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HIGHLIGHT

2020 COPD series

Lung transplant in familial pulmonary fibrosis

Diaphragmatic ultrasound

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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EDITORIAL

Ultrasound of the diaphragm—an essential tool for pulmonologists and intensivists

Luigi Vetrugno[1,2], Daniele Orso[1,2], Tiziana Bove[1,2]

"It is always foolish to give advice: but giving good advice is fatal."
Oscar Wilde

The diaphragm is the major inspiratory muscle, and its continual rise and fall can be likened to the monotonous up-and-down movement of an engine piston. The diaphragm never stops, contracting and relaxing throughout a lifetime, except, of course, during anesthesia or if it is blocked through the use of paralyzing agents in the ICU. The perpetual movement of the diaphragm generates the so-called transdiaphragmatic pressure, the value of which directly correlates with the strength required to achieve adequate ventilation. In the past, only specialized centers equipped for research purposes had the appropriate tools that were necessary for assessing the strength of this muscle, which could be evaluated in two ways. The first modality involves measuring the transdiaphragmatic pressure (in cmH_2O) and employs a double-balloon probe—one balloon is inserted into the esophagus and one is inserted into the stomach. In the second modality, diaphragmatic force is measured indirectly by means of the evaluation of the twitch pressure (in cmH_2O)—the pressure generated at the outside tip of the endotracheal tube. However, in both cases, in order to generate a maximal volitional inspiratory effort in uncooperative patients, cervical magnetic stimulation of the phrenic nerve is required. Needless to say, both techniques are highly invasive and accompanied by limitations. The most important limitation is that unilateral diaphragmatic paralysis can never be excluded, because one hemidiaphragm can compensate for the contralateral one.[1]

Bearing in mind the limitations of the abovementioned techniques, the contemporary use of ultrasound for the assessment of diaphragm function in clinical practice stands to offer some important advantages. Although the ultrasound technique for the evaluation of the diaphragm was originally published some 20 years ago by Wait et al.,[2] Santana et al.,[3] in the article published in the present issue of *Jornal Brasileiro de Pneumologia* (JBP), clearly and accurately described that it is only in the past 10 years that the importance of this approach has been explored in more detail, especially within the ICU.

More than 60% of the patients admitted to the ICU show some form of diaphragm dysfunction in terms of a decrease in unilateral or bilateral diaphragm activity (weakness), abolished function (paralysis), or paradoxical movement. In addition, 80% of the patients develop diaphragm dysfunction during mechanical ventilation (MV).[1-4] A recent study[5] has shown that the most frequent type of shock in the ICU (septic shock) is associated with preferential diaphragmatic atrophy. This preferential loss of diaphragm muscle volume, when compared with that of the psoas muscle, creates a condition called sepsis-induced diaphragmatic dysfunction. That study provides evidence supporting the notion that the loss of diaphragm muscle volume is associated with a loss of strength.[5]

MV is the most frequently used short-term life support technique worldwide. However, although MV provides an unarguably vital form of life support, saving patients from an underlying disease, relieving the work of the diaphragm can rapidly lead to diaphragmatic atrophy and strongly impact the clinical outcome of the patient.[6] The first group to introduce the concept of ventilator-induced diaphragm dysfunction was Vassilakopoulos et al.,[7] who postulated that the rapid disuse of diaphragm fibers during MV is the underlying cause of this condition. Five years later, Levine et al.[8] provided crucial evidence, demonstrating that diaphragm inactivity during MV results in marked atrophy of human diaphragm myofibers. Grosu et al.[9] substantiated that evidence, reporting a 6% reduction in diaphragm thickness within 48 h after initiation of MV in patients in the ICU. Therefore, sepsis and MV in the ICU are now recognized as the two key players that are responsible for diaphragm dysfunction in critically ill patients, and the term "critical illness-associated diaphragm weakness" has been coined in order to refer to all of these mechanisms.[1] However, many other disease processes can affect diaphragm function in terms of its contractile properties, innervation, or indeed both; for example, traumatic injuries, mass effect, inflammatory disease, neurological disease, regional anesthesia, and idiopathic conditions.

In the present issue of the JBP, Santana et al.[3] have provided a detailed review of the literature regarding the technical aspects of how diaphragmatic ultrasound can be used in order to assess diaphragm function during normal breathing, deep breathing, and sniffing. Main findings and clinical applications in critically ill patients are clearly presented. The authors have also evaluated other conditions that can potentially induce diaphragm dysfunction, including asthma, cystic fibrosis, COPD, and neuromuscular disorders.[3] With regards to COPD patients in the ER, diaphragmatic ultrasound has only recently been identified as a tool suited to monitoring patients with acute hypercapnic respiratory failure and severe dyspnea undergoing noninvasive ventilation.[10]

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Figure 1. Looking at the diaphragm with different "eyes".

Santana et al.[3] have also reported how to evaluate diaphragmatic excursion by using the subcostal view in B mode and transverse scanning. This is of particular interest because the longitudinal approach has been reported to be preferable.[11] Normal values of diaphragmatic excursion in healthy volunteers have previously been described.[11] However, the measurement of diaphragmatic excursion (displacement) can only be performed in patients with spontaneous breathing, such as those just admitted to the ICU or intubated patients undergoing a spontaneous breathing trial for weaning purposes. In contrast, ultrasound assessment of diaphragmatic excursion during MV provides erroneous results, because it measures not only the effort exerted by the patient but also the power of the ventilator. Santana et al.[3] claim that the use of the thickening fraction (TF), calculated by means of the diaphragm thickness at end-inspiration (Tdi-insp) and end-expiration (Tdi-exp) at the zone of apposition—TF = [(Tdi-insp − Tdi-exp)/Tdi-exp] × 100 —could be a better indicator of diaphragm activity during MV. TF is an expression of muscular contraction and can therefore be used in order to measure diaphragm activity and assess whether MV support can be managed by the patient in question. Indeed, some patients on MV are exposed to overassistance (excessive unloading of the diaphragm by the ventilator reduces or abolishes inspiratory effort), or underassistance of MV (excessive loading of the diaphragm owing to insufficient ventilator assistance)—both of which causing diaphragm myotrauma. We also know that patient-ventilator dyssynchrony leads to diaphragmatic myotrauma due to eccentric muscle loading.[12] The general consensus to date is that TF should be kept within the normal range, between 15% and 30%, such as in healthy subjects breathing at rest, which seems to be associated with a shorter duration of MV.[6]

At this point, the limitations of diaphragmatic ultrasound also need to be acknowledged. It might be impossible to evaluate a patient presenting with a poor acoustic window; the left hemidiaphragm is difficult to explore; and the level of experience of the operator in performing diaphragmatic ultrasound is important. That being said, with a adequate amount of training proficiency, diaphragmatic ultrasound is a technique that is easy to perform. In conclusion, the well-evidenced central message of the review by Santana et al.[3] is clear: ultrasound is a highly appropriate technique for examining the diaphragm. Use it.

AUTHOR CONTRIBUTIONS

LV designed the editorial. All of the authors participated in drafting and revising the editorial. All authors have read and approved the final version of the manuscript.

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EDITORIAL

Lung transplant in familial pulmonary fibrosis: the road ahead

Anthony Joseph Esposito[1], Souheil Youssef El-Chemaly[1]

Pulmonary fibrosis (PF) is the most common indication for lung transplantation, with the proportion of adult lung transplants performed for interstitial lung disease (ILD) increasing from 38% to 47% over the past decade.[1] Although transplant improves survival of carefully selected patients with PF, recipients tend to have worse outcomes and lower life expectancy than those with other indications.[2] Chronic lung allograft dysfunction (CLAD) is responsible for most of the morbidity and mortality after the first year of transplantation. Approximately 20% of PF cases cluster in families—termed familial PF (FPF)—and, of these, up to one-third have a mutation in a telomere-related gene and/or shortened telomeres in addition to variants in other genes, such as those for surfactant proteins and mucin 5B.[3,4]

In this issue of the *Jornal Brasileiro de Pneumologia*, Bennett et al.[5] report the results of a single-center, retrospective cohort study assessing short- and long-term outcomes of patients with FPF in comparison with those with sporadic PF. The authors identified 9 patients with FPF and 74 with PF from a sample of 160 consecutive patients who underwent lung transplant at their institution in Siena, Italy. Their main conclusion was that there was no statistical difference between groups in CLAD-free and overall survival. Although patients with FPF were more likely to receive bilateral lung transplantation and differed from PF recipients by the choice of induction/maintenance immunosuppression that they received, this conclusion remained valid even after adjustment for these potential covariates. There was also no statistical difference observed in many secondary post-operative outcomes reported, including primary graft dysfunction or acute cellular rejection. Interestingly, patients with FPF were more likely to have lower pre-transplant hemoglobin and hematocrit levels that reemerged 180 days after transplantation. These analyses, as limited as they are by the small sample size, are important to initiate discussions regarding lung transplantation in FPF and, more broadly, in PF associated with genetic variants.

