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## HIGHLIGHT

**Use of a chest X-ray score to predict the clinical course of COVID-19**

**Dyspnea in patients with bronchiectasis**

**High-resolution computed tomography in interstitial lung disease**

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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# Expediente

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# Contents

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# Contents

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# Dyspnea in bronchiectasis: a complex symptom of a complex disease

Adrian Martinez-Vergara[1], Rosa Maria Girón-Moreno[1], Miguel Angel Martínez-García[2]

Dyspnea, as a symptom, and bronchiectasis, as a syndrome, are both complex, heterogeneous entities.[1,2] The pathophysiological mechanisms that explain the presence and evolution of dyspnea in patients with bronchiectasis are quite diverse in origin. They can act synchronously (multifactorial dyspnea), are dynamic (changing over time), and can have different effects in different patients. In addition, dyspnea is difficult to quantify because it is, by definition, a subjective symptom. However, in most studies of bronchiectasis, dyspnea is mentioned as one of the factors most often associated with greater severity and poorer prognosis of the disease (determined by multidimensional scoring systems), as well as with worse quality of life scores.[3]

One common feature of various airway diseases, including bronchiectasis, is that the determination of dyspnea severity provides information that expands and complements findings regarding the nature and impact of the disease on the basis of clinical, radiological, and pulmonary function variables. That might be explained by the unexpectedly weak correlation that the severity of dyspnea shows with deterioration in lung function and the radiological extent of bronchiectasis.[4] In addition, each of the variables most commonly used for the overall evaluation of pulmonary function is usually associated, in varying degrees, with the severity of dyspnea. Each of those pulmonary function variables are therefore probably related, to a greater or lesser extent, to one of the various mechanisms that cause dyspnea in bronchiectasis, such as bronchial obstruction, mucus plugging, pulmonary hyperinflation, parenchymal destruction, and even dyspnea associated with individual comorbidities.[5]

In the present issue of the *Jornal Brasileiro de Pneumologia*, the article authored by Nucci et al.[6] clearly illustrates the complexity of dyspnea in bronchiectasis. The authors analyzed the relationship that dyspnea has not only with various markers of bronchiectasis severity and prognosis but also with several pulmonary function parameters. The analysis involved the rigorous selection of 114 patients with bronchiectasis in whom other diseases that cause dyspnea had been ruled out. Corroborating previous studies, the authors concluded that the severity of dyspnea correlates only weakly with pulmonary function variables and with the radiological extent of bronchiectasis.[4] In other words, none of the functional and radiological variables analyzed achieved, on their own, any significant diagnostic capacity to distinguish patients with fewer symptoms from those with more symptoms (stratified on the basis of a modified Medical Research Council scale score > 1); that is, none of the variables studied had an area under the ROC curve > 0.8 (i.e., excellent diagnostic value), even if we consider the upper limits of their confidence intervals. This finding supports the notion that a single variable (objectively measured) is incapable of evaluating the (subjective) impact of symptoms (dyspnea) in a particular patient.

Another interesting feature of the study conducted by Nucci et al.[6] is the thorough study of respiratory function in all of the patients, which included spirometry, plethysmography, and DLCO measurement. That allowed the authors to determine not only the severity of airway obstruction but also the presence of any restrictive pattern, air trapping, hyperinflation, and even parenchymal impairment or the presence of small airway disease. It is notable that all of these functional variables, when analyzed separately, are capable of distinguishing patients with more symptoms from those with fewer symptoms, although the diagnostic power was modest (area under the ROC curve between 0.62 and 0.68). However, the correlation between individual functional variables was not very high either, confirming once again that each of the functional variables measured provides additional, independent information about the severity of dyspnea in individual patients because those variables are probably associated with one of the pathophysiological mechanisms involved.[5] This finding is interesting because it could clarify some therapeutic aspects of dyspnea. This reminds us of various studies of COPD suggesting that improvements in dyspnea due to the use of bronchodilators are primarily associated with a reduction in air trapping and in pulmonary hyperinflation, which are often found in patients with COPD,[7] as well as in various patients with bronchiectasis.[6] Despite the widespread use of bronchodilators in patients with bronchiectasis, we are continually startled, even after two decades studying this disease, by the paucity of scientific literature on the clinical effects of this type of treatment for bronchiectasis. That is even more notable when compared with the abundance of studies on bronchodilators in other chronic inflammatory airway diseases, such as COPD and asthma—diseases that are closely related to bronchiectasis. Finally, Nucci et al.[6] also found a negligible association between the severity of dyspnea and structural changes on CT scans, probably because the radiological scales generally used in bronchiectasis do not include parameters such as the presence of emphysema, bullae, mucus plugs,

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atelectasis, or other structural lesions that can increase the severity of dyspnea.

It would be interesting to evaluate, perhaps via a further analysis of the data provided by Nucci et al.,[6] the best combination of (simultaneous or sequential) measurements of the different functional variables that would make it possible to predict or assess more accurately the severity of dyspnea in patients with bronchiectasis. This would also involve, however, an evaluation of the costs and availability of those pulmonary function tests at different centers. Finally, the addition of other variables, such as those that measure functional exercise capacity (particularly the six-minute walk distance and incremental shuttle walk distance), could provide valuable complementary information to studies regarding dyspnea in bronchiectasis.[8]

Once again, we are facing an extremely complex disease: bronchiectasis. The severity of the disease needs to be determined as objectively as possible, although other dimensions also need to be taken into account, including its biological activity (biomarker levels) and how well patients live with the disease (quality of life).[1] Such variables will provide further complementary information and contribute to a more realistic evaluation of the overall impact that bronchiectasis has on a given patient. New studies on the subject are likely to be necessary in the future.

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# Interstitial lung diseases: the role of HRCT in in the era of antifibrotic therapy

Alfredo Nicodemos Cruz Santana[1,2], Flavia de Souza Nunes Soares[3,4]

Interstitial lung diseases (ILD) typically represent a major challenge for pulmonologists. That challenge has various facets, such as defining the diagnosis, searching for a possible treatment, and deciding what to do if there is an unfavorable response to the initial treatment, especially in the era before antifibrotic agents.[1-6] Therefore, the Brazilian Thoracic Association has always emphasized the proper diagnosis and treatment of ILD, as well as focusing on advances in this field of pulmonology.[7,8]

In the area of ILD, The use of HRCT has come to play an increasingly more important role in the diagnosis of ILD and even in the planning of its treatment. If an HRCT scan shows a pattern consistent with usual interstitial pneumonia (UIP), there is no need for a lung biopsy to define a diagnosis of idiopathic pulmonary fibrosis (IPF), assuming that the clinical and biochemical findings are consistent with the diagnosis.[9] In addition, HRCT is an important tool for the diagnosis of hypersensitivity pneumonitis (HP), as recently stated in one international guideline for clinical practice.[10]

The use of HRCT plays a role in the management of progressive fibrosing ILD (PF-ILD).[3] It is of note that the pattern of findings on HRCT was selected as one of the selection criteria in a study of the use of an antifibrotic agent in the treatment of PF-ILD.[3] The findings should show reticulation with traction bronchiectasis (with or without honeycombing) and an extent > 10%, although additional findings (including ground-glass opacity, a predominance of alterations in the upper lobes or in the peribronchovascular region, mosaic attenuation, air trapping, and centrilobular nodules) were not criteria for exclusion. In addition, an HRCT finding of an increased extent of fibrotic alterations was one of the criteria to define ILD progression despite the initial treatment (i.e., an unfavorable response to previous treatment).

In a study published in the current issue of the *Jornal Brasileiro de Pneumologia*, Almeida et al.[11] evaluated the prevalence of three different patterns of UIP (typical, probable, and indeterminate) and the prognostic role of HRCT in 244 patients with ILD followed at a referral center between January of 2012 and January of 2016. The diagnosis of ILD was based on the clinical, radiological, and histopathological data (surgical lung biopsy was performed in 28.2% of the patients). Of the 244 subjects evaluated, 52.5% were male, 29.1% had a history of smoking, 9.0% had COPD, 29.1% had diabetes, 18.9% had heart disease, and 17.6% had connective tissue disease. In the sample as a whole, the mean FVC was 70% of the predicted value. On HRCT, the typical UIP pattern was observed in 106 patients (most of whom had IPF or HP); the probable UIP pattern was observed in 114 patients (most of whom had connective tissue disease or IPF); and the indeterminate UIP pattern was observed in 24 patients (most of whom had connective tissue disease or desquamative interstitial pneumonia). The mortality rate was higher among the patients with a UIP pattern on HRCT, regardless of age, gender, smoking history, comorbidities, or pulmonary function.[11]

The study by Almeida et al.[11] had some noteworthy limitations. The authors did not evaluate the possible prognostic role of pulmonary function testing during the clinical follow-up period. They were also unable to determine the impact that ILD treatment had on mortality. In addition, the proportion of patients who could be categorized as having PF-ILD, a novel diagnosis of great clinical importance,[3] was not reported.

Although IPF is considered a rare disease, with a prevalence of 0.5-27.9 cases/100,000 population and an incidence of 0.22-8.8 cases/100,000 population, it is a common indication for lung transplantation.[12] That corroborates the impact that IPF has on the prognosis of patients and on the use of highly complex health care services.

In conclusion, the study by Almeida et al.[11] emphasizes the importance of HRCT findings in ILD and shows that the presence of UIP patterns on HRCT shortens survival, regardless of other factors. Therefore, patients with ILD in whom a UIP pattern is seen on HRCT should undergo clinical follow-up evaluations more frequently, should be evaluated more attentively regarding the use of antifibrotics (as in cases of IPF or PF-ILD), and should be considered potential candidates for lung transplantation (especially those with an FVC < 80% of the predicted value or an $SpO_2$ < 89% during a six-minute walk test).

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# COVID-19: chest X-rays to predict clinical outcomes

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The pandemic caused by the viral agent SARS-CoV-2 has pushed health care systems to the limit worldwide, making their management and even resource rationing the cornerstone in the management of the crisis.[1] Although most patients are asymptomatic or oligosymptomatic, a fraction of those will require hospitalization due to systemic repercussions or respiratory symptoms, and some of those will present with rapid clinical worsening, requiring invasive ventilation and treatment in the ICU.[2] The search for biomarkers that help predict severe outcomes is therefore valuable.

In this issue of the *Jornal Brasileiro de Pneumologia*, Baratella et al.[3] present an interesting retrospective study that aims to evaluate the potential of a simple semiquantitative visual score based on chest X-rays (CXR), as well as of clinical and laboratory parameters, for the prediction of severe outcomes (need for noninvasive ventilation, need for intubation, or death) in patients with COVID-19. The data presented in that study show a possible role of CXR in helping stratify the risk of evolution to severe disease, corroborating data from previous studies in the literature.[4,5] In the study by Baratella et al.,(3) the absence of a severe outcome was significantly associated with a lower proportion of patients with high scores on baseline CXR, and patients with normal baseline CXR results required no noninvasive ventilation or intubation, nor did they die.

Other studies have evaluated the potential of simple CXR scores alone or in association with other clinical and laboratory parameters to predict the outcome in COVID-19. CXR was tested as a prognostic predictor in adults and middle-aged patients by Toussie et al.,[4] and their score was useful in predicting hospital admission after adjusting for demographic factors and comorbidities, and it was also an independent predictor of intubation in hospitalized patients. Schalekamp et al.[2] developed a model for prediction of severity involving clinical and laboratory parameters and a semiquantitative score; higher scores were associated with critical outcomes. In addition, the authors showed that the distribution of the findings might be associated with a worse prognosis; patients with predominantly central or diffuse involvement, as well as those with bilateral pulmonary involvement, were more likely to present with critical outcomes than were those with peripheral distribution or unilateral involvement.[2] Another risk calculator using multiple clinical and laboratory parameters was able to predict severe outcomes, the presence or absence of abnormalities on CXR being considered one of the parameters.(5) Similarly, other studies have shown the potential for quantifying pulmonary involvement on CXR in order to predict the risk of complications in patients with COVID-19.[6]

The use of automated tools using artificial intelligence algorithms is also noteworthy, showing satisfactory agreement between the evaluation of radiologists and of deep learning-based artificial intelligence regarding opacities and disease extension on CXR.[7]

Although evolution of COVID-19 is variable, the imaging aspects follow a relatively similar timeframe that has already been described for both CXR and chest CT. On CXR, findings peak 10-12 days after the onset of symptoms.[8] Patients who sought medical attention later after the onset of symptoms had higher CXR scores in the study by Toussie et al.[4] For the purpose of clinical application of those risk prediction scores, it would be interesting to adjust the CXR scores to the onset of symptoms in order to standardize the date of CXR acquisition.

A potential disadvantage of the radiographic method would be its low sensitivity for detecting mild or early-stage disease, as well as its lower capacity to define some differential diagnoses, such as pulmonary thromboembolism, when compared with chest CT. However, issues such as cost, accessibility, less exposure to radiation, practicality in reading/applying semiquantitative scores, biosafety (such as greater practicality in disinfecting surfaces), mobility (enabling studies to be carried out at the bedside), and facilitation of performing sequential studies make the inclusion of this method valuable in such risk prediction scores.[9]

The use of imaging methods for COVID-19 screening has been discouraged in most clinical settings; it has generally been reserved for individuals with risk factors and probable disease progression or for those with worsening of symptoms. In those cases, such methods can be used in order to assess aspects such as extension of disease and differential diagnosis.(9) A recent consensus of the Fleischner society regarding imaging studies considered the use of CXR or chest CT in COVID-19 patients, making it clear that, when these studies are indicated, the decision on the method to be used ultimately depends on its availability, local resources, and expertise of professionals.[9] CXR has been recommended as an initial method for evaluating patients in the ER and inpatients.[10-12]

The study by Baratella et al.[3] gives a different perspective on the role of imaging methods in the screening and diagnosis of COVID-19, focusing on the screening of patients

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that can potentially present with complications. Although questions about how and which imaging methods can assist in the diagnosis and monitoring of the evolution of COVID-19 patients have yet to be answered (taking into consideration issues of accuracy, availability of resources, and regional policies), the study by Baratella et al.[3] adds evidence to the fact that CXR, alone or as a part of clinical and laboratory multiparametric scores, can assist in risk stratification for predicting severe outcomes in the initial assessment of patients with COVID-19, with consequent implications for the management of clinical care, beds, and resources.[2,4,5]

## AUTHOR CONTRIBUTIONS

PPTST, KLI and EM: conception and planning of the study; interpretation of evidence; drafting and revision of preliminary and final versions; and approval of the final version.

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# Unilateral elevation of the lung base

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

A 65-year-old male smoker (70 pack-years) presented with a 6-month history of irritating cough and weight loss (10 kg). A chest X-ray showed a right perihilar opacity, with elevation of the ipsilateral lung base (Figure 1).

Unilateral elevation of the lung base (UELB) is the most appropriate term to be used in order to describe this abnormality, because X-rays might not eventually reveal the exact position of the diaphragm. UELB may or may not be accompanied by elevation of the diaphragm. In cases in which the diaphragm is in normal position, there is something between the lung base and the diaphragm (most often infrapulmonary pleural effusion).[1]

UELB can be due to abdominal causes (e.g., subphrenic abscess, gastric distention, colonic interposition, hepatic masses, etc.); causes related to the diaphragm itself (e.g., diseases related to phrenic nerve paralysis, diaphragmatic eventration, diaphragmatic hernias, or diaphragmatic tumors); or thoracic causes (e.g., infrapulmonary pleural effusion, pleural masses, and diseases related to decreased lung volume, such as agenesis, hypoplasia, or atelectasis). Clinical and laboratory findings do not normally help much in the differential diagnosis of UELB; which is basically made by imaging.

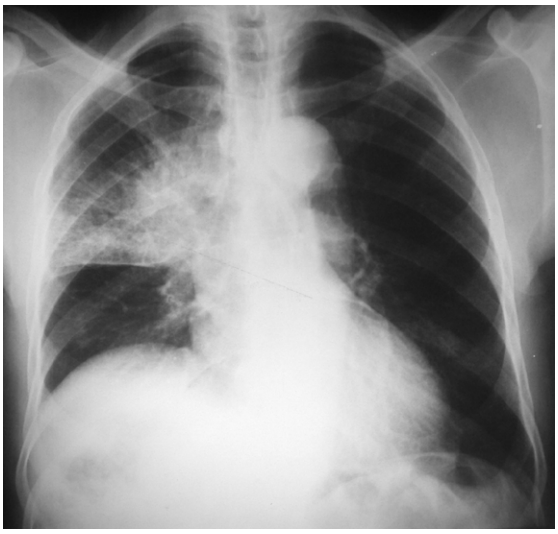

**Figure 1.** Posteroanterior chest X-ray showing an ill-defined right perihilar opacity, with marked elevation of the ipsilateral lung base.

Although the differential diagnosis of UELB can be easily made by CT, ultrasonography, or magnetic resonance imaging (MRI) in most cases, in some situations, the use of simpler methods, such as conventional X-ray imaging, may be sufficient in providing diagnostic certainty.

Infrapulmonary pleural effusion can be diagnosed by horizontal beam X-ray of the chest with the patient in the lateral decubitus position, which demonstrates mobility of the fluid. Unilateral paralysis of the diaphragm caused by phrenic nerve injury can be diagnosed by X-rays obtained during inspiration and expiration or by dynamic tests, such as ultrasonography or MRI, showing immobility of the hemidiaphragm.

In the case of our patient, right diaphragmatic paralysis was confirmed by dynamic MRI, which also revealed a right perihilar mass. Fiberoptic bronchoscopic biopsy of the mass revealed it to be an adenocarcinoma.

Diaphragmatic paralysis occurs when the phrenic nerve is injured as a result of trauma, systemic disease, or neurological disease, causing loss of control of the hemidiaphragms. Symptoms depend on whether one or both hemidiaphragms are affected, on the onset of the paralysis, and on the presence of an underlying lung disease. The differential diagnosis of acquired diaphragmatic paralysis is broad and includes trauma or compression, as well as neurological, muscular, or inflammatory diseases. Unilateral diaphragmatic paralysis is commonly caused by ipsilateral phrenic nerve injury. Currently, the most common cause of unilateral diaphragmatic paralysis is open heart surgery.[2] Another important cause, which was observed in our patient, is phrenic nerve injury due to tumor invasion.

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# Systematic reviews: a brief overview

Natalia Causada Calo[1,2], Juliana Carvalho Ferreira[1,3], Cecilia Maria Patino[1,4]

## SCENARIO

A randomized controlled trial (RCT) was conducted to determine if drug B improves survival when compared with drug A in patients with condition Y. A systematic review (SR) can also answer this same question; however, it is important to differentiate between these study designs.

## THE PROCESS OF A SYSTEMATIC REVIEW

SRs summarize the body of research from primary studies that address a well-defined research question. It also evaluates the quality of the studies and their conclusions using a systematic and reproducible approach.[1] SRs commonly answer questions related to therapy, diagnosis, or prognosis. They are particularly useful when similar studies show conflicting results, when various studies with a small number of participants show inconclusive results, or when practice guidelines are being developed.

The conduct of an SR follows a strict methodological process, which includes the definition of inclusion and exclusion criteria and evaluation of the risk of errors (bias).[1] The process (or "system") for an SR is summarized in Table 1.

First, the PICOT format can be used to define the different components of the research question: the population (P), the intervention or exposure (I), the comparison group (C), the outcome (O), and the type of study design (T). These components will depend on the nature of the study question (intervention, diagnosis, or prognosis). In our hypothetical example, we are interested in comparing the effects of two drugs (interventions) on survival, and the most appropriate study design is an RCT.

Once the question and the detailed study eligibility criteria have been defined, a comprehensive literature search is conducted. This step is elaborate and often requires a librarian who provides the "language" for the search. In contrast to a search that we often conduct as clinicians, in order to conduct an SR, the search has to use clear terms, be comprehensive and reproducible, and be performed across all important medical databases, including the gray literature. Once the search is completed, researchers screen the list of references for eligibility. Typically, two researchers complete this step and the data extraction that follows. A key component of an SR is the evaluation of the quality of the studies included. Different tools are available according to the nature of the question.[2] For RCTs, for example, questions about randomization and allocation concealment are asked. For prognostic studies, it is essential to understand if patient selection is representative.

Once all steps are completed, data are summarized and often analyzed to provide quantitative estimates with their corresponding confidence intervals. This last part corresponds to the meta-analysis, which will be discussed in a forthcoming article. In some cases, an SR does not include a meta-analysis; when this occurs, a transparent report of the methodology should be provided.

## KEY CONCEPTS

- An SR is a summary of the evidence that addresses a well-defined research question in a systematic and reproducible manner.
- One study of interventions, diagnosis, or prognosis alone is unlikely to represent the entirety of the evidence. SRs are useful because they summarize the body of evidence after a comprehensive and reproducible medical literature search and assessment of the risk of bias.

**Table 1.** The process of a systematic review.

| | | |
|---|---|---|
| 1. Definition of the question: PICOT format | Systematic review | Systematic review + Meta-analysis |
| 2. Inclusion and exclusion criteria | | |
| 3. Literature search for studies | | |
| 4. Screening of studies for eligibility | | |
| 5. Data collection from studies | | |
| 6. Assessment of risk of bias of the studies included | | |
| 7. Analysis of results (synthesis) | Meta-analysis | |
| 8. Interpretation of the results | | |
| 9. Conclusions on the estimates | | |

PICOT: P: population; I: intervention/exposure; C: control group or comparator; O: outcome; and T: type of study design.

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- A quantitative analysis (meta-analysis) often accompanies the summary of the evidence, yielding a higher precision in the results than individual studies.

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# Arterial blood gases in the differential diagnosis of hypoxemia

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

## BACKGROUND

Investigation of hypoxemia (low $PaO_2$) invariably benefits from a structured physiological approach based on a careful interpretation of arterial blood gas (ABG) analysis. Determining the underlying mechanism(s) might be particularly challenging when there are multiple potential causes changing over time, either spontaneously or secondary to treatment.

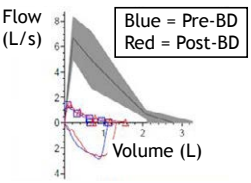
## OVERVIEW

A 71 year-old woman with severe COPD (Figure 1A), GOLD classification B, and modified Medical Research Council scale score 2, presented to the emergency department with worsening dyspnea, productive cough, and abdominal pain. She was confused, lethargic, and hypoxemic ($SpO_2$ = 88% on room air), and presented with mild leukocytosis (12.6 x $10^3$ cells/μL). Inhaled short-acting bronchodilators were optimized, and $O_2$ was administered by nasal cannula (2 L/min). Owing to an unremarkable chest X-ray in the supine position (as per the current pandemic precautions) plus a widened alveolar-arterial $O_2$ pressure gradient [$P(A\text{-}a)O_2$]—Figure 1B—a CT pulmonary angiogram was requested. Despite the absence of pulmonary embolism, an extensive retrocardiac consolidation was observed (Figure 1C). After 7 days of antibiotic therapy, she was discharged on $O_2$ at 1 L/min aiming at a $SpO_2 \approx$ 90-91%. Twenty days later, she returned to the emergency department presenting again with confusion and somnolence; however, her $SpO_2$ was 99%, $O_2$ flow was at 4 L/min, and ABG analysis revealed respiratory acidosis with improved $P(A\text{-}a)O_2$ (Figure 1D). After 3 days on noninvasive ventilation plus $O_2$ at 1 L/min, she was discharged after marked improvement in respiratory acidosis and neurological status.

If $PaO_2$ is substantially lower than alveolar $O_2$ tension ($PAO_2$)—i.e., widened $P(A\text{-}a)O_2$—there are a number of disorders of the lung structure reducing the efficiency of $O_2$ transfer, e.g., diffusion, limitation across the alveolar-capillary membrane (rarely), ventilation-perfusion (V/Q) mismatch, or shunt. In these circumstances, $PaCO_2$ is usually low. Conversely, if $PaO_2$ is reduced in tandem with $PAO_2$ (i.e., normal $P(A\text{-}a)O_2$), $PAO_2$ is low due to reduced inspired $PO_2$ (e.g. altitude) and/or alveolar $CO_2$ tension is increased, suggesting respiratory depression (alveolar hypoventilation).[1,2] The high $P(A\text{-}a)O_2$ in the first ABG analysis (Figure 1B) was secondary to a common cause of V/Q mismatch: an infectious pneumonic consolidation[3]

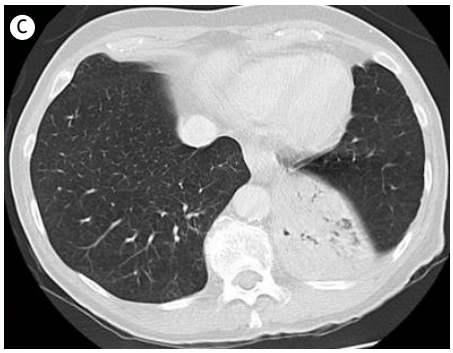
(A)

| | Pre-BD | %predicted | Post-BD | %predicted |
|---|---|---|---|---|
| FVC | 1.12 | 40 | 1.56 | 56 |
| $FEV_1$ | 0.65 | 30 | 0.73 | 33 |
| $FEV_1$/FVC | 0.58 | | 0.47 | |




(B)

| | 1st ED Visit |
|---|---|
| pH | 7.48 |
| $PaCO_2$ (mmHg) | 44.4 |
| $HCO_3$ (mmol/L) | 32.9 |
| $PaO_2$ (mmHg) | 73.5 |
| $SaO_2$ (%) | 95.7 |
| $O_2$ flow (L/min) | 2 |
| $P(A\text{-}a)O_2$ (mmHg) | 67.4 |




(D)

| 2nd ED Visit |
|---|
| 7.35 |
| 72.5 |
| 39.7 |
| 124.0 |
| 98.9 |
| 4 |
| 27.1 |

**Figure 1.** Baseline spirometry (in A) of a 71-year-old woman with a previous diagnosis of COPD who presented at the emergency department with worsening dyspnea and hypoxemia (baseline blood gas analysis in B). A CT pulmonary angiogram revealed pneumonia in the left lower lobe (Figure 1C), which explained an increased alveolar-arterial $O_2$ pressure gradient (expected value, 2.5 + [0.21 × age] = 17.4 mmHg). A few days after the resolution of pneumonia, a second arterial blood gas analysis showed lower alveolar-arterial $O_2$ pressure gradient and hypercapnia, as well as respiratory acidosis induced by the currently excessive high offer of $O_2$ at 4 L/min (in D). BD: bronchodilator; ED: emergency department; $HCO_3$: bicarbonate; and $P(A\text{-}a)O_2$: alveolar-arterial $O_2$ pressure gradient.

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(Figure 1C); in fact, the patient's hypoxemia responded well to a relatively low $FiO_2$, which is not consistent with shunt. ABG analysis also revealed increased bicarbonate levels: when a patient with chronic hypercapnia and showing compensatory bicarbonate accumulation is exposed to a source of a high ventilatory drive (e.g. hypoxemia), $PaCO_2$ may drop down to the normal range; thus, metabolic alkalosis may emerge (Figure 1B).[1] The second ABG analysis showed a different scenario (Figure 1D): at that point in time, the extra source of V/Q mismatch was no longer present, i.e., pneumonia had been resolved. Consequentially, excessively high inspired $O_2$ flows for the improved $P(A\text{-}a)O_2$ increased $O_2$ tension in the alveoli, causing low level of ventilation and inhibiting hypoxic pulmonary vasoconstriction, a well-known cause of hypercapnia (Figure 1D).[4,5]

## CLINICAL MESSAGE

Interpretation of ABG analysis in a hypoxemic patient should consider the clinical history, ongoing treatment, and recent/current inspired $O_2$ flows. The information provided by $P(A\text{-}a)O_2$ should be considered in association with $PaCO_2$ (and pH). A normal $P(A\text{-}a)O_2$ in the presence of hypoxemia signals reduced ambient oxygen or alveolar hypoventilation, shown by elevated $PaCO_2$.

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ORIGINAL ARTICLE

# Characterization of the severity of dyspnea in patients with bronchiectasis: correlation with clinical, functional, and tomographic aspects

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

## ABSTRACT

**Objective:** To characterize a population of patients with bronchiectasis, correlating clinical, radiological, and functional aspects with the severity of dyspnea. **Methods:** This was a cross-sectional study involving adult patients with HRCT-confirmed bronchiectasis, categorized according to the severity of dyspnea (as being mildly or severely symptomatic, on the basis of the modified Medical Research Council scale). We correlated the severity of dyspnea with clinical parameters, functional parameters (spirometry values, lung volumes, and DLCO), and CT parameters. **Results:** We evaluated 114 patients, 47 (41%) of whom were men. The median age (interquartile range) was 42 years (30-55 years). The most common form was idiopathic bronchiectasis. Of the 114 patients, 20 (17.5%) were colonized with *Pseudomonas aeruginosa* and 59 (51.8%) were under continuous treatment with macrolides. When we applied the Exacerbation in the previous year, $FEV_1$, Age, Colonization, Extension, and Dyspnea score, the severity of dyspnea was categorized as moderate in 54 patients (47.4%), whereas it was categorized as mild in 50 (43.9%) when we applied the Bronchiectasis Severity Index. The most common lung function pattern was one of obstruction, seen in 95 patients (83.3%), and air trapping was seen in 77 patients (68.7%). The prevalence of an obstructive pattern on spirometry was higher among the patients with dyspnea that was more severe, and most functional parameters showed reasonable accuracy in discriminating between levels of dyspnea severity. **Conclusions:** Patients with bronchiectasis and dyspnea that was more severe had greater functional impairment. The measurement of lung volumes complemented the spirometry data. Because bronchiectasis is a complex, heterogeneous condition, a single variable does not seem to be sufficient to provide an overall characterization of the clinical condition.

**Keywords:** Bronchiectasis; Dyspnea; Respiratory function tests; Multidetector computed tomography; Plethysmography.

## INTRODUCTION

Bronchiectasis is characterized by abnormal, irreversible dilatation of the airways and can have various causes, including congenital disorders, mechanical bronchial obstruction, respiratory infections, and immunodeficiency.[1-3] It is a chronic, heterogeneous condition of varying severity. It is usually progressive, and the presentation ranges from asymptomatic disease with no functional consequences to advanced disease, such as chronic respiratory failure.[1,2,4]

The interest in and amount of research on bronchiectasis have been increasing in the last decade, leading to advances in the treatment of patients with this disease.[5] In 2008, the Spanish Society of Pulmonology published their first guidelines for the diagnosis and treatment of bronchiectasis.[6] Subsequently, various societies worldwide published their own guidelines; however, recommendations differed considerably across guidelines and different local practices for managing this disease were highlighted.[7-9] More recently, the Brazilian Thoracic Association issued a consensus statement on non-cystic fibrosis bronchiectasis in Brazil.[10] At least some of the differences across guidelines can be explained by the wide variability in the clinical characteristics of the populations studied in different countries. In a recent study conducted in Latin America,[11] the long-term clinical outcomes were similar to those reported in studies conducted in Europe and in the United States.[12-15] However, the authors noted considerable differences between their study population and those evaluated in the latter studies, in terms of age, the etiology of bronchiectasis, the type of bronchial colonization, and the severity of functional impairment.

Because of the great variability in the presentation of bronchiectasis, it is essential that patients with the disease undergo a careful clinical and prognostic assessment.[16]

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Multidimensional scores have been developed to assess disease severity in patients with a diagnosis of non-cystic fibrosis bronchiectasis. Examples of such scores include the **E**xacerbation in the previous year, **F**$EV_1$, **A**ge, **C**olonization, **E**xtension, and **D**yspnea (E-FACED) score[17] and the Bronchiectasis Severity Index (BSI),[13] both of which use a combination of clinical, functional, radiological, and microbiological aspects, with predictive value for mortality, hospital admissions, exacerbations, and quality of life.

There is as yet no single index that can accurately predict disease progression in patients with bronchiectasis. Currently, various phenotypes are recognized as being related to bronchiectasis on the basis of the underlying pathophysiological mechanism of this disease.[18] In addition, there have been improvements in the radiological characterization of patients with bronchiectasis, especially of morphological changes in the (large and small) airways and in the lung parenchyma (consolidation and atelectasis). Such findings can predict clinical outcomes, such as exacerbation, and correlate with the severity of lung involvement, although they do not define the complex, varied clinical presentation of this disease.[19] Therefore, ancillary methods may play an important role in improving the understanding of the heterogeneity of the clinical presentation in patients with bronchiectasis. In patients with bronchiectasis, the use of advanced methods of assessing lung function, such as plethysmography, shows great promise. By identifying specific patterns of air trapping, hyperinflation, and restriction, one can correlate different pathophysiological mechanisms with important characteristics in the management of such patients, such as the fact that dyspnea is closely related to the quality of life of such individuals.[20]

Although some studies have evaluated the use of plethysmography in patients with bronchiectasis,[21] little is known about the role of plethysmography in discriminating between levels of disease severity in such individuals. In addition, those studies are commonly based on European cohorts classically experiencing bronchiectasis that is less severe than that found in Latin American populations.[10,12,22] In the present study, we describe an in-depth assessment of lung function in a sample of individuals diagnosed with bronchiectasis in Brazil. The objective of the present study was to correlate clinical, functional, and radiological parameters with the severity of dyspnea in these individuals in order to determine which ones are most strongly associated with it. Other objectives were to assess lung volumes in relation to spirometry-classified functional patterns and to assess the correlation between functional parameters and a CT score.

## METHODS

This was a cross-sectional study for which data were collected between May of 2014 and October of 2017. We evaluated patients treated at the Bronchiectasis Outpatient Clinic of the University of São Paulo School of Medicine *Hospital das Clínicas*, located in the city of São Paulo, Brazil. The study was approved by the local research ethics committee (Ruling no. SDC 4245/15/072), and all participating patients gave written informed consent.

Patients were sequentially recruited on the basis of the following inclusion criteria: being ≥ 18 years of age; having an HRCT-confirmed diagnosis of bronchiectasis; and having a clinical history of chronic cough with expectoration or recurrent infectious pulmonary exacerbations. Patients who had been diagnosed with cystic fibrosis, asthma, allergic bronchopulmonary aspergillosis, COPD, or active mycobacterial infection were excluded, as were those who had been treated for an infectious exacerbation with oral corticosteroids or antibiotics within the last 30 days, those who had previously undergone lung resection, those with a ≥ 10 pack-year smoking history, those on long-term home oxygen therapy, those with severe, uncontrolled systemic comorbidities, and those who were cognitively unable to perform pulmonary function tests, as well as those who were pregnant.

Clinical data were collected by using an interviewer-administered structured questionnaire designed to obtain information on demographics, severity of dyspnea measured by the modified Medical Research Council (mMRC) scale, frequency of exacerbations in the last 12 months, usual medications, and time since symptom onset. All patients were evaluated for the most common etiologies of bronchiectasis in accordance with our institutional protocol and international guidelines.[23] Data on chronic airway infection were based on sputum examination results in the last 12 months.[24]

Bronchiectasis severity was assessed by the E-FACED score and the BSI,[11,16] both of which are multivariate prognostic scores. The E-FACED score includes six variables (hospitalization in the last year, $FEV_1$, age, colonization with *Pseudomonas aeruginosa*, the radiological extent of bronchiectasis, and the severity of dyspnea, as measured by the mMRC scale), has a maximum score of 9 points, and categorizes disease severity as mild (0-3 points), moderate (4-6 points), or severe (7-9 points).[17] The BSI comprises eight factors: age; body mass index; $FEV_1$; hospital admissions in the last 2 years; exacerbations in the last year; the severity of dyspnea, as measured by the mMRC scale; colonization; and the extent of radiological involvement. The BSI has a maximum score of 25 and also classifies disease severity as mild (0-4 points), moderate (5-8 points), or severe (≥ 9 points).[13]

Participants underwent complete pulmonary function testing (spirometry, plethysmography, and measurement of DLCO). All tests were performed in accordance with the recommendations of the Brazilian Thoracic Association.[25] The reference values for spirometry and plethysmography were those established by Pereira et al.[26] and Neder et al.,[27] respectively. The radiological evaluation consisted of unenhanced HRCT of the chest. Images were acquired in a multislice CT scanner with

160 detector rows (Aquilion Prime; Toshiba Medical Systems Corporation, Otawara, Japan). All scans were assessed by a radiologist specializing in thoracic radiology. The extent and severity of bronchiectasis were classified by the modified Reiff score,[28] the use of which has been previously established in patients with bronchiectasis. The modified Reiff score assesses the number of lobes involved and the degree of the dilatation, with a maximum score of 18 points.[29] Data collection and all procedures were performed on a single day. Study participants, all of whom had previously been diagnosed with bronchiectasis and had been receiving outpatient follow-up care for varying periods, underwent the aforementioned tests in a systematic way and specifically for the purpose of the study.

Patients were divided into two groups on the basis of symptom intensity: those who were mildly symptomatic (mMRC scale score of 0 or 1); and those who were severely symptomatic (mMRC scale score ≥ 2). On spirometry, lung function patterns were classified as obstructive ($FEV_1$/FVC < 0.7 and $FEV_1$ < 80% of predicted) or nonspecific ($FEV_1$/FVC ≥ 0.7 plus $FEV_1$ and FVC < 80% of predicted). On the basis of the Lung volumes, patients were classified as having air trapping (RV/TLC > 40), hyperinflation (TLC > 120% of predicted), or a restrictive lung function pattern (TLC < 80% of predicted).

