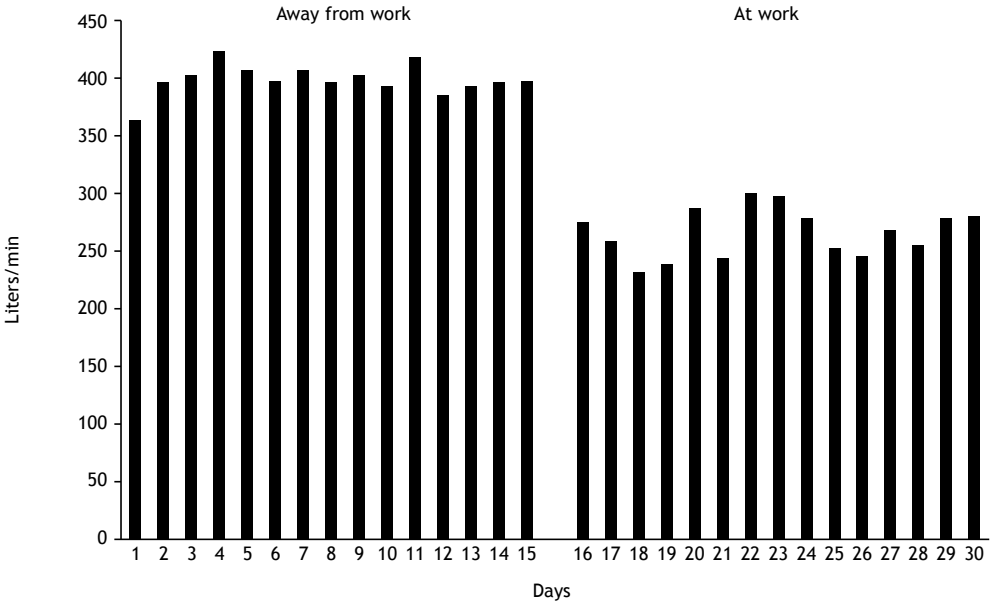

Figure 2. Daily means of serial PEF measurements: periods away from work and periods of work. The patient is a 40-year-old man who had been a carpenter for approximately 21 years. He presented with a 3-year history of progressive rhinitis, dry cough, wheezing, and dyspnea, with attacks. He reported multiple emergency department visits, as well as symptom improvement during periods away from work and with the use of bronchodilators.

Specific bronchial challenge testing

Specific bronchial challenge testing is considered the gold standard for the diagnosis of OA; however, it is difficult to standardize and must be performed in specialized centers, as well as requiring specific test kits, challenge chambers equipped with dosimeters, and a 24-hour hospitalization. Because it is not widely available,[37] its usefulness is limited.[44] Despite its high sensitivity and specificity, false-negative results can occur when individuals are exposed to the wrong agent, when the concentration of the exposure is inadequate, or when individuals are away from exposure.[37] Therefore, specific bronchial challenge testing is recommended when other forms of investigation are unavailable or when the diagnosis remains uncertain.[45]

Immunological tests

Immunological tests such as skin prick tests and specific IgE measurements in blood samples can aid in the diagnosis of sensitizer-induced OA by demonstrating sensitization to an occupational agent. However, the presence of sensitization alone is not sufficient to establish a causal relationship between sensitization and asthma.[46] In addition, standardized tests are currently available for only a few of the more than 400 known allergens, and the lack of standardization limits the validity of the results.[46] Skin prick tests for common aeroallergens (house dust, mites, pollens) can be performed to determine the presence of atopy, which is associated with an increased risk of sensitization to high-molecular-weight agents.[37] However, workers should not be denied a job on the basis of the results of skin prick tests performed during pre-employment medical examination.

Inflammatory markers

Induced sputum cell counts can aid in the diagnosis of OA. An increase in sputum eosinophils following exposure to the causative agent at work in comparison with measurements away from work (and vice versa) is indicative of OA.[10,37] Diagnostic sensitivity and specificity increase when an increased sputum eosinophil count is associated with serial measurements of nonspecific bronchial hyperresponsiveness[47] or serial PEF measurements during periods of work and periods away from work.[6,48] Although only a few studies have examined inflammatory changes in individuals with WEA following exposure to occupational agents (predominantly sensitizers), sputum cell counts appear to be useful in differentiating between OA and WEA.[49] WEA is most commonly associated with no changes in airway inflammation or with neutrophilic airway inflammation, whereas sensitizer-induced OA is most commonly associated with an eosinophilic phenotype.[49] An increase in sputum neutrophils has been reported in individuals with OA caused by exposure to certain low-molecular-weight agents and irritants such as ozone, diesel exhaust particles, and endotoxins.[50] Despite their diagnostic utility, induced sputum cell counts are not widely available, and approximately 20% of individuals are unable to produce sputum samples of adequate quality for analysis.[50]

Few studies have examined the utility of fractional exhaled nitric oxide (FeNO) in the diagnosis of OA, and the results have been inconsistent because

the specificity of FeNO measurements is low in comparison with that of induced sputum cell counts.[7,24] Increased FeNO levels might be related to exposure to occupational sensitizers, most of which are high-molecular-weight agents,[51] although some are low-molecular-weight agents, such as isocyanates.[52,53] Analysis of FeNO changes before and after exposure to a sensitizer can be a useful alternative in patients who are unable to produce adequate sputum samples or perform serial PEF measurements.[7,24,37]

Analysis of exhaled breath condensate (EBC) is a more recent noninvasive method for assessing airway inflammation. In a study in which workers underwent analysis of EBC before and after specific bronchial challenge testing,[54] those suspected of having OA showed a decrease of 0.4 units in EBC pH during periods of work in comparison with periods away from work, with high (90%) specificity for the diagnosis of OA, despite low sensitivity. This preliminary finding suggests that analysis of EBC could be incorporated into the diagnostic workup of OA as an additional test or as an alternative to other tests.[38]

Differentiation between WEA and OA

OA and WEA are not mutually exclusive; an individual with OA can develop WEA, and vice versa. It can be challenging to differentiate between OA and WEA; asthma present before occupational exposure is not always sufficient to discriminate between the two.[10] Immune-mediated OA can affect patients with preexisting asthma (i.e., OA superimposed on previous non-OA), with workers becoming sensitized to a specific agent ("*de novo* asthma").[15] In patients with sensitizer-induced OA, asthma exacerbation caused by exposure to the original causative agent is considered a recurrence of OA. However, workers with OA can also develop asthma exacerbation caused by agents in the workplace that are different from the causative agent of OA.[15] Given that specific bronchial challenge testing is performed in only a few centers and for a minority of agents, the differentiation between OA and WEA in clinical practice is based on a temporal relationship between the onset of asthma symptoms and occupational exposure.[55] Asthma symptoms occurring before an occupational exposure and aggravated by it are suggestive of WEA, provided that the diagnosis of asthma is confirmed by an objective measurement of lung function showing differences between values obtained during periods of work and those obtained during periods away from work.[14]

With regard to the differentiation between WEA and irritant-induced OA, it has been recommended that reactive airway dysfunction syndrome be considered only in individuals without preexisting asthma.[25] However, it has been suggested that acute exposure to high levels of irritants can lead to recurrence of previously quiescent asthma or worsening of previously controlled asthma.[22] There is debate as to whether this accidental worsening of asthma should be categorized as irritant-induced OA or a form of WEA. According to the European Academy of Allergy and Clinical Immunology,[12] irritant-induced OA is asthma in complete remission (no symptoms and no medication use for at least one year) before high-level exposure to irritants, whereas WEA is asthma that is clinically active before high-level exposure to irritants.