In the study by Bennett et al.,[5] only one-third of the patients with FPF and none of those with sporadic PF had genetic analyses available. Of the available data in FPF patients, none had variations in genes for surfactant proteins C/A2 and ABCA2 or for telomerase enzyme-related genes *TERT* and *TERC*; however, assessment of other important telomere-related mutations was unavailable (e.g., *PARN, RTEL1,* and *NAF1*). It is also critical to note that telomere length was not assessed in any of the patients. Despite the lack of genetic data, there are numerous clues that patients in the FPF cohort may have had an underlying telomeropathy. Notably, patients with FPF were more likely to be anemic before surgery and 180 days after surgery, and the majority of those who were anemic were more likely to have macrocytosis.

Mutations in genes that encode proteins involved in telomere maintenance, as well as short telomeres in general, have been implicated in an array of ILDs. In patients with idiopathic pulmonary fibrosis (IPF), multiple mutations in telomere-related genes have been associated with familial IPF in addition to a smaller subset of patients with sporadic disease.[3,4] Furthermore, 25% of patients with sporadic IPF and 37% of those with familial IPF have telomere lengths shorter than the tenth percentile corrected for age, the former occurring even in patients without a known telomere-shortening mutation.[3] Although IPF has the best characterized association, telomeropathies are not limited to this ILD subtype and have been associated with patients with chronic hypersensitivity pneumonitis, nonspecific interstitial pneumonia, unclassifiable PF, and pleuroparenchymal fibroelastosis, among others.[6,7] The presence of short telomeres, regardless of the histological subtype, is associated with a rapid decline in lung function[7]; therefore, discussion of telomere dysfunction solely in the context of FPF alone may underestimate its impact on progressive fibrosing ILDs, which are the ILD subtypes most likely to require lung transplantation. Moreover, the true prevalence of FPF may be underestimated, because recent evidence suggests that up to one in six family members of patients with sporadic PF have unrecognized ILD.[8] These findings provoke the following considerations: should we be performing genetic testing in patients with FPF before transplant? Should we be assessing telomere length regardless of the underlying genetic mutation in order to better risk-stratify patients after transplantation?

Short telomere and/or telomere-related mutations have been associated with higher rates of complications after lung transplantation that extend beyond allograft dysfunction. These include bone marrow suppression, intolerance of immunosuppression, and renal insufficiency.[9-11] With regards to the allograft, short telomeres and telomerase complex mutations have been attributed to higher rates of and more severe primary graft dysfunction, shorter time to the onset of CLAD, and worse post-transplant survival.[12,13] Given the significant evidence that telomeropathies affect both pre- and post-transplant outcomes, should we be screening all patients with PF for short telomeres as part of their pre-transplant evaluation? Some transplant centers have proposed protocols to improve outcomes in these patients that include screening of candidates whose evaluation suggests manifestations of shortened telomeres (early graying, cytopenias or macrocytosis, liver

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dysfunction, family history of ILD).[6] The identification of short telomeres would invite more scrutiny regarding pre-transplant evaluation of the bone marrow and the liver to exclude other manifestations of short telomeres and, more importantly, to mitigate potential post-transplant complications. In the post-transplant period, the preemptive identification of short telomeres could lead to modification of immunosuppression, antiviral prophylaxis, and other potential drugs that could lead to bone marrow toxicity.

In summary, perhaps the most important implications of the study by Bennett et al.[5] do not lie in the conclusions made but in the uncertainties its limitations expose surrounding the pre- and post-transplant evaluation and the management of patients with PF with regards to telomerase dysfunction and telomere length, regardless of their family history. Given the available evidence, it is possible that the overall survival benefit observed in patients with PF who receive a transplant is abrogated in those with short telomeres. Further studies are needed to assess the impact of routine assessment of telomere length in transplant candidates on post-operative care and transplant outcomes in order to develop evidence-based guidelines. Survival after lung transplant lags behind other solid organ transplants; ushering in the era of personalized medicine could lead to improved outcomes.

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Avoidance of hypoxemia in COPD is essential

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Since the publication of a relevant clinical trial by the Nocturnal Oxygen Therapy Trial Group[1] and a similar trial supported by the Medical Research Council,[2] it has been accepted that long-term oxygen therapy (LTOT) in patients with COPD and daytime hypoxemia significantly reduces mortality. LTOT has now become a standard treatment not only for COPD but also for other respiratory diseases. In the two aforementioned studies[1,2] as well as in one recent meta-analysis,[3] it was clarified that the number of hours of daily oxygen use also determines survival. For example, 12 hours of daily oxygen therapy[1] provided little survival benefit over no oxygen therapy,[2] whereas more than 15 hours of daily oxygen therapy provided a clear survival benefit.

It is of note that no further improvement in survival has been demonstrated with the use of LTOT if oxygenation is slightly higher than that defined in the aforementioned trials.[1,2] Although most organizations accept the prescription of oxygen when there is hypoxemia during exercise and sleep, recent randomized controlled trials[4,5] have been unable to prove that supplemental oxygen for patients with nocturnal hypoxemia or moderate hypoxemia alone impacts clinical outcomes.

Sleep studies in patients with COPD have shown that peak hypoxemia occurs during rapid eye movement sleep and has a direct relationship with daytime PaO_2. In the presence of sleep apnea, episodic desaturation also develops and complicates any established hypoxemia.[6] In the present issue of the *Jornal Brasileiro de Pneumologia* (JBP) Prados et al.[7] reported that COPD patients who had severe nocturnal hypoxemia, especially during rapid eye movement sleep, had a greater left ventricular mass and more risk factors, such as slightly higher diastolic blood pressure and mean blood pressure, as well as higher BMI and lower daytime oxygenation. These findings justify additional clinical trials and studies centered on how to prevent, identify, and treat nocturnal hypoxemia in COPD patients with and without sleep apnea.

Hypoxemia in COPD patients contributes to severe organ damage, including (mostly mild to moderate) pulmonary hypertension[8]; polycythemia; systemic inflammation; neurocognitive dysfunction; and skeletal muscle failure.[9] Therefore, hypoxemia itself becomes a primary pathophysiological mechanism. Also in the present issue of the JBP Marcondes et al.[10] showed higher mortality in patients with more severe COPD and more hypoxemia, despite more hours of daily oxygen therapy and a self-reported adherence of 73%. Therefore, it is essential to avoid hypoxemia in patients with COPD or other lung diseases by improving adherence to treatment, including long-term oxygen therapy with or without CPAP in patients with sleep apnea. This is especially true in patients with severe baseline hypoxemia, such as those receiving oxygen therapy 24 h/day. Nonadherence to oxygen therapy can cause much more damage in such cases than in those of patients with less severe hypoxemia.

For years, the only interventions capable of improving survival in COPD patients were smoking cessation and the use of oxygen in the event of hypoxemia, and they remain the most relevant. In most cases, despite repeated efforts, a proportion of patients with COPD persist smoking: 27% in the Prados et al. study[7] and 17% in the study by Marcondes et al.[10] This has been reported worldwide, especially in patients recruited for controlled clinical trials of inhaled drugs, approximately 40% of whom keep smoking. Given that smoking is a persistent risk for premature death, disease, and worsening of COPD, it is imperative to promote smoking cessation.

In conclusion, patients with COPD often fail to adhere to treatment and health recommendations, such as diet and exercise. Therefore, any strategies to improve treatment adherence should be a priority. The studies cited here remind us to strengthen efforts to control hypoxemia and to monitor adherence to treatments, especially those that impact survival and modify the natural course of COPD.

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COPD and pulmonary rehabilitation: new findings from Brazil

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Pulmonary rehabilitation (PR) has been demonstrated to reduce the symptom burden of dyspnea, increase exercise capacity, and improve quality of life in patients with COPD.[1] It is defined as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies which include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviours."[1] In the present issue of the *Jornal Brasileiro de Pneumologia* (JBP), four interesting papers have been published concerning different aspects of PR. They provide novel insights into the usability of the four-meter gait speed (4MGS) maximum test to screen for preserved exercise capacity,[2] the potential effectiveness of upper limb (UL) exercise training for the performance of activities of daily living (ADLs),[3] the effect of PR on serum myostatin levels in patients with COPD,[4] and the outcomes of a PR program between groups of patients with COPD with different exacerbation phenotypes.[5]

As stated in recent guidelines for PR,[1] a thorough patient assessment is key. An important component of the thorough patient assessment concerns the evaluation of exercise capacity. To date, the six-minute walk test (6MWT) and the cardiopulmonary exercise test (CPET) are the two most broadly used test procedures to evaluate exercise capacity. Even though the 6MWT is more practical and simple than is the laboratory-based CPET, it still requires space (a 30-m corridor), time (two 6MWTs with a 30-min interval), and trained personnel. As an alternative, Kon et al.[6] demonstrated the potential use of the 4MGS test as a simple functional assessment tool in patients with COPD. In this issue of the JBP, Tino et al.[2] evaluated four different 4MGS test protocols—combinations of walking at normal pace and at maximum speed along a 4-m course and an 8-m-course. The authors concluded that the 4MGS test at maximum speed along a 4-m course, considering the specific cut-off point of 1.27 m/s, can be used to discriminate preserved exercise capacity in patients with COPD. Preserved exercise capacity was defined by the lower limit of normal, which is equivalent to the mean − 1.645 × standard error, using reference values specific to the Brazilian population.[7] This is an interesting and clinically relevant finding because the 4MGS test at maximum speed is a simple, fast, reliable, and low-cost alternative to evaluating exercise capacity. Moreover, in another study, Kon et al.[8] showed that the 4MGS test results are responsive to PR.