Our statistical analysis compared clinical, functional, and radiological characteristics between mildly and severely symptomatic patients. The Student's t-test was used for variables with normal distribution, the chi-square test was used for the comparison of proportions, and the Mann-Whitney test was used for variables with non-normal distribution. Spearman's correlation coefficient was calculated to determine the relationship between functional variables and the CT (modified Reiff) score.[28] A ROC curve analysis was performed to determine the accuracy of functional and CT variables to predict the severity of symptoms in patients with bronchiectasis (mildly vs. severely symptomatic patients). Differences were considered statistically significant at $p < 0.05$. The IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA) was used for the statistical analysis.

## RESULTS

We evaluated 208 patients, 94 of whom were excluded, for the following reasons: being on long-term home oxygen therapy (n = 38); having undergone lung resection (n = 18); having a > 10 pack-year smoking history (n = 16); having uncontrolled systemic comorbidities (n = 9); having been diagnosed with asthma (n = 6); being unable to perform pulmonary function tests (n = 6); and having active mycobacterial infection (n = 1). Therefore, the final sample comprised 114 patients.

Table 1 presents data on the demographic and clinical characteristics of the study sample. Most of the patients were female and young (mean age, 42.5 years). The bronchiectasis was idiopathic in most cases, although there were also cases in which it was attributed to ciliary dyskinesia or (to a lesser degree) a previous infection. In general, mildly and severely symptomatic patients were comparable in terms of age, gender, time since diagnosis, etiology, and extent of radiological involvement. However, severely symptomatic patients used respiratory medications more frequently, had a higher number of exacerbations, and had worse lung function, as determined by spirometry, by measurement of lung volumes, and by determination of the DLCO.

More than 80% of the patients had an obstructive pattern on spirometry. The most common finding resulting from the measurement of lung volumes by plethysmography was air trapping, seen in 77 patients (67.5%). Of those 77 patients, 24 (31.1%) also had hyperinflation. In addition, among the patients with a confirmed diagnosis of bronchiectasis, the spirometry and plethysmography results were normal in approximately 5% and 7%, respectively. The prevalence of an obstructive pattern on spirometry was higher in the severely symptomatic group than in the mildly symptomatic group (Table 2).

Figure 1 presents the results of the ROC curve analysis of the accuracy of various functional and CT parameters in discriminating between mildly and severely symptomatic patients with bronchiectasis. Spirometric and plethysmographic parameters showed reasonable accuracy in the symptomatic classification of these patients. The most accurate spirometric parameters (Figure 1A) were $FEV_1$—area under the curve (AUC) = 0.684—and $FEF_{25-75\%}$ (AUC = 0.677), whereas the most accurate plethysmographic parameters (Figure 1B) were RV/TLC (AUC = 0.682) and RV (AUC = 0.625). Similarly to the spirometric and plethysmographic parameters, DLCO was able to identify patients who were more severely symptomatic (AUC = 0.684), unlike the CT score,[28] which showed no discriminatory power (AUC = 0.421; Figure 1C).

Patients with bronchiectasis were divided into three groups on the basis of the lung function patterns seen on spirometry, and, subsequently, the patients in each group were classified on the basis of the patterns obtained by measurement of lung volumes by plethysmography. There was a considerable degree of disagreement between spirometry and plethysmography findings, as shown in Table 3. Of the patients who had normal spirometry, 67% had plethysmographic abnormalities. A nonspecific lung function pattern on spirometry was seen in 12 patients (11.4%); however, in only one of those patients was a reduction in TLC confirmed by plethysmography. In addition, patients with an obstructive pattern predominantly had air trapping or hyperinflation on plethysmography.

Table 4 presents the data on correlations between the modified Reiff score and the functional variables assessed in the patients with bronchiectasis. Various spirometric and plethysmographic parameters showed

**Table 1.** Demographic data and clinical characteristics of the patients with bronchiectasis.[a]

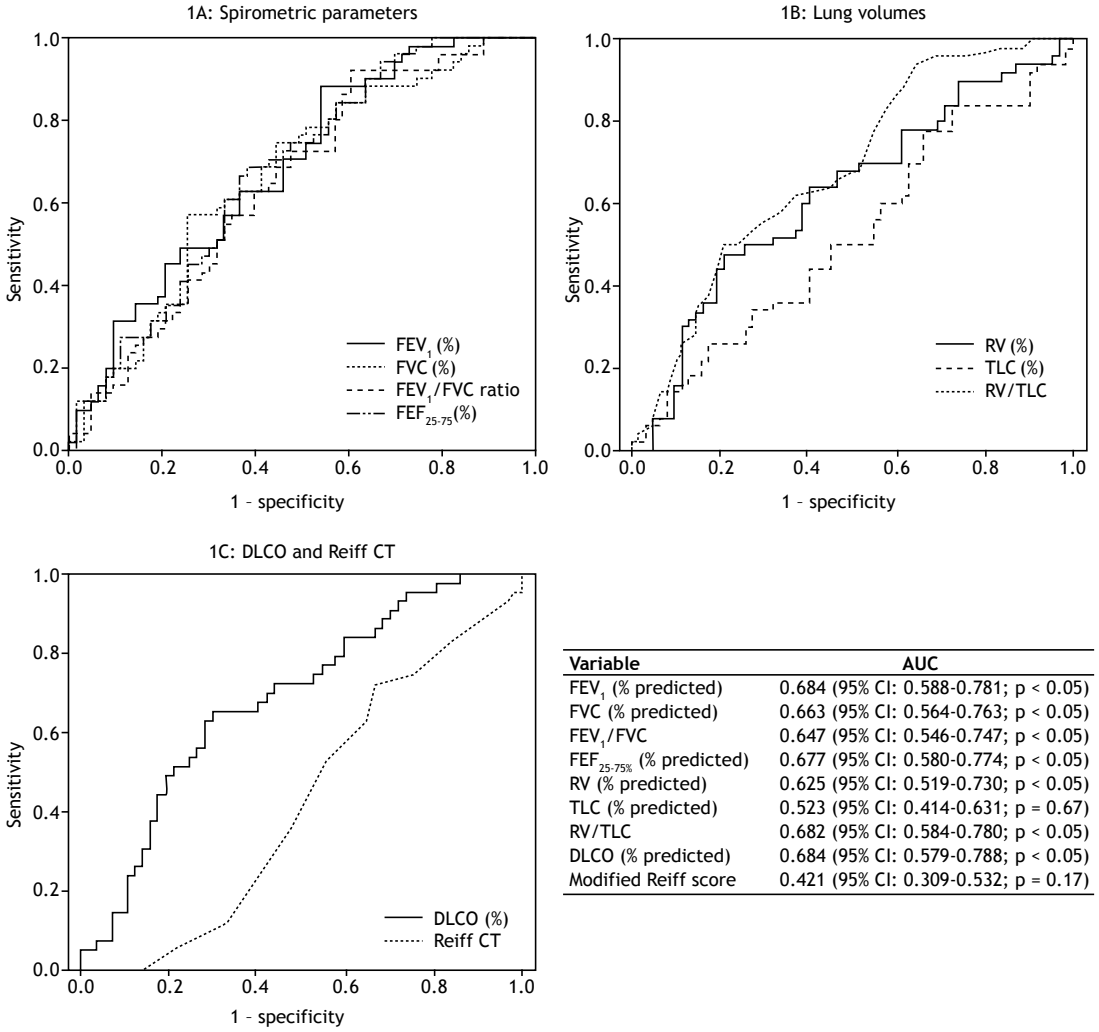
| Variable | Total (N = 114) | Mildly symptomatic (n = 63) | Severely symptomatic (n = 51) | p |
|---|---|---|---|---|
| Male gender | 47 (41) | 29 (46) | 18 (35) | 0.247* |
| Age, years | 42 (30-55) | 41 (27-53) | 47 (34-57) | 0.167† |
| BMI, kg/m$^2$ | 24.4 ± 4.8 | 23.4 ± 4.3 | 25.7 ± 5.1 | 0.009§ |
| Time since diagnosis, years | 11 (4-16.3) | 8 (4-16) | 7 (3-17) | 0.526† |
| Exacerbation | 1 (0-2) | 0 (0-1) | 1 (0-2) | 0.005† |
| Colonization | | | | |
| *Pseudomonas aeruginosa* | 20 (17.5) | 9 (14.2) | 11 (21.5) | 0.346* |
| Other | 8 (7.0) | 6 (9.6) | 2 (3.9) | |
| None | 86 (75.5) | 48 (76.2) | 38 (74.6) | |
| Medications being used | | | | |
| Macrolides | 59 (51.8) | 29 (46.0) | 30 (58.8) | 0.037* |
| Inhaled corticosteroid | 24 (21.1) | 14 (22.2) | 10 (19.6) | |
| Long-acting $\beta_2$ agonist | 7 (6.1) | 2 (3.1) | 5 (9.8) | |
| Inhaled antibiotic | 4 (3.5) | 1 (1.5) | 3 (5.8) | |
| Hypertonic saline | 4 (3.5) | 3 (4.7) | 1 (1.9) | |
| Etiology | | | | |
| Idiopathic | 39 (34.2) | 18 (28.5) | 21 (41.1) | 0.785* |
| Ciliary dyskinesia | 21 (18.4) | 14 (22.2) | 7 (13.7) | |
| Post-infectious | 19 (16.7) | 11 (17.4) | 8 (15.6) | |
| Bronchiolitis | 14 (12.3) | 8 (12.6) | 6 (11.7) | |
| CTD | 6 (5.3) | 3 (4.7) | 3 (5.8) | |
| Immunodeficiency | 4 (3.5) | 3 (4.7) | 1 (1.9) | |
| Other | 11 (9.6) | 6 (9.5) | 5 (9.8) | |
| Lung function | | | | |
| $FEV_1$, % predicted | 48.7 ± 19.81 | 54.66 ± 21.68 | 41.54 ± 14.37 | < 0.001§ |
| FVC, % predicted | 70 ± 17.17 | 74.55 ± 17.80 | 64.9 ± 14.84 | 0.002§ |
| $FEV_1$/FVC | 0.57 ± 0.14 | 0.6 ± 0.15 | 0.52 ± 0.11 | 0.003§ |
| $FEF_{25-75\%}$, % predicted | 27 (11-36) | 25 (13-49) | 14 (9-27.4) | 0.001† |
| TLC, % predicted | 107.0 ± 17.1 | 106.1 ± 16.4 | 108.0 ± 18.0 | 0.573§ |
| RV, % predicted | 201.0 ± 58.0 | 190.7 ± 57.5 | 214.1 ± 56.6 | 0.034§ |
| RV/TLC | 53.0 ± 10.3 | 49.9 ± 10.7 | 56.5 ± 8.6 | < 0.001§ |
| DLCO, % predicted | 70.0 ± 26.4 | 77.6 ± 26.9 | 60.5 ± 22.5 | 0.001§ |
| Modified Reiff score | 7 (7-11) | 7 (4-11) | 8 (6-11) | 0.131† |
| Prognostic scores | | | | |
| E-FACED | | | | |
| Mild disease | 52 (45.6) | 49 (77.8) | 3 (5.9) | < 0.001 |
| Moderate disease | 54 (47.4) | 14 (22.2) | 40 (78.4) | |
| Severe disease | 8 (7.0) | 0 (0) | 8 (15.7) | |
| BSI | | | | |
| Mild disease | 50 (43,9) | 37 (58,7) | 13 (25,5) | 0.001 |
| Moderate disease | 42 (36,8) | 19 (30,2) | 23 (45,1) | |
| Severe disease | 22 (19,3) | 7 (11,1) | 15 (29,4) | |

BMI: body mass index; CTD: connective tissue disease; E-FACED: Exacerbation in the previous year, $FEV_1$, Age, Colonization, Extension, and Dyspnea; and BSI: Bronchiectasis Severity Index. [a]Values expressed as n (%), as mean ± SD, or as median (interquartile range). *Chi-square test. †Mann-Whitney U test. §Student's t-test.

a correlation with the modified Reiff score,[28] RV/TLC being the most strongly correlated.

## DISCUSSION

In the present study, we present an extensive characterization of clinical, functional, and radiological parameters in 114 patients with bronchiectasis and report the impact of those parameters on the severity of dyspnea. Patients who were more severely symptomatic had experienced a higher number of exacerbations in the previous year, used respiratory medications more frequently, and had worse lung function. An obstructive lung function pattern was the most common finding in this population, being more prevalent among severely symptomatic patients. Various functional parameters




| Variable | AUC |
|---|---|
| $FEV_1$ (% predicted) | 0.684 (95% CI: 0.588-0.781; p < 0.05) |
| FVC (% predicted) | 0.663 (95% CI: 0.564-0.763; p < 0.05) |
| $FEV_1$/FVC | 0.647 (95% CI: 0.546-0.747; p < 0.05) |
| $FEF_{25-75\%}$ (% predicted) | 0.677 (95% CI: 0.580-0.774; p < 0.05) |
| RV (% predicted) | 0.625 (95% CI: 0.519-0.730; p < 0.05) |
| TLC (% predicted) | 0.523 (95% CI: 0.414-0.631; p = 0.67) |
| RV/TLC | 0.682 (95% CI: 0.584-0.780; p < 0.05) |
| DLCO (% predicted) | 0.684 (95% CI: 0.579-0.788; p < 0.05) |
| Modified Reiff score | 0.421 (95% CI: 0.309-0.532; p = 0.17) |

**Figure 1.** Accuracy of functional parameters and a CT score in discriminating between patients who were severely symptomatic and those who were mildly symptomatic with dyspnea. AUC: area under the ROC curve; and Reiff CT: modified Reiff score.

were related to the severity of dyspnea. On the basis of our results, we can also state that spirometry alone often fails to provide important information, information that can be complemented by data from complete pulmonary function testing.

We observed that most functional measures (spirometric and lung volume parameters) were associated with the severity of dyspnea, especially variables such as $FEV_1$, RV/TLC, and DLCO, all of which showed better discriminatory power than did other variables. However, those variables showed varying levels of correlation, which suggests that no single functional parameter is sufficiently robust to characterize the intensity of dyspnea in patients with bronchiectasis. The measurement of dyspnea in patients with chronic airway disease is an important prognostic predictor, as has been demonstrated in previous studies involving patients with bronchiectasis[12,13] and patients with COPD.[28] In a large study characterizing a population of patients with a diagnosis of bronchiectasis, the authors did not assess the correlation between the severity of dyspnea and functional parameters.[30] The characterization of dyspnea is a complex process and may be related to various factors in patients with bronchiectasis, as we have recently demonstrated during the validation of a symptom score in this population.[31] Therefore, various factors should be taken into consideration for a careful assessment of the determinants affecting the characterization of dyspnea in patients with bronchiectasis.

In our sample, most patients had an obstructive pattern on spirometry and signs of air trapping on plethysmography. However, previous studies differ regarding this prevalence. Habesoglu et al.[32] performed spirometry in 304 patients with bronchiectasis and demonstrated that only 47.4% of the patients had an obstructive lung function pattern, whereas 20.8% had normal spirometry results. Recently, two studies confirmed the high prevalence of air trapping among patients with bronchiectasis.[33,34] Radovanovic et

**Table 2.** Functional patterns in patients with bronchiectasis, as determined through analysis of spirometry and lung volume data.[a]

| Variable | Total | Mildly symptomatic | Severely symptomatic | p |
|---|---|---|---|---|
| Spirometry | | | | |
| Obstruction | 95 (83.3) | 48 (76.2) | 47 (92.2) | |
| Nonspecific | 13 (10.5) | 9 (14.3) | 4 (7.8) | 0.03 |
| Normal | 6 (5.2) | 6 (9.5) | 0 (0.0) | |
| Plethysmography* | | | | |
| Air trapping (A) | 76 (67.8) | 40 (63.4) | 36 (70.6) | |
| Hyperinflation (H) | 1 (0.9) | 1 (1.6) | 0 (0.0) | |
| A + H | 25 (22.32) | 12 (19.0) | 14 (27.4) | 0.23 |
| Normal | 8 (7.1) | 7 (11.1) | 1 (2.0) | |
| Restriction | 1 (0.9) | 1 (2.6) | 0 (0.0) | |
| Mixed obstruction and restriction | 1 (0.9) | 1 (2.6) | 0 (0.0) | |

[a]Values expressed as n (%). *Two patients (1.8%) had no data because of technical problems during the procedure.

**Table 3.** Information provided by measurement of lung volumes in relation to spirometry-classified functional patterns (n = 112).[a]

| Spirometry | Lung volumes |
|---|---|
| Normal (n = 6) | Air trapping, n = 1 (17%)<br>Hyperinflation, n = 1 (17%)<br>Air trapping + hyperinflation, n = 2 (33%)<br>Normal, n = 2 (33%) |
| Obstruction (n = 94) | Air trapping, n = 65 (69%)<br>Air trapping + hyperinflation, n = 22 (24%)<br>Restriction, n = 1 (1%)<br>Normal, n = 6 (6%) |
| Nonspecific (n = 12) | Air trapping, n = 11 (92%)<br>Restriction, n = 1 (8%) |

[a]One patient in the obstruction group and one patient in the nonspecific group had no data on lung volumes because of technical problems during the procedure.

**Table 4.** Correlation between functional parameters and the modified Reiff score.

| Variable | Modified Reiff score* |
|---|---|
| $FEV_1$, % predicted | −0.343† |
| FVC, % predicted | −0.348† |
| $FEV_1$/FVC | −0.232‡ |
| $FEF_{25-75\%}$, % predicted | −0.303† |
| RV, % predicted | 0.247† |
| TLC, % predicted | 0.012 |
| RV/TLC | 0.356† |

*Spearman's correlation coefficient. †$p < 0.05$. ‡$p < 0.01$.

al.[33] demonstrated the presence of air trapping in 70.2% of their sample, whereas an obstructive pattern was present in only 41.1%. This variability in the identification of patterns on pulmonary function testing can be explained by the different characteristics of the populations studied. Our study sample was characterized by a significant number of patients who were more severely symptomatic and had worse lung function. In populations with milder disease, methods for assessing lung homogeneity (lung clearance index) and the small airways (oscillometry) may even be more sensitive than are traditional methods.[34,35]

The various methods of assessing lung function collect complementary information and can discriminate between different pathophysiological processes in the same patient. When we performed a complete functional assessment, many of the patients classified as normal or as having a nonspecific lung function pattern on spirometry could actually be identified as having air trapping or hyperinflation on plethysmography. The disagreement between spirometric and lung volume parameters is a relevant issue, because, as shown by Martínez-García et al.,[36] obstruction in bronchiectasis is a factor clearly distinct from lung hyperinflation. Obstruction is mainly related to bronchial wall thickening and secretion in the large airways, as proposed by Roberts et al.,[37] whereas hyperinflation is more strongly related to small airways involvement. In addition, plethysmographic parameters such as air trapping, as well as reduced DLCO, are more strongly associated with a worse prognosis in bronchiectasis than are spirometric parameters.[33] Finally, these measures may also behave differently in terms of bronchodilator response, being tools that are more sensitive and characterizing a subgroup with a better clinical course or more favorably affected by specific therapeutic interventions.[33,34]

To our knowledge, ours is the first study to perform a complete functional characterization of a population sample of individuals diagnosed with non-cystic fibrosis bronchiectasis in Brazil and to assess the association of functional, clinical, and radiological variables with the presence of dyspnea. Some studies have characterized populations of patients with bronchiectasis in Brazil, although many of those studies were retrospective and assessed a limited number of parameters. In 1998, Bogossian et al.[38] studied 314 patients with bronchiectasis, comparing symptoms, lung function, and location of bronchiectasis between those with bronchiectasis due to tuberculosis sequelae and those with bronchiectasis of other etiologies. Patients with bronchiectasis due to tuberculosis sequelae were characterized as experiencing more significant functional limitation and having bronchiectasis that was

predominantly located in the upper lobes and on the right side. In 2003, Moreira et al.[39] studied the profile of a population of 170 patients with bronchiectasis, comparing those who received clinical treatment and those who received surgical treatment, in terms of symptoms, bronchial colonization, etiology, and spirometry data. Patients who underwent surgical resection were those with more well preserved lung function, indicating that baseline functional status can even have an impact on the choice of treatment. Subsequently, Faria et al.[40] characterized a broad sample of patients with bronchiectasis, reporting that an obstructive pattern was the most common finding in those individuals, albeit at a lower proportion than that found in our population (43.5% vs. > 80%). However, that study[40] did not consider lung volume measurements, radiological data, or prognostic scores. Finally, in 2015, Lopes et al.[41] primarily assessed the impact of various etiologies of bronchiectasis on clinical findings, lung function data, and CT findings. The authors concluded that etiology, CT score, and severity of dyspnea are independent predictors of $FEV_1$ and DLCO. They also established an association between $FEV_1$ and CT score.

We found that the extent of bronchiectasis seen on CT, as measured by the modified Reiff score,[28] showed weak correlations with functional parameters and with the severity of dyspnea. That finding is in line with those of previous studies. Lynch et al.[42] assessed and reported the relationships that $FEV_1$, FVC, and $FEV_1$/FVC have with the extent of bronchiectasis on CT, the type of bronchiectasis, bronchial wall thickening, air trapping, and mucoid impaction. Dimakou et al.[30] also found that the radiological extent of bronchiectasis correlated only weakly with spirometric parameters. Given the complex, heterogeneous nature of bronchiectasis, the extent to which bronchiectasis affects the respiratory tract should not be assessed by a single method. Chest CT is highly important as a gold standard for the diagnosis of bronchiectasis and provides useful information on potential etiologies. In addition, subjective radiological assessment or radiological assessment by scores, such as the modified Reiff score,[28] allows assessment of regional involvement by bronchiectasis, which is not possible via pulmonary function testing. However, CT scores that include images obtained during inspiration and expiration can be used in order to improve the characterization of small airways involvement and, consequently, of air trapping. By using this methodology, a greater correlation can be found between CT findings and pulmonary function test findings.[42]

Although we systematically characterized a significant sample of patients with a diagnosis of non-cystic fibrosis bronchiectasis, through a detailed description of clinical, functional, and radiological data, our study has some limitations. This was a cross-sectional study, and therefore assessment of causality was not possible; prospective studies are needed in order to determine whether the inclusion of lung volumes in the evaluation adds prognostic value or leads to changes to the follow-up of such patients. In addition, we used a simple CT score that was based solely on the expiratory phase. Therefore, we were unable to assess the correlation between air trapping detected by CT and the various functional parameters measured. Finally, caution should be exercised in extrapolating the results, because the study sample was based on a population with severe lung involvement at a tertiary care hospital and with a lower prevalence of post-infectious etiologies than that commonly found in the Brazilian population.

Patients with bronchiectasis who had more severe dyspnea showed greater functional impairment on spirometry and plethysmography. On spirometry, $FEV_1$, which is a parameter used in the two main prognostic scores in bronchiectasis,[13,17] is an important marker of severity in patients with bronchiectasis. However, spirometry alone is not sufficient to characterize such patients clinically, especially regarding the severity of dyspnea. The measurement of lung volumes by plethysmography can add relevant information because it provides information on small airways involvement and has proven to be a useful complement to the functional assessment in patients with bronchiectasis. Therefore, given the complex nature of bronchiectasis, a combination of clinical, functional, and radiological evaluations is essential for an adequate characterization of the disease, thus making appropriate clinical management and determination of the prognosis.

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ORIGINAL ARTICLE

# Translation and cultural adaptation of the Sleep Apnea Clinical Score for use in Brazil

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Study carried out at the , Universidade do Estado do Rio de Janeiro (RJ) Brasil.

## ABSTRACT

**Objective:** To translate the Sleep Apnea Clinical Score (SACS) into Brazilian Portuguese and adapt it to the cultural setting, validating it for use as a screening method for polysomnography and as a tool to quantify the risk of obstructive sleep apnea syndrome in individuals in Brazil. **Methods:** The translation was performed by two professionals, with subsequent synthesis of the translations. From that version, a back-translation was prepared, revised, and compared with the original by a team of experts. As a pre-test, a consensus version was applied in 20 patients randomly selected from among those under treatment at outpatient clinics at the Piquet Carneiro Polyclinic of the State University of Rio de Janeiro, in the city of Rio de Janeiro, to assess their understanding of the questions. In the validation phase, the Brazilian-Portuguese version of the SACS was applied in 86 patients who subsequently underwent polysomnography, regardless of the SACS result. **Results:** The analyses of the pre-test phase showed that the SACS was easily understood by the patients. In the validation phase, the SACS showed a sensitivity of 45.3% (95% CI: 32.8-58.2%), a specificity of 90.9% (95% CI: 70.8-98.9%), a positive predictive value of 93.5% (95% CI: 79.0-98.2%), a negative predictive value of 36.4% (95% CI: 30.6-42.5%), and an accuracy of 57.0% (95% CI: 45.8-67.6%). **Conclusions:** The Brazilian-Portuguese version of the SACS can be used in order to assess the risk of obstructive sleep apnea syndrome.

**Keywords:** Sleep apnea, obstructive; Polysomnography; Surveys and questionnaires; Translations.

## INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repeated episodes of partial or complete obstruction of the upper airways during sleep, accompanied by a reduction in oxyhemoglobin saturation, together with sleep fragmentation.[1] According to the American Academy of Sleep Medicine, OSAS is defined as the presence of an apnea-hypopnea index ≥ 15 events per hour of sleep, regardless of the presence or absence of symptoms or comorbidities, or an apnea-hypopnea index of 5.0-14.9 events/h with at least one symptom or comorbidity.[2] The main complaints of the patients are sleepiness, nonrestorative sleep, fatigue, insomnia, awakenings with a feeling of asphyxia, habitual snoring, witnessed apnea, mood disorders, and cognitive dysfunction. The most common comorbidities are hypertension, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, and type 2 diabetes mellitus.[2]

Because of the growing recognition of OSAS and its high morbidity and mortality,[3-6] the demand for a diagnosis has increased. The gold standard examination is overnight polysomnography, performed in a sleep laboratory under the supervision of a technician. Therefore, even in high-income countries, there are long waiting lists for this examination.[1,7-9] In attempts to shorten the waiting period and the cost of the OSAS diagnosis, alternative methods have been devised, such methods including the application of questionnaires,[10-13] the use of portable polysomnography equipment for carrying out the examination at home[1,14], and the split-night test, which consists of diagnostic polysomnography and continuous positive airway pressure titration on the same night.[15,16]

One of the instruments developed to assess the risk of an individual having OSAS and the subsequent need to refer the patient for polysomnography is the Sleep Apnea Clinical Score (SACS).[13] The SACS is an objective measure, because it is easily understood, and is rapidly applied, therefore being a useful tool for screening prior to polysomnography.[17-20]

The objective of the present study was to translate the SACS to Brazilian Portuguese and validate it for use in Brazil, considering not only the language but also the cultural adaptation for the target population, as well as demonstrating the reproducibility of the instrument in the country.

## METHODS

### *Ethical aspects*

This project was approved by the Research Ethics Committee of the Pedro Ernesto University Hospital, operated by the State University of Rio de Janeiro, in the city of Rio de Janeiro, Brazil. All participating patients gave written informed consent.

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### Description of the SACS

The SACS is composed of three questions, the measurement of neck circumference, and the evaluation of the presence or absence of hypertension. The total score ranges from 0 to 110, values below 5 indicating a low likelihood of OSAS, whereas values greater than or equal to 15 indicate a high likelihood.[13] The original questionnaire consists of three questions that evaluate the presence of hypertension or use of medication for blood pressure control; the presence of snoring; and the presence of choking, apnea, or sighing during sleep.[13] The first question can only be answered "Yes" or "No". However, the second and third questions can be answered with the following options: "never", "rarely" (1-2 times per year), "occasionally" (4-8 times per year), "sometimes" (1-2 times per month), "often" (1-2 times per week), "almost always" (3-5 times per week), "always" (every night), and "don't know". Patients who answer "almost always" or "always" on the second question are considered positive for snoring. Those who answer "often", "almost always", or "always" on the third question are considered positive for choking, apnea, or sighing during sleep. To complete the score, it is necessary to measure the neck circumference and to know the history of hypertension. That information is entered into a chart that evaluates the score achieved (Chart 1).

### Translation

We contacted the author of the SACS via e-mail and asked permission to translate the instrument into Brazilian Portuguese. After that permission had been granted, we performed a back-translation of the questionnaire. This method was chosen because it is most widely used.[21,22] As summarized in Figure 1, the following steps were used:

1. The original SACS was translated to Brazilian Portuguese by two independent translators who were fluent in English, were specialists in the field of sleep medicine, and knew the purpose of the study so that the translation would be not only literal but also conceptual and from a clinical perspective. The two translations were designated versions 1 and 2.
2. The two versions in Portuguese were reviewed by a multidisciplinary team, composed of two physicians and a nurse, who compared the two versions and created a single consensus version (version P1).
3. The consensus version was back-translated to English by a native speaker of English who was unaware of the purpose of the study and of the original version of the SACS, to ensure that the concepts that had initially been translated into Portuguese held the same meanings as those in the original English-language questionnaire, ensuring a consistent back-translation, even if linguistic changes were needed in order to adapt the instrument for use in the target population. The author of the original article approved the back-translated version.
4. The multidisciplinary team evaluated the back-translated version and compared it with the initial Portuguese-language version (version P1) to identify any linguistic differences. Because they found no inconsistencies, the Portuguese-language version was considered suitable and was designated version P2.

### Cultural adaptation

Version P2 was chosen to be submitted to cultural adaptation through the evaluation of semantic equivalence with a pre-test, as described below.

Version P2 of the SACS was presented to patients at the Pulmonology Outpatient Clinic of the Piquet Carneiro Polyclinic, with the addition of one answer option: "I did not understand the question or the answer options". The patients were instructed to answer only if they clearly understood the question and the answer options; otherwise, they should tick that additional option. Because the SACS is a self-report questionnaire, we selected adult patients who were able to understand the content. In this phase, we excluded illiterate individuals, as well as individuals with poor visual acuity or a cognitive deficit that would have prevented them from reading/understanding the questionnaire.

### Validation of the SACS

The final Portuguese-language version of the SACS was tested in patients referred to the sleep outpatient clinic. The criteria for inclusion in this phase were being an adult (≥ 18 years of age) and having been referred to the sleep outpatient clinic for investigation of possible OSAS. Patients who were unable to read the SACS were excluded, as were those who had previously undergone polysomnography, those who had a confirmed the diagnosis of OSAS, those who were pregnant, those with exacerbated respiratory diseases, and those with psychiatric disorders.

All patients underwent overnight polysomnography in the Sleep Laboratory of the Piquet Carneiro Polyclinic between March 2017 and August 2019, supervised by a technician using a polysomnography system (Alice 5; Philips Respironics, Pittsburgh, PA, USA). The staging of sleep and the marking of related events were carried out by a professional specializing in sleep medicine, in accordance with the Manual of the American Academy of Sleep Medicine.[2] The parameters recorded were the following: electroencephalography (derivations F3-M2, F4-M1, C3-M2, C4-M1, O1-M2, and O2-M1); electrooculography (derivations E1-M2 and E2-M2); electromyography of the mandible and legs; electrocardiography (modified D2 derivation); air flow through a nasal pressure cannula and oronasal thermistor; respiratory effort by thoracic and abdominal plethysmography; pulse oximetry; and body position.

Apnea was defined as a ≥ 90% drop in the amplitude of the thermistor signal for a period of ≥ 10 seconds, and hypopnea was defined as a ≥ 30% drop in the amplitude of the cannula pressure signal during a period ≥ 10 s, with oxygen desaturation ≥ 3% of the baseline value, with or without awakenings.

**Chart 1.** Final version of Sleep Apnea Clinical Score in Brazilian Portuguese.

**Escore clínico da Apneia do Sono (SACS–BR)**

Por favor, responda às seguintes questões:

1. Você tem pressão alta ou toma remédio para controlar a pressão?

( ) Sim ( ) Não

2. "Pessoas que dividem ou que dividiram o quarto comigo, dizem que eu ronco". Por favor, escolha qual a melhor resposta para esta afirmativa:

( ) Nunca
( ) Raramente (1-2 vezes/ano)
( ) Ocasionalmente (4-8 vezes/ano)
( ) Algumas vezes (1-2 vezes/mês)
( ) Frequentemente (1-2 vezes/semana)
( ) Quase sempre (3-5 vezes/semana)
( ) Sempre (todos os dias)
( ) Não sei dizer se ronco

3. "Já me disseram que engasgo, paro de respirar ou suspiro enquanto durmo". Por favor, escolha qual a melhor resposta para esta afirmativa:

( ) Nunca
( ) Raramente (1-2 vezes/ano)
( ) Ocasionalmente (4-8 vezes/ano)
( ) Algumas vezes (1-2 vezes/mês)
( ) Frequentemente (1-2 vezes/semana)
( ) Quase sempre (3-5 vezes/semana)
( ) Sempre (todos os dias)
( ) Não sei dizer se tenho esses sintomas

**Pergunta 1:** se respondido sim, considerar que o paciente tem hipertensão arterial sistêmica (HAS).

Características clínicas: Assinalar se nenhuma, uma ou se as duas respostas abaixo foram positivas.

**Pergunta 2:** considerar positiva se assinaladas as opções "quase sempre" ou "sempre".

**Pergunta 3:** considerar positiva se assinaladas as opções "frequentemente", "quase sempre" ou "sempre".

Medir a circunferência de pescoço (CP) e marcar na tabela abaixo o escore apropriado.

Resultado ≥ 15 indica alta probabilidade de síndrome de apneia obstrutiva do sono (SAOS)

| PREVISÃO de SAOS (circule a pontuação do paciente) | | | | | | |
|---|---|---|---|---|---|---|
| | Sem HAS | | | Com HAS | | |
| | Características clínicas | | | Características clínicas | | |
| CP (cm) | Nenhuma | Uma | Ambas | Nenhuma | Uma | Ambas |
| < 30 | 0 | 0 | 1 | 0 | 1 | 2 |
| 30/31 | 0 | 0 | 1 | 1 | 2 | 4 |
| 32/33 | 0 | 1 | 2 | 1 | 3 | 5 |
| 34/35 | 1 | 2 | 3 | 2 | 4 | 8 |
| 36/37 | 1 | 3 | 5 | 4 | 6 | 11 |
| 38/39 | 2 | 4 | 7 | 5 | 9 | **16** |
| 40/41 | 3 | 6 | 10 | 8 | 13 | **22** |
| 42/43 | 5 | 8 | 14 | 11 | **18** | **30** |
| 44/45 | 7 | 12 | **20** | **15** | **25** | **42** |
| 46/47 | 10 | **16** | **28** | **21** | **35** | **58** |
| 48/49 | 14 | **23** | **38** | **29** | **48** | **80** |
| > 49 | **19** | **32** | **53** | **40** | **66** | **110** |

We calculated the sample size for the inclusion of patients who would undergo polysomnography. A SACS < 5 indicates a 17% post-test likelihood of having OSAS, compared with 81% for a SACS ≥ 15.[13] On the basis of that, we calculated a necessary sample size of 46 patients, considering a type I error of 0.01 and a type II error of 0.01. The sample size was increased to 86 to ensure that all subsequent statistical analyses would be valid.

### *Statistical analysis*

In the descriptive analysis, continuous variables were expressed as mean and standard deviation. The area under the curve was calculated from a ROC curve constructed by the Wilson-Brown method, with the GraphPad Prism statistical package, version 8.0 (GraphPad Software Inc., San Diego, CA, USA). The specificity, sensitivity, positive predictive value, and negative predictive value, as well as their 95% CIs, were calculated with the Medcalc statistical package, version 19.2.0 (MedCalc Software, Mariakerke, Belgium). The reliability of the instrument was determined through the analysis of internal consistency with Cronbach's alpha coefficient. The level of significance was set at 5%.

## RESULTS

The translation of a tool into another language must also encompass the cultural adaptation and the adaptation to the linguistic expressions of the target language that help make the context understandable. In version P2 of the SACS, the phrase "I gasp, choke or snort", in the third question, was translated as *engasgo, paro de respirar ou suspiro* ("I choke, stop breathing, or sigh"), in order to keep the question within the clinical context of the patients with OSAS. The answer options were translated so as to represent the progression of events. Therefore, "sometimes" was translated as *algumas vezes* ("a few times") and "usually" was translated as *quase sempre* ("almost always").

In the pre-test phase, version P2 of the SACS was applied in 20 outpatients. The demographic data of that sample are shown in Table 1. Although all patients were able to read, some of them had had only a few years of schooling. However, none of the patients reported difficulties in understanding the questions or answer options presented in version P2. Although two patients had a complaint regarding the font size, that did not affect their comprehension of the questionnaire.

After the pre-test had been applied, we discussed and evaluated participant understanding and comprehension of the instrument, to ensure that all questions and answer options were well explained. We concluded that the instrument, as translated and revised by the multidisciplinary committee, did not require any further semantic or conceptual alterations. Therefore, we considered version P2 the final version and moved on to the next step: validation.

In this phase (the validation phase), the final version of the SACS was applied in patients who were referred to the sleep clinic for investigation of suspected OSAS. We included 86 randomly selected patients who met the inclusion criteria but not the exclusion criteria and who were scheduled to undergo polysomnography. The demographic data related to those patients are presented in Table 2.

The data obtained with the SACS were correlated with the results of the polysomnography. On the basis of the SACS result, the patients were divided into two groups: those with a low risk of OSAS (SACS < 5) and those with a high-risk (SACS ≥ 15), as shown in Table 3.