Differential diagnosis

The differential diagnosis of WRA should include COPD, hypersensitivity pneumonitis, bronchitis, eosinophilic bronchiolitis, and vocal cord dysfunction; in addition, it should be borne in mind that these conditions can coexist with asthma, albeit not commonly.[10]

Although WRA is diagnosed on the basis of objective measurements to determine a causal relationship between asthma symptoms and occupational exposure, this is not always possible in clinical practice, either because the required tests are not widely available or because patients are not exposed at the time of diagnosis. In a study conducted in the city of São Paulo, Brazil, 50% of patients undergoing medical evaluation were not working, either because they had been dismissed or because they were on sick leave in most cases.[32] In such cases, the diagnosis is made on the basis of careful evaluation of the clinical history and the workplace, as well as on the basis of an understanding of the toxicology of the different exposures.[38,56] Material safety data sheets are sources of information that can help to identify workplace exposures. Occupational hygienists and experienced professionals can aid in establishing a diagnosis and (temporarily or permanently) relocating workers to unexposed areas/duties, when necessary.[15,22]

WRA PATIENT MANAGEMENT

Early diagnosis and complete removal of exposure to the causative agent are the most effective interventions for the prevention and treatment of WRA,[10,57] preventing disease progression and limitations in work activities.[58] Complete removal of exposure is the recommended intervention for patients diagnosed with sensitizer-induced OA. Depending on the severity of asthma and the extent of exacerbating factors at work, individuals experiencing WEA are often able to maintain their jobs/positions after exposure to relevant agents has been controlled/reduced, and this can reduce the socioeconomic impact of work absenteeism.[34] If complete removal of exposure is not sufficient to prevent exacerbation of asthma symptoms, workers should be relocated to unexposed areas/duties.[6] In a systematic review conducted in 2019,[59] removal of exposure and reduction of exposure were reported to improve asthma symptoms when compared with continued exposure, although only removal of exposure was found to improve lung function.

Several studies suggest that WRA is associated with increased rates of prolonged unemployment

and reduced income, primarily in workers who are completely removed from exposure; this is likely due to the need for reassignment to other, less important, jobs and the fact that such workers are often denied job opportunities on the basis of pre-employment medical examination results.[58,59] Therefore, an accurate diagnosis is essential because of the socioeconomic impact of OA.[58] Despite evidence of the importance of early diagnosis, studies suggest that mean time to diagnosis is two to four years after the onset of symptoms, and delayed diagnosis/misdiagnosis can lead to progressive worsening of symptoms.[37]

SOCIAL SECURITY ISSUES

A correct diagnosis of WRA is important because it has implications for formally employed workers regarding social security issues, given that diagnosed cases of WRA must be reported to the Brazilian National Institute of Social Security, even those in which a medical leave of absence is not required. Notification ensures paid medical leave (when applicable) and monthly compensation until retirement in cases in which the disease leads to a functional limitation, a job/career change, or both.[60] In Brazil, workers diagnosed with occupational or work-related disease and on leave for more than 15 days are granted one-year job stability by the social security system.

CHALLENGES IN DEVELOPING COUNTRIES

Worldwide, WRA is underdiagnosed and ineffectively managed, with patients being inadequately compensated for disease-related losses. Epidemiological data on WRA are scarce, and its impact on low- and middle-income countries is likely underestimated.[7] Therefore, there is a need to prioritize research into WRA in order to mitigate the burden of WRA on the working population, the health care system, and the social security system.[61] Improved characterization of WRA can aid in the identification of high-risk industries and occupations, and, consequently, in the creation and implementation of health surveillance programs to establish preventive measures.[54] For example, there is an urgent need for interventions to improve the occupational safety of cleaners, including replacing some cleaning products with less toxic products and providing training on how to prepare and use cleaning products safely.[62] Social security and worker protection systems need to be improved and employers need to be held accountable to provide socioeconomic stability to workers with WRA.

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Brief Intervention for Smoking Cessation During Pregnancy

Andre Bertani[1], Suzana Tanni[1], Irma Godoy[1]

TO THE EDITOR,

The cessation of smoking during pregnancy preserves life and reduces health risks for the mother and the fetus.[1] In Brazil, a study carried out between 2011 and 2012 showed that the prevalence of active smoking during pregnancy was 9.6%.[2] Interventions based on cognitive behavioral therapy, supported by educational material, are indicated as a first-line approach to smoking cessation during gestation.[3]

We conducted a parallel, randomized, controlled clinical trial with a 1:1 allocation ratio of 143 pregnant smokers who attended prenatal services at Primary Care health clinics and the Obstetrics Clinic of the University Hospital of the Botucatu Medical School – UNESP, SP, Brazil. The aim of the study was to determine the influence of a brief intervention based on tailored cognitive behavioral therapy, complemented with a video and a manual including content specifically developed for pregnant smokers, on smoking cessation rates during pregnancy and after delivery.

All participant pregnant smokers signed informed consent, answered a questionnaire, and underwent a 15-minute individual standardized counseling session. In addition, they received a printed manual and a DVD containing a video on both smoking-related content and its consequences to pregnancy and the fetus/newborn. The participants were randomized into an Intervention group (I), in which they were encouraged to participate in up to seven individual treatment sessions held on the same day as the prenatal visits, or a Control group (C), with no additional participation in individual treatment sessions. Abstinence rates were assessed upon each prenatal visit and 40 days after delivery, and the smoking status was confirmed by carbon monoxide measurements. The degree of nicotine dependence was determined using the Fargeström test,[4] and the subjects' motivational stage was assessed according to the Prochaska and DiClemente transtheoretical model.[5] Craving was evaluated by the Brief Questionnaire of Smoking Urges (QSU-Brief), validated for use in Brazil.[6] The study was approved by the Research Ethics Committee of the Botucatu Medical School (Reference No. 430.718).