Following a thorough patient assessment, another cornerstone of PR is multimodality exercise training, which can include endurance training, interval training, resistance training, flexibility training, neuromuscular electrical stimulation, and inspiratory muscle training.[1] To date, the focus on resistance training has often been on the lower limbs. Nevertheless, many problematic everyday tasks in patients with COPD involve the upper limbs (ULs), such as dressing, bathing, and shopping.[9] Dyspnea is reported to be one of the limiting factors to performing ADLs involving the ULs, which can be attributed to the occurrence of dynamic hyperinflation. Interestingly, patients with COPD also perform UL activities at a lower intensity and at a relatively higher muscle effort when compared with healthy subjects,[10] suggesting that also UL muscle function may be a limiting factor. Thus far, Vaes et al.[11] showed that a comprehensive PR program can improve the performance of ADLs in patients with COPD. After an 8-week PR program, the patients in that study needed significantly shorter time to perform ADLs and had lower metabolic load and perception of dyspnea. In this context, Kariagannis et al.[3] systematically reviewed randomized controlled trials to determine whether UL exercise training could improve the performance of ADLs involving the ULs in patients with COPD. The authors demonstrated that UL exercise training is safe and can provide significant improvements in the performance of ADLs involving the ULs. Nevertheless, contradictory results were found in the perception of symptoms during the execution of ADL tasks with the ULs. Of note, the current evidence regarding UL exercise to improve ADL performance should be interpreted with caution and cannot be generalized, because that review[3] was based on five randomized controlled trials with limited sample sizes, the majority of the participants being male. There is a need for well-designed trials since an important goal of PR is to improve ADL performance, because it increases the independence and the ability of patients for self-care.

It has been recognized that muscle and serum levels of myostatin are elevated in patients with COPD, which may contribute to muscle wasting and weight loss,[12,13] or even to a lack of increase in physical capacity following PR.[14] Studies performed in healthy men demonstrated that serum/plasma myostatin levels decreased by approximately 20% after 10 weeks of high intensity resistance training.[15] Previous studies, with contradicting results, evaluated the effect of exercise training on muscle myostatin levels in patients with COPD.[16,17] Nevertheless, for clinical practice, the use of blood instead of muscle samples would facilitate the assessment of myostatin levels. In this

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issue of the JBP, Araujo et al.[4] were among the first to show that even though PR (including aerobic training, lower limb and UL resistance training, education, and nutritional orientation) improved exercise capacity and the level of COPD severity, no changes in plasma myostatin levels were found. Considering that muscle weakness is an important extrapulmonary manifestation in patients with COPD, a better understanding of the role of serum myostatin in the underlying pathways of losing muscle mass is needed.

The natural course of COPD is punctuated by exacerbations, especially in patients with moderate to very severe airflow obstruction.[18] Exacerbations are defined as acute worsening of respiratory symptoms that results in additional therapy, worse clinical outcomes, negative and significant impact on quality of life and on disease progression, as well as higher mortality and health care costs.[19] PR has already been recommended as a nonpharmacological treatment after an exacerbation/hospitalization, because it is feasible and safe and can improve exercise capacity, symptoms, quality of life, and prevention of hospital readmission.[20] Bohn Júnior et al.[5] investigated whether outcomes of PR are different between exacerbation phenotypes. Patients with COPD with two or more exacerbations in the previous year or at least one exacerbation requiring hospitalization had a significantly greater response to a 12-week PR program when compared with those with no exacerbations. Indeed, those with the exacerbation phenotype achieved greater improvements in exercise capacity, regardless of the severity of airflow obstruction (FEV_1%). In addition, greater reductions were found for perception of dyspnea, and there was improvement in prognosis as measured by the BODE index. Baseline 6MWT variables, level of dyspnea, and the BODE index, as well as smoking history, were not different between the groups. The results emphasize that patients with the exacerbation phenotype are ideal candidates for PR.

In summary, a thorough and multicomponent PR program is recommended to alleviate symptom burden, increase exercise capacity, and improve overall health status. Novel findings, as highlighted in this editorial, help improve and tailor PR based on the needs of the patients.

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November 18: World COPD Day 2020. Is it a date to celebrate?

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COPD results from a complex interaction between individual characteristics (genetic predisposition, poor lung development in childhood, aging, and socioeconomic conditions) and exposure to toxic gases and fumes (tobacco smoke, air pollution, and burning of biomass).Current or former smoking remains the major risk factor for COPD.[1]

In recent decades, there has been an increase in both the prevalence of and mortality from COPD. Currently, COPD is identified as the third leading cause of mortality worldwide, accounting for more than three million deaths in 2016 according to WHO data.[2] In Brazil, COPD was ranked the third or fourth leading cause of death in the 2000-2016 period, and there was a downward temporal trend in mortality indicators in all regions, although this trend was stronger in regions with higher socioeconomic indices.[3]

When not fatal, COPD is a major cause of morbidity, which leads to high rates of work absenteeism and early retirement, increased rates of hospitalization, and a consequent increase in disease-related costs. One study showed that, in Brazil, in-hospital morbidity (as defined by number of hospitalizations, length of hospital stay, and hospitalization costs) also decreased, and that this reduction was also more pronounced in regions of greater socioeconomic development.[3]

The treatment of COPD aims to control symptoms, improve quality of life, and reduce exacerbation rates. The use of long-acting bronchodilators is the mainstay of pharmacological treatment, and these drugs are prescribed in accordance with national and international guidelines.[1,4] Whereas there is debate in the literature on whether optimal benefit is achieved by dual or triple therapy, the role of long-acting anticholinergics is well established.[1,5] However, access to these drugs is not uniform throughout Brazil. A study conducted in the state of Bahia[6] showed that most patients diagnosed with COPD did not receive appropriate treatment (83.3% and 63.7%, respectively, according to international and national guidelines), and that more than 50% of the patients did not receive any treatment. Given that the use of long-acting anticholinergics has not been incorporated into the Brazilian Unified Heath Care System in all Brazilian states and that these drugs have not been included in the Brazilian National Ministry of Health clinical protocol and therapeutic guidelines for COPD,[7] the rates of inappropriate treatment can be even higher.

A study conducted in Latin America showed that the COPD underdiagnosis rate can be as high as 4%.[8] If COPD is not clinically suspected by the physician or even by another member of the multidisciplinary team, its diagnosis, treatment, and prevention are compromised. Therefore, Alcântara et al.[9] evaluated the impact that a COPD training program consisting of video classes had on a primary care multidisciplinary team and concluded that the program promoted knowledge acquisition and that this knowledge remained at least three months following the intervention. In addition, the low availability of spirometry in primary care and the physicians' lack of knowledge about the local protocol for dispensing medications are factors that can affect the pharmacological treatment of COPD.[10]

COPD is accompanied by significantly impaired functional exercise capacity, which is caused by airflow obstruction, loss of lean body mass, and, in many cases, hypoxemia. Physical exercise, offered through pulmonary rehabilitation programs, is an important part of treatment.[1,4] The intensity with which the activity is performed is extremely important for the outcome, and the presence of fatigue or dyspnea can prevent the achievement of the objectives. Therefore, studies such as the one by Adolfo et al.,[11] which seek new modalities of physical exercise, are extremely important. In addition, it is important to ensure that COPD patients have access to pulmonary rehabilitation programs.

The use of oxygen therapy is well established and is known to reduce mortality in individuals with resting hypoxemia.[1] Some studies have tried to determine whether patients with exertion-only desaturation or nocturnal desaturation would also benefit from the use of long-term home oxygen therapy.[12,13] Mesquita et al.[12] showed that COPD patients with exertion-only hypoxemia who complied with oxygen therapy had better quality of life scores, but had no improvement in exercise capacity, as measured by six-minute walk distance, or in mortality. A recent study,[13] which would assess the benefit of oxygen therapy for patients with nocturnal desaturation, was discontinued because the minimum number of individuals needed for analysis was not reached and because the recruited individuals had poor treatment adherence.

To date, there have been many advances on pathophysiology, diagnosis, and treatment of COPD. Advances in the fight against smoking and the development of new molecules and inhaler devices have been very important, but we still face a serious problem when it comes to making them available. In Brazil, a continent-sized country with so much inequality, implementing new protocols and revising old ones, all of which containing well-established criteria for dispensing medications, can optimize patient access to treatment. We also need to

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expand patient access to pulmonary rehabilitation programs and understand whether there are benefits to using oxygen therapy in patients other than those with resting hypoxemia. Finally, let us not forget that commitment is required from educational institutions and specialist societies to further the continuing education of non-pulmonologists so that COPD can be diagnosed earlier and earlier. World COPD Day 2020 is on November 18. So, let's celebrate, but let's not forget that there is still much to be done.