The reliability of the SACS was studied through the analysis of internal consistency. Cronbach's alpha coefficient was calculated to be 0.82 (lower limit of the 95% CI: 0.67). The questionnaire showed a sensitivity of 45.3% (95% CI: 32.8-58.2%), a specificity of 90.9% (95% CI: 70.8-98.9%), a positive predictive value of 93.5% (95% CI: 79.0-98.2%), a negative predictive value of 36.4% (95% CI: 30.6-42.5%), and an accuracy of 57.0% (95% CI: 45.8-67.6%). The area under the ROC curve was 0.82 (SE = 0.03; 95% CI: 0.74-0.89; $p < 0.0001$), as shown in Figure 2.

## DISCUSSION

The Portuguese-language version of the SACS was applied in patients in Brazil and was easily understood by those with various levels of education. Because it is a questionnaire with just three simple, objective questions, the level of clarity was the highest possible, as evidenced by the fact that none of the patients reported difficulties in understanding the tool. In addition to the three questions that were validated, the SACS requires the measurement of neck circumference, which, in the present study, was performed by one person (i.e., was not corroborated by a second evaluator).

The SACS was chosen for the translation project because of its ease of use. In Brazil, few health care

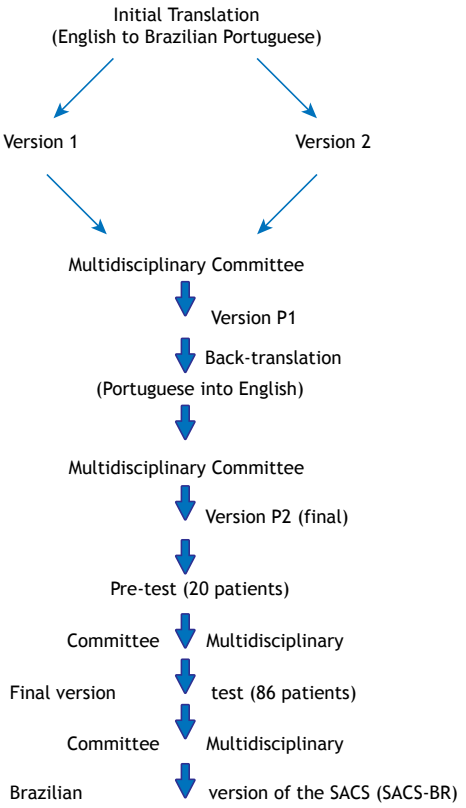


**Figure 1.** Stages in the process of the translation of the Sleep Apnea Clinical Score to Brazilian Portuguese and the cultural adaptation of the instrument for use in Brazil.

**Table 1.** Demographic data for patients who participated in the pre-test of the Sleep Apnea Clinical Score (N = 20).[a]

| Characteristic | Results |
|---|---|
| Male; n (%) | 10 (50) |
| Age, years | 58.25 ± 12.3 |
| Self-reported ethnicity | |
| White | 8 (40) |
| Other | 12 (60) |
| Self-reported level of education | |
| < 9 years of schooling | 2 (10) |
| 9-12 years of schooling | 7 (35) |
| ≥ 12 years of schooling | 9 (45) |
| University degree | 2 (10) |

[a]values expressed in n (%) or mean ± SD.

**Table 2.** Demographic data for the patients who participated in the validation of the Sleep Apnea Clinical Score (N = 86).[a]

| Characteristic | Results |
|---|---|
| Male, n (%) | 41 (48) |
| Age, years | 59.83 ± 10.3 |
| Self-reported ethnicity | |
| White | 41 (48) |
| Other | 45 (52) |
| Self-reported level of education | |
| < 9 years of schooling | 11 (13) |
| 9-12 years of schooling | 26 (30) |
| ≥ 12 years of schooling | 36 (41) |
| University degree | 8 (9) |
| Not stated | 5 (6) |
| Polysomnography results | |
| Normal | 22 (25) |
| Light OSAS | 18 (21) |
| Moderate OSAS | 10 (12) |
| Severe OSAS | 36 (42) |

OSAS: obstructive sleep apnea syndrome. [a]values expressed in n (%) or mean ± SD.

**Table 3.** Apnea-hypopnea index as measured by polysomnography in patients classified as being at low or high risk of presenting obstructive sleep apnea syndrome by the Sleep Apnea Clinical Score.[a]

| AHI, events/h | Low risk (n = 55) | High risk (n = 31) |
|---|---|---|
| < 5 | 20 (34) | 2 (6) |
| 5-15 | 10 (17) | 8 (29) |
| 16-30 | 6 (10) | 4 (17) |
| > 30 | 19 (38) | 17 (47) |

AHI: apnea-hypopnea index. [a]values expressed in n (%).

facilities offer polysomnography, and even fewer of those are within the public health care system. Therefore, it is essential to have a validated questionnaire that will help us select patients for polysomnography.

Flemons et al.[13] stated that neck circumference and hypertension are the most significant independent clinical predictors of OSAS, which is why these two evaluations were included in the SACS. Those authors stated that neck circumference was the independent variable that correlated most strongly with OSAS ($r = 5.89$; $p < 0.0001$).[13] Two of the three questions of the SACS evaluate the characteristics of abnormal nocturnal breathing observed by a partner, including habitual snoring and choking or asphyxia, which were also significant predictors.[13] The authors concluded that, for patients in whom the likelihood of OSAS is high, additional diagnostic tests should be used; a clinical prediction rule like the one they studied can provide a reliable estimate of the likelihood of prior approval for polysomnography. In other words, as clarified by the authors, the SACS was developed to be a tool with a high positive predictive value for the diagnosis of OSAS.[13] That is recognized in the literature, in which the SACS has become established as a questionnaire with high specificity for OSAS.[20]

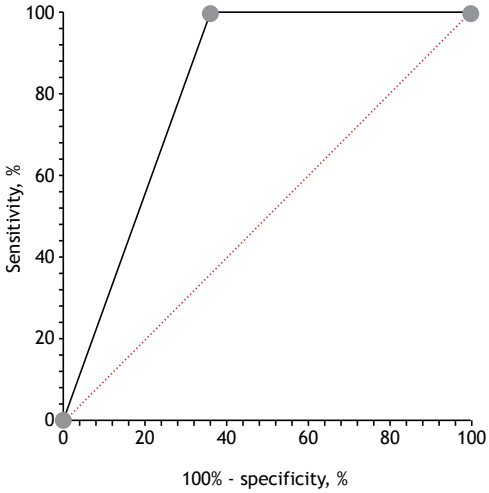


**Figure 2.** Relationship between sensitivity and specificity of the Sleep Apnea Clinical Score.

This means that patients with a SACS ≥ 15 have a high likelihood of actually being diagnosed with OSAS.

In a recent study, Prasad et al.[20] compared nine screening questionnaires designed to assess the likelihood of OSAS. A total of 210 patients underwent polysomnography, and 164 were thus diagnosed with OSAS. Among the various questionnaires compared, the SACS showed the highest positive predictive value (95.2%) and the highest specificity (91.3%) for the diagnosis of OSAS. The authors concluded that the SACS was the most specific tool for the diagnosis of OSAS among the tools evaluated, with values similar to those reported in the original study conducted by Flemons et al.[13] However, the SACS cannot exclude patients from needing the examination when the score is below 15, because it has low sensitivity. Because two of the three questions on the SACS refer to the perception of nocturnal symptoms, individuals who sleep alone do not perceive these changes and deny the presence of snoring or choking. In contrast, patients who sleep accompanied are more likely to respond positively, because their spouses or family members often complain of these symptoms. As a result, patients who sleep alone tend to score lower on the SACS, which could be one of the reasons for the low sensitivity of the tool.

In our sample, the translated, adapted questionnaire produced results similar to those obtained with the original tool. The Portuguese-language version had a specificity of 91%, very close to that reported by Prasad et al.[20]

The SACS has been now been translated to Portuguese, adapted to the cultural setting, and validated for use in Brazil. The present study could function as a reference for health professionals who monitor patients suspected of having OSAS.

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ORIGINAL ARTICLE

# Using the No-Apnea score to screen for obstructive sleep apnea in adults referred to a sleep laboratory: comparative study of the performance of the instrument by gender

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## ABSTRACT

**Objective:** To evaluate the performance of the No-Apnea score, a simplified screening instrument for obstructive sleep apnea (OSA), by gender. **Methods:** This was a cross-sectional study including adults undergoing full polysomnography. The No-Apnea model comprises two items (neck circumference and age) with a total score of 0 to 9. The severity of OSA was categorized, on the basis of the apnea-hypopnea index, as any (≥ 5 events/h), moderate-to-severe (≥ 15 events/h), or severe (≥ 30 events/h). The performance of the No-Apnea instrument was assessed by determining the area under the (ROC) curve (AUC) and by constructing contingency tables. **Results:** We evaluated a total of 6,606 adults (53.8% men). For categorizing the level of OSA severity, the No-Apnea score had a sensitivity of 83.9-93.0% and a specificity of 57.3-35.2%. At all OSA severity levels, the No-Apnea score exhibited higher sensitivity and lower specificity in men than in women. The No-Apnea score proved to be an appropriate screening model for patients in general or when separated by gender or severity of OSA (AUC > 0.7 for all). The discriminatory power of the No-Apnea score to predict any, moderate-to-severe, and severe OSA was similar between genders (p = 0.109, p = 0.698, and p = 0.094, respectively). **Conclusions:** In a sample of adults referred to the sleep laboratory, there was no significant difference between men and women in terms of the discriminatory power of the No-Apnea instrument in for screening for OSA severity.

**Keywords:** Sleep apnea, obstructive/diagnosis; Polysomnography; Sex; Surveys and questionnaires.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep disorder characterized by recurrent episodes of upper airway obstruction, resulting in intermittent hypoxemia, disruptions in sleep, and cardiovascular problems.[1-3] The prevalence of OSA has increased considerably in recent years,[4-6] possibly because of the aging population and the global obesity epidemic. One recent study reported that the overall prevalence of OSA was 32.8% in the city of São Paulo, Brazil.[6]

It is common for sleep laboratories around the world to have a long list of individuals with suspected OSA waiting to get tested. To date, the gold standard test for diagnosing OSA is full polysomnography (PSG). However, it is an expensive test that is not widely available, especially in regions with limited economic resources. Therefore, a screening instrument offering a simplified or home-based diagnostic method can be useful for stratifying patients.

The No-Apnea score is an instrument that comprises only two objective parameters—neck circumference (NC) and age—with a final score ranging from 0 to 9 (a score ≥ 3 indicates a high risk for OSA).[7] ) In the No-Apnea derivation cohort, the area under the ROC curve (AUC) was 0.784, 0.758, and 0.754 for screening for any, moderate-to-severe, and severe OSA, respectively. In fact, despite the simplicity of the No-Apnea score, when compared with two other previously validated models, its discriminatory power showed no statistically significant difference.[7]

As for the clinical history, men with OSA usually display typical symptoms, such as snoring and observed apnea, whereas women often report atypical symptoms, such as insomnia, morning headache, and fatigue.[8-12] In comparison with male patients, female patients typically are older, are more obese, and have more comorbidities—such as hypertension and diabetes mellitus.[10-13] However, NC tends to be greater in men than in women.[14] Based on the polysomnographic findings, women have a lower prevalence of OSA and show evidence of lower quality of sleep than do men.[8-12] As we can see, significant differences can be found between men and women with OSA, not only in the prevalence of the disease but also in the clinical phenotypes associated with it.

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However, despite the several gender-related differences consistently reported in the clinical presentation and polysomnographic findings of the condition,[8-14] analyses of the performance of OSA screening instruments by gender are surprisingly rare. In view of the above, the main objective of the present study was to evaluate the predictive performance and discriminatory power of the No-Apnea score, a simplified model for screening for OSA, by gender.

## METHODS

This was a prospective study, carried out between January of 2017 and March of 2019, with recruitment of individuals who were referred for sleep assessments by their attending physicians. The inclusion criteria were being ≥ 18 years of age and having a suspected sleep disorder. Patients who had previously been diagnosed with OSA were excluded, as were those who were diagnosed through the use of a portable or home monitoring device, those for whom the clinical data were incomplete, and those in whom the PSG was technically inadequate. The study protocol was in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of the Federal University of Rio de Janeiro (Reference no. 1.764.165). All participants gave written informed consent. If the same patient was submitted to more than one PSG, the test with the longest total sleep time was selected for analysis.

The clinical characteristics included gender, age, body mass index (BMI), NC, self-reported comorbidities (smoking, hypertension, and diabetes mellitus), and sleep-related complaints (snoring, observed apnea, nocturnal choking, and morning headache). Patients also completed five instruments, all of which have been validated in the literature: the No-Apnea score[7]; the **S**noring, **T**iredness, **O**bserved apnea, and high blood **P**ressure (STOP) and **S**noring, **T**iredness, **O**bserved apnea, high blood **P**ressure, **B**ody mass index, **A**ge, **N**eck circumference, and **G**ender (STOP-Bang) questionnaires[15]; the **N**eck circumference, **o**besity, **S**noring, **A**ge, and **S**ex (NoSAS) score[16]; and the Epworth Sleepiness Scale (ESS).[17] All of those the instruments have also been validated for use with the Brazilian population.[7,16,18,19] The screening instruments were applied by the PSG technicians immediately prior to the sleep test. The BMI was calculated as the weight in kilograms divided by the height in meters squared (kg/m$^2$), and the NC (in cm) was systematically measured with a measuring tape, as follows[7]: patients were asked to remain erect; and the NC was measured with the upper edge of the measuring tape just below the laryngeal prominence.

### *Screening instruments*

The No-Apnea model evaluates two objective parameters (NC and age), scored as follows: NC of 37.0-39.9 cm = 1; NC of 40.0-42.9 cm = 3; NC of ≥ 43.0 cm = 6; age of 35-44 years = 1; age of 45-54 years = 2; and age of ≥ 55 years = 3. The scores given to each variable are summed, generating a final score ranging from 0 to 9 (a score ≥ 3 indicates a high risk for OSA).[7]

The STOP and STOP-Bang questionnaires[15,18] consist of four and eight yes/no questions, respectively. Each affirmative answer gets a score of 1. The STOP questionnaire contains questions about loud snoring, tiredness, observed apnea, and hypertension (the total score ranging from 0 to 4), whereas the STOP-Bang questionnaire uses those same parameters plus BMI > 35 kg/m$^2$, age > 50 years, NC > 40 cm, and male gender (the total score ranging from 0 to 8). The STOP and STOP-Bang questionnaires use a score of ≥ 2 and ≥ 3, respectively, to identify individuals at risk for OSA.

The NoSAS instrument is scored as follows: an NC > 40 cm gets a score of 4; BMIs of 25-29 kg/m$^2$ and ≥ 30 kg/m$^2$ get scores of 3 and 5, respectively; snoring gets a score of 2; age > 55 years gets a score of 4; and being a male gets a score of 2. The score ranges from 0 to 17 and is considered positive when a patient gets a score ≥ 8.[16]

The ESS is an eight-item instrument that assesses the likelihood of a patient falling asleep in various contexts. Each question is answered on a scale from 0 (never dozes off) to 3 (high chance of dozing off), with a final score ranging from 0 to 24 (a score ≥ 11 indicates excessive daytime sleepiness).[17]

### *Sleep studies*

All polysomnographic evaluations were performed on the same type of device (EMBLA S7000; Embla Systems Inc., Broomfield, CO, USA), at the same sleep center in the city of Rio de Janeiro, Brazil. The recordings consisted of continuous monitoring by electroencephalography, electro-oculography, chin/leg electromyography, and electrocardiography, as well as of airflow, respiratory effort (with chest and abdominal belts), $SpO_2$ (by pulse oximetry), snoring (with a tracheal microphone), and body position (with position sensors). Two pulmonologists performed the manual reading of the exams, as recommended by the American Academy of Sleep Medicine.[20] Both were blinded to the results obtained with the screening instruments. Apnea was defined as a ≥ 90% drop in the baseline airflow value for at least ten seconds was classified as apnea, whereas hypopnea was defined as a ≥ 30% drop for at least 10 seconds accompanied by a ≥ 3% drop in oxygen saturation or a microarousal.[20] The level of OSA severity was classified, on the basis of the apnea-hypopnea index (AHI), as any (AHI ≥ 5 events/h), moderate-to-severe (AHI ≥ 15 events/h), or severe (AHI ≥ 30 events/h).

### *Statistical analysis*

The data were analyzed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA) and are expressed as means ± standard deviation (for numerical variables) or as absolute and relative frequencies (for categorical

variables). We used the chi-square test to compare dichotomous variables, whereas we used the Student's t-test and ANOVA to compare numerical variables. The predictive value of the No-Apnea score was assessed on the basis of its discriminatory power and by contingency tables. The discriminatory power was estimated on the basis of the AUC, which can vary from 0.5 (no discrimination) to 1.0 (perfect discrimination).[21] An AUC > 0.7 was considered clinically significant.[22] The discriminatory power was compared by using a methodology previously described.[23] Sensitivity, specificity, positive predictive value, and negative predictive value were calculated from the contingency tables, and all values are expressed with their respective 95% CIs. A two-tailed p value < 0.05 was considered statistically significant.

## RESULTS

Of a total of 6,820 consecutive individuals who were referred for OSA workup, 214 (3.1%) were excluded on the basis of the study criteria. Therefore, 6,606 patients were enrolled for further analysis: 3,054 (46.2%) were female and 3,552 (53.8%) were male. In comparison with the male patients, the female patients were older, had a higher BMI, and had a lower NC (p < 0.001 for all), as shown in Table 1. Diabetes mellitus was more prevalent in women than in men (p < 0.001). All sleep parameters evaluated were statistically different between genders, except for rapid eye movement sleep (p = 0.334). The mean AHI was higher in men than in women (37.2 ± 29.6 events/h vs. 18.9 ± 22.3 events/h; p < 0.001), whereas the $SpO_2$ nadir was lower in men than in women (80.0 ± 9.8% vs. 83.5 ± 8.8%; p < 0.001), suggesting that OSA was more severe in men than in women. The prevalence of any, moderate-to-severe, and severe OSA was statistically higher in men than in women—88.5% vs. 67.9%, 71.1% vs. 41.9%, and 51.2% vs. 20.9%, respectively (p < 0.001 for all). In addition, the likelihood of having any, moderate-to-severe, and severe OSA was statistically higher in men than in women—OR = 3.626 (95% CI: 3.190-4.121), OR = 3.403 (95% CI: 3.073-3.769), and OR = 3.966 (95% CI: 3.555-4.424), respectively.

The mean No-Apnea score was significantly lower in women than in men (3.2 ± 2.2 vs. 5.5 ± 2.3; p < 0.001). Overall, 75.3% of the patients were classified as being at high risk for OSA (No-Apnea score ≥ 3), the proportion of high-risk individuals being higher among the men than among the women (88.0% vs. 60.4%; p < 0.001). The proportional distribution of women and men by No-Apnea score is shown in Figure 1.

For both genders, an increase in the No-Apnea score from 0 to 9 led to an increase in the prevalence of OSA—that of any OSA increased from 27.6% to 94.4% in women and from 53.5% to 96.6% in men; that of moderate-to-severe OSA increased from 10.8% to 76.7% in women and from 25.4% to 85.2% in men; and that of severe OSA went from 2.0% to 63.3% in women and from 12.7% to 68.3% in men. Similarly, with the progressive increase in the No-Apnea score,

**Table 1.** Characteristics of our study sample.[a]

| Parameters | Total (N = 6,606) | Women (n = 3,054) | Men (n = 3,552) | p |
|---|---|---|---|---|
| Clinical data | | | | |
| Age, years | 44.6 ± 13.8 | 45.9 ± 14.2 | 43.6 ± 13.4 | < 0.001 |
| BMI, kg/m$^2$ | 33.5 ± 7.9 | 34.1 ± 8.4 | 33.0 ± 7.4 | < 0.001 |
| NC, cm | 40.7 ± 4.9 | 37.8 ± 4.0 | 43.2 ± 4.3 | < 0.001 |
| ESS score | 10.0 ± 5.0 | 9.5 ± 5.0 | 10.4 ± 5.0 | < 0.001 |
| Smoking history | 610 (9.2) | 261 (8.5) | 349 (9.8) | 0.074 |
| Hypertension | 2,571 (38.9) | 1,199 (39.3) | 1,372 (38.6) | 0.613 |
| Diabetes mellitus | 792 (12.0) | 435 (14.2) | 357 (10.1) | < 0.001 |
| Loud snoring | 4,322 (65.4) | 1,727 (56.5) | 2,595 (73.1) | < 0.001 |
| Observed apnea | 3,387 (51.3) | 1,228 (40.2) | 2,159 (60.8) | < 0.001 |
| Choking/suffocation | 2,731 (41.3) | 1,274 (41.7) | 1,457 (41.0) | 0.581 |
| Morning headache | 3,396 (51.4) | 2,045 (67.0) | 1,351 (38.0) | < 0.001 |
| Polysomnographic data | | | | |
| Total sleep time, min | 342.2 ± 69.4 | 340.1 ± 69.6 | 344.1 ± 69.2 | 0.031 |
| REM sleep, % | 16.1 ± 7.7 | 16.2 ± 7.8 | 16.0 ± 7.7 | 0.334 |
| NREM sleep, % | 83.4 ± 7.7 | 83.2 ± 7.8 | 83.6 ± 7.7 | 0.021 |
| Arousals/h | 30.8 ± 25.8 | 22.2 ± 20.5 | 38.2 ± 27.6 | < 0.001 |
| AHI, events/h | 28.7 ± 28.0 | 18.9 ± 22.3 | 37.2 ± 29.6 | < 0.001 |
| AI, events/h | 15.6 ± 24.2 | 7.5 ± 16.1 | 22.6 ± 27.7 | < 0.001 |
| HI, events/h | 13.1 ± 12.8 | 11.3 ± 12.4 | 14.6 ± 12.9 | < 0.001 |
| Mean $SpO_2$, % | 93.4 ± 3.4 | 93.9 ± 3.3 | 93.0 ± 3.5 | < 0.001 |
| Minimum $SpO_2$,% | 81.6 ± 9.5 | 83.5 ± 8.8 | 80.0 ± 9.8 | < 0.001 |

BMI: body mass index; NC: neck circumference; ESS: Epworth Sleepiness Scale; REM: rapid eye movement; NREM: non-REM; AHI: apnea-hypopnea index; AI: apnea index; and HI: hypopnea index. [a]Values expressed as mean ± SD or n (%).

there was a trend toward a linear increase in the mean AHI (Figure 2): from 5.1 ± 8.6 events/h to 42.8 ± 28.8 events/h in women ($p < 0.001$); and from 12.1 ± 16.1 events/h to 46.8 ± 27.1 events/h in men ($p < 0.001$).

Table 2 shows the performance of the No-Apnea score by gender. Overall, for screening different levels of OSA severity, the sensitivity of the No-Apnea model ranged from 83.9% to 93.0%, whereas its specificity ranged from 57.3% to 35.2%. Regardless of the level of severity, the No-Apnea model had higher sensitivity and lower specificity in men than in women.

Table 3 shows the discriminatory power calculated for each of the five screening instruments: the No-Apnea score, the STOP questionnaire, the STOP-Bang questionnaire, the NoSAS score, and the ESS. The No-Apnea proved to be a useful screening tool for all patients included in the study and for patients dichotomized by gender (AUC > 0.7 for all OSA severity levels). In women, the AUC obtained ranged from 0.719 (95% CI: 0.701-0.737) to 0.741 (95% CI: 0.721-0.760), whereas in men, it ranged from 0.702 (95% CI: 0.685-0.720) to 0.763 (95% CI: 0.738-0.788). The discriminatory power of the No-Apnea score for any, moderate-to-severe, and severe OSA was comparable between the genders ($p = 0.109$, $p = 0.698$, and $p = 0.094$, respectively). The other models also had similar performances for both genders, except for the ESS, which performed better in men than in women for any, moderate-to-severe, and severe OSA ($p = 0.007$, $p = 0.009$, and $p = 0.015$, respectively).

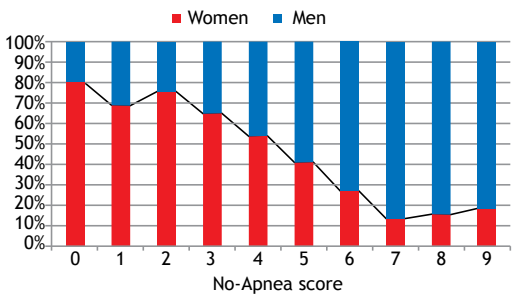


**Figure 1.** Proportion of women and men per No-Apnea score (from 0 to 9): women predominated at scores of 0-4, whereas men predominated at scores of 5-9.

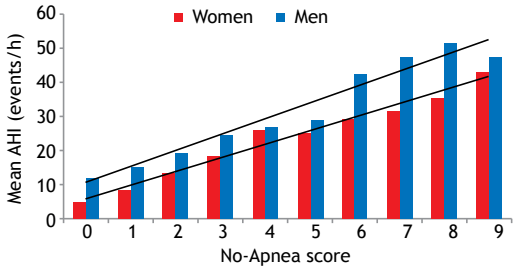


**Figure 2.** Mean apnea-hypopnea index (AHI) detected by overnight polysomnography per No-Apnea score (from 0 to 9) in women (n = 3,054) and in men (n = 3,552). As the No-Apnea score increases, there is a trend toward a linear increase in the AHI in men and women ($p < 0.001$ for both).

## DISCUSSION

The main finding of our study was that, in adult individuals who were referred to a sleep laboratory, the No-Apnea score can be a useful screening tool for OSA. The instrument showed appropriate predictive performance and discriminatory power for the purpose of screening for OSA at all levels of severity and in both genders.

An advantage of using OSA screening instruments like the No-Apnea score is the possibility of appropriately referring high-risk patients for evaluation with portable diagnostic methods, thereby reducing the long waiting lists at sleep laboratories.[24,25] In addition, because the No-Apnea score comprises only objective variables, it can be used in individuals who sleep alone and whose subjective sleep information is not always easily available.

In the present study, we found several clinical and polysomnographic differences between genders that have already been extensively reported in the literature.[8-14] We found a predominance of OSA in men, which is in keeping with the findings of population-based studies[6] and studies conducted in sleep laboratories,[18] albeit different that what has been reported in studies of patients in the preoperative period of bariatric surgery[26] or of patients with insomnia.[27] One previous study showed that the prevalence of OSA was lower in women than in men, despite the fact that the women in the sample had higher BMIs and were older.[28] The following factors have been implicated in the gender-related difference in OSA[29-31]: hormonal influences and menopause (in women); craniofacial structure; and upper airway length.

There are several OSA screening instruments available, and their performance may vary depending on the tests used to diagnose OSA, the type of population evaluated, and the AHI cutoff used.[32] It is possibly more important that screening tests for diseases like OSA have high sensitivity than that they have high specificity, especially in a population with a high pretest probability.[32,33] Preeminent among the several OSA screening models described in the literature are the Berlin questionnaire,[34] the STOP-Bang questionnaire,[15] and the NoSAS score.[16] Although the gender-related differences in the symptoms and prevalence of OSA are well established, few studies have effectively evaluated whether there are also gender-specific differences in the performance of the screening instruments.

A study assessing the applicability of the fractional exhaled nitric oxide test as a screening method for OSA found that the No-Apnea score was a useful screening tool for any, moderate-to-severe, and severe OSA, for which the AUC reported was 0.786, 0.713, and 0.717, respectively.[35] A subsequent study, involving a cohort of morbidly obese patients, found that the No-Apnea score had appropriate discriminatory power for screening for OSA.[36] The authors found no gender-specific differences in performance for the screening for any ($p = 0.973$) and moderate-to-severe OSA ($p = 0.817$),

**Table 2.** Predictive performance of the No-Apnea score in screening for obstructive sleep apnea.[a]

| Variables | Total (N = 6,606) | Women (n = 3,054) | Men (n = 3,552) |
|---|---|---|---|
| AHI ≥ 5 events/h (any OSA) | | | |
| Sensitivity | 83.9 (83.4-84.5) | 72.5 (71.3-73.6) | 91.5 (91.0-92.0) |
| Specificity | 57.3 (55.2-59.5) | 65.1 (62.6-67.5) | 38.9 (34.8-43.0) |
| PPV | 88.1 (87.5-88.7) | 81.5 (80.2-82.8) | 92.0 (91.5-92.5) |
| NPV | 48.7 (46.9-50.5) | 52.7 (50.7-54.7) | 37.3 (33.4-41.3) |
| AHI ≥ 15 events/h (moderate-to-severe OSA) | | | |
| Sensitivity | 89.5 (88.6-90.2) | 80.5 (78.6-82.3) | 94.0 (93.3-94.7) |
| Specificity | 44.0 (42.9-45.1) | 54.0 (52.6-55.3) | 26.8 (24.9-28.5) |
| PPV | 68.4 (67.8-69.0) | 55.8 (54.5-57.0) | 75.9 (75.3-76.5) |
| NPV | 75.5 (73.5-77.3) | 79.3 (77.3-81.2) | 64.6 (60.1-68.8) |
| AHI ≥ 30 events/h (severe OSA) | | | |
| Sensitivity | 93.0 (92.0-93.9) | 85.6 (82.8-88.0) | 95.6 (94.7-96.4) |
| Specificity | 35.2 (34.6-35.8) | 46.2 (45.5-46.8) | 19.9 (19.0-20.8) |
| PPV | 45.9 (45.4-46.4) | 29.6 (28.6-30.4) | 55.6 (55.0-56.0) |
| NPV | 89.5 (88.0-90.8) | 92.4 (90.9-93.7) | 81.2 (77.3-84.6) |

AHI: apnea-hypopnea index; OSA: obstructive sleep apnea; PPV: positive predictive value; and NPV: negative predictive value. [a]Values expressed as estimate (95% CI).

**Table 3.** Comparison between the five obstructive sleep apnea screening models in terms of their discriminatory power, by gender.[a]

| Variables | Total (N = 6,606) | Women (n = 3,054) | Men (n = 3,552) | p |
|---|---|---|---|---|
| AHI ≥ 5 events/h (any OSA) | | | | |
| No-Apnea score | 0.784 (0.771-0.798) | 0.741 (0.721-0.760) | 0.763 (0.738-0.788) | 0.109 |
| STOP questionnaire | 0.711 (0.695-0.726) | 0.695 (0.675-0.714) | 0.705 (0.678-0.732) | 0.514 |
| STOP-Bang questionnaire | 0.796 (0.783-0.809) | 0.755 (0.737-0.773) | 0.767 (0.742-0.792) | 0.374 |
| NoSAS score | 0.776 (0.762-0.790) | 0.719 (0.699-0.738) | 0.740 (0.713-0.768) | 0.146 |
| ESS | 0.572 (0.555-0.589) | 0.543 (0.521-0.564) | 0.591 (0.562-0.621) | 0.007 |
| AHI ≥ 15 events/h (moderate-to-severe OSA) | | | | |
| No-Apnea score | 0.759 (0.747-0.771) | 0.719 (0.701-0.737) | 0.724 (0.705-0.743) | 0.698 |
| STOP questionnaire | 0.687 (0.684-0.700) | 0.675 (0.656-0.695) | 0.680 (0.661-0.700) | 0.713 |
| STOP-Bang questionnaire | 0.773 (0.762-0.784) | 0.731 (0.713-0.748) | 0.743 (0.725-0.761) | 0.340 |
| NoSAS score | 0.752 (0.740-0.764) | 0.699 (0.680-0.717) | 0.704 (0.684-0.724) | 0.705 |
| ESS | 0.576 (0.562-0.590) | 0.548 (0.527-0.568) | 0.586 (0.566-0.607) | 0.009 |
| AHI ≥ 30 events/h (severe OSA) | | | | |
| No-Apnea score | 0.758 (0.746-0.770) | 0.727 (0.707-0.748) | 0.702 (0.685-0.720) | 0.094 |
| STOP questionnaire | 0.689 (0.676-0.702) | 0.689 (0.666-0.711) | 0.679 (0.662-0.697) | 0.516 |
| STOP-Bang questionnaire | 0.780 (0.769-0.791) | 0.745 (0.725-0.765) | 0.739 (0.722-0.755) | 0.679 |
| NoSAS score | 0.750 (0.738-0.762) | 0.708 (0.686-0.729) | 0.680 (0.663-0.698) | 0.066 |
| ESS | 0.589 (0.575-0.603) | 0.555 (0.529-0.580) | 0.594 (0.577-0.614) | 0.015 |

AHI: apnea-hypopnea index; OSA: obstructive sleep apnea; STOP: Snoring, Tiredness, Observed apnea, and high blood Pressure; STOP-Bang: Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and Gender; NoSAS: Neck circumference, obesity, Snoring, Age, and Sex; and ESS: Epworth Sleepiness Scale. [a]Values for area under the ROC curve (95% CI).

although they did find the score to perform better in screening for severe OSA in women than in men (p = 0.033).[36] The No-Apnea score has also been validated in a cohort of patients with insomnia, showing an appropriate predictive performance.[37] As previously reported,[7,36,37] its discriminatory power is similar to that of other instruments with positive evaluations in the literature, such as the STOP-Bang questionnaire[15] and the NoSAS score.[16]

In a study of 502 patients (465 men and 37 women) who underwent portable monitoring sleep studies, a STOP-Bang score ≥ 3 predicted an AHI ≥ 5 events/h with an AUC of 0.72.[38] Sensitivity and specificity rates were calculated separately for men and women but achieved similar results, the sensitivity being 98.8% and 100.0%, respectively, whereas the specificity was 4.0% and 0.0%, respectively. However, that study[38] had significant limitations that are worth mentioning:

few women were included; all participants were evaluated with unsupervised sleep studies; and no comparisons were made between the men and the women in terms of the AUC.

Another study, involving 1,426 individuals undergoing full PSG, found that observed apnea and snoring were reported more often in men, whereas the presence of tiredness and hypertension was similar between genders.[39] However, gender-specific AUCs have not been reported for the STOP-Bang questionnaire. A study involving 251 patients (76% women) undergoing preoperative evaluation for bariatric surgery applied four different instruments (the ESS, the Fatigue Severity Scale, the STOP-Bang questionnaire, and the NoSAS score) and found that, except for the ESS, all of the instruments performed better in women than in men.[40]

A study of 403 women and 532 men found that the performance of the STOP-Bang questionnaire in screening for OSA in women was influenced by the BMI, whereas NC seemed to be more relevant in the screening of men.[41] That study also showed that the STOP-Bang questionnaire had extremely low specificity in men: 11.9% for any OSA (AHI ≥ 5 events/h), 7.9% for moderate-to-severe OSA (AHI ≥ 15 events/h), and 7.0% for severe OSA (AHI ≥ 30 events/h). In our study, the No-Apnea score also showed low specificity in men: 38.9% for any OSA (AHI ≥ 5 events/h), 26.8% for moderate-to-severe OSA (AHI ≥ 15 events/h), and 19.9% for severe OSA (AHI ≥ 30 events/h). However, our values were higher than those found for the STOP-Bang questionnaire.[41]

The present study has some limitations. The sample was composed of patients referred to a single sleep laboratory (i.e., preselected individuals with a high pretest probability), which could limit the generalizability of our findings. In addition, it did not include many individuals of other ethnicities, who could have different anthropometric characteristics.

In conclusion, the present study, involving adult individuals who were referred to a sleep laboratory, identified several clinical and polysomnographic differences between genders. Nevertheless, the No-Apnea score showed appropriate performance in screening for suspected OSA across all severity levels. Because the prevalence of OSA increases in parallel with increases in the No-Apnea score, this model can be used to aid in classifying risk in individuals referred to sleep laboratories, regardless of gender.

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ORIGINAL ARTICLE

# High resolution computed tomography patterns in interstitial lung disease (ILD): prevalence and prognosis

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## ABSTRACT

**Objective:** To correlate the prevalence and prognosis of each HRCT pattern of typical, probable, and indeterminate usual interstitial pneumonia (UIP) with the clinical multidisciplinary diagnosis of interstitial lung disease (ILD). **Methods:** We included all patients with a multidisciplinary diagnosis of ILD with an HRCT pattern of typical UIP, probable UIP, or indeterminate for UIP. Clinical and histopathological data, pulmonary function tests, and survival status were retrospectively obtained. The final diagnosis was validated by a multidisciplinary team. **Results:** A total of 244 patients were included in the study, with a mean age of 68 ±13 years and being 52.5% males. In a total of 106 patients with typical UIP pattern, 62% had the multidisciplinary diagnosis of IPF, 20% had chronic hypersensitivity pneumonitis (CHP), and 10% had connective tissue disease-related ILD (CTD-ILD). Out of the 114 cases with probable UIP, CTD-ILD corresponded to 39%, IPF to 31%, desquamative interstitial pneumonia to 11%, drug-related lung disease to 9%, and CHP to 8%. In the 24 patients with CT indeterminate for UIP, CTD-ILD was the final diagnosis in 33%, followed by desquamative interstitial pneumonia (21%), and IPF (13%). Patients with typical UIP were more likely to die or had lung transplantation in the follow-up (17.9% and 11.3%, respectively). **Conclusion:** IPF, CHP, and CTD-ILD were the main differential diagnoses in patients with HRCT patterns of typical, probable and indeterminate UIP. Patients with HRCT typical UIP pattern were more likely to die or had lung transplantation in the follow-up.

**Keywords:** High resolution computed tomography; Interstitial lung disease; Idiopathic pulmonary fibrosis; Usual interstitial pneumonia.

## INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) represents one of the most common interstitial lung diseases (ILD), characterized by progressive, fibrotic interstitial pneumonia of unknown cause, and the finding of usual interstitial pneumonia (UIP) pattern on both high-resolution computed tomography (HRCT) and on anatomopathological exam.[1-4] IPF diagnosis is challenging, requiring multidisciplinary collaboration from pulmonologists, radiologists, and pathologists to integrate clinical data as well as interpretation of the radiological patterns of the disease.[5]

A new revision of the diagnostic recommendations of IPF based on the latest clinical trials and expert consensus was published by the ATS/ERS/JRS/ALAT in September 2018.[3] The diagnostic algorithm recommends all patients with ILD to undergo a thorough investigation to rule out specific causes of the disease, including investigation of environmental exposure, medication use, and serological tests. If no alternative cause is identified, the HRCT pattern must be considered. The radiological categories of UIP in this recent review are: UIP, probable UIP, indeterminate for UIP and alternative diagnosis.[3] The radiological pattern of UIP is defined by bilateral reticulation and honeycombing, with peripheral traction bronchiectasis and bronchiolectasis, which are predominantly basal and subpleural.[1,3,5] Probable UIP differs from UIP by the absence of honeycombing, which are clusters of thick-walled cystic spaces of similar diameters typically located in the dorsal, basal and subpleural regions of the lung.[3] On the other hand, the indeterminate pattern presents evidence of basal and subpleural fibrosis but with other findings that do not suggest any specific diagnosis.[3] Thus, in the right clinical context, CT pattern of UIP are accurate to diagnose IPF without a biopsy.[5] However, in the case of probable UIP, indeterminate or CT pattern consistent with an alternative diagnosis, a multidisciplinary discussion can decide which other exams are necessary to establish the diagnosis, although ATS/ERS/JRS/ALAT suggests performing a surgical lung biopsy.[3]

In light of the contribution of the HRCT to the diagnosis of fibrosing ILD, our goal was to describe the prevalence and survival of the different multidisciplinary diagnosis of ILD associated with the CT patterns of UIP (UIP, probable and indeterminate).

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## METHODS

### *Study population*

We included consecutive patients aged >18 years with a multidisciplinary diagnosis of IPF or any other ILD with HRCT showing a pattern of UIP, probable UIP and indeterminate for UIP, at our reference center from January 2012 to January 2016. Diagnosis was determined either by surgical lung biopsy or by multidisciplinary discussions. Histological pattern of UIP on surgical lung biopsy and clinical-radiologic diagnosis was based on the ATS/ERS/JRS/ALAT.[3] Patients were excluded if they were not followed-up at our center after the initial CT scan. Clinical data, including demographics, occupational exposure, smoking history, comorbidities at the time of the first appointment, pulmonary function tests, histopathological data, and deceased status were retrieved using medical records. This retrospective study was approved by the local ethics committee (number 1.763.960).

### *CT protocols and imaging analysis*

HRCT was performed with 1.0 mm thick sections throughout the entire lung during inspiration and expiration in the supine position. All CT scans were performed in 64MDCT GE LightSpeed 64 VCT (GE Healthcare, Waukesha, Wisconsin). The CT scanning protocol was spiral mode, 120 kVp, 2000 mA, 0.5- s rotation time, 0.5-mm collimation and HRCT kernel was applied. CT images were reconstructed with 1-mm slice thickness in axial, coronal and sagittal.

Paired inspiratory and expiratory images were independently evaluated by two thoracic radiologists with more than 8 years of experience. All cases had their HRCT patterns reviewed and reclassified into the three groups of UIP according to the new criteria in the 2018 ATS/ERS/JRS/ALAT guideline.[3] A UIP pattern was defined by the presence of basal and subpleural predominance plus honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis. The criterion of indeterminate for UIP, according to the guideline, was the presence of basal and subpleural fibrosis with mild reticulation, ground-glass opacities and/or distortion and other findings that do not suggest a specific etiology.[3] Radiologists interobserver agreement was assessed by calculating the kappa statistic (κ) and was interpreted according to a previous study.[6]

### *Multidisciplinary diagnostic criteria*

A multidisciplinary group with the integration of pulmonologist, rheumatologist, radiologist, and pathologist was responsible for reviewing the final clinical diagnosis in selected cases. These multidisciplinary conferences occur monthly to evaluate patients with probable or indeterminate for UIP HRCT pattern, patients with non-characteristic disease or suspected for a different etiology other than IPF or also those with clinical evolution discordant to the previously established diagnosis. The initial approach was to rule out other causes of interstitial lung disease. Selected cases underwent surgical lung biopsy in case of a "possible UIP pattern" (per the ATS 2011 guidelines, since it is a retrospective study) when clinically tolerable by the patient [2]. Therefore, the final diagnosis was established considering the clinical, radiological and histopathological findings.

### *Statistical analysis*

Data were presented as frequency and percentage or mean ± standard deviation (SD) or median (IQR). Initial group comparisons were performed using ANOVA test for continuous variables and Chi-square tests for categorial. Cox regression analysis was performed and hazard ratios (HR) were calculated to investigate the potential factors associated with higher overall mortality. Only variables that showed a $p<0.10$ were included in the multivariate analysis. In all other cases, *p* values were two-tailed and considered statistically significant with an alpha of 0.05. Statistical analyses were performed using the SPSS v.18 (IBM, Chicago, IL).

## RESULTS

A total of 244 patients were included in the study, and their characteristics are described in Table 1. Among those, 106 presented a UIP pattern, 114 had probable a UIP pattern, and 24 had an indeterminate pattern for UIP. Cases of UIP and probable UIP patterns and their histopathological correlation are shown in Figures 1 and 2. Most patients in our sample were male (52.5%), had a mean age of 68 ±13 years and were non-smokers (70.9%). The median length of follow-up was 2 years in the total sample, in which 31 (12.7%) of our total sample died, and 17 (7%) had pulmonary lung transplantation. Compared to those with probable and indeterminate pattern of UIP, patients with UIP patterns were more often smokers (37.7% vs. 24.6% and 12.5%, respectively; p = 0.017), and were more likely to undergone lung transplantation (11.3% vs. 3.5% and 4.2%; p = 0.021).

About the prevalence of final diagnosis, 43% (n=105) of the 244 patients had IPF, 25.8% (n=63) had CTD-ILD, followed by CHP with 12.3% (n=30), desquamative interstitial pneumonia (7.4%, n=18), drug-related lung disease (5.3%, n=13), unclassifiable fibrosis (2%, n=5), bronchiolocentric interstitial pneumonia (1.6%, n=4), pneumoconiosis (1.2%, n=3) and lymphoid interstitial pneumonia (1.2%, n=3). In total, 69 patients were diagnosed by SLB and the remaining 175 by multidisciplinary consensus based on clinical and radiological findings.

The prevalence of each individual diagnosis stratified according to the CT pattern of UIP is shown in Table 2. The most prevalent diagnosis in patients with UIP pattern on HRCT were IPF (n=66, 62%) and chronic hypersensitivity pneumonitis (CHP) (n=21, 20%). On the

**Table 1.** Baseline patient characteristics.

| Parameter | Total (N=244) | Probable UIP (N=114) | Indeterminate UIP (N=24) | UIP (N=106) | *p* |
|---|---|---|---|---|---|
| Sex | | | | | .391 |
| Male | 128 (52.5) | 55 (48.2) | 15 (62.5) | 58 (54.7) | |
| Female | 116 (47.5) | 59 (51.8) | 9 (37.5) | 48 (45.3) | |
| Age, y | 68±13 | 69±14 | 68±10 | 68±11 | .945 |
| Smoking history | 71 (29.1) | 28 (24.6) | 3 (12.5) | 40 (37.7) | .017 |
| Clinical conditions | | | | | |
| Cardiomyopathy | 46 (18.9) | 20 (17.5) | 3 (12.5) | 23 (21.7) | .390 |
| COPD | 22 (9.0) | 5 (4.4) | 5 (20.8) | 12 (11.3) | .021 |
| Diabetes mellitus | 71 (29.1) | 28 (24.6) | 3 (12.5) | 40 (37.7) | .998 |
| IPF | 83 (38.4) | 36 (31.6) | 3 (12.5) | 44 (56.4) | <.001 |
| Lung cancer | 25 (10.2) | 12 (10.5) | 4 (16.7) | 9 (8.5) | .551 |
| Lung transplantation | 17 (7.0) | 4 (3.5) | 1 (4.2) | 12 (11.3) | .021 |
| PH | 18 (7.4) | 6 (5.3) | 0 | 12 (11.3) | .066 |
| CTD | 43 (17.6) | 23 (20.2) | 4 (16.7) | 16 (15.1) | .332 |
| Lung function | | | | | |
| $FEV_1$, L | 1.82±0.65 | 1.92±0.76 | 1.80±0.45 | 1.73±0.58 | .483 |
| $FEV_1$, % | 71±20 | 74±20 | 70±20 | 67±20 | .259 |
| FVC, L | 2,22±0.83 | 2,34±0.97 | 2,22±0.83 | 2,10±0.70 | .500 |
| FVC, % | 68±19 | 70±18 | 68±19 | 66±21 | .521 |
| $FEV_1$/ FVC, ratio | 1.04±0.11 | 1.05±0.12 | 1.04±0.11 | 1.04±0.10 | .476 |
| Follow-up | 2.2±1.6 | 2.3±1.6 | 2.2±1.6 | 2.1±1.6 | .366 |
| Death | 31 (12.7) | 10 (8.8) | 2 (8.3) | 19 (17.9) | .037 |

COPD: chronic obstructive pulmonary disease; IPF: idiopathic pulmonary fibrosis; PH: pulmonary hypertension; CTD: connective tissue disease; $FEV_1$: the forced expiratory volume in one second; FVC: forced vital capacity. Data were presented as N° (%) or mean ±SD.

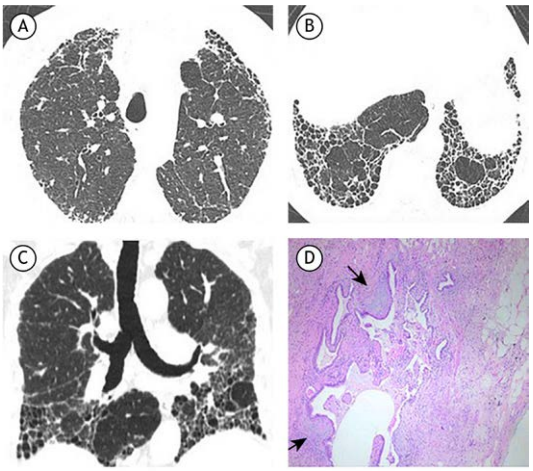


**Figure 1.** UIP CT and anatomopathological pattern. (A-C) Axial and coronal HRCT images of a patient with UIP showing basal and subpleural predominance with honeycombing and reticular pattern. (D) Surgical lung biopsy demonstrating dense scarring with fibroblast foci (arrows) in a subpleural localization (H&E,40x).

other hand, the most common diagnosis associated with the "probable" and "indeterminate" UIP patterns was connective tissue disease-associated interstitial lung disease (CTD-ILD) (n=44, 39%; n=8, 33%, respectively). In the group of probable UIP pattern, IPF

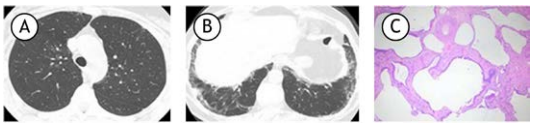


**Figure 2.** Probable UIP CT and anatomopathological pattern. (A and B) HRCT images showing basal predominant reticular abnormality without honeycombing. (C) Higher power evaluation of the surgical lung biopsy sample shows fibrosis with microscopic honeycombing but no fibroblast foci (H&E, 40x).

(32%, n=36) represented the second most common diagnosis, whereas for indeterminate desquamative interstitial pneumonia (n=5, 21%) had the second position in prevalence. The rate of agreement between radiologists was 94.05% (κ = 0.730; 95% confidence interval, 0.60–0.80).

Death events during follow-up were statistically higher for UIP pattern (n=19, 17.9%) compared to probable (n=10, 8.8%) and indeterminate UIP (n=2, 8.3%) (Table 1). Cox regression analysis is shown in Table 3. In the multivariate analysis, the UIP pattern on HRCT (HR = 2.44, 95% CI 1.05-5.64**)** and lung cancer (HR = 4.20, 95% CI 1.79-9.82) were the only variables positively associated with higher mortality after controlling for age, smoking history, and cardiomyopathy.

**Table 2.** Distribution of prevalence ILD according to the HRCT pattern.

| Final diagnosis | Total (N=244) | Probable UIP (N=114) | Indeterminate UIP (N=24) | UIP (N=106) | *p* |
|---|---|---|---|---|---|
| Drug-related lung disease | 13 (5.3) | 10 (8.7) | 3 (12.5) | - | 0.015 |
| CTD | 63 (25.8) | 44 (38.6) | 8 (33.3) | 11 (10.3) | <0.001 |
| IPF | 105 (43) | 36 (31.5) | 3 (12.5) | 66 (62.2) | <0.001 |
| HP | 30 (12.2) | 9 (7.8%) | - | 21 (19.9) | 0.004 |
| DIP | 18 (7.3) | 13 (11.4%) | 5 (20.8) | - | <0.001 |
| LIP | 3 (1.2) | - | 3 (12.5) | - | <0.001 |
| BIP | 4 (1.6) | 2 (1.7%) | 2 (8.3) | - | 0.015 |
| Unclassified | 5 (2) | - | - | 5 (4.7) | 0.036 |
| Pneumoconiosis | 3 (1.2) | - | - | 3 (2.9) | 0.138 |

IPF: idiopathic pulmonary fibrosis; CTD: connective tissue disease; HP: Hypersensitivity pneumonitis; DIP: Desquamative interstitial pneumonia; LIP: Lymphoid interstitial pneumonia; BIP: Bronchiolocentric interstitial pneumonia. Data were presented as N° (%) or mean ±SD.

**Table 3.** Cox regression analysis for overall mortality among HRCT findings and other independent factors.

| Parameter | Univariate analysis[a] | | Multivariate analysis[b] | |
|---|---|---|---|---|
| | HR (95% CI) | *p* | HR (95% CI) | *p* |
| HRCT findings | | .026 | | .037 |
| Indeterminate UIP | 1.44 (0.30-6.89) | | 1.72 (0.36-8.19) | |
| UIP | 2.66 (1.10-6.42) | | 2.44 (1.05-5.64) | |
| Female | 1.44 (0.65-3.17) | .365 | | |
| Age, y | 1.02 (0.99-1.06) | .107 | 1.01 (0.98-1.04) | .347 |
| Smoking history | 1.77 (0.79-3.95) | .017 | 1.95 (0.88-4.28) | .109 |
| Clinical conditions | | | | |
| Cardiomyopathy | 2.94 (1.32-6.51) | .008 | 2.05 (0.93-4.50) | .077 |
| COPD | 1.32 (0.39-4.41) | .646 | | |
| DM | 0.73 (0.25-2.07) | .558 | | |
| PH | 1.40 (0.43-4.49) | .571 | | |
| Lung cancer | 4.68 (2.05-10.6) | <.001 | 4.20 (1.79-9.82) | .001 |
| Lung function | | | | |
| $FEV_1$, % | 0.99 (0.96-1.03) | .888 | | |
| FVC, % | 0.98 (0.94-1.02) | .339 | | |
| $FEV_1$/ FVC, ratio | 3.89 (0.37-40.0) | .258 | | |

HRCT: high resolution computed tomography; HR: hazard ratio; UIP: usual interstitial pneumonia; COPD: chronic obstructive pulmonary disease; PH: pulmonary hypertension; $FEV_1$: the forced expiratory volume in one second; FVC: forced vital capacity; DM: Diabetes mellitus; CI = confidence interval. [a]All parameters at a significance level of p-value less than 0.10 in the univariate analysis were included in a multivariable model; [b]Model adjusted for HRCT findings, age, smoking history, cardiomyopathy, lung cancer, lung transplantation and CTD.

## DISCUSSION

Our study correlated the final multidisciplinary diagnosis with HRCT patterns of UIP, probable UIP, and indeterminate for UIP, based on clinical, radiological and pathological criteria to diagnose UIP of the latest ATS/ERS/JRS/ALAT guideline.[3] The majority of patients with typical UIP pattern had a final multidisciplinary diagnosis of IPF with CHP and CTD-ILD being the most prevalent differentials with this pattern. Most patients (97.1%) with a final multidisciplinary diagnosis of IPF had a typical or probable UIP pattern on CT. Notably, three patients with indeterminate UIP pattern were also diagnosed with IPF after a multidisciplinary evaluation. Patients with UIP pattern had a significantly higher mortality compared to the other two HRCT patterns.

Few studies have reported the general prevalence of interstitial lung diseases since their diagnosis is difficult in some cases and requires a specialized multidisciplinary team. It is known that the prevalence and etiological distribution of the ILD in a population varies according to the region worldwide. Most current studies are more focused on IPF; they determined the prevalence of IPF is higher in the United States and Europe (ranging from 10 to 60 cases per 100,000), compared to South America and East Asia,[1,7-12], and is indeed actually raising compared to previous years.[7-9] One explanation for this fact is due to an increase in knowledge about the disease, with greater awareness of diagnosis and treatment.[9] While in North America IPF, CTD-ILD, and CPH represent the most prevalent forms of ILD (corresponding to 20% each), a study in a French population put CTD-ILD (16%) and IPF (11.6%) as the top etiologies of ILD.[1,10] In contrast, the distribution of ILD in an Indian population was

47.3% of CHP, 13.9% of CTD-ILD, and 13.7% of IPF.[13] The distribution of ILD in our study mirrored that of the American studies, having IPF, CHP and CTD-ILD, as the most prevalent differential diagnoses of fibrosing ILD.

Our results are also in agreement with previous studies that have shown a high concordance between UIP pattern on HRCT and a multidisciplinary diagnosis of IPF.[5,14-17]. Chung et al.[18] showed that the correspondence of histopathological diagnosis of UIP is more often seen in those with definite and probable UIP on CT, compared to those with an indeterminate pattern. In a study with 214 subjects with IPF, Yagihashi et al.[19] found that 97,1% of the patients with an HRCT pattern of UIP had histologically definite or probable UIP. But they also showed that a large group of patients (94.7%) with "inconsistent with UIP" pattern on HRCT ended up with a pathological diagnosis of UIP, suggesting that the term "inconsistent" is actually misleading and not accurate. Likewise, a study with 59 subjects performed in a center with expertise in ILD demonstrated a high specificity of diagnosis of a new-onset IPF based on a clinical assessment or HRCT features alone, despite a relatively low sensitivity.[20]

It should be highlighted that HRCT alone without the appropriate clinical context cannot accurately establish the diagnosis of IPF since the pattern of UIP can be seen in other causes of ILD,[5] as demonstrated in our study. In light of that, both ATS/ERS/JRS/ALAT guideline and Fleischner Society's review emphasize the importance of differentiating CHP and CTD-ILD from IPF in patients with advanced fibrosing ILD,[3,5] in which the CT features often overlaps.[5,21] Although CHP is characterized by upper and middle-lobe predominant and peribronchovascular fibrosis with ground-glass opacities, poorly defined centrilobular nodules, mosaic attenuation and air trapping, it may eventually be subpleural and present honeycombing, mimicking UIP.[22, 23] In our service we use the diagnostic algorithm for CHP suggested by Vasakova et al.[22] that includes evaluation of occupational and environmental history, physical examination, HRCT pattern, serum specific IgGs, bronchoalveolar lavage (BAL)and lung biopsy in selected cases. If the patient has a positive history of exposure and/or IgGs with typical HP HRCT pattern and BAL showing lymphocytosis, the diagnosis of HP can be made with confidence. Otherwise, a biopsy is indicated.[22]

The same issue is also true for connective tissue disease. Chung et al.[24] recently demonstrated that 57.4% of patients with interstitial pneumonia with autoimmune features (IPAF) presented with UIP HRCT features.ATS/ERS/JRS/ALAT recommends that all patients with ILD should undergo serological tests to rule out CTD, although they do not have a consensus on which tests to perform routinely.[3] In our service, our initial approach includes serologies for C-reactive protein, erythrocyte sedimentation rate, antinuclear antibodies and rheumatoid factor.[2,25] Young patients, females and patients with signs and symptoms of CTD or positive serological tests are evaluated by a rheumatologist.[2,3,25] The prognosis of these diseases in cases of advanced fibrosis seems to be the same as for IPF, but when diagnosed in the early stages and treated correctly, it is substantially better.[2,23] These results confirm the importance of a multidisciplinary approach, correlating the clinical, radiological and pathological findings, especially in those patients with a non-characteristic clinical-radiological profile.

The patients with CT pattern of typical UIP were more likely to die or had lung transplantation compared to the other two patterns of UIP. This result is expected given the higher mortality of patients with IPF and also previous articles demonstrated worse outcome in those patients with definitive UIP on HRCT according to the 2011 ATS guidelines.[16,26-28] This fact may occur because UIP pattern on HRCT is more common in patients with a late stage of the disease, unlike the early stages, when radiological findings may be more atypical.[16,26-28]

Our study has a few limitations. First are the limitations inherent to the retrospective nature of the study. Second, since the patients were recruited in a single transplant reference center, the regional variability influences the results,because environmental factors, ethnicity, cultural habits and occupational risks are known to be related to the development of interstitial lung diseases.[9,10] Third, we do not have the histopathological data of all patients in particular to those with IPF, given the recent literature that supports withholding unnecessary biopsies to those patients. Thus, some degree of clinical uncertainty is often present in the benefit of the patient and also acknowledged by the Fleischer Society[5] and the ATS/ERS/JRS/ALAT guidelines.[3] We did not include patients with HRCT finding compatible with an alternative diagnosis, which could contribute to the overall distribution of the ILDs in our study.

In summary, we presented the prevalence of different multidisciplinary diagnosis of ILDs according to the latest HRCT patterns of UIP, probable UIP, and indeterminate for UIP by the 2018 ATS/ERS/JRS/ALAT guidelines. CHP and CTD-ILD were the primary differential diagnoses of IPF in patients with UIP pattern. Also, patients with HRCT typical UIP pattern were more likely to die or had lung transplantation in the follow-up.

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ORIGINAL ARTICLE

# Severity of lung involvement on chest X-rays in SARS-coronavirus-2 infected patients as a possible tool to predict clinical progression: an observational retrospective analysis of the relationship between radiological, clinical, and laboratory data

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## ABSTRACT

**Objective:** To investigate the diagnostic accuracy of a chest X-ray (CXR) score and of clinical and laboratory data in predicting the clinical course of patients with SARS coronavirus 2 (SARS-CoV-2) infection. **Methods:** This is a pilot multicenter retrospective study including patients with SARS-CoV-2 infection admitted to the ERs in three hospitals in Italy between February and March of 2020. Two radiologists independently evaluated the baseline CXR of the patients using a semi-quantitative score to determine the severity of lung involvement: a score of 0 represented no lung involvement, whereas scores of 1 to 4 represented the first (less severe) to the fourth (more severe) quartiles regarding the severity of lung involvement. Relevant clinical and laboratory data were collected. The outcome of patients was defined as severe if noninvasive ventilation (NIV) or intubation was necessary, or if the patient died. **Results:** Our sample comprised 140 patients. Most of the patients were symptomatic (132/138; 95.7%), and 133/140 patients (95.0%) presented with opacities on CXR at admission. Of the 140 patients, 7 (5.0%) showed no lung involvement, whereas 58 (41.4%), 31 (22.1%), 26 (18.6%), and 18 (12.9%), respectively, scored 1, 2, 3, and 4. In our sample, 66 patients underwent NIV or intubation, 37 of whom scored 1 or 2 on baseline CXR, and 28 patients died. **Conclusions:** The severity score based on CXR seems to be able to predict the clinical progression in cases that scored 0, 3, or 4. However, the score alone cannot predict the clinical progression in patients with mild-to-moderate parenchymal involvement (scores 1 and 2).

**Keywords:** Coronavirus infections; Radiography, thoracic; Pneumonia; Respiratory insufficiency; Severe acute respiratory syndrome.

## INTRODUCTION

In December 2019, an epidemic caused by the SARS coronavirus 2 (SARS-CoV-2) occurred in China. The most incident symptoms and clinical signs are related to impairment of the respiratory system.[1,2] Forms of interstitial pneumonia can be diagnosed and can sometimes require invasive ventilatory support. A rapid accurate assessment of pulmonary parenchymal damage is needed in order to design a tailored therapeutic plan.[1,3-6] CT is currently deemed the most sensitive imaging tool when coronavirus disease 2019 (COVID-19) is suspected, based on the detection of specific and highly suggestive signs (e.g., ground-glass opacities with or without consolidation in the lung periphery),[2,5-11] and recently published studies have investigated the potential role of artificial intelligence based on CT images to assess the severity of the disease and to predict the final clinical outcome.[12-14] However, chest X-rays are frequently requested in patients with acute pulmonary symptoms admitted to the ER, as well as in critical patients in the ICU, being a technique that is inexpensive, is largely available at the bedside, and has low radiation exposure. The relatively low sensitivity of chest X-rays in patients with a SARS-CoV-2-related interstitial pneumonia[15-17] could be overcome by combining chest X-rays with clinical and laboratory data, including arterial blood gas (ABG) analysis.

This pilot retrospective study aims at investigating the diagnostic accuracy of a chest X-ray score and of clinical and laboratory data in predicting the outcome of patients with SARS-CoV-2 pulmonary infection.

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## METHODS

### Study population

A pilot retrospective multicenter study was carried out in three Italian institutions (Cattinara Hospital and Maggiore Hospital, both located in the city of Trieste; and *Azienda Ospedaliera Universitaria*, in the city of Sassari). Patients with SARS-CoV-2 infection, confirmed by a positive RT-PCR result from nasopharyngeal swabs performed at admission to the ER between February and March of 2020, were retrospectively identified. Patients were included if they were ≥ 18 years of age and had a chest X-ray performed at the onset of the respiratory symptoms. The most relevant clinical and epidemiological data, including smoking status, major comorbidities, and signs and symptoms at the onset of the disease were collected from the medical records of all patients (Table 1).

The clinical course of the patients was considered nonsevere when there was no hospitalization or when only oxygen therapy was necessary during hospital stay. The clinical course was considered severe when there was a need for noninvasive ventilation (NIV) or intubation or if the patient died, considered as a composite outcome and as single outcomes.

### Chest X-ray imaging

Chest X-rays were obtained using the following equipment: Definium 8000 (GE Healthcare, Chalfont St Giles, United Kingdom) and Visitor T30R (Villa Sistemi Medicali, Buccinasco, Italy) in the hospitals in Trieste; and Mobilett XP Hybrid (Siemens Healthineers, Erlangen, Germany) in the *Azienda Ospedaliera Universitaria* in Sassari. All chest X-rays were performed in a single frontal projection in a posteroanterior view if the patient was able to maintain the standing position; in the remaining cases, an anteroposterior view in the sitting or supine position was acquired.

All chest X-rays were independently evaluated by two radiologists with experience in thoracic imaging (15 and 6 years' experience, respectively); discrepant interpretations of the images were resolved by consensus. The radiologists used a semi-quantitative score in order to quantify the extent of pulmonary involvement (by less or more dense consolidations) on the chest X-rays (Figure 1). This severity score was adapted from the one proposed by Feng et al.[18] for patients with pneumonia secondary to avian influenza virus infection and was calculated as follows: each lung was divided craniocaudally into three main zones. The upper zone included the parenchymal region above the carina, the middle zone included the parenchyma below the carina and above the inferior pulmonary vein, and the lower zone involved the parenchyma below the inferior pulmonary vein; given their anatomical extent, the middle and lower zones were further divided into a lateral and a medial area (i.e. five regions per lung for a total of ten regions). A maximum of 10% of parenchymal involvement was assigned for each area. If an area was partly spared, a score of 5% was considered. The scores of each lung were summed up to provide the final severity score. A score of 0 was defined as a total lung involvement of 0%, whereas a score of 1, 2, 3, and 4 indicated a total lung involvement in the range of 1-25%, 26-50%, 51-75%, and 76-100%, respectively.

Patients underwent a follow-up chest X-ray if there was worsening of the clinical symptoms, if a chest device was placed, or if the response to therapy needed to be assessed. These follow-up exams were scored as well.

### Laboratory data

Baseline laboratory data obtained within 24 h from admission were recorded, including white blood cell (WBC) count, C-reactive protein (CRP), and ABG analysis (pH, $PaO_2$, $PaCO_2$, $SaO_2$, and $HCO_3$). In the present study, the major parameter obtained from the ABG analysis was the $PaO_2/FiO_2$ ratio, classified as follows: a $PaO_2/FiO_2$ ratio > 300 (normal); between 300 and 200 (mild hypoxia); between 200 and 100 (moderate hypoxia), and < 100 (severe hypoxia).[19]

### Statistical analysis

An *ad hoc* electronic database was created to compile all of the variables in our study. Qualitative variables were described as absolute and relative frequencies. Quantitative variables were expressed as means and standard deviations or as medians and interquartile ranges (IQR) in case of parametric or nonparametric distribution, respectively. Qualitative variables were compared with the chi-square test or the Fisher's exact test when appropriate, whereas the Mann-Whitney test was used in order to detect any statistical differences in the comparison of nonparametric quantitative variables.

For correlations between the chest X-ray scores and the clinical outcomes of patients only the baseline chest X-rays were considered. Intraclass correlation coefficients were computed to assess interobserver reproducibility. Logistic regression analyses were carried out to assess the relationship of independent clinical, epidemiological, and demographic variables with individual and composite severe outcomes (i.e., NIV, intubation, or death). A two-tailed p-value < 0.05 was considered statistically significant. The Stata statistical software package, version 16 (StataCorp LP, College Station, TX, USA) was used for data processing and statistical analysis.

## RESULTS

The study involved 140 patients, 86 (61.1%) being male. The median age was 71 (IQR: 58.8-80.0) years. Only 26 patients (18.7%) were current smokers. The most common comorbidity was hypertension, in 79 patients (56.8%), followed by diabetes, in 38 (27.3%). Almost all of the patients were symptomatic at admission to the ER (n = 134; 95.7%). Common symptoms were fever (in 87.1%), dyspnea (in 56.8%), and cough (in 50.0%). During follow-up, 73 of the 140 patients met the composite severe outcome criteria,

**Table 1.** Characteristics of the study patients (N = 140) at baseline and outcomes.[a]

| Characteristic | | Result |
|---|---|---|
| Male, n (%) | | 86/140 (61.4) |
| Age, years | | 71 [58.5-80.0] |
| Age bracket, n (%) | < 50 years | 18/140 (12.9) |
| | 50-75 years | 72/140 (51.4) |
| | > 75 years | 50/140 (35.7) |
| Smoking status, n (%) | Never smoker | 100/139 (71.9) |
| | Current smoker | 26/139 (18.7) |
| | Former smoker | 13/139 (9.4) |
| RT-PCR, n (%) | | 139/139 (100.0) |
| **Comorbidities** | | |
| Presence of comorbidity, n (%) | | 116/139 (83.5) |
| BMI > 30 kg/m$^2$, n (%) | | 23/139 (16.6) |
| COPD, n (%) | | 15/139 (10.8) |
| Diabetes, n (%) | | 38/139 (27.3) |
| Hypertension, n (%) | | 79/139 (56.8) |
| CHD, n (%) | | 29/139 (20.9) |
| Liver disease, n (%) | | 6/139 (4.3) |
| Cancer, n (%) | | 24/139 (17.3) |
| Kidney disease, n (%) | | 23/138 (16.7) |
| Immunodeficiency, n (%) | | 0/139 (0.0) |
| **Symptoms** | | |
| Presence of a symptom, n (%) | | 132/138 (95.7) |
| Fever, n (%) | | 121/139 (87.1) |
| Cough, n (%) | | 69/138 (50.0) |
| Sputum, n (%) | | 17/138 (12.3) |
| Dyspnea, n (%) | | 79/139 (56.8) |
| **Baseline chest X-rays** | | |
| Time from the onset of symptoms to performing X-ray, days | | 4 [1-8] |
| Chest X-ray score, n (%) | No lung involvement | 7/140 (5.0) |
| | Lung involvement, 1-25% | 58/140 (41.4) |
| | Lung involvement, 26-50% | 31/140 (22.1) |
| | Lung involvement, 51-75% | 26/140 (18.6) |
| | Lung involvement, 76-100% | 18/140 (12.9) |
| **Baseline laboratory data** | | |
| WBC/mL | | 5,920 [4,145-8,850] |
| CRP, mg/L | | 29.6 [11.6-101.4] |
| pH | | 7.45 ± 0.04 |
| $PaO_2$, mmHg | | 62.7 [53.4-76.6] |
| $PaCO_2$, mmHg | | 34.5 ± 5.2 |
| $SaO_2$, % | | 94.7 [91-96] |
| $HCO_3$, mmol/L | | 24.5 ± 2.7 |
| $PaO_2/FiO_2$ ratio | | 279.0 [173.5-333.5] |
| Mild hypoxia, n (%) | | 25/97 (25.8) |
| Moderate hypoxia, n (%) | | 25/97 (25.8) |
| Severe hypoxia, n (%) | | 13/97 (13.4) |
| **Outcome** | | |
| Oxygen therapy, n (%) | | 96/140 (68.6) |
| NIV, n (%) | | 38/140 (27.1) |
| Intubation, n (%) | | 28/140 (20.0) |
| Death, n (%) | | 28/138 (20.9) |
| Recovery, n (%) | | 41/113 (36.3) |
| Patient management, n (%) | Discharge | 9/115 (7.8) |
| | Hospitalization | 66/115 (57.4) |
| | ICU | 40/115 (34.8) |

BMI: body mass index; CHD: coronary heart disease; WBC: white blood cell; CRP: C-reactive protein; and NIV: noninvasive ventilation. [a]Values expressed as mean ± SD or median [interquartile range], except where otherwise indicated.

and 28 (20.9%) died. The mean time between hospital admission and death was 7.0 ± 3.8 days (Table 1).

Of the 140 patients, 7 (5%) had no lung involvement (were scored 0) on the baseline chest X-ray, 58 (41.4%) were scored 1, 31 (22.1%) were scored 2, 26 (18.6%) were scored 3, and 18 (12.9%) were scored 4. Follow-up X-rays of the chest were performed in 74 patients, all of which showing scores ≥ 1—mean follow-up period = 6 days (range: 1-17 days). Scores of 1, 2, 3, and 4 were found, respectively, in 14, 11, 23, and 26 patients. None of the patients with a baseline score of 3 or 4 showed a decrease in their follow-up scores (Table 2). The intraclass correlation coefficient to assess interobserver reproducibility was 0.95 (95% CI: 0.93-0.96).

Routine blood tests were performed in all patients at admission to the ER, and ABG analyses were performed in 97 patients (69.0%).

A nonsevere clinical course (no NIV, intubation, or death) was associated with a statistically significant smaller proportion of patients with a score of 3 or 4 on the baseline chest X-ray (10.5% and 4.5%, respectively; Table 3). None of the patients who were scored 0 on the baseline chest X-ray score had a severe clinical course. Patients with a severe clinical course had significantly higher median absolute WBC (p = 0.02) and CRP (p = 0.0006). In addition, the median $PaO_2/FiO_2$ ratio was lower in patients with severe disease—207.5 (IQR: 127.5-285.0)—in comparison with that of those with nonsevere disease—326.0 (IQR: 279.0-387.5; p < 0.0001; Figure 2).

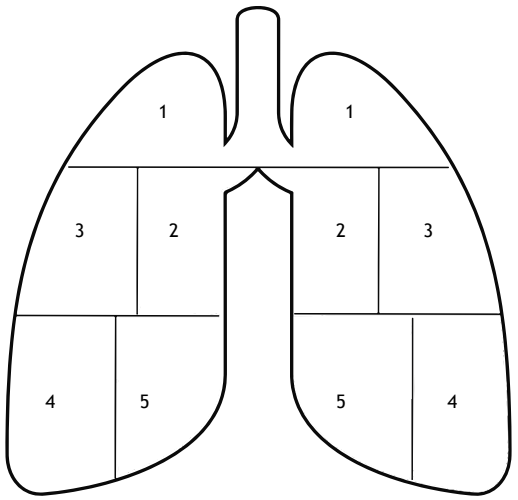


**Figure 1.** Chest X-ray score. Each lung is divided into three main zones (upper, middle, and lower) comprising five regions (for a total of ten regions), with a maximum of 10% of parenchymal involvement for each region.

Table 3 shows the demographic, radiological, and laboratory characteristics of the study patients, by outcome—composite outcome (NIV/intubation/death) and each of the outcomes separately. No radiological differences were found between those who underwent NIV and those who did not, whereas the proportion of patients with a score of 4 was higher among those who were intubated (25%; p = 0.03) or died (35.7%; p < 0.0001). Median $PaO_2/FiO_2$ ratio was statistically lower in patients who underwent NIV (n = 254; p = 0.04), were intubated (n = 181; p = 0.005), or died (n = 167; p = 0.002). Median absolute WBC was significantly higher only in patients who died (9,330 cells/mL; p = 0.001), whereas median CRP was statistically more elevated in patients under NIV (90.8 mg/L; p = 0.001) and in those who died (71.1 mg/L; p = 0.02).

Logistic regression analyses showed that severe outcomes (NIV, intubation, or death) were associated with diabetes (OR: 4.1; p = 0.049) and moderate hypoxia (OR: 19.0; p = 0.02). The same risk factors were found for the individual outcome "intubation" (Tables S1-S4 in the supplementary material).

## DISCUSSION

In our study, we performed a semi-quantitative analysis of lung involvement based on chest X-rays in patients with SARS-CoV-2 infection. Of the 140 patients, 133 (95.0%) showed lung opacities at admission, and 89 (63,5%) presented with mild-to-moderate lung involvement (scores 1 and 2).