The sample size was calculated to identify a difference of 20% in the abstinence rate between groups, with a power of 90% and an alpha of 5% for tests of proportion. The required sample size was 117 individuals. Associations of primary outcome (smoking status 40 days after delivery) to the subjects' characteristics, adherence, degree of dependence, motivational stage, use of educational material, and economic class were performed by logistic regression analysis.

The main characteristics of the participants are shown in Table 1. The individuals from the Control group were older than those from the Intervention group (29.5 ± 6.1 years vs. 24.3 ± 7.2 years, $p < 0.001$). Most of the pregnant women were in a stable union (66.9%), had only an elementary school level (57.4%), and belonged to the D and C2 Brazilian economic classes (58.1%), with no differences between groups. A statistically significant difference in the proportion of passive smoking (69% vs. 36%, $p<0.001$) and of pregnant women in the contemplative stage (76.7% vs. 32%, $p < 0.001$) was found in the Intervention group compared to the Control group. In addition, a statistically significant difference in the smoking cessation rates was observed in the Intervention group as compared to the Control group (55.8% vs. 34%, $p = 0.026$). In the logistic regression model, the status 'active smoking after delivery' was associated with smoke loads >10 pack-years, participation in only one counseling session, exposure to secondhand smoke, and lack of use of educational material. Gestational age was also included in the logistic regression model, but a significant difference was not found. However, when analyzing the differences between medians, Gestational age was statistically different between groups (Table 1).

Our results showed that prenatal care educational programs with content related to the effects of smoking during pregnancy effectively enhanced smoking cessation, which increased with program intensity. The findings reported by Ferreira-Borges,[7] who evaluated the impact of a twelve-minute counseling session and a booklet containing related information on smoking during pregnancy, corroborate our results regarding abstinence rate, confirmed by measuring the carbon monoxide in exhaled air, which was 33% in the Intervention group and 8.3% in the Control group ($p = 0.026$).[7] Other studies assessing interventions during prenatal visits related to the problems that smoking may cause in pregnancy compared cessation strategies with routine prenatal guidance alone.[8,9] In previous studies, biochemically confirmed smoking cessation rates varied between 35% and 39% in the Intervention groups and between 18.9% and 30% in the Control groups.[8,9] Regression analysis showed a positive association of being a smoker 40 days after delivery with a smoke load >10 pack-years, secondhand smoke exposure, no use of educational material, and participation in only one counseling session. An important finding was the negative association between active smoking 40 days after delivery and a contemplative

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Table 1. Baseline characteristics of the studied groups.

Variables	I n = 77 (60.6%)	C n = 50 (39.4%)	p value
Age (years), mean ± SD	29.5 ± 6.1	24.3 ± 7.2	<0.001
Stable union, n (%)	47 (61.0)	38 (76.0)	0.119
Smoke load, cigarretes/day (range)	18 (8 - 28)	13 (5 - 23)	0.263
High nicotine dependence, n (%)	43 (56.0)	34 (68.0)	0.236
Intense craving prepartum, n (%)	10 (13.7)	29 (58.5)	0.007
Intense craving postpartum, n (%)	11 (14.2)	26 (53.1)	0.013
Previous cessation attempts, n (%)	38 (49.0)	14 (28.0)	0.027
Secondhand smoking, n (%)	53 (69.0)	18 (36.0)	<0.001
Contemplative stage, n (%)*	59 (77.0)	16 (32.0)	<0.001
Gestational age (weeks), n (%)*	12 (8-16)	24 (12-28)	<0.001

I: Intervention group. C: Control group. *Contemplative stage and Gestational age at baseline.

motivational stage towards cessation, indicating that the reinforcement of smoking cessation counseling during pregnancy provides positive results, regardless of the motivational stage. Stotts et al. also concluded that pregnant women who were contemplative at baseline migrated to the action stage and ceased smoking after treatment.[10] Secondhand smoking and the number of cigarettes/day have also been previously described as risk factors for continuing smoking during gestation and after delivery.[8,10]

Similar to our findings, a study comparing an experimental group of pregnant women who were provided brief counseling and a video and self-help manual with content aimed at smoking cessation with a control group that received only routine prenatal care showed a significant positive association between adherence to the intervention and abstinence after follow-up.[9] In the present study, 81% of the pregnant women in the Intervention group participated in 4 or more sessions. Delivering the sessions during prenatal consultations was probably a key feature to obtain this result.

Some limitations should be considered in our study. The majority of women included in the study belonged to a high-risk pregnancy group; however, even in a sample with these characteristics, the intervention was successful. In addition, it was not possible to determine the long-term abstinence rate because the 6 and 12-month smoking status were not evaluated.

In conclusion, the results obtained in our study showed that the brief intervention supplemented with educational material had a positive effect on smoking abstinence rates in pregnant women. The incorporation of this intervention model during prenatal consultations opens the possibility of using similar approaches in other services. Our results reinforce the importance of more intense interventions with greater attention to those exposed to higher smoking levels, including secondhand smoking. Regardless of the motivational status and the degree of nicotine dependence, counseling and educational materials were effective in this group of pregnant women.

FINANCIAL SUPPORT

This study received financial support from the São Paulo Research Foundation (FAPESP – Fundação de Amparo à Pesquisa do Estado de São Paulo – Process No. 2013/14910-9).

AUTHOR CONTRIBUTIONS

ALB conducted the interviews with the pregnant women, gave them counseling, tabulated the data, and wrote the manuscript. SET performed the regression analysis. IG supervised the research procedures and revised the final version of the manuscript.

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J Bras Pneumol. 2021;47(4):e20210170
https://dx.doi.org/10.36416/1806-3756/e20210170

Applicability of the chronic obstructive pulmonary disease assessment test as a measure of health status in patients with sequelae of pulmonary tuberculosis

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TO THE EDITOR,

Pulmonary tuberculosis often results in sequelae associated with airway obstruction and/or functional limitations, leading to lower tolerance to exercise and reductions in health status (HS) and, consequently, in quality of life (QoL), particularly in patients treated for more than six months.[1]

Considered as one of the leading causes of death worldwide, tuberculosis is estimated to have affected 10 million individuals in 2019, resulting in approximately 1.2 million deaths, despite the fact that the cumulative incidence of the disease fell by 9% between 2015 and 2019. Brazil was among the 30 countries with the highest number of cases of tuberculosis worldwide in 2019.[2]

Practical instruments for the measurement of HS and QoL are required in order to assess improvement.[3] The objective of this study was to investigate the applicability of the chronic obstructive pulmonary disease (COPD) assessment test (CAT) as an instrument to evaluate the HS of individuals with sequelae of pulmonary tuberculosis and limitations regarding exercise.