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Nodules with fat density

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

A 52-year-old male former smoker (30 pack-years) with no symptoms or comorbidities had a routine chest X-ray, which revealed a nodule at the right lung base. A chest CT identified a smooth-bordered nodule in the right lower lobe measuring approximately 1 cm in diameter and with a mean density of −30 HU (Figure 1).

A nodule is defined as a focal rounded opacity measuring up to 3 cm in diameter. An opacity greater than 3 cm in diameter is termed a mass, and an opacity smaller than 1 cm in diameter is termed a small nodule. Nodules can be solitary or multiple, and their density can indicate soft tissue, ground-glass pattern, water, calcium, air (cavitated nodules), or fat. A solitary pulmonary nodule is a common problem for radiologists and pulmonologists, having numerous causes of benign and malignant etiology. Differential diagnosis from lung cancer is the major challenge.

Some imaging criteria, such as nodule stability for more than 2 years or presence of specific patterns of calcification (e.g., calcification of the whole nodule, central/bull's eye calcification, eggshell calcification, etc.), are suggestive of benignity. However, one of the most reliable findings indicative of benignity is the presence of fat within the nodule. Fat is confirmed when the measured density is between −30 and −150 HU.

Two benign tumors can have the aforementioned density values: lipomas and hamartomas.[1,2] Hamartomas are benign neoplasms composed of variable proportions of mesenchymal tissues, such as cartilage, fat, connective tissue, and smooth muscle. Hamartomas often have heterogeneous density, with focal areas of fat and/or calcification.[2] Lipomas are benign mesenchymal tumors composed of adipose tissue. Although lipomas are a common form of soft tissue tumor, intrapulmonary lipomas are very rare. Most intrapulmonary lipomas are asymptomatic and are generally incidentally found on routine X-rays, presenting as solitary opacities indistinguishable from malignant neoplasms. On CT, the presence of intranodular fat is a reliable indicator of benignity. Magnetic resonance imaging also allows distinction between the different components of the lesion, including fat.[1] One caveat should be made regarding the benignity of nodules with fat: the possibility of their being metastatic liposarcoma. In such cases, however, the discovery of lung metastases rarely precedes the diagnosis of the primary tumor.

Our patient received a diagnosis of pulmonary lipoma on the basis of the CT findings. He is being followed, and the nodule has shown no changes since its detection 5 years prior.

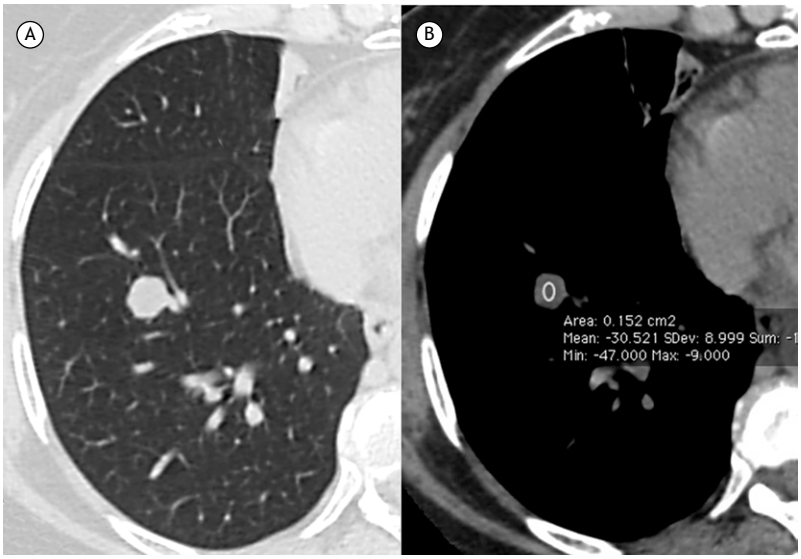

Figure 1. Chest CT in lung (A) and mediastinal (B) windows shows a well-defined nodule, measuring approximately 10 mm in diameter, in the right lower lobe. Note in B that the nodule has fat density (mean density, −30 HU).

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Meta-analyses: a primer for clinicians

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PRACTICAL SCENARIO

Investigators conducted a systematic review (SR) study that included eight randomized controlled trials (RCTs) comparing drug A vs. drug B for the treatment of condition Y. The outcome of interest was 30-day all-cause mortality. Each study reported an effect estimate (OR) to compare the two drugs. Investigators then generated a pooled estimate to summarize the overall effect across the studies. How is that achieved in a meta-analysis?

WHAT IS A META-ANALYSIS?

A meta-analysis is a statistical approach that combines results from individual studies identified in an SR and calculates a pooled estimate of the magnitude and direction of treatment effects.[1] Consequently, the overall sample size and the precision of the estimate increase, and the width of confidence intervals decreases. The combined treatment effect is estimated by calculating a weighted average across individual study estimates. The weight assigned to each study result is related to the precision of each estimate, which in turn is related to the sample size of the study. Therefore, larger studies have a greater influence on the final pooled estimate.

Frequently, a meta-analysis follows an SR of individual RCTs or observational studies. Depending on the nature of the research question, a meta-analysis can be used to answer questions about intervention effectiveness, diagnostic/prognostic test accuracy, and disease burden (prevalence and incidence).

SRs often include studies with distinct features that lead to clinical, methodological, and statistical heterogeneity. Clinical heterogeneity arises from differences in study participants, interventions, or outcome definitions. Methodological heterogeneity arises, for example, when some of the RCTs included are blinded, and others are not. In a meta-analysis, statistical heterogeneity is formally assessed by calculating the I^2 statistic, which ranges from 0% to 100%. An $I^2 > 50\%$ indicates high heterogeneity, which should raise the question of whether it is reasonable to perform a meta-analysis or not and to prompt the search of potential underlying reasons for heterogeneity.

FOREST PLOTS: A VISUAL SUMMARY OF META-ANALYSIS RESULTS

A forest plot[2] is the key graphical representation of the major findings of an SR and meta-analysis. In our example (Figure 1), each row represents one of the 8 RCTs included in the SR with their respective effect estimates (OR and 95% CI). The bottom row represents the pooled estimate of the effect, that is, the result of the meta-analysis. Each individual study has a different relative weight; for example, study 7 has the largest weight, which is likely associated with a high precision of the estimate (smaller CI). Notably, specific estimates of most individual studies are not statistically significant (95% CI includes the value of 1), whereas the pooled estimate shows a statistically significant beneficial effect of drug A vs. drug B. The heterogeneity of the study was 45%, estimated by the I^2 statistic.

SRs combined with meta-analyses are often considered as one of the highest levels of analysis in evidence-based medicine because they combine the results of various RCTs/observational studies and offer a more precise estimate of the effect size of a given intervention. They can be very useful for clinical decision making, although their results are only as good as the studies included in the analysis.

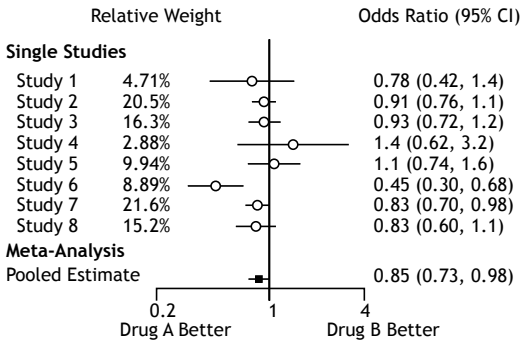

Figure 1. An example of a forest plot.

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Absence of airflow obstruction on spirometry: can it still be COPD?

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BACKGROUND

An FEV_1/FVC ratio < 0.7 has been widely used to define airflow obstruction, because, on average, it correlates well with more sophisticated measurements of expiratory flow limitation. In fact, the cut-off point of 0.7 is at the core of the definition of COPD according to the GOLD.[1] It follows that most physicians assume that a post-bronchodilator (BD) FEV_1/FVC ratio ≥ 0.7 effectively rules out COPD.

OVERVIEW

A 59-year-old, heavy former smoker (45 pack-years) woman who had complaints of exertional dyspnea (mMRC = 3) received a provisional diagnosis of COPD. Although there was partial improvement with the use of inhaled formoterol (mMRC = 2), she was referred to the pulmonology department for reassessment of diagnosis since her post-BD FEV_1/FVC ratio had always been ≥ 0.7 (Figure 1A). Additional lung function tests, however, showed mild gas trapping (↑RV) and moderately ↓DLCO (Figure 1B). Considering that the exertional symptoms of the patient could be a mere reflection of severe deconditioning, a cardiopulmonary exercise test was performed to determine whether there was any evidence that "the lungs" could have explained her breathlessness. As shown in Figure 1C, this was indeed the case: a) dyspnea scores, either as a function of work rate or minute ventilation ($\dot{V}_E$), were typically above the upper limit of normal[2]; b) there was evidence of critical constraints to tidal volume expansion (Figure 1C, arrow) as tidal volume prematurely reached ≈70% of the inspiratory capacity and ≈0.5 L of inspiratory reserve volume, that is, the end-inspiratory lung volume was too close to TLC,[3] and peak $\dot{V}_E$ approached the estimated maximal voluntary ventilation. Moreover, a chest CT showed emphysema and thickened bronchial walls (Figure 1D).