HRCT has greater sensitivity and specificity in identifying viral pneumonia when compared with chest X-rays, especially in an early phase of the disease.[13,15] Even though the sensitivity of CT is greater than is that of chest X-ray,[14-16] the latter remains the first imaging technique of choice in patients with respiratory illnesses due to its wide availability, rapidity, low radiation exposure, and low costs.[17] Furthermore, the use of portable X-ray machines can minimize the risk of transmission and diffusion of the disease, because the infection is contained inside the isolation room of the patient.[20] Wong et al.[16] showed that chest X-rays are useful for demonstrating the presence of pulmonary abnormalities in patients with SARS-CoV-2 infection and

**Table 2.** Chest X-ray findings during the follow-up period (n = 78).

| Chest X-ray score | Baseline | Follow-up | p |
|---|---|---|---|
| No lung involvement, n (%) | 1 (1.3) | - | - |
| Lung involvement, 1-25%, n (%) | 35 (44.9) | 15 (19.2) | 0.0006 |
| Lung involvement, 26-50%, n (%) | 17 (21.8) | 11 (14.1) | 0.21 |
| Lung involvement, 51-75%, n (%) | 14 (18.0) | 25 (32.1) | 0.04 |
| Lung involvement, 76-100%, n (%) | 11 (14.1) | 27 (34.6) | 0.003 |
| Chest x-ray score, median (IQR) | 2 (1-3) | 3 (2-4) | < 0.0001 |

IQR: interquartile range.

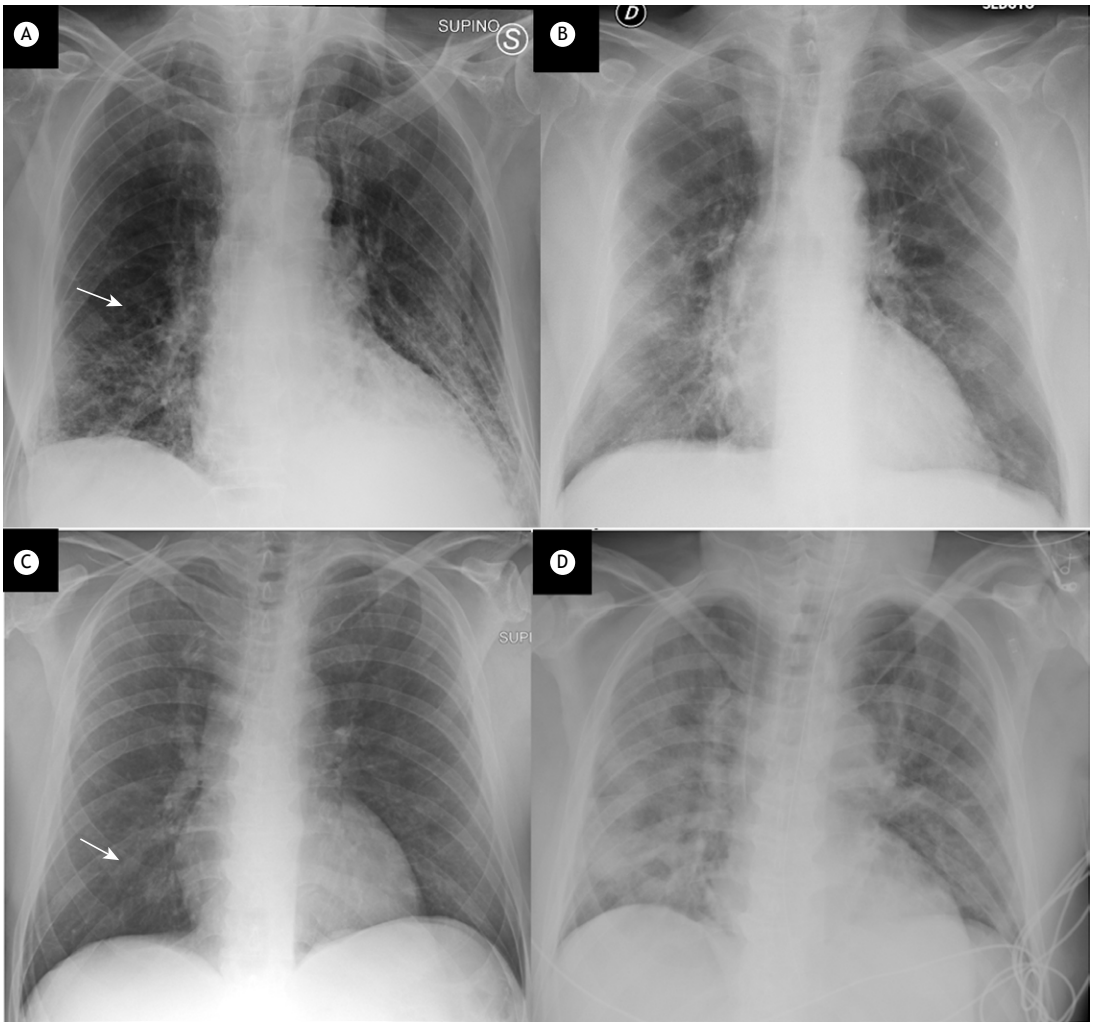


**Figure 2.** In A and B, chest X-rays of a 72-year-old male patient. In A, the chest X-ray was scored 2 due to right perihilar opacities (arrow). The patient presented with a $PaO_2/FiO_2$ ratio = 86 and CRP = 58 mg/L at admission to the ER; NIV was required. In B, a follow-up chest X-ray seven days later was scored 2 again (bilateral opacities). In C and D, chest X-rays of a 62-year-old male patient. In C, the chest X-ray was scored 1 due to unilateral opacity (arrow). The patient presented with a $PaO_2/FiO_2$ ratio = 103 and CRP = 165 mg/L at the onset of symptoms. In D, a chest X-ray performed two days later was scored 4 due to the presence of bilateral and diffuse opacities. The patient was referred to the ICU and intubated.

for providing a baseline for both future examinations and the monitoring of response to therapy. Our study demonstrated the probable predictive role of X-rays in patients with no lung involvement (score 0) and in those with extensive lung disease (scores 3 and 4). In patients with mild lung parenchymal involvement (scores 1 and 2), the chest X-ray score alone was unable to predict the clinical outcome.

Follow-up X-rays of the chest are generally required to evaluate possible complications, the radiological progression of the disease, and the response to therapy, as well as to assess the placement of chest devices (e.g., central venous catheter, endotracheal cannula, pleural tube, etc.). Although the correlation of a follow-up chest X-ray score with the outcome of patients was not analyzed in the present study, this should be investigated in future studies in order to determine whether there is a correlation between radiological and clinical progression of the disease, as well as to further evaluate the predictive value of a chest X-ray score obtained at baseline.

In our study, baseline CRP levels were significantly higher in patients who needed NIV, died, or met the composite outcome criteria (NIV/intubation/death). A recent study suggested that CRP levels correlate with a CT scan severity score and may predict SARS-CoV-2 lung infection or unfavorable outcomes in patients with viral pneumonia.[21] Our data confirm the relationship between CRP and poor prognosis even in patients with mild-to-moderate lung impairment.

Our results showed that baseline WBC counts were significantly higher in patients requiring NIV, in those who met the composite outcome criteria, and in those who died. This is in line with one meta-analysis[22]

**Table 3.** Demographic, radiological, and laboratory characteristics of the study patients, by outcome—composite outcome (noninvasive ventilation/intubation/death) and each of the outcomes separately.[a]

| Characteristic | | NIV/intubation/death | | |
|---|---|---|---|---|
| | | No (n = 67) | Yes (n = 73) | p |
| Male, n (%) | | 37 (55.2) | 49 (67.1) | 0.15 |
| Age, years | | 71 [54-80] | 71 [60-80] | 0.42 |
| Chest X-ray score, n (%) | No lung involvement | 7 (10.5) | 0 (0.0) | 0.005 |
| | Lung involvement, 1-25% | 33 (49.3) | 25 (34.3) | 0.07 |
| | Lung involvement, 26-50% | 17 (24.4) | 14 (19.2) | 0.38 |
| | Lung involvement, 51-75% | 7 (10.5) | 19 (26.0) | 0.02 |
| | Lung involvement, 76-100% | 3 (4.5) | 15 (20.6) | 0.005 |
| $PaO_2/FiO_2$ ratio | | 326.0 [279.0-387.5] | 207.5 [127.5-285.0] | < 0.0001 |
| WBC/mL | | 5,600 [4,000-7,220] | 6,980 [4,230-9,920] | 0.02 |
| CRP, mg/L | | 20.6 [4.4-71.8] | 59.1 [18.8-134.6] | 0.0006 |
| **Characteristic** | | **NIV** | | |
| | | **No (n = 102)** | **Yes (n = 38)** | **p** |
| Male, n (%) | | 60 (58.8) | 26 (68.4) | 0.30 |
| Age, years | | 72.0 [60.0-81.0] | 66.5 [58.0-72.0] | 0.03 |
| Chest X-ray score, n (%) | No lung involvement | 7 (6.9) | 0 (0.0) | 0.19 |
| | Lung involvement, 1-25% | 42 (41.2) | 16 (42.1) | 0.92 |
| | Lung involvement, 26-50% | 23 (22.6) | 8 (21.1) | 0.85 |
| | Lung involvement, 51-75% | 17 (16.7) | 9 (23.7) | 0.34 |
| | Lung involvement, 76-100% | 13 (12.8) | 5 (13.2) | 0.95 |
| $PaO_2/FiO_2$ ratio | | 285.5 [185.5-354.5] | 254 [127.5-292.0] | 0.04 |
| WBC/mL | | 6,140 [4,445-8,930] | 4,935 [4.020-8,520] | 0.33 |
| CRP, mg/L | | 22.1 [9.0-82.9] | 90.8 [19.5-155.5] | 0.001 |
| **Characteristic** | | **Intubation** | | |
| | | **No (n = 112)** | **Yes (n = 28)** | **p** |
| Male, n (%) | | 62 (55.4) | 24 (85.7) | 0.004 |
| Age, years | | 71.5 [57.0-81.0] | 67.5 [62.5-72.0] | 0.30 |
| Chest X-ray score, n (%) | No lung involvement | 7 (6.3) | 0 (0.0) | 0.35 |
| | Lung involvement, 1-25% | 48 (42.9) | 10 (35.7) | 0.49 |
| | Lung involvement, 26-50% | 28 (25.0) | 3 (10.7) | 0.13 |
| | Lung involvement, 51-75% | 18 (16.1) | 8 (28.6) | 0.13 |
| | Lung involvement, 76-100% | 11 (9.8) | 7 (25.0) | 0.03 |
| $PaO_2/FiO_2$ ratio | | 287.5 [223.0-352.0] | 181.0 [138.0-240.0] | 0.005 |
| WBC/mL | | 5,765 [4,070-8,835] | 6,860 [4,450-9,140] | 0.34 |
| CRP, mg/L | | 39.6 [11.8-102.7] | 20.8 [10.7-68.4] | 0.49 |
| **Characteristic** | | **Death** | | |
| | | **No (n = 110)** | **Yes (n = 28)** | **p** |
| Male, n (%) | | 68 (61.8) | 16 (57.1) | 0.65 |
| Age, years | | 67.0 [56.0-76.0] | 81.5 [75.0-86.5] | < 0.0001 |
| Chest X-ray score, n (%) | No lung involvement | 7 (6.4) | 0 (0.0) | 0.34 |
| | Lung involvement, 1-25% | 51 (46.4) | 6 (21.4) | 0.02 |
| | Lung involvement, 26-50% | 25 (22.7) | 6 (21.4) | 0.88 |
| | Lung involvement, 51-75% | 19 (17.3) | 6 (21.4) | 0.91 |
| | Lung involvement, 76-100% | 8 (7.3) | 10 (35.7) | < 0.0001 |
| $PaO_2/FiO_2$ ratio | | 285 [222-348] | 167 [77-209] | 0.002 |
| WBC/mL | | 5,610 [4,010-8,000] | 9,330 [5,115-11,500] | 0.001 |
| CRP, mg/L | | 25.7 [10.5-92.1] | 71.1 [19.8-147.8] | 0.02 |

WBC: white blood cell; CRP: C-reactive protein; and NIV: noninvasive ventilation. [a]Values expressed as median [interquartile range], except where otherwise indicated.

that investigated biochemical and immune biomarker abnormalities associated with severe illness and mortality in patients with COVID-19. The results showed that patients who died had a significant increase in the WBC count, due to both an increase in the neutrophil count and a decrease in the lymphocyte count.

SARS-CoV-2 infects alveolar epithelial cells in the lungs and causes pneumonia or ARDS (in severe cases).[23] In our study, the degree of hypoxia of the patients was assessed using the $PaO_2/FiO_2$ ratio. Severely ill patients had a lower baseline $PaO_2/FiO_2$ ratio values than did nonseverely ill patients. In addition, the patients who died had a significantly lower $PaO_2/FiO_2$ ratio at baseline. These results confirm that a low $PaO_2/FiO_2$ ratio at baseline is predictive of poor outcomes in patients with COVID-19, similarly to what occurs in patients with ARDS caused by other conditions. Patients with such characteristics should be promptly evaluated by ICU specialists for early intubation and respiratory maneuvers with the patient in the prone position, which have been shown to reduce lung stress and strain in patients with ARDS.[24]

These considerations might have clinical relevance in both low- and high-income countries and highlight the potential role of routine clinical and laboratory parameters integrated with chest X-rays, a low-cost and largely available technique, to stratify infected patients according to their risk of worsening.

Our study has limitations. Firstly, no control CT scans were available, which might have caused underdetection of opacities on chest X-rays. Only 2 patients underwent a CT scan within two days after the onset of symptoms because of a discrepancy between clinical symptoms and the radiological severity of the disease. Those patients presented with doubtful findings on their chest X-rays but had severe respiratory insufficiency. Another limitation was the small sample size, which is due to the nature of the study, and our results therefore require confirmation with a greater number of patients.

In conclusion, the severity score based on chest X-rays seems to be able to predict the clinical outcome in patients with COVID-19 when there is no lung involvement (score 0) and in severe cases (scores 3 and 4). However, a radiographic score alone is unable to predict the clinical outcome in patients with mild-to-moderate parenchymal involvement (scores 1 and 2). In these cases, the score should be associated with clinical and laboratory data in order to identify, at the onset of symptoms, those patients who may require ventilatory support during hospitalization.

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ORIGINAL ARTICLE

# Smoking history: relationships with inflammatory markers, metabolic markers, body composition, muscle strength, and cardiopulmonary capacity in current smokers

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## ABSTRACT

**Objective:** To determine the relationships that smoking history has with inflammatory markers, metabolic markers, body composition, muscle strength, and cardiopulmonary capacity in current smokers. **Methods:** This was a cross-sectional study involving 65 smokers (age range: 18-60 years). On three non-consecutive days, each participant was evaluated in terms of smoking history, pre-existing comorbidities, lung function (by spirometry), peripheral muscle strength (by dynamometry), body composition (by bioelectrical impedance analysis), levels of metabolic/inflammatory markers, and maximum cardiopulmonary capacity (by treadmill exercise test). We evaluated the relationships that smoking history has with inflammatory markers, metabolic markers, body composition, muscle strength, and cardiopulmonary capacity, using logarithmic transformation of the data and calculating Pearson's correlation coefficient and for partial correlations adjusted for age, gender, body mass index (BMI), and comorbidities. To identify the influence of smoking history on pre-existing comorbidities, we used a logistic regression model adjusted for age, BMI, and duration of smoking. **Results:** Smoking history correlated significantly, albeit weakly, with triglyceride level ($r = 0.317$; $p = 0.005$), monocyte count ($r = 0.308$; $p = 0.013$), and waist circumference ($r = 0.299$; $p = 0.017$). However, those correlations did not retain their significance in the adjusted analysis. In the logistic regression model, smoking more than 20 cigarettes/day correlated significantly with the presence of metabolic diseases (OR = 0.31; 95% **CI:** 1.009-1.701; $p = 0.043$). **Conclusions:** In this sample of smokers, smoking history correlated positively with the triglyceride level, the monocyte count, and waist circumference. The prevalence of metabolic disease was highest in those who smoked more than 20 cigarettes/day.

**Keywords:** Tobacco; Smoking; Triglycerides; Monocytes; Waist circumference; Body composition.

## INTRODUCTION

Smoking is considered a chronic disease.[1] Tobacco use causes more than 7 million deaths per year[2] and is responsible for the development of various conditions,[3] such as atherosclerotic diseases, which cause mild inflammation and can lead to dyslipidemias[4] and sarcopenia through a catabolic response of the skeletal muscles.[5]

Smoking affects the lipid profile, reducing the level of HDL, which is cardioprotective, as well as increasing total cholesterol, LDL, and triglyceride levels.[6] As a consequence, it causes endothelial dysfunction, oxidative stress, dyslipidemias, atherosclerosis, and cardiovascular diseases.[6]

Smoking can also change body composition, which, in turn, affects glucose homeostasis, diminishing pancreatic β-cell function and leading to insulin resistance. This process negatively influences the waist-to-hip ratio and the visceral fat profile of smokers, predictors of morbidity and mortality[7] that are hallmarks of metabolic syndrome, which results in arterial hypertension, insulin resistance, abnormal cholesterol levels, and fat deposition in the abdominal region.[8]

Smoking is an external agent that attacks the respiratory system, leading to an increase in local defense cells, such as monocytes, lymphocytes, eosinophils, leukocytes, and neutrophils.[9] Chronic smoking affects the functioning of the peripheral immune system and can lead to low-grade chronic inflammation.[9] In addition, it can predispose an individual to the development of COPD, generating an abnormal inflammatory response in the lungs, loss of skeletal muscle mass, and muscle dysfunction.[10] The proteolysis triggered by tobacco use results in muscle

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atrophy and a consequent decrease in cardiopulmonary capacity.[10,11]

The magnitude of the negative impact of smoking is related to what is known as the smoking history. Although smoking fewer cigarettes per day for a longer period of time has been shown to be more harmful than is smoking more cigarettes per day for a shorter period of time,[12] calculating the number of pack-years is still considered an appropriate way to investigate the relationship between smoking history and the risk profile in this population.

The objective of the present study was to evaluate the relationships that smoking history has with inflammatory markers, metabolic markers, body composition, and muscle strength, as well as cardiopulmonary capacity, in current smokers.

## METHODS

We evaluated 65 smokers between 18 and 60 years of age (Figure 1). All of the procedures performed in this study were approved by the Research Ethics Committee of the School of Science and Technology of São Paulo State University, Presidente Prudente Campus (Reference no. 53299816.9.0000.5402). All participants gave written informed consent.

The study included smokers who were clinically stable and had a body mass index (BMI) < 40 kg/m$^2$. Individuals who did not complete all evaluations were excluded from the study, as were those who had changed their medication in the last 30 days, those who had a pre-existing chronic respiratory diseases ($FEV_1$/FVC ratio < 0.7), those who had cancer, those who had an uncontrolled cardiac or metabolic disease, and those who used nicotine replacement therapy or antidepressants as smoking cessation aids.

### *Study design*

This was a cross-sectional study in which participants were evaluated on three non-consecutive days. All tests were done in the morning in a temperature- and humidity-controlled environment (22.0°C ± 2.2°C and 56.6% ± 6.9%, respectively). Participants were instructed not to consume tobacco, alcohol, caffeine, analgesics, or barbiturates 12 h before the evaluations. All evaluations were overseen by specialized professionals.

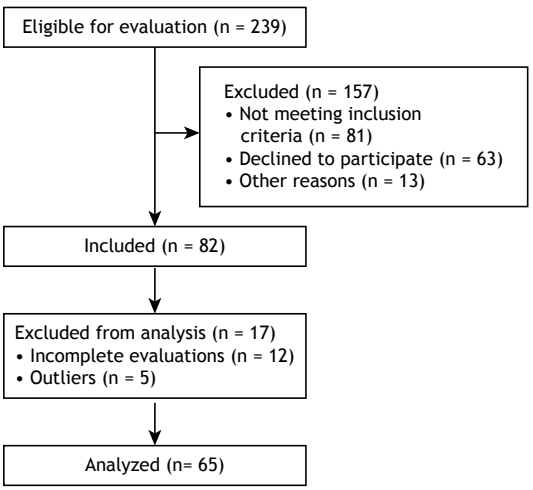


**Figure 1.** Study flowchart.

On the first day of evaluations, participant histories were taken and personal data (gender, age, weight, and height) were collected, as were data related to smoking (duration of smoking, number of cigarettes/day, smoking history, and level of nicotine dependence) and pre-existing comorbidities (cardiovascular or metabolic diseases such as systemic arterial hypertension, type 2 diabetes mellitus, and dyslipidemia). On the same day, lung function was evaluated by spirometry and peripheral muscle strength was evaluated by dynamometry. On the second day, body composition was evaluated by bioelectrical impedance analysis and peripheral venous blood was drawn for biochemical analysis. On the third day, each participant underwent a treadmill exercise test to determine maximum cardiopulmonary capacity and maximum oxygen consumption ($VO_{2max}$).

### *Procedures*

Each participant answered questions about the number of cigarettes smoked per day and duration of smoking. Their level of nicotine dependence was assessed with the Fagerström test,[13] which classifies nicotine dependence into five levels[14]: very low (0 to 2 points); low (3 to 4 points); moderate (5 points); high (6 to 7 points); and very high (8 to 10 points). For each participant, the smoking history (pack-years) was calculated with the following formula: *the number of cigarettes smoked per day* divided by 20 and multiplied by *the number of years of smoking*.

The level of exhaled carbon monoxide was measured with a portable carbon monoxide monitor (Micro CO; Micro Medical Ltd., Rochester, England). Participants were instructed to take a deep breath and hold it for 15-20 s and then exhale slowly and constantly.[15] The exhaled carbon monoxide level was measured before the other evaluations to make sure that they had gone 12 h without smoking. The cut-off point to be achieved in order to go on to the other tests was 10 ppm.[16]

Lung function was evaluated with a portable MIR-Spirobank spirometer, version 3.6 (Medical International Research, Rome, Italy). The results were interpreted in accordance with the standards of the American Thoracic Society/European Respiratory Society,[17] and we employed reference values for the Brazilian population.[18] The lung function pattern was established in relation to the lower limit of normal (LLN) for an obstructive pattern ($FEV_1$/FVC ratio < LLN and FVC ≥ LLN), a restrictive pattern ($FEV_1$/FVC ratio ≥ LLN and FVC < LLN), and a mixed pattern ($FEV_1$/FVC ratio < LLN and FVC < LLN).[19]

An electronic dynamometer (Power Din Standard; CEFISE, São Paulo, Brazil) was used in order to

estimate peripheral muscle strength for the muscle groups responsible for the following movements[20]: shoulder flexion, elbow flexion, shoulder abduction, knee extension, and knee flexion. Each test was performed three times, with specific dynamometer cables connected to the load cell and to the computer, and a one-minute interval between each attempt. Peak force and mean force were measured (in kgf). The highest values obtained for each variable and segment were recorded for analysis.

The InBody 720 device (InBody, Cerritos, CA, USA) was used for assessing body composition, including weight, BMI, body fat percentage, muscle mass, fat mass, waist circumference, and waist-to-hip ratio. The device has eight electrodes: four for each hand—in contact with the palm (E1 and E3) and thumb (E2 and E4); and four for each foot—in contact with the sole (E5 and E7) and heel (E6 and E8).[21,22] Participants were instructed to fast for 12 h and not to engage in moderate or vigorous exercise for 24 h before the evaluation.

After the 12-h fast, 14-mL samples of peripheral venous blood were collected by qualified professionals using disposable and sterilized materials. The blood specimens were collected into three vacuum tubes, centrifuged for 15 min at 3,500 rpm to separate the product to be analyzed and have the levels of triglyceride, total cholesterol, HDL, LDL, and glucose determined. The biological material was stored at −70°C, in accordance with the manufacturer's instructions. Glucose and lipid profile analyses were run on a spectrophotometer (SpectraMax Plus 384; Molecular Devices LLC, San Jose, CA, USA). Complete blood count and platelet count were performed by a specialized laboratory in an automated hematology analyzer (STKS; Coulter Electronics of Canada, Burlington, Canada).

For the evaluation of the maximal functional capacity, participants were submitted to a treadmill exercise test at an initial speed of 5.0 km/h, a constant incline of 1%, and speed increases of 0.5 km/h every 2 min. The test was continued until voluntary fatigue ($VO_{2max}$).[23] The HR and $SpO_2$ were monitored continuously; the subjective perception of exertion was rated according to the Borg dyspnea scale. In addition, the ventilatory variables were determined breath by breath with a pulmonary function testing system (Quark PFT; Cosmed, Rome, Italy), which was previously calibrated for each test in accordance with the manufacturer's specifications.

The $VO_{2max}$ was presumed to be the highest mean oxygen consumption in the last 30 s of exercise, when at least two of the following three criteria were met: HR > 90% of the age-predicted maximum (220 − age); respiratory exchange ratio > 1.10; and variation in $VO_2$ between the penultimate and final stages of the exercise < 2.1 mL/kg per min. If a participant became fatigued before the end of the stage, the $VO_{2max}$ was calculated with the following equation:

$$VO_{2peak} = Scom + (t/180) \times I$$

where *Scom* stands for the last stage completed by the participant; *t* stands for the time spent in the last incomplete load (the duration of each stage being 180 s); and *I* stands for the speed increment (0.5 km/h).

### *Statistical analysis*

We tested the data for normality with the Shapiro-Wilk test and found that they had a non-normal distribution. The data were therefore expressed as medians and interquartile ranges (IQRs). We evaluated the relationships that smoking history had with inflammatory markers, metabolic markers, body composition, muscle strength, and cardiopulmonary capacity, using logarithmic transformation to decrease the variability of the nonparametric variables, except for qualitative data, such as gender and comorbidities. For those data, we used Pearson's correlation coefficient and partial correlations adjusted for age, gender, BMI, and comorbidities. The responses were classified (by correlation coefficient) as weak (< 0.4), moderate (≥ 0.4 and < 0.5), or strong (≥ 0.5).[24] We then used a linear regression model adjusted for the same confounders.

The logistic regression model adjusted for age, BMI, and duration of smoking was used in order to identify the influence of smoking history on pre-existing comorbidities. The participants were divided into two groups: those who smoked ≤ 20 cigarettes/day (n = 12) and those who smoked > 20 cigarettes/day (n = 53). Comorbidities were classified as present (1) or absent (0). The increase in relative risk was calculated with the following formula: [Exp(B) − 1] × 100. All analyses were carried out with the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA). A significance level of 5% was used for all tests.

## RESULTS

Table 1 shows the general characteristics of our sample (N = 65), including smoking history, as well as demographic, anthropometric, and lung function data. Based on the LLN, 57 participants (88%) had a normal spirometry pattern, whereas 2 (3%) had an obstructive pattern, 4 (6%) had a restrictive pattern, and 2 (3%) had a mixed pattern.

Table 2 shows the data on inflammatory markers, metabolic markers, muscle strength, cardiopulmonary capacity, and the presence of comorbidities in our study sample. All of the participants with cardiovascular disease had systemic arterial hypertension. Of the 6 participants with metabolic disease, 5 had dyslipidemia and 1 had type 2 diabetes mellitus.

Figure 2 shows the analyses of the Pearson's correlation coefficients, in which we found that smoking history showed weak positive correlations with the triglyceride level (r = 0.317; p = 0.005), monocyte count (r = 0.308; p = 0.013), and abdominal circumference (r = 0.299; p = 0.017). No significant correlations were found between smoking history and

the covariates in the partial correlations adjusted for age, gender, BMI, and comorbidities.

Finally, the logistic regression revealed that participants who smoked more than 20 cigarettes/day had an OR of 3.1 for metabolic diseases when compared with participants who smoked fewer than 20 cigarettes/day (p = 0.043; 95% CI: 1.009-1.701).

## DISCUSSION

Although we found smoking history to correlate with monocyte count, triglyceride level, and waist circumference, the correlations were weak and did not withstand adjustment. Another important finding of our study was that participants who smoked more than 20 cigarettes/day were at a 31% higher risk of developing metabolic disease than were those who smoked fewer than 20 cigarettes/day.

Reynolds et al.[25] found that exposure to smoking causes changes in monocyte gene expression. When monocytes enter the subendothelial spaces of blood vessels, they can predispose the organism to the development of atherosclerosis. This happens because monocytes respond to chemotactic factors and start migrating and adhering to a layer of endothelial cells, potentially differentiating into macrophages thereafter. Those macrophages absorb low-density lipoproteins and turn into foam cells that gradually accumulate in the vessels, contributing to the development of atherosclerotic lesions.[26,27] Merianos et al.[28] found that adolescent smokers had increased levels of triglycerides. Consequently, such individuals are at an increased risk of atheromatous plaque formation.[27]

A study involving a sample of smokers and nonsmokers in Switzerland (all of whom were White and 35-75 years of age) identified a trend towards a dose-response effect between the number of cigarettes smoked and waist circumference.[29] In the present study, we also observed a weak positive correlation between smoking history and waist circumference. Waist circumference can also be associated with an increase in insulin resistance and have an indirect relationship with obesity, because an increased waist circumference is a marker for the development of diabetes, hypertension, metabolic syndrome, atherosclerosis, and cardiovascular diseases.[30,31]

According to a systematic review with meta-analysis,[32] a one-cigarette-per-day increase in consumption increases the waist circumference by

**Table 1.** General characteristics of the study sample (N = 65).[a]

| Characteristics | Results |
|---|---|
| Demographic data | |
| Gender (female/male), n/n | 33/32 |
| Age, years | 43.0 (31.5-49.0) |
| Anthropometric data | |
| Height, m | 1.7 (1.6-1.7) |
| Weight, kg | 68.6 (60.6-80.0) |
| Body mass index, kg/m$^2$ | 25.5 (21.6-29.0) |
| Body fat, % | 29.8 (22.8-35.9) |
| Lean mass, kg | 25.8 (22.7-32.1) |
| Fat mass, kg | 22.3 (14.0-27.7) |
| Waist-to-hip ratio | 1.0 (0.9-1.0) |
| Waist circumference, cm | 88.0 (81.0-100.0) |
| Visceral fat, cm$^2$ | 96.7 (59.5-118.5) |
| Smoking history | |
| Cigarettes/day | 20.0 (10.0-20.0) |
| Duration of smoking, years | 23.0 (14.0-32.5) |
| Smoking history, pack-years | 18.5 (11.4-30.0) |
| Fagerström test | 6.0 (4.0-7.0) |
| Lung function, % of predicted | |
| FVC | 91.0 (84.5-101.5) |
| $FEV_1$ | 91.0 (83.0-100.0) |
| $FEV_1$/FVC | 99.0 (92.0-103.0) |
| PEF | 76.0 (67.0-87.0) |
| $FEF_{25-75\%}$ | 87.0 (74.0-112.5) |
| Lung function pattern, n (%) | |
| Normal | 57 (88) |
| Obstructive | 2 (3) |
| Restrictive | 4 (6) |
| Mixed | 2 (3) |

BMI: body mass index; and $FEF_{25-75\%}$: forced expiratory flow between 25% and 75% of FVC. [a]Data expressed as medians and interquartile ranges, except where otherwise indicated.

**Table 2.** Metabolic markers, inflammatory markers, muscle strength, cardiopulmonary capacity, and comorbidities in our sample of current smokers (N = 65).[a]

| Variables | Results |
|---|---|
| Inflammatory markers, cells/mm$^3$ | |
| Leukocytes | 96.6 (59.5-118.5) |
| Neutrophils | 4,425.4 (3,320.9-5,637.9) |
| Monocytes | 657.6 (528.0-782.1) |
| Eosinophils | 219.0 (115.9-296.9) |
| Lymphocytes | 2,367.0 (2,020.8-3,054.5) |
| Metabolic markers, mg/dL | |
| Total cholesterol | 257.7 (220.4-311.8) |
| HDL | 41.8 (35.4-47.2) |
| Triglycerides | 140.5 (130.9-167.7) |
| Glucose | 90.1 (83.0-106.8) |
| LDL | 175.5 (140.4-243.6) |
| Muscle strength, kgf | |
| Knee extension | 22.0 (16.5-28.5) |
| Knee flexion | 12.4 (9.0-16.4) |
| Shoulder abduction | 5.6 (3.5-7.6) |
| Shoulder flexion | 5.7 (3.8-7.5) |
| Elbow flexion | 9.9 (6.2-13.7) |
| Cardiopulmonary capacity | |
| $VO_2$, L/min | 1.8 (1.6-2.0) |
| $VO_2$, mL/kg/min | 26.2 (22.2-32.6) |
| Comorbidities, n | |
| Cardiovascular | 13 |
| Metabolic | 6 |

$VO_2$: oxygen consumption. [a]Data expressed as medians and interquartile ranges, except for comorbidities, which are expressed as n.

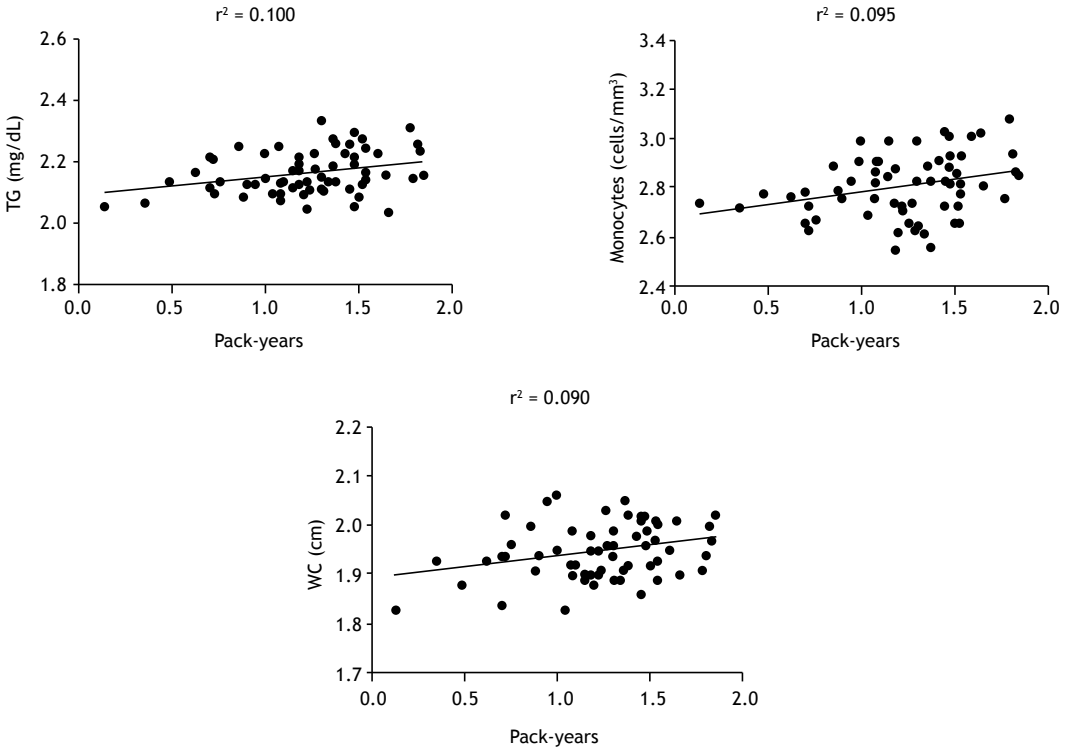


**Figure 2.** Pearson's correlation coefficients for the relationships that smoking history has with triglyceride (TG) levels, monocyte count, and waist circumference (WC).

0.14% even when the BMI remains constant, that is, greater smoking intensity is associated with a propensity for central fat distribution. That may also explain the positive correlation that we found between waist circumference and smoking history, given that the magnitude of changes in the abdominal region is directly proportional to the number of cigarettes smoked.

In the present study, smoking history was not found to correlate with monocyte count, triglyceride level, or waist circumference after adjustments for gender, age, BMI, and comorbidities. Therefore, these factors may be interfering in this relationship in addition to the smoking history. Several factors can trigger the development of diseases; in this case, smoking is a modifiable risk factor, as are BMI and comorbidities, whereas gender and age are not.[33]

The fact that smoking history was not found to correlate with and lipid profile-related variables (total cholesterol, HDL, and LDL) corroborates the findings of a study conducted by Rom et al.,[34] who also found no such correlations. However, in a review of the literature, Chelland Campbell et al.[6] found that smokers have higher levels of lipid-profile related variables than nonsmokers. Contrary to the findings of our study, Marano et al.[35] found that the levels of inflammatory markers were higher in smokers than in nonsmokers, a finding that could be explained by their small sample size.

Our finding that smoking history did not correlate with muscle strength or cardiopulmonary capacity corroborates those of Wüst et al.[36] who found that, in the absence of COPD, smokers did not present muscle weakness or changes in the contractile properties of the quadriceps muscle, although they did show more fatigue. It is likely that this correlation was not seen in our study because our sample was composed of current smokers without COPD. However, we can presume that the individuals in our sample are at a higher risk of developing COPD and other diseases, with the consequent loss of muscle mass related to the systemic inflammation caused by COPD and to smoking itself, which activates protein degradation pathways.[11,37]

Our study has some limitations, including the small sample size and the fact that we did not measure cytokine levels, as well as the lack of a control group, which could have helped us understand the results in a more consistent way. Therefore, we suggest that further prospective studies be carried out to investigate the relationship between smoking history and the development of metabolic diseases, drawing comparisons between smokers and healthy nonsmokers without comorbidities, as well as between normal-weight and overweight individuals.