This was a cross-sectional, observational study. Patients with radiological evidence of sequelae of pulmonary tuberculosis who had completed treatment and consented to participate in the study were included. Meanwhile, individuals that were unwilling to cooperate, who had limited cognitive or intellectual ability, were clinically unstable, or that had any musculoskeletal lesion that could affect their physical capability, as well as patients with any comorbidity that could cause dyspnea, angina, or severe arrhythmias, were excluded from the study.

The evaluations included: analysis of medical records and interview; chest X-ray; physical examination (vital signs and anthropometry); mini-mental state examination (MMSE); the Modified Borg Scale (MBS), and physical fitness, assessed using the 6-minute walk test (6MWT) and maximum inspiratory and expiratory pressure (MIP and MEP, respectively). The Saint George Respiratory Questionnaire (SGRQ) and the CAT were used to evaluate the participants' HS.

All analyses were conducted using the Sigmastat software, version 3.1 (Systat Software, Inc., Point Richmond, California, USA). Differences and correlations were considered statistically significant when p-values were < 0.05.

The Institutional internal review board approved the study protocol under reference CAAE: 10481219.9.0000.5257. All participants signed an informed consent form.

This was a convenience sample obtained from the electronic database at the Thoracic Diseases Institute of Rio de Janeiro Federal University. A total of 46 individuals with sequelae of pulmonary tuberculosis who had been treated with the Brazilian Ministry of Health's standardized drug regimen were contacted. Among them, 16 were included in the study, eight of whom were women. The mean age of the individuals was 49.2 (± 15.2) years, and the mean body mass index was 23.7 (± 4.6) kg/m^2. Five of the participants were former smokers, with a mean smoking load of 34.8 pack-years. The mean MMSE score obtained was 26 (± 2.3), thus enabling the application of the instruments to evaluate HS and QoL.

The patients' complaints were mainly dyspnea (31.2%) and chest pain (18.7%). The most common X-ray findings were localized interstitial infiltrates (50%), low lung volume (31.2%), and nodular opacity (37.5%). Data collected at the time of physical examination, including hemodynamics, pulse oximetry, and perceived effort, as well as predicted measures and values related to physical fitness, cardiopulmonary response, respiratory muscle strength, and health status correlation, are shown in Table 1.

Upon physical evaluation, the participants' results regarding the 6MWT and MBS were normal, as well as their hemodynamic response.[4,5] Nevertheless, the strength of the respiratory muscles, determined by MIP and MEP, remained adequate, indicating a reduction in the participants' pulmonary vascular resistance and/or peripheral muscle force, with no negative effects on the respiratory muscles.[6,7]

The SGRQ is specific for respiratory diseases. The overall score serves to assess HS and QoL, while the questionnaire is subdivided into domains related to symptoms, activity limitation, and the social and emotional impacts of the disease. According to this instrument, QoL, whether overall or for an individual domain, is considered impaired when

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ISSN 1806-3756

Table 1. Characteristics of the physical, functional, and health status of the participants.

Parameter	Mean and SD at baseline (% predicted)
SBP	133.8 ± 24.3
DBP	75.8 ± 12.4
SpO_2	96.8 ± 1.7
Heart Rate	82.1 ± 19.1
MBS	0.8 ± 1.1
6MWT	531 ± 101.1 (84.9)
MIP	100 ± 20 (97.4)
MEP	94.1 ± 23.4 (89.1)
SGRQ (total)	33.6 ± 26.1
Symptoms	38.3 ± 27.1
Activity Limitation	43.2 ± 27.7
Impact	29.3 ± 23.2
CAT	12.7 ± 8.4

SD: standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; SpO_2: oxygen saturation; MBS: Modified Borg Scale; 6MWT: 6-minute walk test; MIP: maximum inspiratory pressure; MEP: maximum expiratory pressure; SGRQ: Saint George Respiratory Questionnaire; CAT: Chronic obstructive pulmonary disease assessment test.

the value obtained is over 10%, while changes ≥ 4% following an intervention are indicative of a significant change in QoL.[8] The participants of the present study had a mean overall score of 33.6 (± 26.1) (symptoms 38.3 ± 27.1; activity limitation 43.2 ± 27.7; social and emotional impacts of the disease 29.3 ± 23.2).

Developed and validated in 2009, the CAT has the advantage of being a short, simple instrument to evaluate HS in patients with COPD in clinical practice.[4] The instrument consists of eight multiple-choice questions, with possible answers scoring from 0 to 5. The final score is reached by tallying the score for each question, with the impact of the disease being classified as follows: a) low: 6-10; b) medium: 11-20; c) high: 21-30; and d) very high: 31-40 points.[4] The CAT was previously used to evaluate HS in a cohort of individuals with a history of pulmonary tuberculosis associated with pulmonary hypertension.[9] Although the instrument had not yet been validated for use in that population, the mean score obtained was 14.76 ± 5.88; no statistically significant difference was found between the subgroups of smokers and non-smokers ($p = 0.25$). The score obtained in the present study was quite similar, with a mean overall score of 12.7 ± 8.4, thus indicating a medium impact on HS. The correlation of the CAT and the SGRQ scores was significant ($p < 0.0001$; $r = 0.84$).

The possibility of a preexisting pulmonary disease, particularly among individuals exposed to smoking, was a limitation of the present study since the functional differences among the participants were not evaluated according to the predominant pulmonary disorder (restrictive and/or obstructive). Nevertheless, patients could benefit from individualized cardiopulmonary rehabilitation irrespective of the type of disorder.[1,10]

Despite the limitation regarding the small sample size, it is reasonable to suggest that the CAT is as applicable as the SGRQ for the evaluation of HS in individuals with sequelae of pulmonary tuberculosis and exercise limitations. However, larger studies are needed in order to establish the usefulness of this highly practical instrument.

AUTHOR CONTRIBUTIONS

DFMT: conception and planning of the study, interpreting the evidence, writing and reviewing the preliminary and final versions of the manuscript. ACSN: interpreting the evidence, writing the preliminary versions of the manuscript. SFD: interpreting the evidence, writing the preliminary versions of the manuscript. APC: conception and planning of the study, interpreting the evidence, and reviewing the final version of the manuscript. FCQM: conception and planning of the study, interpreting the evidence, reviewing the final version of the manuscript.