Although there is ongoing controversy regarding the best cut-off point to define airflow obstruction (a fixed FEV_1/FVC ratio < 0.7 or age- and sex-based lower limit of normal), a reduced FEV_1/FVC ratio has been considered an indispensable criterion for the diagnosis of COPD.[1] There is mounting evidence that subjects showing intermediate FEV_1/FVC ratios (i.e., greater than the lower limit of normal but smaller than 0.7) have higher hospitalization and death rates,[1] more cardiovascular comorbidities, and worse exercise tolerance and dyspnea[4] than do subjects with no obstruction using both criteria. Occasionally, however, FVC decreases roughly in tandem with FEV_1 as RV increases despite a preserved TLC, reflecting increased small airway collapse/closure at low lung volumes during the forced maneuver.[5] In fact, a sizeable number of symptomatic smokers with no spirometric evidence of obstruction may show gas

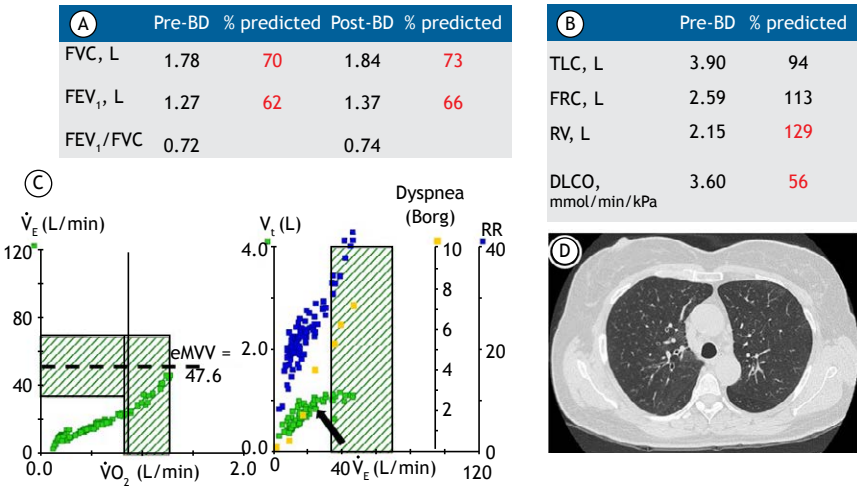

Figure 1. Physiological and structural investigations in a 59-year-old, former heavy smoker woman with complaints of chronic dyspnea. There was a proportional reduction in FEV_1 and FVC, leading to a preserved pre- and post-bronchodilator FEV_1/FVC ratio (in A), increased RV and reduced DLCO (in B), mechanical ventilatory limitation to exercise (in C; see text for further elaboration), and emphysema plus thickened airway walls on a chest CT (in D) that jointly indicate the presence of COPD. BD: bronchodilator; FRC: functional residual capacity; eMVV: estimated maximal voluntary ventilation; $\dot{V}_E$: minute ventilation; $\dot{V}O_2$: oxygen uptake; and V_T: tidal volume.

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trapping and/or ↓DLCO plus structural changes in keeping with COPD.[1] Indeed, some such individuals may benefit clinically from a more proactive approach toward early treatment with BDs.[1]

CLINICAL MESSAGE

The key pathophysiological characteristic of the current definition of COPD (a persistently ↓FEV_1/FVC ratio) is **not** *sine qua non* in smokers showing gas trapping and/or ↓DLCO and/or emphysema on CT. As such, there is a surge of interest in adding CT variables to the definition of COPD,[1] although we strongly believe that the abovementioned physiological variables should also be taken into consideration. The bottom line is that the diagnosis of COPD in subjects with a high pre-test probability of the disease but a preserved FEV_1/FVC ratio requires a more holistic approach, involving assessment of clinical (dyspnea), physiological (lung volumes and DLCO), and anatomical (emphysema) abnormalities.

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Evaluation of the left ventricle in patients with COPD and nocturnal hypoxemia

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ABSTRACT

Objective: To verify association between left ventricular (LV) mass and thickness and the presence of significant nocturnal hypoxemia in patients with COPD with mild diurnal hypoxemia. **Methods:** A cross-sectional study carried out in clinically stable outpatients with COPD and mild hypoxemia (oxygen saturation ≥90 to ≤94%, identified by noninvasive oximetry) in a clinic specialized in the treatment of respiratory diseases in Goiânia-GO. All patients were submitted to clinical evaluation, spirometry, polysomnography, echocardiography, arterial blood gas analysis, 6-minute walk test and chest X-ray. **Results:** Patients with significant nocturnal hypoxemia had echocardiographic parameters associated with increase of LV musculature when compared to patients with mild nocturnal hypoxemia. The LV volume/mass ratio was significantly lower in the group with significant nocturnal hypoxemia (ratio 0.64 ± 0.13 versus 0.72 ± 0.12, p = 0.04), the thickness diastolic diameter of the interventricular septum and the diastolic thickness of the LV posterior wall were significantly higher in this group (9.7 ± 0.92 versus 9.1 ± 0.90 p = 0.03), (9.7 ± 1.0 versus 8.9 ± 1.0, p = 0.01. The time in REM sleep with saturation below 85% significantly predicted septum thickness (adjustment for BMI, age and mean blood pressure, r^2 = 0.20; p = 0.046). **Conclusion:** We observed association between severe REM sleep hypoxemia and echocardiographic parameters indicating increased LV mass in individuals with COPD and significant nocturnal hypoxemia. This suggests that this subgroup of individuals may benefit from an echocardiographic evaluation of the left ventricle.

Keywords: Chronic Obstructive Pulmonary Disease; Left ventricular hypertrophy; Echocardiography.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the main causes of global morbidity and disabilities and, according to the World Health Organization (WHO),[1] more than 210 million people worldwide have COPD, which could become in 2020, the third leading cause of death in the world.[2] In Brazil, it is estimated that there are more than 7 million adults affected.[3]

This disease causes pulmonary and extrapulmonary changes that lead to a decrease in the individual's quality of life, reduction in exercise tolerance, increase in the number of hospitalizations and risk of cardiovascular morbidities.[4] The uncorrected chronic hypoxemia caused by COPD triggers mechanisms that contribute to left ventricular (LV) hypertrophy, through systemic inflammation, release of oxygen radicals and activation of the sympathetic nervous system. LV hypertrophy deserves attention due to the damage caused in patients with this condition, such as: arrhythmias, reduced coronary perfusion, thromboembolic events and a significant 38% increase in mortality in patients with COPD.[5]

Abnormalities caused by mild to severe hypoxemia in the right ventricle are already well described in the literature,[6] but the relationship between chronic respiratory disease and left ventricular disorders is not well established.[7] Thus, the present study aims to verify the association between increased LV mass and/or thickness and significant nocturnal hypoxemia in patients with COPD. Early identification and consequent treatment can have great impact on the prevention of cardiovascular complications in these patients.

METHODS

The present work is a subproject of the research "Association between Night Hypoxemia and Depression in Patients with Chronic Obstructive Pulmonary Disease

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(COPD): A Case-control Study", carried out according to good clinical practices and approved by the Ethics Committee of the Goiânia General Hospital, under protocol nº 198.344/2013. The main research was initially carried out as a cross-sectional study to estimate the prevalence of OSA and nocturnal hypoxemia, followed by a case-control study, comparing patients with COPD and mild hypoxemia with major depression (cases) with patients without major depression (controls). This work evaluates the data collected in a cross-sectional study of the initial sample of patients with COPD and mild hypoxemia.

Study location

The main research study was conducted at the CLARE Clinical Research Center, an outpatient clinic specialized in the care of pulmonary diseases, in Goiânia, Goiás.

Inclusion criteria

Individuals with COPD who were not undergoing home oxygen therapy, clinically stable, aged 40 or over, admitted between April 1 and September 31, 2013 at the CLARE Clinical Research Center.

After signing the Informed Consent Term (ICF), an oximetry was performed to include only patients with mild daytime hypoxemia (oxygen saturation ≥90% to ≤94%). The patients subsequently underwent clinical evaluation (anamnesis and physical examination), answered validated questionnaires for dyspnea from the Medical Research Council, COPD Assessment Test (CAT) health impairment, socioeconomic level (Associação Brasileira de Empresas de Pesquisa, 2009[8]), and performed spirometry, 6-minute walk test, polysomnography, echocardiogram, arterial blood gas analysis and chest radiography. Individuals with oxygen saturation ≤85% for at least 5 minutes during sleep were considered to have significant nocturnal hypoxemia.[9]

Exclusion criteria

Pregnancy, recent myocardial infarction (less than three months ago), medical history of asthma or any other concomitant lung disease, history of cancer diagnosis, presence of renal failure or dialysis, presence of insulin- dependent, presence of PaO2 <60mmHg at rest, presence of radiographic evidence of any significant abnormality not attributable to COPD and inability to understand or complete all questionnaires, tests and interviews.