Smokers are at an increased risk of developing various diseases, especially metabolic disorders, which, once developed, can lead to the appearance of other diseases. In clinical practice, professionals should be alert to the accumulation of fat in the abdominal region and the number of cigarettes smoked per day,

promoting smoking cessation or, when that is not possible, raising awareness about the importance of reducing the number of cigarettes smoked per day, engaging in physical activity, and having a more controlled, balanced diet.

In summary, we found a positive correlation between smoking history and triglyceride levels, monocyte count, and waist circumference. The prevalence of metabolic diseases was highest in those who smoked more than 20 cigarettes per day.

## AUTHOR CONTRIBUTIONS

All authors made significant individual contributions to the development of this study. TSG, IBT, CPS, MP, and DR contributed to the study conception and design; TSG and CPS collected the data; TSG, IBT, and BSAS analyzed and interpreted the data; IBT conducted the statistical analysis; TSG, IBT, CPS, MP, and DR secured the research funding; and all authors participated in the writing of the manuscript and critical review of the intellectual content.

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ORIGINAL ARTICLE

# Impact of a respiratory ICU rotation on resident knowledge and confidence in managing mechanical ventilation

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## ABSTRACT

**Objective:** To develop and apply a competency-based test to assess learning among internal medicine residents during a respiratory ICU rotation at a university hospital. **Methods:** We developed a test comprising 19 multiple-choice questions regarding knowledge of mechanical ventilation (MV) and 4 self-assessment questions regarding the degree of confidence in the management of MV. The test was applied on the first and last day of a 30-day respiratory ICU rotation (pre-rotation and post-rotation, respectively). During the rotation, the residents had lectures, underwent simulator training, and shadowed physicians on daily bedside rounds focused on teaching MV management. **Results:** Fifty residents completed the test at both time points. The mean score increased from 6.9 ± 1.2 (pre-rotation) to 8.6 ± 0.8 (post-rotation; $p < 0.001$). On questions regarding the approach to hypoxemia, the recognition of patient-ventilator asynchrony, and the recognition of risk factors for extubation failure, the post-rotation scores were significantly higher than the pre-rotation scores. Confidence in airway management increased from 6% before the rotation to 22% after the rotation ($p = 0.02$), whereas confidence in making the initial MV settings increased from 31% to 96% ($p < 0.001$) and confidence in adjusting the ventilator modes increased from 23% to 77% ($p < 0.001$). **Conclusions:** We developed a competency-based test to assess knowledge of MV among residents before and after an rotation in a respiratory ICU. Resident performance increased significantly after the rotation, as did their confidence in caring for patients on MV.

**Keywords:** Education, medical; Respiration, artificial; Surveys and questionnaires; internship and residency; Competency-based education; Educational measurement.

## INTRODUCTION

Since the polio epidemic in Copenhagen in 1952,[1-3] mechanical ventilation (MV) has been the key element in the care of patients with respiratory failure[4] and continues to be the most widely used technique for providing life support .[5]

The use of MV is associated with significantly higher daily costs for patients receiving treatment in the ICU.[6] In addition to the costs, the need for MV continues to be associated with high mortality, in Brazil and in other countries, despite scientific advances in the area.[4,7,8]

Strategies that result in shorter ICU stays or less time on MV could lead to substantial reductions in the total cost per inpatient.[9] In addition, the appropriate adjustment of MV settings could reduce mortality in various clinical scenarios.[4,10-13] Therefore, instruction regarding the indications for and management of MV is essential to ensure the appropriate training of residents who will treat critically ill patients. Given that most ICU patients in Brazil and elsewhere are treated by clinicians who are not intensivists,[14-16] an MV curriculum for residents is important not only residency programs in intensive care but also in those in internal medicine.

There are few data in the literature on whether and how residency programs provide appropriate training in the management of MV.[17,18] In a study conducted by Willcox et al.,[19] emergency medicine residents reported that, although they frequently treated patients on MV, they felt that they had not received sufficient instruction on the management of MV. In a study involving medical students, residents, and emergency medicine physicians in Brazil, 85% of the participants believed that they had not received enough information about MV during their medical training and considered themselves underqualified to care for patients on MV.[20] In addition, there is no

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consensus on how to assess resident knowledge of MV. Although the development of validated assessment tools to measure learning is the most highly recommended method,[21,22] the effective application of such tools still presents a challenge in all areas of medicine.[23]

For an assessment to be considered well-planned, competencies and learning objectives in MV must first be established.[18,24]

In the present study, we developed and applied a test to assess the knowledge and learning of internal medicine residents who completed a supervised rotation at a university hospital respiratory ICU. Our hypothesis was that their knowledge of MV and confidence in managing patients on MV would increase after a 30-day respiratory ICU rotation focused on MV management.

## METHODS

### *Location and participants*

This study was carried out in the Respiratory ICU of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP, University of São Paulo School of Medicine Hospital das Clínicas), located in the city of São Paulo, Brazil, between September of 2014 and August of 2015. The study was approved by the local research ethics committee. Given that it was a project designed to assess resident performance, an activity that is within the scope of the medical residency program, the requirement for informed consent was waived.

The study participants were second-year internal medicine residents at the HCFMUSP. The study inclusion criteria were being an internal medicine resident at the HCFMUSP and being an intern in the HCFMUSP respiratory ICU during the study period. The exclusion criterion was not completing the assessments during the rotation.

### *Test development*

We developed a multiple-choice question test based on clinical cases, initially comprising 22 questions. The questions were developed on the basis of lists of competencies and learning objectives in MV in adult individuals, described in the literature,[18,24] as well as on the basis of our respiratory ICU residency program. Most questions were based on clinical cases, and a given case could be used for multiple questions.

First, the questions were discussed with our senior team, consisting of five MV specialists with more than 10 years of experience in ICUs, all of whom were involved in researching and teaching MV. On the basis of those discussions, 3 questions were excluded because they were not considered highly relevant for assessing knowledge of MV. Therefore, the final version of the test comprised 19 questions. To improve clarity, the group of specialists modified some of those questions, and the consensus opinion was that the final version of the test (Chart S1, supplementary material) was appropriate.

The key knowledge topics addressed on the test were cardiopulmonary physiology, interpretation of waveforms, adjustment of ventilator settings, and ventilator mode recognition (Chart 1). In addition to the questions regarding adjustment of MV, we included 4 self-assessment questions about the degree of confidence in airway management, in applying noninvasive ventilation (NIV), in making the initial MV settings, and in adjusting basic ventilator modes. Those four questions were scored on a Likert scale with 5 possible answers, ranging from 0 (I am not at all confident) to 4 (I am completely confident). The scores were later regrouped into two categories: low confidence (0, 1, and 2); and high confidence (3 and 4).

### *Data collection*

The test was administered to residents twice during their rotation in the HCFMUSP respiratory ICU. The rotation lasted 30 days, and the test was administered on the first and last days of that period (pre-rotation and post-rotation, respectively).

During the between-test interval, the residents were responsible for the care of patients on MV, making changes to the ventilator settings with the help of pulmonology residents, pulmonologists, and intensivists, who were responsible for supervising the residents during their ICU rotation. Rotation activities included daily multidisciplinary rounds to discuss cases and plan treatment, with a focus on MV, as well as to provide overall care to the patients. Rounds lasted an average of two hours, with the participation of a supervising physician, all residents, and the ICU respiratory therapist. In addition, the residents participated in bedside discussions that focused on the care of patients on MV, involving ventilator waveform interpretation and ventilator setting adjustments. Those discussions were based on the needs of the resident. Whenever the MV settings were going to be changed in the morning, the supervising physician and the residents gathered at the bedside to discuss the ventilator settings. Throughout the day, depending on the complexity of each case, the settings were reviewed, and the residents had the opportunity to adjust the settings under the supervision of the pulmonology residents or supervising physicians. The residents had four one-hour lectures addressing the following topics: ventilator modes; MV in acute respiratory distress syndrome (ARDS) and severe hypoxemia; MV in patients with obstructive lung disease; and weaning from MV. The lectures combined a traditional expository model, in which ventilator waveforms were drawn on a whiteboard, and a participatory model, in which the residents posed questions and made suggestions. In addition, MV simulations were carried out using online software (xlung Excellence in teaching mechanical ventilation management simulator; Pulmocenter, Fortaleza, Brazil). The practical training with the virtual tool lasted approximately 90 min, and, using standardized clinical cases, the residents were encouraged to suggest adjustments to the virtual ventilator settings

and evaluate the result of their decisions. The same supervising physicians were responsible for teaching the residents throughout the study period.

The primary outcome variable was the test score, normalized to vary from 0 to 10. The secondary outcome variables were the degrees of confidence (high or low) for the four key competencies addressed in the self-assessment questions.

### *Statistical analysis*

We tested the primary outcome variable for normality with the Shapiro-Wilk test. We used paired t-tests to compare the pre- and post-rotation total scores, whereas we used McNemar's test to compare the pre- and post-rotation rates of correct answers to each knowledge question and to compare the pre- and post-rotation scores on the questions regarding confidence. The level of significance was set at $p < 0.05$. We used the R statistical program, version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

During the study period, 59 residents completed an rotation at the HCFMUSP respiratory ICU, and 50 of those residents completed the test at both time points. The mean score increased from 6.9 ± 1.2 (pre-rotation) to 8.6 ± 0.8 (post-rotation; $p < 0.001$), with a mean pre-rotation to post-rotation difference of 1.67 (95% CI: 1.3-2.0; Figure 1).

Table 1 shows the proportion of individuals who answered each question correctly at each of the two time points, and Table S1 (supplementary material) describes the knowledge topic assessed by each question and its correspondence with a list of competencies described in the literature.[18,24] The questions with the highest pre-rotation rates of correct answers were those assessing knowledge of how to calculate respiratory system compliance and resistance, of the characteristics of the basic MV modes, of protective ventilation in ARDS, and of permissive hypercapnia. In contrast, the questions regarding the recognition of asynchrony and of risk factors for extubation failure had the lowest pre-rotation rates of correct answers.

We found that the post-rotation rates of correct answers to questions regarding the treatment of hypoxemia, the recognition of patient-ventilator asynchrony, the risks of high inspiratory pressures, and the recognition of risk factors for extubation failure were significantly higher than the pre-rotation ones. The pre-rotation and post-rotation rates of correct answers were both low for only one question, which addressed particularities in the ventilatory management of patients with COPD (Table 1).

The questions regarding the degree of confidence in managing MV after the rotation were answered by 48 residents. Comparing the pre- and post-rotation scores on those questions (Figure 2), we found that the degree of confidence increased from 6% to 22% for airway management ($p = 0.02$), from 96% to 100% for applying NIV ($p = 0.47$), from 31% to 96% for making the initial MV settings ($p < 0.001$), and from 23% to 77% for adjusting the ventilator modes increased ($p < 0.001$).

## DISCUSSION

In the present study, we found that the overall performance of second-year internal medicine residents on a clinical case-based test assessing knowledge of MV was moderately good; however, their performance on questions assessing knowledge related to core competencies, such as the recognition of asynchrony and of risk factors for extubation failure, was poor. After a 30-day rotation in a respiratory ICU, their overall performance was significantly higher on most questions. Resident confidence in caring for patients on MV, which was low at the beginning of the rotation, increased significantly as a result of the training.

Although MV management is considered an important skill for residents of various specialties,[17] studies have shown that physicians and other health professionals who work in ICUs have difficulty in interpreting ventilator waveforms,[25] show poor adherence to protective MV

**Chart 1.** Competencies associated with the knowledge questions on the test.

| |
|---|
| Recognize patterns of respiratory system resistance/compliance and their relationships with prevalent diseases |
| Apply the basic mechanical ventilation modes in patients with acute respiratory failure |
| Interpret ventilator waveforms |
| List risk factors for a difficult airway |
| Recognize acute respiratory failure due to ARDS and pathophysiological mechanisms of hypoxemia |
| Select ventilator settings consistent with protective ventilation in patients with ARDS |
| List strategies for securing the airway in a patient who is difficult to intubate |
| Describe the advantages and risks of rescue measures for refractory hypoxemia and their indications |
| Appropriately indicate the need for ventilatory support in patients with acute respiratory failure due to neuromuscular disease |
| Recognize risk factors for extubation failure |
| Adjust ventilator settings according to the clinical status and laboratory test results of the patient |
| Identify particularities in the ventilatory management of patients with certain lung diseases |
| List indications for noninvasive mechanical ventilation |

ARDS: acute respiratory distress syndrome.

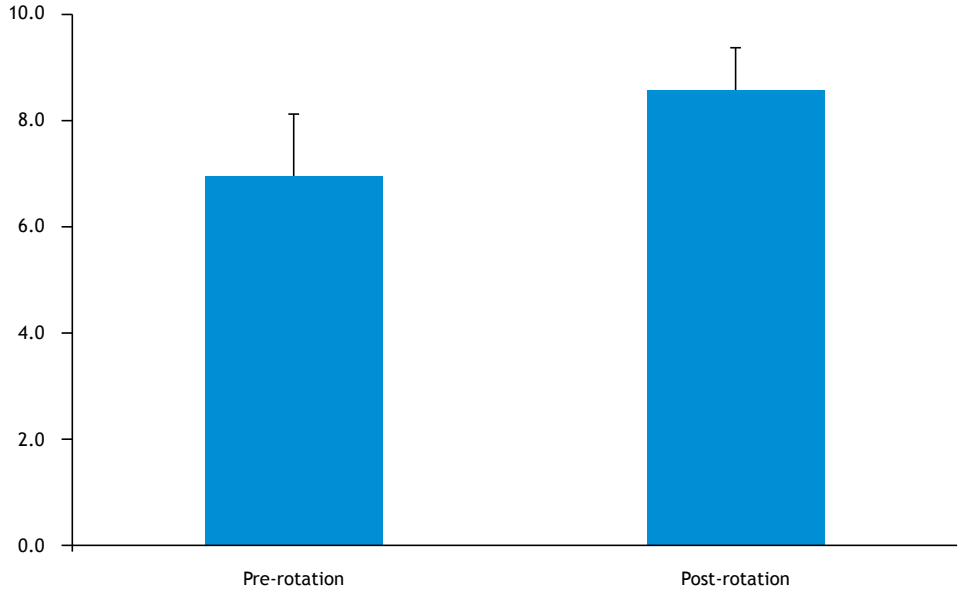


**Figure 1.** The blue bars represent the means and the error bars represent the standard deviation of the pre- and post-rotation scores (on a scale from 0 to 10).

**Table 1.** Knowledge topics assessed and participant performance on each question before and after the respiratory ICU rotation (N = 50).[a]

| Knowledge topic assessed | Question | Pre-rotation[a] | Post-rotation[a] | p |
|---|---|---|---|---|
| Recognize patterns of resistance and compliance of the respiratory system and their relationships with prevalent diseases | 4 | 48 (96) | 49 (98) | 1 |
| Apply the basic mechanical ventilation modes in patients with acute respiratory failure | 5 | 45 (90) | 49 (98) | 0.22 |
| Interpret ventilator waveforms | 3 | 42 (84) | 48 (96) | 0.08 |
| | 6 | 47 (94) | 49 (98) | 0.62 |
| | 19 | 16 (32) | 37 (74) | < 0.001 |
| List risk factors for a difficult airway | 7 | 39 (78) | 43 (86) | 0.39 |
| Recognize acute respiratory failure due to ARDS and pathophysiological mechanisms of hypoxemia | 8 | 40 (80) | 43 (86) | 0.51 |
| | 9 | 30 (60) | 45 (90) | < 0.001 |
| Select ventilator settings consistent with protective ventilation in patients with ARDS | 10 | 47 (94) | 50 (100) | 0.24 |
| List strategies for securing the airway in a patient who is difficult to intubate | 11 | 22 (44) | 35 (70) | 0.002 |
| Describe the advantages and risks of rescue measures for refractory hypoxemia and their indications | 12 | 23 (46) | 32 (64) | 0.07 |
| Appropriately indicate the need for ventilatory support in patients with acute respiratory failure due to neuromuscular disease | 13 | 31 (62) | 42 (84) | 0.003 |
| Recognize risk factors for extubation failure | 14 | 18 (36) | 35 (70) | < 0.001 |
| Adjust ventilator settings according to the clinical status and laboratory test results of the patient | 15 | 42 (84) | 45 (90) | 0.51 |
| | 16 | 33 (66) | 43 (86) | 0.02 |
| Identify particularities in the ventilatory management of patients with certain lung diseases | 1 | 26 (52) | 31 (62) | 0.30 |
| | 2 | 47 (94) | 49 (98) | 0.48 |
| | 19 | 16 (32) | 37 (74) | < 0.001 |
| List indications for noninvasive mechanical ventilation | 17 | 38 (76) | 49 (98) | 0.003 |
| | 18 | 27 (54) | 43 (86) | 0.001 |

Pre-rotation: test administered on the first day of the rotation; post-rotation: same test administered on the last (30th) day of the rotation; and ARDS: acute respiratory distress syndrome. [a]Values expressed as number of participants (%).

protocols in patients with ARDS[12,26] and feel poorly prepared to care for patients on MV.[20] This is probably due, in part, to the fact that instruction in MV is not well standardized, because there is no widely used list

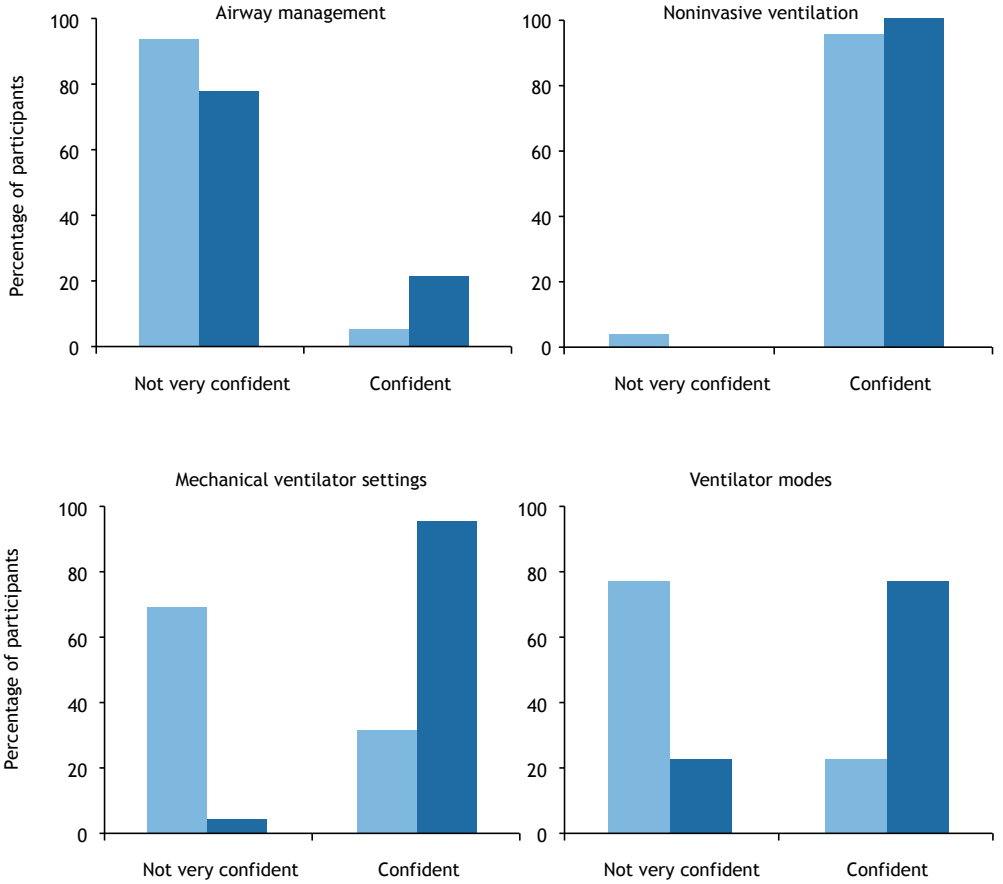


**Figure 2.** Proportion of participants (n = 48) by degree of confidence as measured by the self-assessment questions before the rotation (light blue) and after the rotation (dark blue).

of competencies in MV, nor is there consensus on how to develop a specific curriculum in MV and to quantify learning.[18,24,27-29]

In the present study, the pre-rotation total score was moderately high, reflecting the knowledge of MV that was acquired during the ICU rotations in the first year of the residency program. However, the increase in the mean total score after the rotation shows a significant gain of knowledge after the training focused on MV management, a gain that was also observed in a study involving residents who underwent intensive training in MV.[27]

We found that the rate of correct answers to the question assessing protective ventilation in patients with ARDS increased from 94% (pre-rotation) to 100% (post-rotation), a rate that is higher than the 52% reported by Cox et al.[17] in another study involving medical residents. That difference might be due to the fact that protective ventilation has come to be more widely used in recent years and that the study by Cox et al.[17] was published more than a decade ago. With regard to managing NIV, we found rates of correct answers of 76% (pre-rotation) and 98% (post-rotation), compared with 73% in the Cox et al. study.[17] With regard to adjusting ventilator settings to correct auto-positive end-expiratory pressure, the rate of correct answers in the Cox et al. study[17] was 65%, whereas we found rates of 84% (pre-rotation) and 96% (post-rotation).

The rate of correct answers to some questions was low before the rotation but improved significantly after the rotation. That could be attributed to the training and discussions that took place during the rotation, corroborating findings from similar studies.[27] The high rate of correct answers to some questions before the rotation may be related to knowledge of MV gained during previous rotations or to the varying degree of difficulty of the questions.

We found that resident confidence in managing MV before the rotation varied depending on the question. The residents reported a high degree of confidence only in applying NIV, and that remained unaltered after the rotation. That finding differs from one reported by Tallo et al.,[20] who found that only 23% of the participants in their study felt confident enough to initiate NIV. However, in comparison with ours, the sample evaluated in that study[20] was more heterogeneous, including final-year medical students and emergency physicians, which may have contributed to the difference relative to our finding.

The participants in our study had low confidence in airway management, in making the initial MV settings, and in adjusting ventilator modes before the rotation, corroborating previous findings.[20] Their confidence increased significantly for those three skills but remained relatively low for airway management. Although airway management in an emergency setting was not a learning objective of the rotation, the low degree of resident confidence even after the rotation indicates the need for additional training in this area.

Our study has some limitations that should be taken into account when interpreting our results. First, this was a single-center study. Therefore, performance on the test may be associated with the prior knowledge level of the residents selected for admission to our residency program; with specific training, provided in our residency program, in rotations in emergency rooms and ICUs; and with the particularities of the rotation in our respiratory ICU. Second, the test was developed only by professionals in our department, which again may represent the specific view of our residency program. Third, education experts have conflicting opinions on multiple choice tests to measure learning and many now consider the use of simulations to be a more appropriate means of assessment.[29-31] Finally, there is no list of validated and widely accepted MV competencies. Nevertheless, our study has some strengths. We conducted an objective assessment based on clinical cases with scenarios similar to those that residents are exposed to in ICUs in real life. In addition, when we developed the questions, we took into consideration the pre-defined learning objectives in our residency program and in the literature.[24] Furthermore, this was the first study to assess knowledge of MV in a low- or middle-income country.

In terms of future directions, it is essential for residency programs that train physicians who will work in ICUs to have a well-structured MV curriculum based on well-defined learning objectives and competencies, including diversified teaching strategies that combine theoretical classes, discussions, simulations, and bedside teaching.[27,28,31,32] The validation of a list of competencies in MV that can be adopted by various medical residency programs would also be quite useful to ensure that the training provided to residents is appropriate.[24] Finally, the development of tools that are more effective in assessing competency in MV, not only in terms of knowledge, but also in terms of skills and attitudes, such as tools based on simulations or structured objective assessments, would further contribute to improving residency programs so that the training given to physicians working in ICUs in Brazil is appropriate for the care of critically ill patients on MV, which could result in reduced mortality and reduced ICU costs.

In conclusion, we have developed a test, based on lists of competencies in MV, that made it possible to assess the knowledge and learning of second-year internal medicine residents before and after a 30-day rotation in a respiratory ICU, as well as to determine their degree of confidence in the management of MV. At the beginning of the rotation, resident performance on some core topics was insufficient and their confidence in their skills related to the application of MV was low. After the rotation, the performance of the residents improved significantly, as did their confidence in caring for patients on MV.

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## SUPPLEMENTARY MATERIAL

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REVIEW ARTICLE

# Social determinants of health and catastrophic costs associated with the diagnosis and treatment of tuberculosis

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## ABSTRACT

The epidemiological relevance of tuberculosis is directly related to the socioeconomic profile of a given country. Vulnerability to tuberculosis is influenced by biological factors (e.g., malnutrition, HIV infection, and age) and social factors (e.g., unhealthy housing, high population density, inappropriate working conditions, and lack of access to health services). In many cases, multiple vulnerabilities occur in conjunction. We propose here a reflection on tuberculosis from the point of view of the social determinants of health, as well as the costs associated with its diagnosis and treatment in Brazil, based not only on data in the international literature but also on evidence related to the national context. Given the magnitude of tuberculosis as a socially mediated disease, there is an evident need for greater involvement of health professionals and of the scientific community to implement relevant operational and research measures to understand the social conditions influencing the health-illness continuum for tuberculosis patients. Although the recent economic crisis in Brazil has contributed to increased mortality from all causes, including tuberculosis, health and social protection expenditures have mitigated detrimental health effects. The evidence presented here underscores the importance of public social protection policies for minimizing the effects of tuberculosis indicators, with the aim of eliminating tuberculosis in Brazil.

**Keywords:** Tuberculosis; Social determinants of health; Cost of illness; Costs and cost analysis.

## INTRODUCTION

In recent decades, there have been advances in tuberculosis control worldwide. The incidence of tuberculosis decreased by 2% between 2017 and 2018, and 53 million deaths were averted between 2000 and 2016. Despite these results, tuberculosis remains a global health priority. In 2018, there were an estimated 10 million new cases of tuberculosis, approximately 1.5 million individuals having died from the disease.[1] In that same year, tuberculosis was one of the ten leading causes of death worldwide, ranking above HIV/AIDS as the leading cause of death from a single infectious agent. Tuberculosis morbidity and mortality are directly related to the socioeconomic profile of a given country, being higher in poorer countries, where 95% of tuberculosis-related deaths occur.[1]

Brazil remains on the list of countries with the highest burden of tuberculosis. In 2019, 73,864 cases of the disease were reported in the country, and 4,490 individuals (including men, women, and children) died from the disease in the country.[2] According to the World Health Organization (WHO), Brazil ranks 20th for disease burden and 19th for tuberculosis/HIV coinfection.[1-3]

The distribution of tuberculosis in Brazil is directly related to differences in socioeconomic conditions across municipalities. In municipalities in which socioeconomic conditions are better (in accordance with new Brazilian National Tuberculosis Control Program criteria), the tuberculosis incidence rate increased by 1.8%, from 31.8/100,000 population in 2015 to 32.3/100,000 population in 2018 ($p = 0.004$). In municipalities in which socioeconomic conditions are poor, the tuberculosis incidence rate increased by 2.7%, from 52.2/100,000 population in 2015 to 53.7/100,000 population in 2018 ($p < 0.001$).[2]

The End TB Strategy, approved by the World Health Assembly in 2014 and by Brazil in 2017, with the implementation of the Brazilian National Plan to End Tuberculosis as a Public Health Problem,[4] includes the following targets for achievement by 2035: a 90% reduction in the tuberculosis incidence rate; a 95% reduction in the number of tuberculosis-related deaths; and elimination of catastrophic costs caused by tuberculosis.

The strategy is based on three pillars; the second pillar focuses on "bold policies and supportive systems", emphasizing the importance of social support for successful tuberculosis control.[4,5]

Vulnerability to tuberculosis is influenced by biological factors affecting the immune response to *Mycobacterium tuberculosis*, as occurs in young children and patients with comorbidities such as HIV infection and diabetes mellitus. Vulnerability to tuberculosis is also influenced

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by social factors, exposing individuals to a greater risk of contact with *M. tuberculosis* and subsequent illness due to conditions of precarious housing conditions, malnutrition, inappropriate working conditions, and lack of access to health services. In addition, patients with tuberculosis disease are faced with loss of work productivity and the high costs associated with the diagnosis and treatment of tuberculosis. In many cases, multiple vulnerabilities occur in conjunction, especially in shantytowns in poor countries and poor areas of large cities, where individual immune status is influenced by social determinants of health (SDOH) that increase the risk of active tuberculosis and latent tuberculosis infection.[6]

We propose here a reflection on tuberculosis from the point of view of SDOH and the costs associated with the diagnosis and treatment of tuberculosis in Brazil, based not only on data in the international literature but also on national evidence regarding the association between living conditions (i.e., access to education, health care, appropriate housing, and decent work) and the incidence of tuberculosis, as well as the impact that social support measures have on disease control.

## METHODS

To provide a theoretical basis for the topics covered here, we conducted a narrative review of studies published between January of 2000 and November of 2019. The included studies were identified by database searching. The search strategy included title searches with the terms "social determinants of health" and "catastrophic costs" combined with the term "tuberculosis". We searched for studies published in any of the following languages: Portuguese, English, Spanish, French, and Italian. We searched the following databases: SciELO, MEDLINE (PubMed), and Google Scholar. We also searched the Brazilian National Ministry of Health website and the WHO website. A total of 230 studies were retrieved. Of those, 68% were published in the 2015-2019 period and 96% were in English. To identify additional studies, we carried out a hand search of the references cited in the studies retrieved by database searching. A total of 6 studies were thus identified as eligible for full review.

## SOCIAL DETERMINANTS OF HEALTH AND THEIR ASSOCIATION WITH TUBERCULOSIS IN BRAZIL AND THE WORLD

According to the WHO, SDOH are the social, political, economic, environmental, and cultural conditions in which people are born, grow up, live, work, and age, including the local health care system, all of which influence their health status.[7,8] According to the Brazilian National Commission on the Social Determinants of Health,[9] SDOH are social, economic, cultural, ethnic/racial, psychological, and behavioral factors increasing the risk of disease, causing health problems to the population. SDOH have also been defined as inequities in the conditions in which people are born, live, and age, driven by inequities in power, money, and resources. By yet another definition, SDOH are factors and mechanisms by which societal conditions affect health and that can be altered by informed action.[10-12]

Societal conditions affect health by the following factors and mechanisms[9,13]:

- physical/material factors—income inequality and a lack of investment in social infrastructure influence the production of health and disease;
- psychosocial factors—individual perceptions and experiences in unequal societies are harmful to health;
- ecosocial perspectives—frameworks that seek to integrate social and biological reasoning and a dynamic, historical, and ecological perspective;
- social capital—wear and tear on relationships of support and security among people and among groups of people, through which economic (income-related) issues negatively influence health status.

Brazil has a population of 208.5 million inhabitants, of whom 13.5 million (6.5%) live in extreme poverty (i.e., on a monthly per capita income of less than 145 Brazilian reals [R$]) and 52.5 million (18.7%) live in poverty (i.e., on a monthly per capita income of less than R$ 420) as defined by the World Bank.[14] Recent data from the Brazilian Institute of Geography and Statistics show that 29.5 million people currently living in poverty have no access to sewerage; 13.5 million have no access to piped water; and 11.1 million have no access to garbage collection services. Poverty or low income plays a central role in school dropout rates and delayed academic achievement among individuals in the 15- to 17-year age bracket, with 11.8% dropping out of school during high school and 33.6% having delayed educational attainment. Extreme poverty affects a highly vulnerable group of individuals that are not generally well-equipped to enter the labor market.[15]

Tuberculosis and poverty are correlated; poverty is associated with poor health, and poor health can lead to poverty, reducing job opportunities and resulting in a vicious cycle that tends to worsen.[6] Tuberculosis predominantly affects poorly educated adult males in their economically productive years. Tuberculosis is directly associated with living in "subnormal agglomerations" (i.e., slums), lack of access to primary health care, malnutrition, and poor diet quality, as well as with abuse of alcohol, tobacco, and other drugs.[16,17] Poor living conditions and lack of access to information (resulting from a low level of education) increase the risk of tuberculosis. A low level of education can limit patient understanding of the importance of appropriate treatment and the risks of noncompliance with tuberculosis treatment, creating further obstacles to the elimination of the disease and contributing to the emergence of drug-resistant strains (multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis).[18-20]

Comorbidities such as diabetes mellitus, HIV infection, mental health disorders, silicosis, and chronic immunosuppressive conditions, as well as malnutrition, together with abuse of alcohol, tobacco, and other drugs, are predictive factors for noncompliance with tuberculosis treatment and increased health care costs.[7,21-23]

In a systematic review of the association between tuberculosis and socioeconomic indicators in Brazil, major risk factors for the development of tuberculosis included having no regular income, having a history of incarceration, being undernourished, being separated or widowed, and having few assets. In addition, alcoholism, unemployment, and a low level of education were associated with poor tuberculosis outcomes (death, treatment abandonment, and treatment failure).[24,25]

According to the WHO and the United Nations Human Settlements Programme, of 6.908 billion people in the world, approximately 1 billion (14.5%) lived in slums in 2010 and, by 2050, the number of slum dwellers will have doubled.[17] Slum dwellers live in extremely precarious conditions, including overcrowding, poor sanitation, poor housing conditions, poor transportation infrastructure, and increased violence.[26] In an ecological study conducted in 5,565 Brazilian municipalities, household crowding and the unemployment rate were the socioeconomic variables most commonly associated with the incidence of tuberculosis.[27] In contrast, the Accelerated Growth Program implemented in the Rocinha *favela* in the city of Rio de Janeiro, Brazil,[28] resulted in a reduction in the incidence of tuberculosis, achieved by urban interventions such as street widening and improved air circulation, showing that better living conditions can improve tuberculosis control.

## CATASTROPHIC COSTS ASSOCIATED WITH THE DIAGNOSIS AND TREATMENT OF TUBERCULOSIS

Tuberculosis disease and treatment costs fall on the household budget, further aggravating poverty and resulting in lost work time, which in turn results in economic losses not only for families but also for the country, reducing the national workforce.[29-33]

Costs associated with tuberculosis diagnosis and treatment include direct costs, indirect costs, and coping costs. Direct medical costs are medical expenses such as medications, hospital/physician fees, laboratory tests, and imaging tests. Direct nonmedical costs are expenses such as transportation, food, and lodging, which can be assessed separately before and after the diagnosis of tuberculosis. Indirect costs are income reductions partially or fully attributable to disease-related work disability. Indirect costs include lost work productivity for patients and family caregivers.[34-37] Finally, coping costs are those incurred by patients and family caregivers when they cannot pay for care using their own income and therefore borrow money, use savings, sell assets, or cut down on spending for food/education.[37,38]

Difficulty gaining access to health care and the high costs involved can delay the diagnosis of tuberculosis and be economically catastrophic for households. Catastrophic costs are defined as the sum of direct, indirect, and coping costs to the patient ≥ 20% of total annual household income.[36-39]

The TB-specific indicator designated "catastrophic total costs due to TB" is different from the "catastrophic health care expenditures" indicator, which is used as an indicator of overall progress toward universal health coverage because catastrophic TB costs incorporate not only medical care expenditures for treatment but also indirect costs. The TB-specific indicator is restricted to patients diagnosed with and treated for tuberculosis, whereas catastrophic health care expenditures include health care costs for all household members and for all health conditions.[37]

## IMPACT OF SOCIAL PROTECTION PROGRAMS ON TUBERCULOSIS OUTCOMES

Social protection sits at the intersection between health and social interventions and is an essential component of efforts to achieve ambitious health targets, including the end of tuberculosis. Social support provides tuberculosis patients with financial resources that can reduce financial hardship from direct and indirect health care costs, as well as reducing poverty and social vulnerability.[40-43]

Cash transfer programs are forms of social protection based on the provision of cash to vulnerable households with the objective of reducing risk, vulnerability, and chronic poverty, as well as improving human capital.[44,45]

Studies conducted in Brazil have shown that social protection has a positive impact on tuberculosis treatment outcomes. The *Programa Bolsa Família* (PBF) is a conditional cash transfer program for poor families (i.e., families living on a monthly per capita income of R$ 89-178) and extremely poor families (i.e., families living on a monthly per capita income of ≤ R$ 89).[46,47] The first study conducted in Brazil and examining the association between the PBF and tuberculosis treatment by correlating data from the Brazilian Tuberculosis Case Registry Database, the *Cadastro Único* database (which is used in order to identify and characterize low-income families), and the PBF payroll showed that the cure rate was 5% higher among tuberculosis patients who were PBF beneficiaries than among those who were not.[48]

Brazil's Family Health Strategy (FHS) facilitates access to health care and has led to higher rates of tuberculosis treatment success regardless of patient participation in a cash transfer program. A study conducted in the city of Rio de Janeiro examined the impact of the FHS and PBF on tuberculosis treatment outcomes.[49] Treatment was successful in 80% of the tuberculosis patients exposed to the FHS, being successful in 74% of those exposed to the PBF and in 64% of those exposed to neither program. Treatment

success rate was highest (82%) in those exposed to both programs.

A meta-analysis of nine randomized clinical trials (a total of 1,687 participants) showed a modest association between social protection strategies and tuberculosis treatment success (RR = 1.09; 95% CI: 1.03-1.14).[40] Social protection strategies had the greatest impact on the rate of treatment abandonment, showing that they improve access to health care and, consequently, adherence to tuberculosis treatment.[40,50]

In addition to having deleterious effects on the health of tuberculosis patients, SDOH and economic determinants of health have an impact on overall mortality in Brazil. A recent study showed that the economic recession in Brazil between 2014 and 2016 contributed to increases in mortality in the country, particularly among men, Black/Brown individuals, and individuals in the 30- to 59-year age bracket. However, health and social protection expenditures mitigated detrimental health effects, especially among vulnerable populations.[51]

## FINAL CONSIDERATIONS

Given the magnitude of tuberculosis as a socially mediated disease, there is an evident need for greater involvement of health professionals, managers, and the scientific community to implement relevant operational and research measures to understand the social conditions influencing the health-illness continuum for tuberculosis patients. The evidence presented here underscores the importance of public social protection policies for minimizing the effects of tuberculosis indicators, with the aim of eliminating them in Brazil.