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J Bras Pneumol. 2021;47(4):e20210020
https://dx.doi.org/10.36416/1806-3756/e20210020

Bronchiolitis obliterans due to toxic epidermal necrolysis - a serious condition with a good therapeutic response

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TO THE EDITOR,

Bronchiolitis obliterans (BO) is a rare disease that can result from a large number of clinical conditions. The injury and inflammation of the small airways can be caused by different stimuli, such as viral diseases, gastroesophageal reflux, prolonged exposure to pollutants, autoimmune diseases, post-organ or bone marrow transplantation, and less frequently, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[1,2] Clinically, BO is characterized by progressive dyspnea and dry cough, which progress from weeks to months.[1] Spirometry may be normal or exhibit an obstructive, restrictive, or mixed pattern.[1] High-resolution computed tomography (HRCT) of the chest can show early alterations, even with normal spirometry, with hypodense areas presenting reduced vascular caliber, suggestive of air trapping.[1,3]

SJS and TEN are different spectra of the same disease, differing by the extent of skin detachment.[4] This disease is characterized by severe skin reactions, with acute eruptions of the skin and mucous membranes that can affect the respiratory system, leading to laryngeal edema, epiglottitis, bronchiolitis, pneumonitis, and, in rare cases, pneumothorax.[4] Persistent pulmonary sequelae associated with SJS or TEN are considered uncommon, but when the involvement of the respiratory mucosa is extensive, the disease appears, in most reports, as severe, progressive, and with a poor prognosis.[2,3,5,6]

Here we describe a case of BO secondary to TEN, which presented with a favorable clinical outcome. This is the first case reported in adults in Brazil, according to searches on the PubMed database. The patient was a 32-year-old woman, who at the time was single, unemployed, from the state of Ceará, nonsmoker, and without previous lung diseases. She had a medical history of epilepsy, having used phenobarbital for 8 years. The patient evolved with TEN secondary to the use of such medication. She exhibited extensive involvement of oral, vaginal, corneal, and respiratory mucosa, having remained on mechanical ventilation in the ICU for 45 days due to acute respiratory failure. In the hospital ward, the patient persisted with dyspnea upon minimal exertion, wheezing, coughing with mucoid sputum, and oxygen dependence. She was discharged after 15 days and was referred to the Pulmonology Service of the Walter Cantídio University Hospital. At consultation, she complained of dyspnea (m-MRC 3) and reported the need for oxygen at night and oral corticosteroid use (prednisone 20 mg per day). Upon physical examination, the patient exhibited impaired overall condition; she was oriented, tachydyspneic, and presented bilateral amaurosis and normal cardiac auscultation. Pulmonary auscultation revealed diffusely diminished breath sounds, without adventitious sounds, and oxygen saturation was 93% in room air. Initial spirometry showed marked obstructive ventilatory disorder, with reduced FVC (pre-BD FEV1: 0.61 (23.9%), post-BD FEV1: 0.61 (23.9%), pre-BD FVC: 1.10 (37.4%), post-BD FVC: 1.05 (35.6%), pre-BD FEV1 / FVC: 55.32%, post-BD FEV1 / FVC: 57.78%). Chest radiography showed diffuse hyperinflation and a small focal condensation on the right base. The HRCT scan of the chest showed a diffuse mosaic attenuation pattern, with extensive areas of regional hyperinflation and discrete reticular infiltrates associated with a ground-glass area bilaterally dispersed in the anterior segments, notably in the left lung (Figure 1). Treatment with inhaled Budesonide / Formoterol was started, and progressive weaning from systemic corticosteroids was carried out. The patient evolved with significant improvement in dyspnea and weaning from oxygen therapy. She has been followed-up in the service for 6 years, with control of symptoms (m-MRC 1) and progressive improvement in lung function, and, in the last evaluation, she exhibited 930 mL pre-BD FEV1 (FEV1 pre-BD: 0.93 (38.4%), FEV1 post-BD: 0.97 (40.4%), FVC pre-BD: 1.63 (57.8%), FVC post-BD: 1.64 (58.3%), FEV1 / FVC pre-BD: 57%, FEV1 / FVC post-BD: 59.4%) and a 156-meter increase in the 6-minute walk test.

TEN is caused by hypersensitivity to immune complexes, triggered mainly by drugs, with anticonvulsants being one of the most involved classes.[2,4,5] This reaction leads to injury to the epidermis and mucous membranes and is characterized as TEN when more than 30% of the epidermis presents necrosis.[4,5] In TEN, mucosal lesions are more commonly seen in the upper airways, but in the case of BO, a rare and severe complication associated with this syndrome, mucosal lesions reach the terminal bronchioles.[4,5]

In the healing process of these lesions, fibrin production and tissue invasion occur by inflammatory cells, such as lymphocytes and macrophages, as well as the proliferation of myofibroblasts and blood capillaries, leading to the

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ISSN 1806-3756

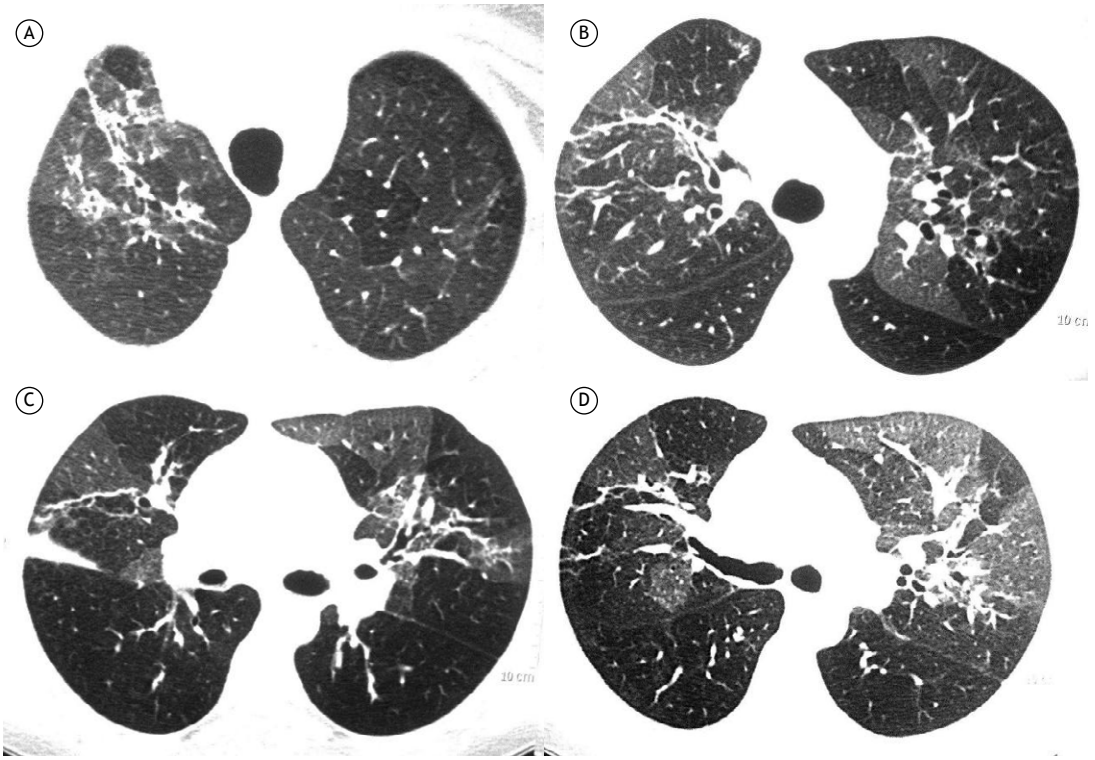

Figure 1. HRCT performed two months after hospital admission, showing pulmonary parenchyma with a pattern of attenuation in diffuse mosaic, with extensive areas of regional hyperinflation and discrete reticular infiltrates associated with ground-glass areas dispersed bilaterally in the anterior segments, notably in the left lung.