Sample size calculation

The t-test was used to determine whether the thickness of the left ventricular (LV) infero-septal wall differs significantly between groups of COPD patients with and without significant nocturnal hypoxemia. The sample was calculated to be able to detect a difference of 15% or more in the thickness of the LV infero-septal wall. A previous study reported that the mean and standard deviation of the LV infero-septal wall thickness in a group of COPD patients was 11 ± 1.9. For α (two-tailed) = 0.05 and power = 0.80, at least 42 individuals with COPD are required.

The results were analyzed using the Stata version 13.1 program (StataCorp, Texas, USA), using a 5% significance level ($p < 0.05$). Shapiro-Wilk test was used to assess the normality of the data. Quantitative variables with normal distribution were described using mean and standard deviation, quantitative variables that did not have normal distribution were described using median and interquartile range, and qualitative variables were described using proportions.

The t-test was used to compare the means; the Wilcoxon test was used for comparisons of medians; and the chi-square test or Fisher's exact-test was used for dichotomous variables. Linear regression was selected to estimate the association between time with saturation below 85% in REM sleep and interventricular septum thickness (IVS), while adjusting for BMI, age and mean arterial pressure.

RESULTS

During the study period, 230 COPD patients were admitted to the CLARE Clinical Research Center outpatient clinic and assessed for eligibility. Of these, 24 patients (10.4%) were excluded due to home oxygen therapy or refusal to participate. Of the remaining patients, 93 patients (40.4%) were excluded because of oximetry ≥ 95% or <90%, 42 patients (18.3%) were excluded due to FEV1/FVC> 70, and 07 patients (3.0%) were excluded due to the presence of radiological evidence of significant changes not attributable to COPD and PaO2 <60mmHg. Figure 1 describes the flow for selecting participants.

The study sample comprised mostly of elderly patients with COPD and advanced disease (GOLD D), with a predominance of males (56.3%), low socioeconomic level, normal Body Mass Index (BMI), the majority of ex-smokers and hypertensive patients (57.8%) with controlled disease. The groups with and without significant nocturnal hypoxemia were different in relation to BMI, PaCO2 and oxygen saturation. There was no statistically significant difference between the two groups, considering blood pressure or percentage of hypertensive patients. The group with significant nocturnal hypoxemia (26.6%) had a higher BMI, higher PaCO2 and less oxygen saturation. (Table 1).

There were more individuals with OSA in the group with significant nocturnal hypoxemia as well as the mean saturation at wake and during sleep were significantly lower in that group (Table 2).

Evaluating the mean saturation of REM sleep versus non-REM sleep, it was found that the median REM

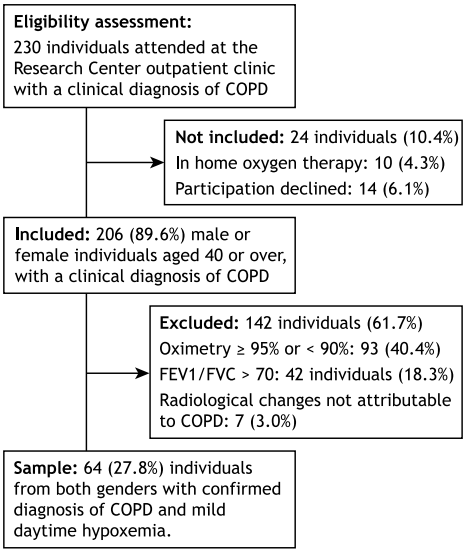

Figure 1. Flow for selecting participants. FEV1 / FVC: forced expiratory volume ratio in the first second and forced vital capacity.

sleep is significantly lower than that of non-REM sleep in both groups: with significant nocturnal hypoxemia (88% versus 91%, respectively p = 0.001) and without significant nocturnal hypoxemia (93% versus 93.5%, respectively p = 0.02).

Regarding echocardiographic parameters, the volume-to-mass ratio was significantly lower in the group with significant nocturnal hypoxemia (ratio 0.64 ± 0.13 versus 0.72 ± 0.12, p = 0.04), the diastolic thickness of the SIV and the LV posterior wall (PP) diastolic thickness were significantly greater in this same group (9.7 ± 0.92 versus 9.1 ± 0.90 p = 0.03), (9.7 ± 1.0 versus 8, 9 ± 1.0, p = 0.01 (Table 3, Figures 2 and 3). The time with saturation below 85% in REM sleep positively correlates to the thickness of the interventricular septum, r = 0.32, p = 0.01, and significantly predicts the interventricular septum thickness (interventricular septum thickness in mm = 8.21 + 0.022 time with saturation ≤85% + 0.03BMI + 0.017 mean arterial pressure -0.02 age, r^2= 0.20; p = 0.046).

Table 1. Characteristics of patients with COPD and mild daytime hypoxemia seen at a clinical center specialized in the treatment of respiratory diseases, Goiânia, Goiás (GO), during the study period.

	All patients	With Significant Nocturnal hypoxemia	Without Significant nocturnal hypoxemia	p
	n = 64	n = 17	n = 47	
Age, years	69.7 ± 8.8	69.4 ± 6.2	69.8 ± 9.6	0.85
Gender male, n (%)	36 (56.3)	7 (41.2)	29 (61.7)	0.15
BMI, kg/m^2	25.1 ± 5.2	27.6 ± 6.6	24.2 ± 4.4	0.02*
Cervical circumference, cm	36.6 ± 4.9	37.4 ± 5.9	36.3 ± 4.4	0.43
Socioeconomic score	17 (14;24)†	16 (16;19)†	17 (14;25)†	0.72
Smoking (packs/year)	47.5 (26;60)†	54 (26;60)†	39 (25;60)†	0.42
Active smoking n (%)	17 (26.6)	5 (29.4)	12 (25.5)	
Ex-smoker n (%)	42 (65.6)	10 (58.8)	32 (68.1)	0.74
Never smoked n (%)	5 (7.8)	2 (11.8)	3 (6.4)	
PAS, mmHg	129.7 ± 18.3	128.2 ± 20.4	130.2 ± 17.6	0.70
DBP, mmHg	74.5 ± 8.3	77.1 ± 9.9	73.6 ± 7.6	0.15
MAP, mmHg	92.9 ± 10.5	94.1 ± 12.6	92.4 ± 9.5	0.57
Hypertension, n (%)	37 (57.8)	11 (64.7)	26 (55.3)	0.50
COPD GOLD A	6 (9.4)	1 (5.9)	5 (10.6)	
n (%) GOLD B	10 (15.6)	3 (17.7)	7 (14.9)	0.76
GOLD C	2 (3.1)	0 (0)	2 (4.3)	
GOLD D	46 (71.9)	13 (76.4)	33 (70.2)	
FEV1 post-Bd (liters)	1.29 ± 0.6	1.21 ± 0.5	1.32 ± 0.6	0.51
FEV1 post -Bd (%)	50.2 ± 18.6	49.6 ± 17.9	50.4 ± 19.0	0.87
FEV1/FVC post -Bd (%)	51.3 ± 12.1	55.7 ± 13.3	49.7 ±11.4	0.08
PaO2, mmHg	71.9 ± 9.8	68.1 ± 11.8	73.4± 8.7	0.06
PaCO2, mmHg	35.1 ± 5.2	37.5 ± 5.7	34.2 ± 4.7	0.03*
Sat O2, blood gas analysis (%)	93.8 ± 2.1	92.9 ± 2.2	94.2 ± 1.9	0.02*
Pulmonary hypertension, n (%)	3 (4.7)	1 (5.9)	2 (4.3)	
PAPs normal, n (%)	30 (46.9)	10 (58.8)	20 (42.6)	0.38
PAPs indeterminate, n (%)	31 (48.4)	6 (35.3)	25 (53.1)	
6MWT distance (% predicted)	92.2 (82.4;107.7)†	95.1 (88.7;107.8)†	89.1 (76.7;107.7)†	0.13
CAT (0-40)	17 ± 7.1	16 ± 6.1	17.3 ± 7.5	0.51

Data are presented as mean ± SD, n (%) or median (interquartile range: p25; p75) †. BMI: Body Mass Index; PAS: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV1: forced expiratory volume in one second; post-BD: post-bronchodilator; FVC: forced vital capacity; PAPs: pulmonary artery systolic pressure; 6MWT: 6-minute walk test; CAT: COPD Assessment Test. Pulmonary hypertension: PAPs> 40. Undetermined PAP: patients without tricuspid regurgitation. *Statistically significant difference.