## AUTHOR CONTRIBUTIONS

All authors conceived and designed the study; collected, analyzed, and interpreted the data; drafted and revised the manuscript for intellectual content; and gave final approval of the version to be published.

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REVIEW ARTICLE

# Are smoking, environmental pollution, and weather conditions risk factors for COVID-19?

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## ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is probably systemic, has a major respiratory component, and is transmitted by person-to-person contact, via airborne droplets or aerosols. In the respiratory tract, the virus begins to replicate within cells, after which the host starts shedding the virus. The individuals recognized as being at risk for an unfavorable COVID-19 outcome are those > 60 years of age, those with chronic diseases such as diabetes mellitus, those with hypertension, and those with chronic lung diseases, as well as those using chemotherapy, corticosteroids, or biological agents. Some studies have suggested that infection with SARS-CoV-2 is associated with other risk factors, such as smoking, external environmental pollution, and certain climatic conditions. The purpose of this narrative review was to perform a critical assessment of the relationship between COVID-19 and these potential risk factors.

**Keywords:** Coronavirus infections; COVID-19; Air pollution; Smoking; Tobacco use disorder.

## INTRODUCTION

In recent decades, life-threatening viral epidemics have emerged in various regions of the world. Serious outbreaks of Ebola virus disease, severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle Eastern respiratory syndrome coronavirus (MERS-CoV), as well as outbreaks of influenza, particularly more severe types of influenza, such as H1N1.[1]

Because of the severity and worldwide dissemination of the current outbreak of the new coronavirus (designated SARS-CoV-2) infection, the World Health Organization (WHO) has stated that the coronavirus disease 2019 (COVID-19) has become a pandemic. On April 16, 2020, COVID-19 had reached 210 countries and territories, having caused over 100,000 deaths and infected approximately 2 million people, the overall fatality rate being 3.4%. Previous case-fatality rates for SARS-CoV and MERS-CoV epidemics were 10% and 37%, respectively.[1]

COVID-19, Caused by a highly contagious virus,[2] is probably systemic, has a major respiratory component, and is transmitted by person-to-person contact, via airborne droplets or aerosols. In the respiratory tract, the virus begins to replicate within cells, after which the host starts shedding the virus.[3,4]

The role of smoking has been little remembered and even less discussed in this current public health situation. Other factors, such as environmental pollution and climatic conditions, also need to be understood better. The purpose of this narrative review was to perform an assessment of the current knowledge about these risk factors and their importance in the COVID-19 pandemic.

## SMOKING

Smoking has been associated with unfavorable outcomes in COVID-19.[5,6] Smokers, who are more vulnerable to respiratory viruses than are nonsmokers, have a greater risk of severe influenza infection and more severe clinical conditions. Therefore, smokers, when compared with nonsmokers, have a higher risk of hospitalization (OR = 1.5; 95% CI: 1.3-1.7) and ICU admission (OR = 2.2; 95% CI: 1.4-3.4) after having influenza infections.[7] In addition, during the MERS-CoV outbreak, smokers had higher mortality rates than did nonsmokers.[8,9] The use of electronic cigarettes and heated tobacco devices have also been related to a higher frequency of respiratory infections, especially viral ones.[10-15]

The mechanism of this increased susceptibility appears to be multifactorial, including structural changes, such as increased permeability of the bronchial mucosa, impaired mucociliary clearance, greater pathogen adherence, rupture of the respiratory epithelium, peribronchial inflammation, and fibrosis. There is also a decrease in the production of antibodies and defense immune cells.[10,16] In addition to those mechanisms, the association between SARS-CoV-2 and smoking can be facilitated by the rituals of smoking, involving repeated hand-to-face movements.[17]

Studies on respiratory syncytial virus, which has a similar structure to that of SARS-CoV-2, have shown that inhaling tobacco smoke increases the rate of viral transmission and the severity of infections, confirming the association between tobacco smoke and some viral infections and possibly explaining the severity of COVID-19

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in certain groups of individuals. Tobacco use has been considered a risk factor for MERS-CoV.[18]

The need for clarification of that association was reinforced by the fact that the highest proportion of deaths from COVID-19 occurred in males in China.[19] These finding might be related to the fact that the number of smokers, as well as their smoking history, is a lot greater among males than among females in that country (288 million vs. 12.6 million in 2018).[20] This fact is likely to be at least a cofactor that increases the chance of males to develop pulmonary, heart, and neoplastic diseases. These data are in line with the findings of the WHO-China Joint Mission on Coronavirus Disease 2019, which has reported higher case-fatality rates in men than in women (4.7% vs. 2.8%).[21-23]

Other studies have also reported a higher prevalence of COVID-19 in men. Guan et al.,[24] evaluating 1,099 critical patients with COVID-19 in 552 hospitals in 30 provinces in China, found a proportion of 58.1% of male patients. In addition, Yang et al.[25] found that males accounted for 67% of the patients in their sample. Liu et al.[26] identified that tobacco use was more frequent in the group of patients with unfavorable outcomes when compared with nonsmokers (27.3% vs. 3.0%, p = 0.018).However, Zhang et al.,[27] evaluating 140 patients with COVID-19 in China, found no differences regarding gender. In that same publication, the authors reported only 1.4% of male patients as current smokers, although the proportion of cases with COPD included in the sample was much higher. Guan et al.[24] showed a greater number of current smokers (12.6%) and former smokers (1.9%) in their study. Nevertheless, the authors could point out that being a current smoker was significantly related to presenting with more severe symptoms. The small proportion of smokers in those two studies,[24,27] when compared with the high prevalence of smoking in China (50.5%),[22] might indicate a smaller chance of an association of smoking with the incidence and severity of COVID-19.[20]

Two meta-analyses reached contradictory results. Lippi et al.[28] identified no association between smoking and disease severity. However, Vardavas & Nikitara[29] showed that current smoking was associated with a risk of developing more severe symptoms 1.4 (95% CI: 0.98-2.00) times greater and a risk of needing mechanical ventilation 2.4 (95% CI: 1.43-4.04) times greater. Mehra et al.[30] studied patients with COVID-19 admitted to 169 hospitals in Europe (64.6% of the sample), Asia (18.2% of the sample), and North America (17.2% of the sample). Of those, 2.5% of the cases had COPD, and the proportions of former and current smokers were 16.8% and 5.5%, respectively. The individuals were classified as survivors (n = 8,395, 22.5% being current or former smokers) and nonsurvivors (n = 515, 25.0% being current or former smokers). The authors concluded that smoking had an OR of 1.79 (95% CI: 1.29-2.47) for in-hospital mortality.[30] Additional analyses involving other series of cases adjusted for other factors are necessary in order to clarify the association between the severity of COVID-19 and current smoking.

The possibility of this association has been investigated regarding biological aspects. The angiotensin-converting enzyme 2 (ACE2) is likely to be related to the severity of symptoms and unfavorable outcomes of COVID-19. SARS-CoV-2 penetrates human cells by binding to the extracellular domain of the ACE2 receptor.[31,32] This enzyme acts on the renin-angiotensin system, fragmenting the molecule of angiotensin 2, a potent inflammatory and vasoconstrictor agent, and producing angiotensin-(1-7), which has a significant anti-inflammatory action.[33,34] Therefore, anti-ACE2 antibodies or the blockade of their receptor prevent the virus from binding, contributing to a greater severity of the disease in the elderly, as well as in those with diabetes or hypertension.[35] In those groups of patients, there is a clear decrease in the expression of ACE2, making it difficult to form degradation products, which have anti-inflammatory action, whereas there would be greater amounts of ACE2, which is an inflammatory agent. These two mechanisms could partially explain the greater severity of the clinical course of the disease. Younger patients have a higher expression of angiotensin-(1-7), which has anti-inflammatory action, and tend to present with less severe disease, although much more frequently.[35,36]

Smith & Sheltzer[37] found that samples of lung tissue collected from smokers had 40-50% more ACE2 receptors than did those collected from nonsmokers, even when the analysis was controlled for age, sex, race, and body mass index. Smokers with a history of > 80 pack-years showed a 100% increase in ACE2 receptors when compared with smokers with a history of < 20 pack-years. In that same study,[37] the authors found that smoking cessation led to decreased levels of ACE2 in the lungs, i.e., the increase in the expression of ACE2 was shown to be potentially reversible. This type of upregulation of ACE2 was also found in patients with idiopathic pulmonary fibrosis, but not in those with asthma, sarcoidosis, or cystic fibrosis, which reinforces the association of smoking with the upregulation of ACE2, but this association does not occur in other respiratory diseases.[38]

The greater amount of ACE2 receptors in the lungs of smokers, possibly induced by nicotine itself, would bring more opportunities for the virus to enter the cells. This might at least partially explain why those individuals are more likely to develop severe forms of COVID-19.[39] In addition, since smoking cessation is associated with a decreased expression of ACE2, it can be speculated that there would also be a reduction in susceptibility to severe forms of COVID-19.[40,41]

Literature reviews have shown that smoking conventional cigarettes or using electronic cigarettes or heated tobacco devices is associated with a greater expression (upregulation) of ACE2, and there is also a clear dose-dependent relationship in this effect.[23,41,42]

The low prevalences of smoking and of COPD in COVID-19 reports are noteworthy, especially when we consider that most studies are from China, where the prevalence of smoking is very high; however, when such frequencies have been assessed in other countries, these prevalences have also been low.[30,42] Preliminary data from an American case series show that the prevalences of chronic lung disease and of current smoking, respectively, are 9.2% and 1.3%.[43]

In contrast to the mechanisms described, another hypothesis is beginning to be raised. Tobacco use could attenuate the normal response of the immune system, through which the body would be more tolerant and less reactive to the aggression caused by the virus. Nonsmokers would maintain the ability to respond immediately to this type of insult through the cytokine release syndrome, i.e., immunocompetent individuals would more readily respond to the aggression, explaining their greater severity and high mortality due to COVID-19.[44]

Clinical and epidemiological data mainly from Chinese cohorts, but also from other countries, when analyzed separately or by means of meta-analyses, are controversial regarding the role of smoking as a risk factor and as a risk of greater severity of the disease. However, experimental and clinical studies point to a greater expression of ACE2 in smokers, acting as a possible link between smoking and COVID-19, although such mechanisms are yet to be fully understood. Since this association remains unclear, the WHO strongly advises smokers to quit smoking to minimize the direct and indirect (passive smokers in the household) risks.[45] The current COVID-19 pandemic is an opportune time to divulge those messages to users of any form of tobacco, who are probably very concerned about their health.

We can infer that the increase in smoking cessation rates might impact on community transmission of SARS-CoV-2. In previous viral epidemics, there was evidence that multifaceted approaches to smoking cessation, by means of behavioral and pharmacological interventions, could play a significant role in both situations, i.e., viral epidemic and smoking.[46] Overtime, smoking cessation normalizes part of the architecture of the respiratory epithelium, with a decrease in hyperplasia and downregulation of ACE2 levels.[47]

Since much remains to be clarified about this relationship, cohort and experimental studies from other countries are necessary. Nevertheless, considering the innumerable damages caused by smoking to human health, especially to the respiratory tract, smoking cessation during the COVID-19 pandemic might contribute to a better evolution of the disease, a decreased risk of death, and smaller contamination rates.[48.49]

## ENVIRONMENTAL POLLUTION

Air pollution is well recognized as a cause of prolonged systemic inflammation affecting the innate immune system, especially in the respiratory tract. Despite this knowledge, few studies have identified air pollution as a potential factor for the spread of SARS-CoV-2 and, eventually, as a cofactor that influences lethality related to the current COVID-19 pandemic.[49-52]

The Italian Society of Environmental Medicine, in one of the few notes in the literature, showed that air pollution might have played a significant role in the spread of the COVID-19 outbreak in northern Italy, but they reported no evidence that, by worsening the health of individuals, it could also have interfered with SARS-CoV-2-related case fatality.[50] That region is considered one of the most polluted in Europe according to the European Environment Agency.[48]

Therefore, in addition to the already known routes of transmission by droplets and aerosols, it is possible that the inhalation of particulate matter (PM) has some role in the spread of COVID-19, since infectious diseases might be related to the inhalation of viral agents adsorbed to PM, especially those with a diameter between 2.5 and 10 μm (coarse PM), < 2.5 μm (fine PM), and ≤ 0.1 μm (ultrafine PM).[49-51] Ultrafine MP might transport coronavirus from tracheobronchial regions to the most peripheral areas of the lungs.[52] This mechanism might have greater implications in countries and cities with high rates of environmental pollution, such as China and Milan. Polluting agents with oxidative potential might reduce the immune defense against the virus, exacerbating the COVID-19 infection.[49]

Animal and human studies have confirmed that the inhalation of coarse and fine PM induces systemic inflammation by means of increased expressions of various agents, such as IL-1, IL-4, IL-6, TNF-α, and TGF-β1, which is directly related to longer periods of exposure. This phase is called the cytokine-storm syndrome.[51,53] These mechanisms might at least partially explain the relevant number of COVID-19 cases, with greater case fatality rates in regions with high environmental pollution rates. However, the clear plunge in air pollution rates as a result of social distancing might have also influenced the decrease in the severity of the outbreak in various cities and regions.[51]

In the near future, SARS-CoV-2 is likely to become a seasonal infectious agent. Therefore, knowledge of its frequency, survival conditions in the more diverse environments, contamination mechanisms, its pathophysiological cascade, and its virulence need to be clarified in detail.[54]

## CLIMATIC CONDITIONS

Although the relationship between SARS-CoV and climatic conditions has already been demonstrated, a more severe phase occurring during cold weather,[55,56] this variable has yet to be fully studied in relation to SARS-CoV-2. However, it is very likely that climatic conditions are related to various parameters of COVID-19.

The increase in the incidence of influenza is known to be associated with low temperatures, low humidity, and greater temperature changes.[57] Those climatic factors are also related to a higher frequency of deaths from respiratory diseases.[58] Breathing dry air causes damage to the respiratory mucosa and reduces the effectiveness of mucociliary clearance, making the individual more susceptible to viral infections. However, droplets exhaled in high humidity environments tend to be heavier and float for less time, reducing contamination, and the opposite occurs in low humidity environments. Although these factors have yet to be studied regarding the COVID-19 pandemic, it is very likely that they are also valid for the current coronavirus outbreak.[59]

The few studies available relating COVID-19 and climate conditions have found an increase in the doubling time of COVID-10 cases when there is an increase in daily temperature, but no relationship was found with an increase in temperature regarding mortality rates.[54,60] Wu et al.[61] reported that a 1ºC increase in temperature was associated with a 3.08% (95% CI: 1.53-4.63%) reduction in new daily cases and a 1.19% (95% CI: 0.44-1.95%) reduction in the number of deaths. The same authors stated that a 1% increase in relative air humidity was related to a daily decrease in new cases of 0.85% (95% CI: 0.51-1.19%) and a decrease of new deaths of 0.51% (95% CI: 0.34-0.67%).

Ma et al.[62] analyzed 2,299 deaths from COVID-19 between January 20 and February 29, 2020, in Wuhan, China, against meteorological and pollution parameters. The authors found an association between the decrease in death rates from COVID-19 and the increase in humidity. Inhaling dry air causes epithelial damage and reduced mucociliary clearance, making the individual more susceptible to viral respiratory infections. These findings are in accordance with previous publications relating the increase in deaths from respiratory diseases to the decrease in temperature,[63] particularly when there is very intense cold and low humidity.[64]

Other factors that might influence the assessments of any outbreak should be considered, such as government interventions, availability of human resources and materials to treat the population, availability of hospital beds, among others. The outbreak of influenza in Japan, concurrently with COVID-19, has been less intense than in previous years. This might have occurred due to the lesser virulence of the agent, but also due to SARS-CoV-2-related restrictive measures, especially those of social distancing, such as closing schools and prohibiting large events and agglomerations. The search for medical care related to influenza might have also been altered by the severity of the COVID-19 epidemic.[65]

## FINAL CONSIDERATIONS

Pandemics pose major challenges for individuals and health care systems. Those that are more prepared or consider such difficult times as windows of opportunity to prepare for future outbreaks will have better results. Different types of measures have a marked influence on the spread of the virus and the resulting diseases.

This article reviews the influence of smoking, environmental pollution, and climatic conditions on the incidence and severity of COVID-19. As for environmental pollution and climate, it is urgent that the global outcry result in objective actions from various government bodies and society so that everyone can do their part. As for smoking, we are facing the opportunity and challenge to stop tobacco use in order to reduce the risk of acquiring or having more severe forms of COVID-19 and of other diseases. Even though the relationship between smoking and COVID-19 needs to be further clarified, there is no doubt that among the major risk factors for presenting with severe forms of the disease are smoking itself and smoking-related diseases.

## AUTHOR CONTRIBUTIONS

JMC: review of the literature, preparation of the text, and approval of the final version. IG: critical review of the literature and participation in the preparation of the manuscript.

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# Tuberculosis in elderly patients in the city of Cali, Colombia: a hospital-based cohort study

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## TO THE EDITOR:

Elderly patients are at an increased risk of tuberculosis because of immune system alterations affecting cell-mediated responses.[1] Several studies have shown that tuberculosis incidence and mortality rates are significantly higher in patients over 80 years of age than in those in any other age group.[2] Elderly patients are also at an increased risk of developing age-related diseases such as cancer and cardiovascular disease.[3] In Colombia, tuberculosis remains a public health problem, and, with the increase in life expectancy, it has become an issue in the elderly population. In addition, data on tuberculosis treatment outcomes and adverse reactions in patients over 65 years of age are limited.

Here, we report 108 cases of tuberculosis in elderly patients treated at Fundación Valle del Lili, a university hospital located in the city of Cali, Colombia, where the tuberculosis notification rate in 2015 was 40 cases per 100,000 population. All cases were recorded in the institutional tuberculosis database between January 1st, 2011 and December 31st, 2016. The inclusion criteria were as follows: being 65 years of age or older and having been diagnosed with tuberculosis on the basis of an AFB-positive sputum smear, a positive culture for *Mycobacterium tuberculosis*, or a positive GeneXpert result. Cases of nontuberculous mycobacterial infection were excluded, as were suspected but unconfirmed cases of tuberculosis.

Descriptive statistics were calculated for all variables. The chi-square test or Fisher's exact test was used in order to compare categorical variables, and a t-test was used in order to compare continuous variables. A subanalysis was performed on patients in the 65- to 79-year age bracket (the non-octogenarian group) and on those ≥ 80 years of age (the octogenarian group). Patients for whom there was information regarding treatment outcomes were evaluated and divided into two groups, namely, treatment success and treatment failure. Survival analysis was performed with the Kaplan-Meier method. Differences in survival between the two age groups were assessed by the log-rank test. A value of $p < 0.05$ was considered significant for all statistical analyses. All analyses were performed with the Stata statistical software package, version 14.0 (StataCorp LP, College Station, TX, USA).

Patient clinical and sociodemographic characteristics, as well as comorbidities, risk factors for tuberculosis, and treatment outcomes, are summarized in Table 1. The most common comorbidities in the non-octogenarian group were diabetes, in 36%; COPD, in 23%; and malignancy, in 21%. In the octogenarian group, the most common comorbidities were COPD, in 46%; malignancy, in 14%; and diabetes, in 7%. Diabetes was less common in the octogenarian group than in the non-octogenarian group, whereas COPD was more common in the former than in the latter. There was a significant difference between the two groups regarding diabetes ($p = 0.004$) and COPD ($p = 0.017$). With regard to tuberculosis presentation, there were no differences between the two groups.

Of the sample as a whole, 25 (23%) had a diagnostic delay of 31-90 days and 39 (36%) had a diagnostic delay of more than 90 days. In the treatment success and treatment failure groups, respectively, 10 (22%) and 7 (32%) had a diagnostic delay of 31-90 days, whereas 15 (33%) and 4 (18%) had a diagnostic delay of more than 90 days.

Of the 108 patients included in the study, 106 were started on antituberculosis therapy and 2 died before receiving treatment. Thirty-six patients (34%) were lost to follow-up, and 20 (18%) died after treatment initiation. Forty-one patients were excluded from our analysis because they did not complete tuberculosis treatment at our institution or because they were lost to follow-up. There were no significant differences between the treatment success and treatment failure groups regarding risk factors for tuberculosis, the exception being malignancy ($p = 0.013$).

At five years of follow-up, 24 (21.77%) had died, the remaining 84 being censored at follow-up. Five-year overall survival for tuberculosis was 78.23%. There were no differences in survival between the non-octogenarian and octogenarian groups ($p = 0.5936$).

Twenty patients (18%) died after tuberculosis treatment initiation. Of those 20 patients, 10 (50%) died of tuberculosis. Of those, 1 died of central nervous system tuberculosis. Other causes of death included lung cancer, in 10%; hepatocellular carcinoma, in 5%; gastrointestinal bleeding, in 15%; intra-abdominal bacterial infection,

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**Table 1.** Descriptive statistics and univariate analysis results in tuberculosis patients in the 65- to 79-year age bracket (the non-octogenarian group) and in those ≥ 80 years of age (the octogenarian group).[a]

| Variable | Total sample (N = 108) | | Non-octogenarian patients (n = 80) | | Octogenarian patients (n = 28) | | p |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Age, years[b] | 74.0 (65.0-91.0) | | 72.0 (67.5-76.0) | | 84.0 (81.0-86.0) | | |
| Male sex | 64 | 59 | 50 | 63 | 14 | 50 | 0.247 |
| Ethnic group[c] | | | | | | | |
| Hispanic American | 71 | 66 | 58 | 68 | 17 | 61 | |
| Afro-Colombian | 7 | 6 | 6 | 8 | 1 | 3 | 1 |
| European ancestry | 6 | 6 | 3 | 3 | 3 | 11 | |
| Native South American | 3 | 3 | 3 | 3 | - | - | |
| Comorbidities | | | | | | | |
| Diabetes | 31 | 29 | 29 | 36 | 2 | 7 | 0.004 |
| COPD | 31 | 29 | 18 | 23 | 13 | 46 | 0.017 |
| Malignancy | 19 | 18 | 17 | 21 | 4 | 14 | 0.451 |
| End-stage renal disease | 5 | 5 | 4 | 5 | 1 | 3 | 1 |
| HIV infection | 4 | 4 | 4 | 5 | - | - | 0.571 |
| Chronic hepatitis C | 2 | 2 | 2 | 3 | - | - | |
| Bariatric surgery | 1 | 1 | 1 | 1 | - | - | 1 |
| Solid organ transplantation | 1 | 1 | 1 | 1 | - | - | 1 |
| Risk factors for TB | | | | | | | |
| Cigarette smoking | 36 | 33 | 30 | 38 | 9 | 32 | 0.648 |
| Previous TB treatment | 14 | 13 | 10 | 13 | 4 | 14 | 0.811 |
| Household contact | 8 | 7 | 6 | 8 | 2 | 7 | 1 |
| Positive tuberculin skin test | 2 | 2 | 2 | 3 | - | - | 0.487 |
| Drug abuse | 2 | 2 | 2 | 3 | - | - | 1 |
| Duration of symptoms prior to TB diagnosis, days[d] | | | | | | | |
| ≤ 30 | 38 | 35 | 18 | 23 | 7 | 28 | 0.302 |
| 31-90 | 25 | 23 | 32 | 42 | 6 | 24 | |
| ≥ 91 | 39 | 36 | 27 | 35 | 12 | 48 | |
| TB presentation | | | | | | | |
| Pulmonary | 87 | 81 | 64 | 80 | 23 | 82 | 0.805 |
| Extrapulmonary | 21 | 19 | 16 | 20 | 5 | 18 | |
| Pleural | 4 | 4 | 4 | 5 | - | - | 0.571 |
| Central nervous system | 3 | 3 | 3 | 4 | - | - | 0.567 |
| Osteoarticular | 3 | 3 | 2 | 3 | 1 | 4 | 1 |
| Genitourinary | 3 | 3 | 2 | 3 | 1 | 4 | 1 |
| Disseminated | 3 | 3 | 3 | 4 | - | - | 0.567 |
| Spinal | 2 | 2 | 1 | 1 | 1 | 4 | 0.453 |
| Gastrointestinal | 1 | 1 | - | - | 1 | 4 | 0.259 |
| Lymph node | 1 | 1 | 1 | 1 | - | - | 1 |
| Cutaneous | 1 | 1 | - | - | 1 | 4 | 0.259 |
| Treatment outcomes | | | | | | | |
| Treatment success | 45 | 42 | 33 | 41 | 12 | 43 | 0.618 |
| Loss to follow-up | 37 | 34 | 25 | 31 | 9 | 32 | |
| Death | 20 | 18 | 15 | 19 | 5 | 18 | |
| Transfer | 4 | 4 | 4 | 5 | - | - | |
| Treatment failure | 2 | 2 | 3 | 4 | 2 | 7 | |

TB: tuberculosis. [a]Data expressed as n (%), except where otherwise indicated. [b]Data expressed as median (interquartile range). [c]Missing data for 21 patients. [d]Missing data for 6 patients.

in 10%; cryptococcosis/HIV coinfection, in 5%; and stroke, in 5%. Case-fatality rates were similar between the non-octogenarian and octogenarian groups (19% vs. 18%).

Tuberculosis carries a high disease burden and a high morbidity in Colombia and across Latin America, where elderly individuals, who constitute approximately 3% of the Colombian population, are at risk of acquiring the disease. This is due to the epidemiological transition and several other factors, including immunosenescence, malnutrition, comorbidities, polypharmacy, and concurrent socioeconomic disparities.[1]

The clinical presentation of tuberculosis in elderly patients can be atypical, meaning that the classic symptoms (fever, sweating, weight loss, and cough) are either not present or, if present, due to decompensated comorbidities.[4] A high index of suspicion should therefore be maintained. In elderly patients, the most common presentation of tuberculosis is pulmonary tuberculosis, and there is a low prevalence of

cavitary disease.[5] Although there is no difference in the recommended tuberculosis treatment regimen between elderly patients (over 65 years of age) and younger patients, there is a higher risk of drug-drug interactions in the former, especially between rifampin and antihypertensive or hypoglycemic agents.[6] These drug-drug interactions can reduce tuberculosis treatment success rates.

In a meta-analysis published in 2018, moderate-quality evidence showed an association of pulmonary tuberculosis with comorbid malignancy and an increased risk of in-hospital mortality (OR = 1.85; 95% CI, 1.01-3.40).[7] These results are consistent with our findings that there were more cases of malignancy in the treatment failure group.

Most of the elderly patients in the present study had pulmonary tuberculosis and experienced a diagnostic delay. They had unfavorable treatment outcomes, with high case-fatality rates, and some were lost to follow-up.[8-10] These losses could be attributable to limitations of program coordination, with patients being transferred to and treated in different hospitals and health care centers, which is a constant problem in Latin America.

Tuberculosis control programs should evaluate care models to improve tuberculosis treatment success rates and health care coordination. The results of the present study can form the basis for future studies and contribute to changes in health policies related to tuberculosis control programs, including cost-effectiveness studies and more frequent follow-up of this population.

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# Triple-matched defects on ventilation/perfusion scintigraphy and computed tomography: the importance of the reticular reversed halo sign

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## TO THE EDITOR:

An 87-year-old female patient with a history of heart failure and nondialysis chronic kidney disease was hospitalized for dyspnea and cough. She had a low pretest probability of pulmonary embolism (PE), as assessed by the original Wells score (< 2). Her laboratory test results were as follows: hemoglobin, 12.0 g/dL; mild leukocytosis (11,570 cells/mm$^3$); serum urea, 94 mg/dL; serum creatinine, 1.94 mg/dL (estimated glomerular filtration rate, as determined by the Modification of Diet in Renal Disease equation, 26 mL/min/1.73 m$^2$); elevated C-reactive protein (11.34 mg/dL); and elevated D-dimer (2,536 ng/mL). A chest X-ray showed peripheral opacities in the middle and lower left lung fields, as well as signs of a small ipsilateral pleural effusion. Planar ventilation/perfusion (V/Q) scintigraphy revealed a segmental matched V/Q defect in the left lower lobe, where the radiographic changes had been seen (constituting a triple-matched defect), leading to consideration of an intermediate (20-79%) probability of PE; that is, the procedure was considered nondiagnostic (Figures 1A-C). One caveat is that the diagnostic performance of planar V/Q scintigraphy is lower than that of V/Q single-photon emission CT, especially for segmental and subsegmental emboli.[1,2] Unenhanced chest CT showed peripheral opacities in the left lower lobe, as well as a reversed halo sign (RHS) with a reticular pattern within the halo (Figure 1D), together with a small ipsilateral pleural effusion. The presence of a reticular RHS in a juxtapleural location raised the possibility of pulmonary infarction. Prophylactic measures were implemented to prevent contrast-induced nephropathy, and dual-energy

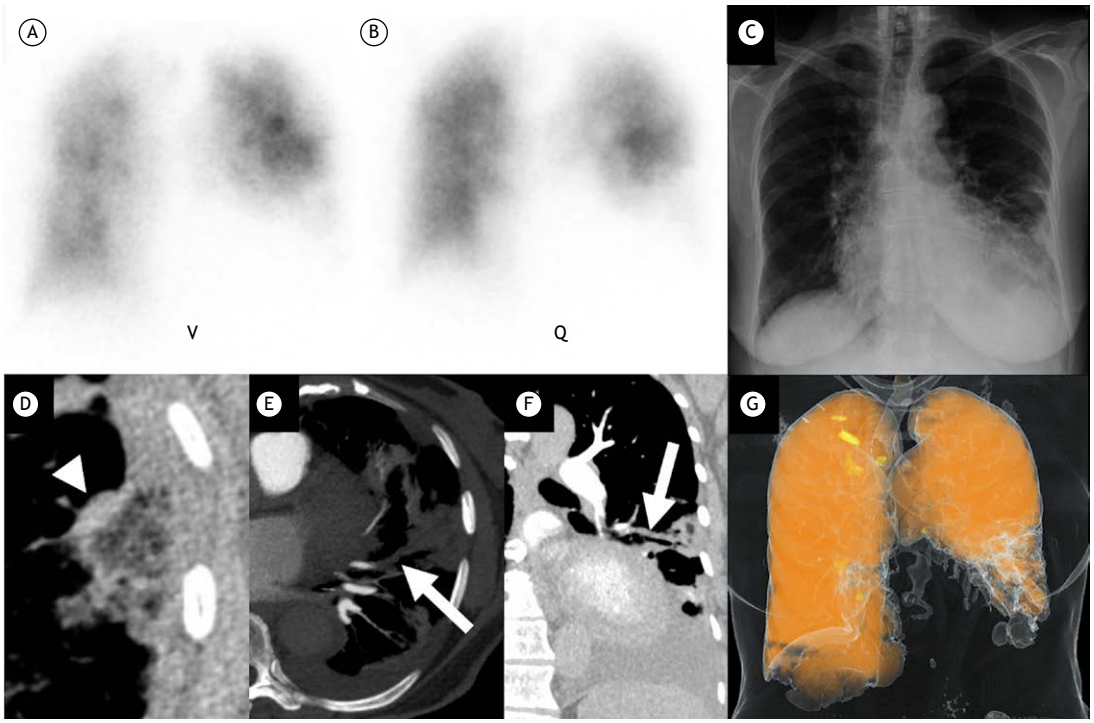


**Figure 1.** Planar ventilation/perfusion (V/Q) scintigraphy (anterior view, in A and B) and chest X-ray (frontal view, in C) reveal a triple-matched defect in the left lower lobe. An axial CT image (in D) shows a reversed halo sign (RHS) with low-attenuation areas within the halo (reticular RHS; arrowhead) in a juxtapleural location, a finding suggestive of pulmonary infarction. On CT angiography, an axial maximum intensity projection image (in E) and an oblique coronal image (in F) show a complete filling defect in the subsegmental arterial branch (arrow) supplying the opacified area in the left lower lobe. A color-coded pulmonary blood volume map from dual-energy pulmonary CT angiography (in G) shows an iodine defect in the left lower lobe.

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pulmonary CT angiography was performed, confirming the presence of subsegmental PE (Figures 1E and 1F); color-coded iodine perfusion maps revealed an iodine defect in the left lower lobe (Figure 1G). Although dual-energy CT allows visualization of blood volume but not blood flow and does not provide true perfusion imaging, it allows selective visualization of contrast medium distribution with high spatial resolution (iodine color map) and eliminates registration problems with no additional radiation exposure.[3] In our patient, dual-energy CT showed a perfusion defect beyond an obstructive clot. Although this was not essential for diagnostic confirmation, it was very illustrative in terms of imaging.

According to the original and revised Prospective Investigation of Pulmonary Embolism Diagnosis II criteria, a solitary moderate-size or large triple-matched defect in the lower lung zone on V/Q scintigraphy and chest X-ray indicates an intermediate probability of PE and is nondiagnostic, respectively, a moderate defect covering 25-75% of a lung segment and a large defect covering > 75% of a lung segment.[4,5] In patients with PE, pulmonary infarction has an incidence that ranges from 10% to 30% and typically presents on CT as pleural-based wedge-shaped opacities in cases of occlusion or subocclusion of segmental/subsegmental arterial branches, often in association with the RHS.[6,7] The RHS is defined as a focal area of ground-glass opacity surrounded by a more or less complete ring of consolidation.[8,9] Although it was originally described in the context of organizing pneumonia, it has been shown to be associated with several other lung diseases, including PE.[7,10,11] In immunocompetent patients, an RHS with reticulation within the halo (reticular RHS) in a juxtapleural location is highly suggestive of pulmonary infarction, usually secondary to thromboembolic disease.[12-14]

In an appropriate clinical context, the presence of a reticular RHS on unenhanced CT scans and nondiagnostic V/Q scans increase the likelihood of PE. In very specific situations, it might allow us to avoid the use of contrast media. Multicenter studies are needed in order to investigate this possibility.

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# COVID-19 morbidity and mortality in 2020: the case of the city of Rio de Janeiro

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## DEAR EDITOR:

In March of 2020, community transmission of severe acute respiratory syndrome coronavirus 2 was confirmed in Brazil. In the present study, we investigated possible changes in trends, as well as the levels of morbidity and mortality, associated with coronavirus disease 2019 (COVID-19) during the pandemic in the city of Rio de Janeiro, Brazil, using time series analyses. Further details about the data used in this study—cases and deaths occurring between March 6 and July 22, 2020 (a period of 139 days) in the city—are available at . We collected data on the daily numbers of new cases of and deaths from COVID-19 during that period.

For the numbers of COVID-19 cases and deaths in 2020, we compared periods. For cases, we compared the 74-day period from March 6 to May 18 with the 65-day period from May 19 to July 22. For deaths, we compared the 62-day period from March 6 to May 6 with the 77-day period from May 7 to July 22.

Because this was a relatively short time series, we chose to use the Prais-Winsten and Cochrane-Orcutt regression to adjust the models for both outcomes (COVID-19 cases and deaths). The models included a constant, a term indicating a change in level from the first to the second period, and another term indicating a change in trend (slope) from the first to the second period.

The model is expressed as follows:

$$Y_t = (\hat{\beta}_0 + \hat{\beta}_1 \times \textit{total days} + \hat{\beta}_2 \times 1 + \hat{\beta}_3 \times \textit{days after the pre-prediction period}) + e_t$$

where $Y_t$ is the absolute effect for a given period of time, $\hat{\beta}_0$ is the constant, $\hat{\beta}_1$ is the parameter related to the total investigation time, $\hat{\beta}_2$ is the parameter related to the prediction period, $\hat{\beta}_3$ is the parameter related to the duration of the effect to be estimated, and $e_t$ is the random error.

Between March 6 and July 22, there were 68,334 new COVID-19 cases and 7,887 COVID-19-related deaths. The mean number of cases in the first and second periods were 181.66 ± 208.86 and 844.48 ± 553.34, respectively, whereas the mean number of deaths per day in the first and second periods were 12.32 ± 14.51 and 92.51 ± 46.92, respectively.

The serial correlation coefficient for cases was 7.17 (95% CI: 3.18-11.16; $p < 0.001$), indicating an increase in the number of cases. Starting on the 75th day, the trend was reversed, indicating a decrease in the number of cases (coefficient = −21.87; 95% CI: −28.07 to −15.67; $p < 0.0001$). We detected a change in the level of cases in the second period (coefficient = 887.56; 95% CI: 642.88-1.132.25; $p < 0.0001$), as shown in Figure 1A.

The serial correlation coefficient for deaths was 0.73 (95% CI: 0.14-1.31; $p < 0.02$), which indicates growth. Starting on May 7, the trend reversed, indicating a decrease in the number of deaths (coefficient = −1.53; 95% CI: −2.24 to −0.83; $p < 0.0001$). The regression model estimates for the change in level were significant, indicating a mean increase of 90.11 COVID-19 deaths (95% CI: 63.64-116.58; $p < 0.0001$) in the second period, as shown in Figure 1B.

Since the beginning of the epidemic in the city of Rio de Janeiro, the municipal testing policy has made RT-PCR tests available for inpatients and for patients with suspected COVID-19 seen in emergency departments, although no tests have been made available at primary health care clinics. Our findings indicate that, in the first two months after the onset of the epidemic, the number of deaths was low, although there was thereafter a significant increase in morbidity and mortality, associated with the high transmissibility of the disease, the lack of knowledge about the biological behavior of the virus, and the lack of a specific treatment or vaccine.