hyperproliferation of granulation tissue, with collagen deposition in the submucosa and consequent progressive concentric narrowing and bronchial lumen distortion, characterizing chronic inflammation.[2]

As the structure of the bronchial wall, including the smooth muscle layer and elastic fibers, is not destroyed and is surrounded by fibrosis tissue, the histological pattern is characterized by constrictive bronchiolitis, which can lead to partial or complete bronchiole obstruction, aspects that determine the severity of the condition.[2,6] The presence of bronchial cartilage involvement has also been described as a factor associated with a worse prognosis.[2,6]

Currently, biopsy has been dispensed with for the diagnosis of BO, which is based on clinical and radiological criteria, when there is a clinical history and compatible pathological history, associated with pulmonary function test with a fixed obstructive pattern and tomography with a mosaic attenuation pattern, with vascular attenuation and central bronchiectasis.[3,5,7]

Ideally, the effective treatment of TEN prevents these serious respiratory sequelae from being generated.[8] For that, early recognition of the syndrome and the causative agent is necessary, and the exposure to the agent must be stopped immediately, given that the disease has rapid evolution.[4]

According to the literature, when BO is already installed, the prognosis is generally unfavorable, with a fatal outcome in most cases in adults.[2,3,5,6,8] There is no specific treatment established for this disease, with poor outcomes based on corticosteroid treatment, in most cases.[3,8] Differently, in the case reported, the patient evolved with good control of respiratory symptoms and improved lung function, thus making inhalation therapy an option to be considered.

AUTHOR CONTRIBUTIONS

ALBPF: conception and planning of the study, writing and reviewing the preliminary and final versions of the manuscript, approval of the final manuscript. RCR: conception and planning of the study, reviewing the preliminary and final versions of the manuscript, approval of the final manuscript. RCPP: conception and planning of the study, approval of the final manuscript. JFF: writing and reviewing the preliminary and final versions of the manuscript, approval of the final manuscript. MAH: reviewing the preliminary and final versions of the manuscript, approval of the final manuscript.

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J Bras Pneumol. 2021;47(4):e20210143
https://dx.doi.org/10.36416/1806-3756/e20210143

Use of sildenafil in late postoperative period of congenital diaphragmatic hernia

Mário Cícero Falcão[1], Ana Paula Andrade Telles[1], Marcela Ludwig Macedo da Aguiar[1], Juliana Zoboli Del Bigio[1]

TO THE EDITOR

Congenital diaphragmatic hernia (CDH) occurs in about 1 in 3,300 live births. It is a congenital defect of the diaphragm with herniation of the abdominal viscera into the thorax. Abnormal pulmonary development leads to hypoplasia and pulmonary hypertension, which are the main determinants of morbidity and mortality for these patients.[1]

Between 2015 and 2019, 83 patients with CDH were admitted to the Neonatal Intensive Care Center-2 (NICC-2) of the Child and Adolescent Institute of the Clinics Hospital of the University of São Paulo School of Medicine (*HCFMUSP*), São Paulo, Brazil. Of these, 42 (50.6%) were discharged from the hospital and enrolled in a specialized follow-up outpatient clinic, in which six patients (14.2%) used sildenafil. The other 36 patients had normal pulmonary pressure and therefore there was no indication for use of sildenafil.

NICC-2, aligned with the most up-to-date guidelines, uses systematized protocols for the CDH approach.[1,2] This protocol is multidisciplinary and begins with the admission of the newborn shortly after birth in the surgical room or obstetric center. It includes resuscitation in the delivery room, transfer to CTIN-2 for monitoring, ventilation assistance, central and arterial venous accesses, drug treatment of pulmonary hypertension, fluid control, comfort measures, and pain reduction.[3]

All these measures aim not only to stabilize the newborn for surgical correction of the congenital defect, but also to allow an adequate recovery in the postoperative period, increasing its survival. Moreover these newborns are referred to a specialized follow-up outpatient clinic.

The main characteristics of the children on sildenafil after hospital discharge were the following: 83.3% were male, 100% were Cesarean born, average birth weight was 3058.3 ± 306.2 grams, mean gestational age was 38.3 ± 1.0 weeks, and in relation to karyotype, three had 46XY, one had mosaicism 46X0/46XY and two families did not agree with the test. As there may be an association of CDH with trisomy, especially 18 and 21, it is recommended to perform fetal karyotype routinely[4].

Regarding the type of CDH, five children (83.3%) had the defect on the left side and all required a prosthetic patch during surgery to repair the diaphragm. Congenital anomalies were found in three (50%) different cases (hypoplasia of the aortic isthmus, ventriculomegaly and hydrocephalus).

Table 1 shows the doses of sildenafil used, as well as the time of use and evolution of pulmonary hypertension measured by echocardiography.[5]

According to "The Canadian Congenital Diaphragmatic Hernia Collaborative"[1], the treatment of pulmonary hypertension in CDH consists in using the following drugs: inhaled nitric oxide - indicated in the treatment of pulmonary hypertension without left ventricular dysfunction, but in the absence of clinical response and/or echocardiography, its use should be discontinued (grade II evidence); milrinone - drug of choice in the treatment of pulmonary hypertension with cardiac dysfunction (grade I evidence); sildenafil - used in pulmonary hypertension refractory to nitric oxide and/or in conjunction with nitric oxide (grade II evidence); prostaglandin E - used to keep the ductus arteriosus patent and reduce the right overload in newborns with pulmonary hypertension and right ventricular failure or in imminent ductus arteriosus closure (grade II evidence).

After the instability phase, the drugs of choice by enteral route for treatment of pulmonary hypertension are sildenafil and bosentan.[6] In our country, sildenafil is chosen over bosentan because of the high costs involved.

After several controversies, sildenafil was released to control neonatal pulmonary hypertension in the following conditions: as adjuvant to inhaled nitric oxide or to facilitate weaning, as primary treatment of persistent pulmonary hypertension of the newborn when nitric oxide is not available or contraindicated and as first option in the chronic treatment of pulmonary hypertension in bronchopulmonary dysplasia and CDH.[7,8,9]

In our sample, 14.2% of the children required sildenafil after hospital discharge (average of 144 days), with doses between 2 and 4 mg/kg. In a similar study, Behrsin et al.[10] reported that 17% used the drug after discharge at a dose of 8 mg/kg/day, with a median of 343 days. This showed a consistency in the dose, but with a much longer period of use of sildenafil, probably due to severities other than pulmonary hypertension. Furthermore, the discontinuation of sildenafil was gradual (0.5 mg/kg/week) in the Australian study,[10] which was not performed in our sample because the drug was discontinued and there was no rebound effect on pulmonary hypertension, showing no need for drug discontinuation. Our protocol does not establish a specific time for the use of sildenafil as it depends on the pulmonary hypertension reversal.