Table 2. Sleep parameters of patients with COPD and mild daytime hypoxemia seen at a clinical center specializing in respiratory diseases, Goiânia, Goiás (GO), during the study period.

	Significant nocturnal hypoxemia		p
	Yes	No	
	n = 17	n = 47	
Epworth sleepiness scale	8.3 ± 4.2	7.5 ± 4.4	0.55
Total time in bed, min	432.4 ± 46.6	422.5 ± 52.6	0.49
Sleep period, min	404.8 ± 41.4	386.8 ± 42.8	0.17
Wake up before sleep, min	33.5 (17-40)†	30.5 (18-39)†	0.92
Wakefulness after sleep onset, min	38 (18-51)†	29.5 (17-38)†	0.46
Sleep efficiency	69.7 (63.7-79.4)†	70.6 (58.5-82.5)†	0.66
Sleep latency REM, min	152 (59-226.5)†	108.3 (67.5-152.5)†	0.48
Micro wake-up/TTS hour	20.4 (7-28.7)†	10.4 (6.1-19.8)†	0.21
REM sleep duration, min	70.6 ± 20.6	54.3 ± 25.9	0.04*
Duration of non-REM sleep, min	254.6 ± 46.4	237.8 ± 51.8	0.28
Sleep stage I (% of TTS)	5.3 (3.3-6.5)†	5.7 (4.1-6.7)†	0.57
Sleep stage II (% of TTS)	59.3 ± 11.1	59.4 ± 12.3	0.96
Sleep stage III/IV (% of TTS)	15.3 ± 8.4	16.2 ± 9.0	0.70
REM stage (% of TTS)	20.1 ± 5.8	18.6 ± 8.4	0.49
Apnea/hypopnea index (TTS)	15.3 (10.2-30.5)†	5.9 (3.2-9.8)†	0.0002*
Presence of OSA (%) (AIH≥15)	9 (64.3)	5 (35.7)	0.0001*
Mean saturation, wakefulness (%)	92 (90-93)†	94 (93-95)†	0.0002*
Mean sleep saturation (%) (TTS)	91 (89-92)†	94 (92-95)†	0.0001*
Mean sleep saturation (%) (REM)	88 (85-89)†	93 (91-94)†	<0.00001*
Mean sleep saturation (%)(n-REM)	91 (88-92)†	93.5 (91-95)†	0.001*
Minimum sleep saturation (%) (TTS)	73 (72-77)†	87 (83-91)†	<0.00001*

Data are presented as mean ± SD, n (%) or median (interquartile range: p25; p75)†. TTS: total sleep time; OSA: obstructive sleep apnea. REM: *rapid eye movement*; AIH: *the apnea-hypopnea index*. *Statistically significant difference.

Table 3. Echocardiographic variables of patients with COPD and mild daytime hypoxemia seen at a clinical center specializing in respiratory diseases, Goiânia, Goiás (GO), during the study period.

	Significant nocturnal hypoxemia		p
	Yes	No	
	n = 17	n =47	
Left atrial diameter (mm)	33.8 ± 3.7	32.1 ± 3.8	0.13
Right ventricular diameter (mm)	21 (20-21)†	21 (20-21)†	0.14
Diastolic left ventricular diameter (mm)	46 (40-51)†	46 (42-50)†	0.73
Systolic left ventricular diameter (mm)	27 (26-30)†	29 (25-31)†	0.70
Diastolic thickness of the interventricular septum (mm)	9.7 ± 0.92	9.1 ± 0.90	0.03*
Diastolic thickness of the LV posterior wall (mm)	9.7 ± 1.0	8.9 ± 1.0	0.01*
Volume/mass ratio	0.64 ± 0.13	0.72 ± 0.12	0.04*
Left atrium/aorta relationship	1.2 ± 0.2	1.1 ± 0.2	0.16
Left ventricular mass (g)	154.3 ± 39.4	143.8 ± 39.3	0.35
LV ejection fraction (%)	70 (64-74)†	69 (65-72)†	0.33
LV mass/body surface ratio (g/m^2)	91.2 (69.5-101.2)†	81.3 (69.4-106.3)†	0.80
LV cavity shortening (%)	40 (35-43)†	39 (36-41)†	0.64
LV septum/posterior wall thickness ratio	1 (1-1)†	1 (1-1.1)†	0.42
LV end diastolic volume (ml)	97 (70-124)†	97 (79-118)†	0.73
LV stroke volume (ml)	68.1 ± 20.7	67.7 ± 20.1	0.95
LV end stroke volume (ml)	27 (25-35)†	32 (22-38)†	0.70
LV systolic dysfunction, n (%)	0 (0)	2 (4.3)	0.54
LV diastolic dysfunction, n (%)	14 (82.4)	32 (68.1)	0.21

Data are presented as mean ± SD, n (%) or median (interquartile range: p25; p75)†. LV: left ventricle. *Statistically significant difference.

DISCUSSION

Our COPD sample showed characteristics representative of these patients in Brazil, corroborating the data published by the PLATINO study in Brazil, in which 18% of men and 14% of women were affected with COPD.[10] Thus, both the study by Mueller et al.,[11] who evaluated the systemic effects of nocturnal hypoxemia in COPD patients without obstructive sleep apnea syndrome (male gender corresponded to 71.4% of the total sample), and the present study (male gender corresponded to 56.3% of the sample) showed predominance of males.

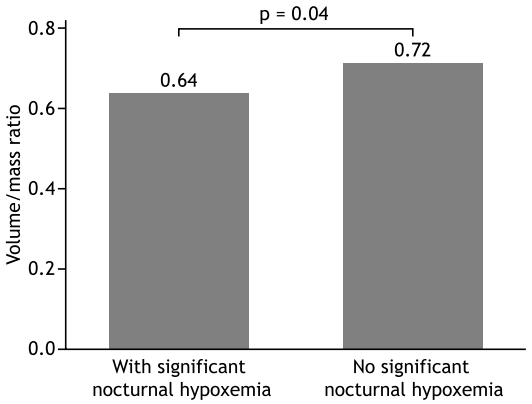

Figure 2. Mean volume/mass ratio of patients with COPD and mild daytime hypoxemia seen at a clinical center specializing in respiratory diseases, Goiânia, Goiás (GO), during the study period.

The same was observed regarding the socio-economic level of the sample. Tando,[12] states that low socioeconomic conditions are a risk factor for COPD. Likewise, Prescott et al.,[13] reinforces that the negative impact of socioeconomic status on the pulmonary function of patients with COPD is only second to the impact of smoking. In the socioeconomic score used in the present study, patients with significant nocturnal hypoxemia reached 16 points and those without significant nocturnal hypoxemia reached 17 point, both in class C2 (mean family income of 726 reais), reinforcing the influence of socioeconomic status in COPD.

Systemic arterial hypertension (SAH) was observed in 57% of the individuals evaluated. It was considered the most frequent comorbidity in patients with COPD in Costa's et al.[14] research, and it affects 42.2% of the participants in this study. Also, we observed no statistically significant difference between the groups with and without significant nocturnal hypoxemia in relation to the level of blood pressure, and in relation to the prevalence of hypertensive patients. Thus, the LV hypertrophy found in the group with nocturnal hypoxemia was not due to inadequate control of blood pressure or the greater amount of hypertension in the group with significant nocturnal hypoxemia, as arterial hypertension is a well-established risk factor for LV hypertrophy.[15]

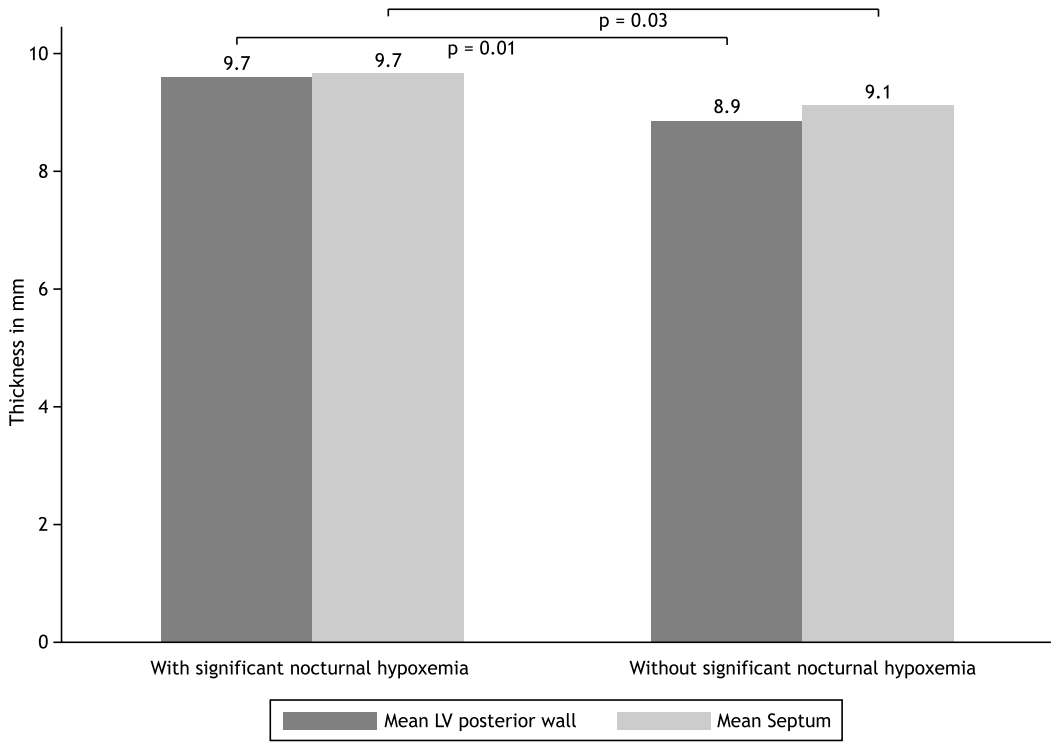

Figure 3. Mean posterior wall of the LV and interventricular septum of patients with COPD and mild daytime hypoxemia seen at the clinical center specialized in the treatment of respiratory diseases, Goiânia, Goiás (GO), during the study period. LV: left ventricle.