According to the Brazilian National Ministry of Health, by the second half of May, there were more than 240,000 confirmed COVID-19 cases and just over 16,000 thousand deaths attributed to the disease in the country. At that time, nearly 140,000 patients had been hospitalized with suspected COVID-19 in Brazil.

Measures have been put in place to control the pandemic. Although social distancing was adopted as the main policy to confront COVID-19 in Brazil, the country lacked important coordinated actions, such as investments in a unified information system; greater availability of diagnostic tests for suspected cases; rerouting of the operational flow at health care facilities; and streamlining of patient care with the construction of field hospitals and purchasing of equipment.[1,2]

In terms of COVID-19 mitigation measures, two different scenarios were observed in Brazil. The first is related to a short period of time in which there was no mitigation, whereas the second is related to a period with medium-level mitigation measures in place. This second scenario differs from that seen in other countries, such as France, Spain, and Switzerland, which adopted stricter measures with the imposition of a total lockdown after the cumulative number of cases reached 50 (intense

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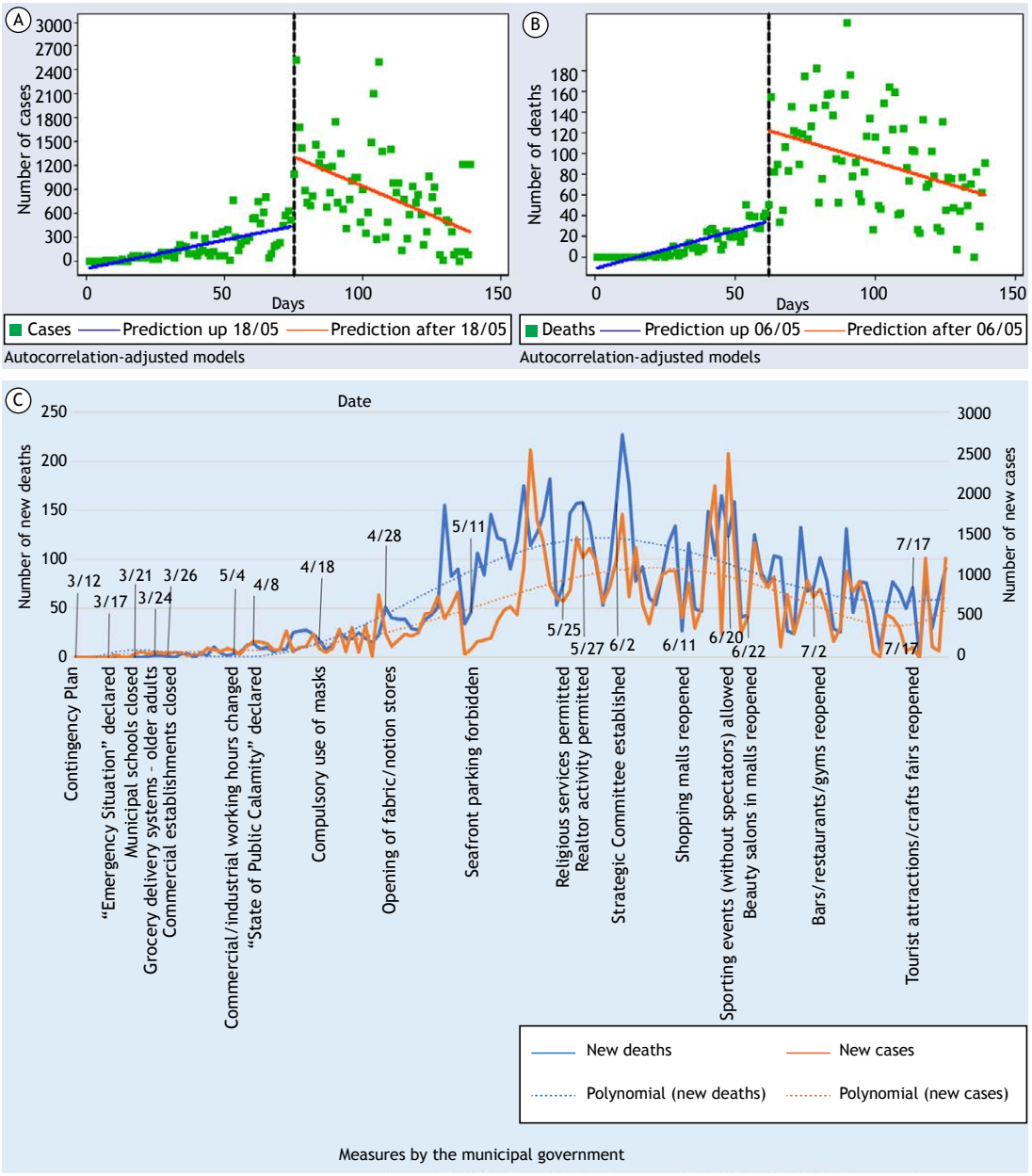


**Figure 1.** Time series of COVID-19 morbidity and mortality in the city of Rio de Janeiro (RJ)—March 6 to July 22, 2020. A: Number of cases. B: Number of deaths. C: Effects of the passing of municipal decrees on the number of COVID-19 cases and deaths.

mitigation scenario). Germany, Italy, and the United Kingdom took longer to implement such actions.[3]

Despite the containment measures implemented, the estimated capacity of an infected individual to infect others ($R_0$) in the state of Rio de Janeiro and in the greater metropolitan region of the city of Rio de Janeiro was 2.4 in early May,[4] which suggests that the number of cases was growing and that other measures would be needed to contain the spread of the disease.

The successful use of nonpharmacological disease mitigation measures in China has given rise to effectiveness studies.[5-7] Many researchers argue that nonpharmacological intervention measures can, by lowering the occupancy rate of ICU beds and the number of deaths, avoid the collapse of the health care system, which could be overwhelmed by severe cases that require hospitalization.[8-10]

Predominant among the obstacles that hindered the control of COVID-19 in Brazil are the high turnover of health ministers during the pandemic, the belief that there was no need for stricter mitigation measures, the constant pressure to resume economic activities, and the delay in providing government aid to the

vulnerable population, which led to long lines at banks and consequent agglomerations of individuals.

Although we saw a significant increase in the number of deaths and new cases in May, the measures adopted to face the pandemic were eased, mainly in late May/early June (Figure 1C). Additional surveillance activities could contribute to increasing compliance with the mitigation measures in place.

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# Lung function and respiratory symptoms in charcoal workers in southern Brazil: an eight-year cohort study

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## TO THE EDITOR:

In southern Brazil, charcoal production is an artisanal, nonmechanized process that involves felling trees, transporting logs, burning wood in brick kilns, and monitoring the wood burning process. Workers are exposed to charcoal smoke and dust, often with no personal protective equipment. The kilns are family owned and located adjacent to their dwellings, likely leading to lifetime exposure. The objective of the present study was to assess whether there were significant changes in respiratory symptoms and spirometry results after an eight-year period.

In 2008, we evaluated 67 individuals working at 41 kilns, the mean number of years working at kilns being 19.1 years.[1] Participants completed a structured questionnaire and underwent spirometry. Of the 67 workers evaluated in 2008, 9 had obstructive lung disease, as assessed by spirometry. Of those, 5 were diagnosed with bronchial asthma and 4 were diagnosed with COPD. In addition, 4 participants (5.8%) died and 1 (1.5%) was lost to follow-up. In 2016, 62 individuals (92.5%) were located for follow-up. Of those, 11 (16.4%) declined to participate. Therefore, 51 (82.2%) completed the questionnaire and underwent spirometry again. All spirometry tests were performed with a Microlab 3500 spirometer (Micro Medical Ltd., Rochester, England) before and after administration of a bronchodilator (400 µg of albuterol). All procedures were performed in accordance with the American Thoracic Society/European Respiratory Society guidelines.[2] The study was approved by the local research ethics committee (CAAE no. 50237415.5.0000.5348). All participants gave written informed consent.

Normality of data distribution was assessed with the Kolmogorov-Smirnov test. Continuous variables were presented as means and standard deviations, and the Student's t-test was used in order to assess changes in spirometric variables. Descriptive statistics (absolute and relative values) were calculated, and McNemar's test was used in order to assess changes in respiratory symptoms. The level of significance was set at 0.05. All statistical analyses were performed with the IBM SPSS Statistics software package, version 24.0 (IBM Corporation, Armonk, NY, USA).

Of the 67 individuals who were evaluated in 2008, 51 (80.9%) were evaluated again in 2016, the mean age being 54 ± 13 years. Of those 51 individuals, most (n = 38; 74.5%) were male. In addition, 35 (68.6%) remained as charcoal workers, whereas 16 (31.4%) did not. The most common upper airway symptoms were sneezing, in 35 (68.6%); nasal obstruction, in 14 (27.5%); and nasal discharge, in 13 (25.5%). The most common lower airway symptoms were cough, in 14 (27.5%); expectoration, in 19 (37.3%); and chronic expectoration, in 8 (15.7%). The prevalence of respiratory symptoms did not change after eight years, the exception being that of sneezing, which increased from 39.2% in 2008 to 68.6% in 2016 ($p < 0.05$).

Lung volumes were found to have decreased after eight years of exposure in smokers and nonsmokers alike. In both subgroups, there was a significant reduction in FVC in liters and as a percentage of the predicted value, as well as in $FEV_1$ in liters. All 51 workers showed a decline of 48 mL/year in pre-bronchodilator FVC and of 37 mL/year in pre-bronchodilator $FEV_1$. Nonsmokers showed a mean decline of 44 mL/year in FVC and of 35 mL/year in $FEV_1$. Smokers experienced a significant decrease in mean FVC and $FEV_1$ (58 mL/year and 39 mL/year, respectively). It is of note that the participants who remained as charcoal workers and those who were smokers experienced a more pronounced decline in FVC and $FEV_1$ after bronchodilator administration. Among workers ≥ 40 years of age (n = 44), there was no significant decrease in FVC after eight years, but there was a significant decrease in $FEV_1$. After bronchodilator administration, there was a significant decrease in mean FVC and $FEV_1$ (65 mL/year and 45 mL/year, respectively; $p < 0.001$ for both). Table 1 shows the changes in spirometric values over the course of eight years, by sex, work status (i.e., still working in the production of charcoal or no longer working in the production of charcoal), smoking status, and age.

Our study showed a significant decrease in lung volumes (i.e., a decrease of 51 mL/year in FVC and of 38 mL/year in $FEV_1$) after bronchodilator administration. Reduced lung capacity is associated with aging and is an expected physiological outcome in most individuals,[3] being influenced by the environment and, in particular, air quality. One study[4] examined lung function and showed that a decline of ≤ 20 mL/year in $FEV_1$ can be considered normal in individuals ≤ 40 years of age. In individuals > 40 years of age, a decline of approximately 38 mL/year in $FEV_1$ can be considered normal.[4] In the present study, however, 7 (13.7%) of the workers who were ≤ 40 years of age experienced a decline of 62 mL/year in $FEV_1$ after bronchodilator administration. This suggests that working in charcoal production can lead to a more pronounced decline in $FEV_1$ over time.

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**Table 1.** Changes in $FEV_1$ (in mL/year) and FVC (in mL/year) in charcoal workers in Brazil in the 2008-2016 period, by smoking status, work status (i.e., still working/no longer working in charcoal production), sex, and age.

| Variable | n | Pre-bronchodilator | | | | Post-bronchodilator | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | $\Delta FEV_1$ | p | ΔFVC | p | $\Delta FEV_1$ | p | ΔFVC | p |
| Total sample | 51 | −37 | < 0.001 | −48 | < 0.001 | −38 | < 0.001 | −51 | < 0.001 |
| Smoking status | | | | | | | | | |
| Nonsmoker | 37 | −35 | < 0.001 | −44 | < 0.001 | −34 | < 0.001 | −43 | < 0.001 |
| Smoker | 14 | −39 | < 0.002 | −58 | < 0.001 | −50 | < 0.001 | −72 | < 0.001 |
| Working in charcoal production in 2016 | | | | | | | | | |
| No | 16 | −28 | < 0.006 | −45 | < 0.003 | −35 | < 0.008 | −42 | < 0.023 |
| Yes | 35 | −39 | < 0.001 | −49 | < 0.001 | −40 | < 0.001 | −54 | < 0.001 |
| Working in charcoal production in 2016 + smoking status | | | | | | | | | |
| No + nonsmoker | 09 | −17 | < 0.079 | −24 | < 0.086 | −21 | < 0.053 | −16 | < 0.408 |
| No + smoker | 07 | −43 | < 0.037 | −72 | < 0.016 | −53 | < 0.050 | −73 | < 0.028 |
| Yes + nonsmoker | 28 | −40 | < 0.001 | −51 | < 0.001 | −37 | < 0.001 | −50 | < 0.001 |
| Yes + smoker | 07 | −35 | < 0.037 | −45 | < 0.064 | −48 | < 0.003 | −70 | < 0.002 |
| Sex | | | | | | | | | |
| Male | 38 | −36 | < 0.001 | −48 | < 0.001 | −42 | < 0.001 | −65 | < 0.001 |
| Female | 13 | −31 | 0.001 | −45 | < 0.001 | −37 | 0.001 | −61 | 0.001 |
| Age | | | | | | | | | |
| ≤ 40 years | 7 | −36 | 0.009 | −18 | 0.008 | −62 | 0.001 | −37 | < 0.001 |
| > 40 years | 44 | −35 | 0.010 | −53 | 0.055 | −45 | < 0.001 | −65 | < 0.001 |

Participants > 40 years of age had a decline of 45 mL/year in $FEV_1$ after bronchodilator administration. Charcoal workers are similar to firefighters in terms of occupational smoke exposure. In a study evaluating 1,146 firefighters in the USA over a three-year period in the 1970s, $FEV_1$ and FVC were found to have decreased by 30 mL/year and 40 mL/year, respectively.[5]

Our study has two major limitations: 19% of the original sample was lost to follow-up, and the absence of a control group precluded comparisons with individuals not exposed to charcoal smoke/dust. Nevertheless, the present study presents interesting data regarding a very common occupation in Brazil, comparing spirometry results over an eight-year period.

In conclusion, although charcoal workers showed no increase in respiratory symptoms (except for sneezing), there was a reduction in lung volumes over the course of eight years, especially in those who were smokers and ≤ 40 years of age.

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# Assessment of pulmonologists' receptivity to a structured radiology report for interstitial lung disease

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## TO THE EDITOR:

Interstitial lung disease (ILD) encompasses a group of more than 200 disorders, which are classified together because they affect the tissue and space around the alveoli.[1,2] Depending on the specific disorder, other lung compartments are also affected.[1,2] Despite the extent of this group, there are some international guidelines that can aid in diagnosis. In cases of suspected idiopathic ILD, there is the 2013 consensus statement, which defines imaging patterns for all interstitial pneumonias,[1] and there is the 2018 clinical practice guideline for idiopathic pulmonary fibrosis.[2]

In this context, structured radiology reports (SRRs) are a vital tool and have grown in importance in imaging studies.[3] SRRs stand on three pillars. The first pillar is the presence of headings, such as "indication" and "impression".[3] The second pillar includes subheadings, such as "organs" and "systems". The third pillar is standardization of language and elements of the report form, which is the most relevant pillar, because it is the limited, standardized language that provides most of the benefits of SRRs. First of all, SRRs reduce ambiguous language,[4] enabling more effective analysis, creating opportunities for research, and providing support for clinical decisions. In addition, this method of reporting makes it possible for radiologists to provide comprehensive reports, with greater adherence to guidelines, even when they face unusual conditions or when they usually find it difficult to remember all the elements of international guidelines and recommendations.[3,4] One study revealed that radiologists from a large university center reached a proportion of only 60.8% of conformance with the Fleischner Society guidelines for the management of pulmonary nodules.[5] SRRs tend to improve these numbers and could provide recommendations automatically, based on appropriate information.[2-5]

In order to achieve the aforementioned benefits, we developed, on the basis of previous experiences and with the approval of the Research Ethics Committee of the Santa Casa Sisters of Mercy Hospital of Porto Alegre, located in the city of Porto Alegre, Brazil, an SRR containing CT findings consistent with ILD (Chart 1).[1,2,6,7] In order to assess pulmonologists' acceptance of and opinions about this SRR, radiologists completed the SRR of a total of 58 examinations requested by 20 pulmonologists because of suspected ILD, that is, no definite diagnosis, for three months. Subsequently, a questionnaire was developed and sent to the pulmonologists, 16 of whom agreed to complete it anonymously online. Participants were questioned regarding the SRR itself, the reliability of the medical reports, and their preferred mode of receiving the reports.

The analysis of the responses received showed that most pulmonologists were between 40 and 60 years of age, 10 (62.5%) reported having read the reports in full, and all trusted the radiologist's opinion—12 (75%) trusted it completely. The mode of presentation of the report was the item of greatest disagreement; slightly more than half of the participants preferred printed images and reports (to reports stored in the cloud or on CDs). Thirteen (81.3%) of the participants found it important that the reports included a description of the technique used in the examination.

The greatest agreement was found for topics related to the SRR itself. Almost all participants (15/16) reported preferring structured to narrative free-text reports and stated that the presence of several differential diagnoses helped them think about all of the hypotheses. In this sense, 14 (87.5%) stated that the SRR made the management of patients with ILD much easier, and all participants reported some degree of facilitation.

The participants' acceptance of the SRR reinforces the benefits of this type of report and encourages its use to improve communication between radiologists and pulmonologists, thus facilitating the diagnosis of ILDs.

## AUTHOR CONTRIBUTIONS

KLI, ASSJ, and EM: conceptualization and planning of the study, as well as interpretation of the evidence. JPSDB: writing and review of the preliminary drafts and final version. BH: writing and review of the preliminary drafts and final version; approval of the final version.

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**Chart 1.** Structured radiology report for interstitial lung disease on chest CT.

**STRUCTURED REPORT FOR INTERSTITIAL LUNG DISEASE - COMPUTED TOMOGRAPHY OF THE CHEST**

**Technique:** Examination performed without intravenous contrast medium, using high resolution technique and slice thickness of 1 mm for the assessment of lung parenchyma. Further acquisitions were made during forced expiration.
**Clinical information:**
**Motion artifacts:** yes/no
**Interstitial evaluation:**
**Honeycombing:** yes/no
**Traction bronchiectasis:** yes/no
**Signs of loss of lung volume:** yes/no
**Predominant apicobasal gradient:** yes/no
If yes: upper third/middle third/lower third
**Predominant axial distribution:** yes/no
If yes: subpleural/peribronchovascular/diffuse
**Overall pulmonary fibrosis extent:**
Upper third: ____% Middle third: ____% Lower third: ____%
**Emphysema:** yes/no
Emphysema subtype: centrilobular/paraseptal/bullous
Extent: Mild (< 5%); Moderate (5-30%); Severe (> 30%)
**Lymph node enlargement:** yes/no
Location: mediastinal/hilar/axillary
**Increased diameter of the pulmonary artery:** yes/no
**Air trapping:** yes/no
**Diffuse lung cysts:** yes/no
**Extensive ground-glass pattern:** yes/no
**Micronodular interstitial pattern:** yes/no
**Consolidation:** yes/no
**Other findings:** (Free text)
**IMPRESSION:**
**Interstitial lung disease pattern on chest CT:**
**1. Consensus statement for interstitial lung diseases (updated)**
1. Usual interstitial pneumonia
2. Nonspecific interstitial pneumonia
3. Desquamative interstitial pneumonia
4. Acute interstitial pneumonia
5. Organizing pneumonia
6. Respiratory bronchiolitis/interstitial lung disease
7. Lymphocytic interstitial pneumonia
8. Unclassifiable interstitial pneumonia
9. Pulmonary fibroelastosis

**2. Idiopathic pulmonary fibrosis clinical guideline**
1. Definitive usual interstitial pneumonia
2. Probable usual interstitial pneumonia
3. Indeterminate usual interstitial pneumonia
4. Alternative diagnoses to usual interstitial pneumonia

**Comparison made with a previous examination performed on** DD/MM/YYYY. **Any variation in the pattern of fibrosing lung disease, as compared with the previous study:** (Free text)
**Possible diagnosis:**
Chronic hypersensitivity pneumonitis. Connective tissue disease. Asbestosis. Drug-induced interstitial pneumonia. There is no imaging support for suggestion of a diagnosis.

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# Changes in endothelial cell-derived extracellular vesicles after acute exercise in patients with COPD: a pilot study

Dario Nieri[1,2], Tommaso Neri[1], Sabrina Santerini[3], Stefania Lombardi[4], Alessandro Celi[1]

## TO THE EDITOR:

Endothelial dysfunction and peripheral muscle impairment are known to be extrapulmonary manifestations of COPD.[1,2] Quantification of endothelial cell-derived extracellular vesicles (EEV) has been proposed as a possible method to evaluate endothelial function.[3] In addition, EEV could be markers of emphysema and predictors of prognosis in COPD.[4] Although physical activity is currently recommended for COPD patients,[2] the effect of a single bout of exercise on endothelial response in such patients is unknown. It has been proposed that vascular function after an acute bout of exercise in healthy individuals follows a biphasic pattern (a transient decrease followed by normalization or even improvement).[5] However, to our knowledge, this has yet to be studied in patients with COPD. We conducted a pilot study to evaluate whether EEV might be considered as a marker of endothelial response after acute exercise in patients with COPD. We hypothesized that there would be an increase in EEV counts after acute exercise.

We enrolled patients with a confirmed diagnosis of COPD in accordance with current guidelines,[2] a post-bronchodilator $FEV_1$ between 30% and 70% of the predicted value, and no severe comorbidities. A group of healthy subjects was enrolled as controls. The study was approved by the local research ethics committee, in compliance with the Declaration of Helsinki, and all participants gave written informed consent. After clinical evaluation, all participants were submitted to biochemical blood testing and pulmonary function tests (visit 0). At visit 1, all subjects underwent an incremental, symptom-limited cardiopulmonary exercise test (CPET) on a cycle ergometer, using an incremental ramp protocol based on their baseline pulmonary function in order to complete the test in 6-10 min. During CPET, data on metabolic, ventilatory, and central hemodynamic variables were collected (Table 1). At visit 2, participants underwent a constant-load CPET after a 3-min warm-up period and at 70% of the maximum workload achieved during the incremental test. In order to measure plasma EEV, peripheral blood samples were collected at rest (T0), at peak of exercise (Tmax, i.e., immediately after the subject stopped pedaling because of exhaustion), and at recovery (Trec, i.e., 1 h after completion of CPET). Both incremental and constant-load CPETs were performed in the morning, approximately 2 h after a light breakfast (excluding coffee), with an interval of 5-7 days between tests. Smokers were asked to refrain from smoking three days prior to the tests. Platelet-poor plasma was obtained by two rounds of centrifugation (1,500 *g* for 15 min and 13,000 *g* for 2 min). For the characterization of plasma extracellular vesicles (EV), multiparametric flow cytometry was performed using a BD FACS Canto flow cytometer (BD Biosciences, San Jose, CA, USA) as described in one study[6] with modifications. EEV were initially discriminated by size as events (light scatter distribution within the 0.5- to 0.9-μm bead range) and then specifically identified as positive events for peridinin chlorophyll protein complex-labeled annexin V, carboxyfluorescein diacetate succinimidyl ester, allophycocyanin-labeled anti-CD62e, and phycoerythrin-labeled anti-CD31.

Data are presented as medians and interquartile ranges. The two-sample Kolmogorov-Smirnov test and the Friedman test for repeated measures were used. All statistical analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

A total of 17 subjects (12 COPD patients and 5 controls) were enrolled. The anthropometric characteristics were similar between the groups. The COPD group showed moderate airflow obstruction and a moderate decrease in DLCO on spirometry (Table 1). EEV response differed between the two groups. No differences were found in the control group regarding EEV levels at T0, Tmax, and Trec—11.8 (37.6) events/min; 14.8 (31.1) events/min; and 19.6 (30.1) events/min, respectively ($p = 0.678$). In the COPD group, we found a significant decrease in EEV levels at Tmax—3.4 (14.1) events/min—when compared with those at T0—6.7 (16.9) events/min ($p = 0.024$)—and those at Trec—7.8 (35.1) events/min ($p = 0.002$). No difference was found between T0 and Trec. We arbitrarily assigned to T0 an EEV level of 100% and calculated EEV levels at Tmax and at Trec, as well as relative baseline variations. No differences were found in the control group. In the COPD group, however, EEV levels at Tmax were significantly lower than at T0—62.3% (27.6%) vs. 100.0% (0.0%); $p = 0.024$—and at Trec—62.3% (27.6%) vs. 109.5% (156.7%); $p = 0.002$. This decrease in EEV levels at Tmax, with a return to baseline levels at Trec, was observed in 11 of the 12 COPD patients.

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**Table 1.** Anthropometric measurements, clinical features, pulmonary function results, together with metabolic, respiratory, and central hemodynamic variables collected during cardiopulmonary exercise testing.[a]

| Variable | Group | | p |
|---|---|---|---|
| | COPD (n = 12) | Control (n = 5) | |
| Age, years | 70.5 (7.0) | 65.0 (9.0) | N/S |
| Male/female, n/n | 8/4 | 4/1 | N/S |
| Smoking status, n | | | |
| Current smoker | 2 | 0 | N/A |
| Former smoker | 10 | 5 | |
| Never smoker | 0 | 0 | |
| Smoking history, pack-years | 35.0 (36.8) | 4.0 (18.0) | 0.005 |
| Dyspnea, mMRC scale score | 2.0 (1.0) | 0.0 (0.0) | 0.005 |
| BMI, kg/m$^2$ | 24.2 (7.9) | 25.9 (5.5) | N/S |
| $FEV_1$, L | 1.20 (0.35) | 3.38 (1.01) | 0.002 |
| $FEV_1$, % predicted | 56.5 (22.0) | 110.0 (23.0) | 0.002 |
| $FEV_1$/FVC | 0.45 (0.17) | 0.76 (0.07) | 0.002 |
| TLC, L | 6.44 (2.53) | 7.48 (1.30) | N/S |
| TLC, % predicted | 114.0 (25.0) | 106.0 (16.0) | N/S |
| DLCO, mL · min$^{-1}$ · mmHg$^{-1}$ | 13.0 (9.9) | 28.2 (7.8) | 0.002 |
| DLCO, % predicted | 58.0 (28.8) | 104.0 (20.0) | 0.002 |
| HR at rest, bpm | 84.0 (14.0) | 68.0 (23.5) | N/S |
| Blood pressure at rest, mmHg | 132 (10)/74 (7) | 117 (23)/78 (17) | N/S |
| $VO_2$peak[b], mL/kg × min | 16.3 (10.1) | 22.3 (7.9) | N/S |
| $VO_2$peak, % predicted | 74.0 (49.0) | 82.0 (21.5) | N/S |
| Maximum workload[b], W | 79.0 (52.0) | 169.0 (63.5) | 0.022 |
| Maximum workload, % predicted | 70.0 (46.0) | 104.0 (31.5) | 0.038 |
| Oxygen pulse[b], mL/beat | 15.2 (4.1) | 17.4 (7.4) | N/S |
| Breathing reserve[b], L | 9.7 (18.4) | 85.1 (39.9) | 0.002 |
| Endurance time[c], s | 227.5 (132.5) | 380.0 (157.5) | 0.053 |
| $VO_2$peak[c], mL/kg × min | 14.6 (6.2) | 18.5 (12.3) | N/S |
| $VO_2$peak, % pred | 60.0 (33.0) | 71.0 (40.5) | N/S |
| Hemoglobin, g/dL | 14.7 (2.0) | 15.2 (2.0) | N/S |
| White blood cell count, cells/mm$^2$ | 7,735 (2,412.5) | 5,310 (3,545) | N/S |
| Serum creatinine, mg/dL | 0.91 (0.35) | 0.81 (0.32) | N/S |
| Alanine aminotransferase, U/L | 16.0 (7.5) | 26.0 (16.5) | N/S |
| Aspartate aminotransferase, U/L | 19.0 (7.0) | 22.0 (7.5) | N/S |
| NT-proBNP, pg/mL | 95.0 (108.3) | 56.0 (27.5) | 0.038 |
| CRP, mg/dL | 0.24 (0.30) | 0.12 (0.49) | N/S |
| Fibrinogen, mg/dL | 333.0 (100.0) | 288.0 (74.0) | N/S |

N/S: not significant; N/A: not applicable; mMRC: modified Medical Research Council; BMI: body mass index; % pred: % of the predicted value; $VO_2$: oxygen consumption; NT-proBNP: N-terminal pro-brain natriuretic peptide; and CRP: C-reactive protein. [a]Values expressed as median (interquartile range), except where otherwise indicated. [b]Data collected during incremental cardiopulmonary exercise testing. [c]Data collected during constant-load cardiopulmonary exercise testing.

To our knowledge, no studies have investigated the behavior of circulating EEV after exercise in COPD patients. Although circulating EV levels are expected to increase in healthy subjects, results vary with regard to the cellular origin of EV and changes in EV levels after exercise.[7] One study[8] found an increase in apoptotic EEV levels in a sample of 17 patients with COPD after endothelial stimulation induced by shear stress; therefore, it is difficult to compare those results with ours. Decreased circulating EEV levels after exercise appear to be characteristic of the pathophysiology of COPD and might represent exaggerated EEV clearance at peak of exercise in such patients. In athletes, physical exercise has been reported to protect the vascular system and promote an in-vitro uptake of EEV into endothelial cells that is associated with a protection of target cells against apoptosis.[9] Similarly, it is possible that acute exercise could cause (either protective or detrimental) endothelial activation only in patients with COPD: the decrease in EEV we observed could be the result of exaggerated EEV clearance by the endothelium; because the pathogenesis of COPD involves the pulmonary capillary bed,[10] we can speculate about an activation of an altered pulmonary endothelium

specifically during exercise in these patients (whereas in controls, in whom pulmonary function is expected to be normal, we found no significant decrease in EEV). Whether or not this phenomenon actually involves the pulmonary vascular bed specifically should be the topic of further investigations using the von Willebrand factor as an endothelial-cell marker to determine the origin of EEV.

## AUTHOR CONTRIBUTIONS

DN, TN, and AC: study conception and design; DN, TN, SS, and SL: laboratory analysis and tests; DN, TN, and AC: data analysis; DN, TN, and AC: preparation of the manuscript; DN, TN, SS, SL, and AC: review and approval of the manuscript.

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# Hemophagocytic syndrome: a potential COVID-19 complication

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A 62-year-old male smoker who was an alcoholic and had diabetes was being treated for mediastinitis after surgical myocardial revascularization when he presented with worsening of the respiratory pattern despite overall improvement, requiring endotracheal intubation. The patient underwent a CT scan of the chest that showed findings consistent with COVID-19 (Figures 1A and 1B), which was later confirmed by RT-PCR. Seventeen days after the diagnosis of COVID-19, the patient presented with pancytopenia and increased levels of ferritin and IL-2 receptor. Hemophagocytic syndrome (HPS) was therefore suspected. A myelogram confirmed the diagnosis of HPS. Treatment consisted of i.v. immunoglobulin for two days. Thirteen days after the diagnosis of HPS, the patient experienced decreased oxygen saturation and tachypnea. A new CT scan of the chest showed new cavitating pulmonary lesions, superimposed on the pulmonary findings of COVID-19 (Figures 1C and 1D). Bronchoscopy revealed grossly necrotic tissue and bronchial infection with *Aspergillus fumigatus* (Figure 1E). The patient was started on anidulafungin in an attempt to contain the fungal infection; however, given the severity of his condition, he died three days after treatment initiation.

HPS is a rare and severe complication characterized by fever, hepatosplenomegaly, cytopenia, and activated macrophages in hematopoietic organs. It is often related to infectious diseases, and it can increase the risk of developing opportunistic infections.[1] New evidence indicates that HPS can occur in the context of COVID-19,[2,3] carrying an ominous prognosis.

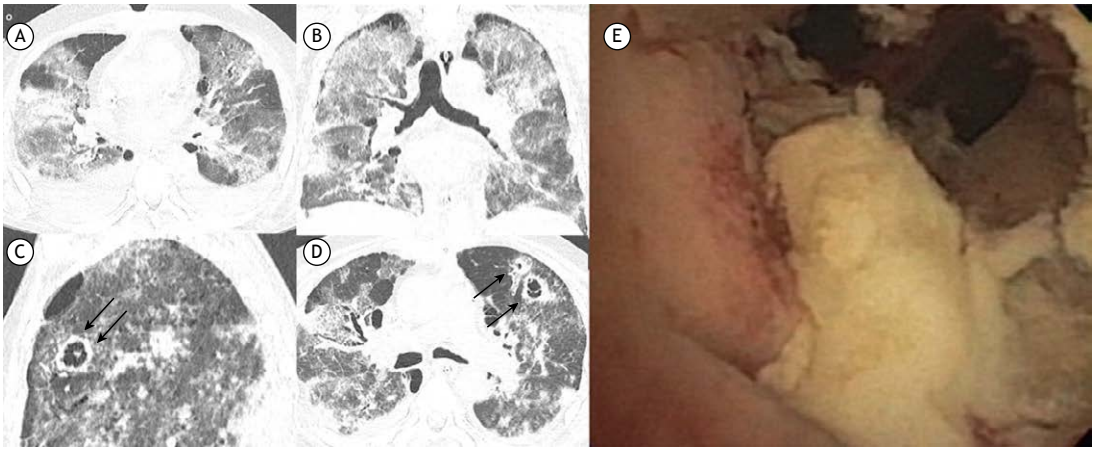


**Figure 1.** In A and B, respectively, axial and coronal CT scans of the chest showing extensive bilateral ground-glass opacities, associated with fine reticulation and small foci of consolidation, consistent with COVID-19. Note also bilateral pleural effusions. In C and D, respectively, sagittal and axial CT images of the chest showing cavitated pulmonary lesions (arrows) in the left upper lobe, superimposed on the findings of COVID-19. In E, bronchoscopic findings of grossly necrotic tissue and yellowish secretion, suggesting fungal colonization.

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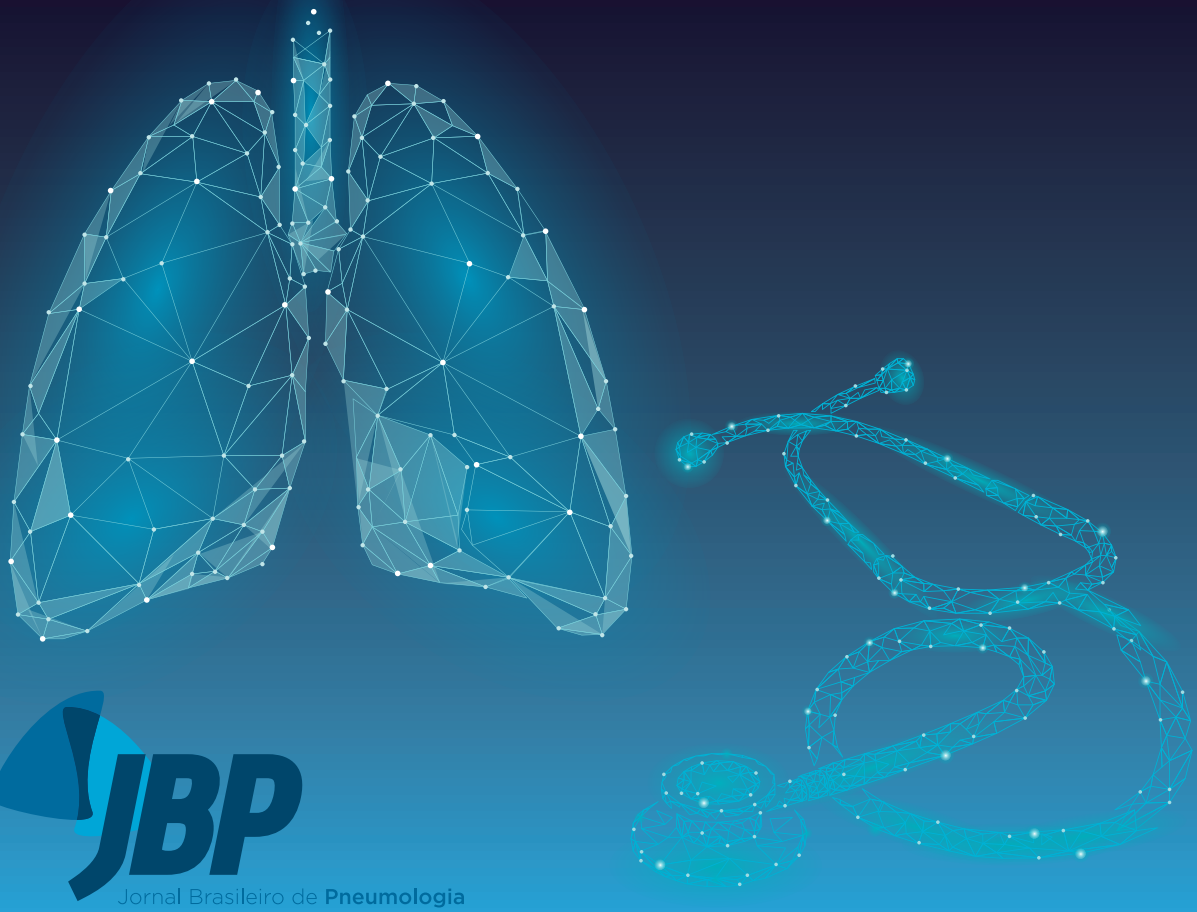

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