The side effects of sildenafil were categorized into gastrointestinal (diarrhea, dyspepsia), vascular (epistaxis, flushing, headache) and neurological (abnormal vision, hyperactivity, insomnia, myalgia, pyrexia),[2] but such an event was not observed in the medical records regarding the use of sildenafil.

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Table 1. Variable doses of sildenafil used, time of use and evolution of pulmonary hypertension.

Case	Dose of sildenafil (g/kg/dose)	Time of use (days)	Echocardiography PASP at discharge (mmHg)	Echocardiography at sildenafil discontinuation
1	4	71	85	Absence of indirect PH signs*
2	2	124	70	PASP=31 mmHg
3	2	266	73	Absence of indirect PH signs*
4	2	77	65	Absence of indirect PH signs*
5	2	120	58	Absence of indirect PH signs*
6	2	210	60	Absence of indirect PH signs*

PASP = pulmonary artery systolic pressure at hospital discharge. PH = pulmonary hypertension. *Indirect signs of PH on echocardiography = pulmonary artery dilation, changes in pulmonary valve movement and pattern of the flow velocity curve of the right ventricular outflow tract.[5]

In conclusion, the prescription of sildenafil for pulmonary hypertension control was effective and showed no side effects. It is noteworthy that several of these effects are subjective (dyspepsia, headache, hyperactivity, abnormal vision, myalgia, pyrexia) and difficult to evaluate and/or measure in young infants as they may go unnoticed in the follow-up appointment. Thus, in these children should be asked about all the side effects listed above. Moreover, families should be instructed to monitor these side effects and report on them so that appropriate action is taken.

It is worth emphasizing that this is the first Brazilian report describing the outpatient use of sildenafil for treatment of pulmonary hypertension in children with corrected CDH.

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J Bras Pneumol. 2021;47(4):e20210083
https://dx.doi.org/10.36416/1806-3756/e20210083

Thoracic textiloma with atypical localization

Antônio Carlos Portugal Gomes[1], Gláucia Zanetti[2], Edson Marchiori[2]

A 68-year-old man was admitted to the emergency ward presenting with cough and chest pain that had started 3 days earlier. The patient denied fever or other symptoms and had a history of cardiac surgery with myocardial revascularization 1 month before. Physical examination and laboratory findings were unremarkable. Chest computed tomography (CT) showed an elongated heterogeneous mass containing gas bubbles and metallic densities in the anterior, paramediastinal region of the left hemithorax (Figure 1), suggestive of a retained surgical sponge. Surgical exploration revealed a well-encapsulated surgical gauze sponge in the left hemithorax. The patient's postoperative recovery was uneventful. After 2 years, he remains asymptomatic.

Textiloma (also known as gossypiboma) is the term used to describe a mass in the body composed of a sponge or other retained surgical material surrounded by foreign-body reaction. It is a rare complication following thoracic surgery. CT is the most effective imaging method for the detection of a retained intrathoracic textiloma. Although some cases are clinically silent and discovered only upon routine radiological examination, textilomas can have severe medical consequences, including infection and abscess formation. Surgical treatment is indicated in almost all cases.[1,2]

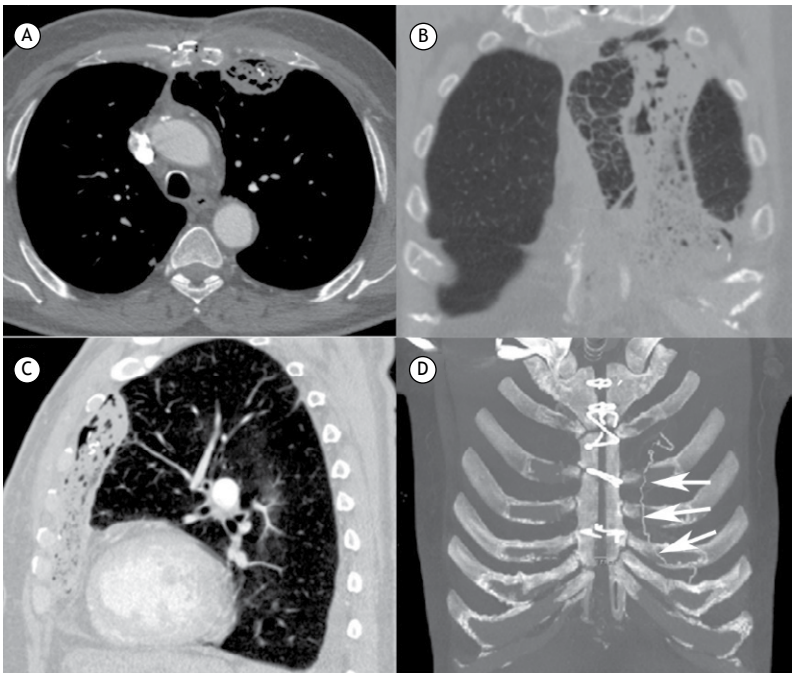

Figure 1. Axial (A) contrast-enhanced chest computed tomography image showing a heterogeneous oval mass containing gas bubbles and metallic densities in the anterior region of the left hemithorax, suggesting extrapulmonary origin. Coronal (B) and sagittal (C) reformatted images demonstrating that the mass was elongated, projecting into the anterior portion of the left hemithorax, in the paramediastinal topography, and in close contact with the pleural surface. Note the interlobular septal thickening in the pulmonary parenchyma between the mass and the mediastinum. Coronal reformatted image with maximum intensity projection (D) showing a dense and irregular linear object in the left hemithorax, compatible with radiopaque filaments (arrows). Note also the signs of sternotomy.

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Post COVID-19 vaccine adenopathy: first Brazilian report

Joshua Araújo Viana[1,2], Eduardo Kaiser Ururahy Nunes Fonseca[1,2], Márcio Valente Yamada Sawamura[1,2]

A 50-year-old man with a previous neurological deficit presented fever, axillary discomfort in the upper right limb, and a convulsive episode 24 hours after application of the Pfizer-BioNTech COVID-19 vaccine in the right arm. He underwent chest computed tomography (Figures 1. A and B) on the same day, which evidenced axillary fat stranding associated with lymph node enlargement.

Lymphadenopathy was one of the most frequent adverse effects reported after vaccination with the Pfizer-BioNTech and Moderna COVID-19 vaccines, and its imaging findings are well-described.[1-3]

The Brazilian medical community may have little familiarity with these findings since the Pfizer vaccine was introduced in the country only in early May.

Such findings may be of concern if misinterpreted as suspicious, particularly in oncologic patients.[1-3] Physicians should be aware of the possible occurrence of lymphadenopathy and inquire patients about their recent vaccination. In some cases, such as the patient in question (Figures 1. C and D), comparisons with other recent imaging exams can assist in distinguishing metastatic or reactive axillary lymph nodes. In addition, recent studies reinforce that lymphadenopathy is more commonly described on the same side as the vaccine application site, a fact that could be a clue for its diagnosis.[1-3]

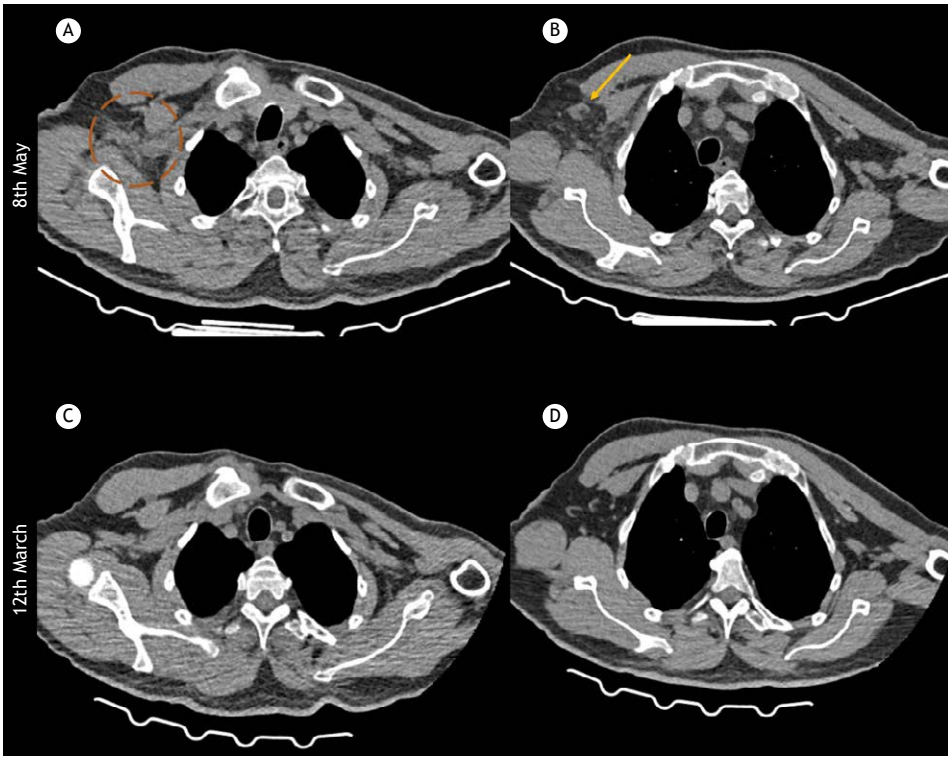

Figure 1. A and B - Axial CT hours after the vaccine, indicating enlarged lymph nodes (arrow) associated with regional fat stranding (circle) in the ipsilateral axillary region of the injection site; C and D – Previous CT of the same patient, approximately 60 days prior to vaccination, showing small axillary lymph nodes with preserved fatty hilum.

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ISSN 1806-3756

Time course of exercise capacity in patients recovering from COVID-19-associated pneumonia. Authors' reply

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"I have come here to bury Caesar, not to praise him."
William Shakespeare. Julius Caesar, Act 3, Scene *2*

The early phase of the COVID-19 pandemic forced health systems to undertake continuous organizational changes, often more empiric than evidence-based ones.[1] In addition, rehabilitation professionals had to revise programs in a newly changed environment: spaces, equipments, and aids could not be used as in the past; the professionals could not wear their usual "clothes," but had to wear personal protective equipment.[2] This was a process that required time and a solid scientific basis to guarantee adequate treatment.

The pandemic has been associated with an increase of "last-minute" and retrospective publications with a high level of retractions.[3] However, we could not wait for well-designed prospective randomized controlled trials before starting interventions in daily clinical practice. Therefore, we believe that, despite all the inbuilt limitations of observational, uncontrolled, or retrospective studies, the scientific community had to answer the emerging questions posed by the pandemic, including those in the field of rehabilitation, in order to make use of the available data timely.

That is why we thank Borghi-Silva et al.[4] for their editorial, who showed interest in our study[5] and gave constructive criticism, most of which we agree with. We were and are well aware of the unavoidable limitations of that[5] and other studies[6] published by our group on that topic and will not annoy the readers in an attempt to "defend" our work.

However, we are happy to provide a few answers and comments. Comparing the inpatients undergoing rehabilitation with those discharged, the former group presented with lower six-minute walk distance (6MWD) in % of predicted values [median = 65% (IQR, 58-82) vs. 98 (IQR, 74-109); p = 0.0007)]; higher oxygen desaturation ($p < 0.0001$), and lower Short Physical Performance Battery scores ($p = 0.03$), with no other differences (unpublished data). Patients undergoing rehabilitation might have experienced faster/better functional recovery, although all of the enrolled subjects with a 6MWD < 75% of predicted improved, even those not undergoing rehabilitation.

We find the issue raised by Borghi-Silva et al.[4] regarding the best way to assess physical performance other than the 6MWD used in our study very interesting.[5] Recently, we have reviewed the types of measures used in order to assess physical performance in COVID-19 survivors.[6] We found that a wide variety of tests have been used, making comparisons among the studies difficult. All such measures show impairment in physical performance in those patients. However, the quality of most of the studies was considered low or fair.[6] Therefore, we agree on the need to standardize a common battery of evaluations to improve the characterization of functional limitations of patients.

Another issue discussed in the editorial[4] and in our study[5] was the need to follow up those patients strictly. In addition to presenting with lung function damage, they might show impairment in their physical performance six months after the infection.

In conclusion, we thank again Borghi-Silva et al.[4] for their stimulating comments, addressing at least two important issues in the COVID-19 era: the need of rigorous methodology in scientific research (analysis and reporting of data even in emergency conditions) and the attention that clinicians must pay to long-term functional limitations associated with COVID-19 (and the measures to assess them).

"Things without all remedy should be without regard: what's done is done."
William Shakespeare. Macbeth. Act 3, Scene 2.

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The Jornal Brasileiro de Pneumologia (J Bras Pneumol, Brazilian Journal of Pulmonology) ISSN-1806-3756, published once every two months, is the official organ of the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Society) for the publication of scientific papers regarding Pulmonology and related areas.

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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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(Assistente Editorial - Luana Campos)

Online submission of articles:

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