The study sample had normal BMI; however, the mean BMI of the group with significant nocturnal hypoxemia was higher than in the group without abnormal sleep (27.6 kg/m^2 versus 24.2 kg/m^2). This was also observed in the study Chaouat et al.,[16] which found an association between high BMI and nocturnal desaturation. Pujante et al.[17] found a high prevalence (76.2%) of OSA in patients with morbid obesity, as well as a high prevalence (78.6%) of changes in LV mass in morbidly obese patients affected by OSA. In other studies, Avelar et al.,[18] Mirzaaghazadeh et al.,[19] Papachatzakis et al.,[20] Gupta et al. [21], most patients with OSA presented significantly higher BMI and waist circumference, since obesity is an important risk factor for OSA, which in turn leads to nocturnal hypoxemia.[22]

However, OSA is not the exclusive cause of significant nocturnal hypoxemia, which can also be caused by COPD, by decreased functional residual capacity due to hypotonia of the intercostal muscles, decreased ventilatory response to hypoxia and hypercapnia, and by worsening ventilation/perfusion disproportion at night.[23] We observed OSA in 64.3% of patients with significant nocturnal hypoxemia, and in 35.7% of patients without significant nocturnal hypoxemia. According to Senaratna et al.,[24] in the general population, the prevalence ranges from 9 to 38%, and Tufik et al.[25] found OSA index in 32.8%, which was similar to that found in the sample without hypoxemia. This shows that the prevalence of OSA in the general population and in COPD patients without nocturnal hypoxemia remained very close, while the excess of OSA in the group with hypoxemia partially justifies the greater nocturnal desaturation in this group.

Zanchet and Viegas[26] found that 52% of the patients studied (with COPD, without sleep apnea and with mild hypoxemia during wakefulness) presented nocturnal desaturation. This was also seen in the present study since, even in the group without significant hypoxemia, the minimum sleep saturation was low (87%). We also observed that the mean wakefulness saturation was significantly lower in individuals with significant nocturnal hypoxemia (92% versus 94%), and this reproduced during sleep (88% versus 93% in REM sleep). Thus, we conclude that the presence of mild hypoxemia during wakefulness is a predictive factor of lower levels of the mean saturation during sleep, as demonstrated by Lewis et al.[27] A decrease in oxygen saturation was observed when in REM sleep compared to non-REM sleep in both groups. This drop in both groups is probably due to physiological changes in respiratory mechanics during sleep. The decrease in the sensitivity of the chemoreceptors, the respiratory motor drive and muscle contraction cause changes in the ventilation/perfusion ratio and increase in resistance to airflow. Although unimportant in healthy individuals, these changes can lead to pronounced nocturnal hypoxemia in REM sleep in patients with COPD.[4]

Regarding the daytime PaO2 and PaCO2 values, Plywaczewski et al.[28] demonstrated that patients with PaO2 values below 65 mmHg and PaCO2 above 45 mmHg were more likely to have nocturnal desaturation. We found similar results. The group with significant nocturnal hypoxemia had significantly lower levels of saturation (92.9% versus 94.2%) and higher PaCO2 (37.5 versus 34.2) compared to the group without significant nocturnal hypoxemia.

According to Mendes,[29] studies on the relationship between pulmonary function and cardiac remodeling in hypertensive individuals are still scarce. Vonk-Noordegraaf et al.[6] did not find an increase in LV mass or changes in their imaging parameters when comparing a group of 25 COPD patients with mild hypoxemia with healthy controls, however, nuclear magnetic resonance was used to assess the heart and not echocardiography. In post-mortem studies, left hypertrophy and its magnitude have been shown to be well correlated with the duration of right ventricular (RV) pressure overload.[30] In addition, due to ventricular interdependence, structural changes in the RV also change the structures of the LV.[6] The present study brings important findings to reinforce this scientific evidence regarding the LV changes that can be produced by respiratory diseases.

Three parameters that are related to left ventricular hypertrophy were altered in a group of patients experiencing significant hypoxemia at night (mass volume ratio, diastolic thickness of the interventricular septum and diastolic thickness of the posterior LV wall). As explained in the study by Dempsey et al.,[22] severe hypoxia induces increases in sympathetic nervous activity, including sympathetic nervous activity in the renal system, activating the Renin-Angiotensin-Aldosterone System. This stimulation of the mineralocorticoid receptor induces not only inflammation, but also oxidative stress, which leads to endothelial dysfunction and vascular remodeling, important mechanisms in the pathogenesis of cardiac hypertrophy. Even in healthy individuals, REM sleep is associated with intense sympathetic activation, up to 226% of the baseline value in wakefulness, possibly linked to changes in muscle tone.[31] In patients with nocturnal hypoxemia, such as those with OSA, this sympathetic nervous system hyperactivity can persist even when the individual is awake, being directly or indirectly involved in several other effects of hypoxemia, including oxidative stress, lipid dysfunction, inflammation systemic, endothelial dysfunction and accelerated atherosclerosis.[32] The increase in hypoxemia during REM sleep in patients with COPD is caused by a reduction in the minute volume secondary to depression of the ventilatory response to chemical stimuli associated with reduced activity of the accessory musculature of ventilation, that occurs at this stage of sleep. With the diaphragmatic function compromised by possible hyperinflation and the reduction of accessory respiratory muscle activity, there is a reduction in the functional residual capacity, which increases the closing volume, alters the ventilation-perfusion ratio and causes a decrease in oxygenation.[33] The intensification of hypoxemia, in turn, accentuates the activation of the sympathetic

nervous system, which leads to hemodynamic changes during REM sleep, playing an important role in the production of left ventricular hypertrophy.[34]

Left ventricular characteristics were analyzed in patients with significant nocturnal hypoxemia with COPD and mild daytime hypoxemia and data were found that indicate an increase in LV mass when compared with a group without significant nocturnal hypoxemia. Left ventricular mass has been shown to be an important predictor of cardiovascular outcomes, such as heart failure and coronary artery disease, with a higher cardiovascular risk with increased LV muscle, regardless of the presence of ventricular hypertrophy criteria.[35,36] In addition, randomized clinical trials demonstrate that a therapeutic intervention that reduces LV mass results in a decrease in mortality and morbidity.[3,4] Thus, by showing a greater LV mass in the group with significant hypoxemia during sleep, we identify the presence of greater cardiovascular risk in these patients.[37,38]

In the literature, data from studies relating COPD and left ventricular cardiac function are scarce and not conclusive. Thus, as a significant portion of COPD patients present nocturnal hypoxemia, our findings have relevant clinical implications for the prognosis of these patients, since LV hypertrophy in its uncompensated phase can result in left ventricular dysfunction, constituting an important factor in increasing cardiovascular morbidity and mortality. Thus, in addition to the clinician's usual concern with treating the hemodynamic consequences of lung disease in the right ventricle, we show that, in a subgroup of patients (with significant nocturnal hypoxemia), it is important to consider whether the respiratory disease affects the left ventricle to avoid the complications associated with your dysfunction.

We evaluated COPD patients with mild hypoxemia (oxygen saturation ≥90 to ≤94%) since isolated nocturnal hypoxemia in individuals with oxygen saturation ≥ 95% at rest is unlikely,[27] suggesting that this subgroup of patients would not need to be evaluated for nocturnal hypoxemia. Considering that COPD patients with oxygen saturation <90% are more likely to have PaO2 <60 mmHg at rest and come to need home oxygen therapy in case of pulmonary hypertension or cor pulmonale, this group of patients must have an echocardiogram. Thus, a subgroup of individuals with COPD is formed with oxygen saturation between 90 and 94%, of which there is little publication on the presence of nocturnal hypoxemia. This nocturnal hypoxemia could generate a higher cardiovascular risk, since patients with mild daytime hypoxemia may present disproportionate drops in oxygen saturation during sleep, which can cause arrhythmias and pulmonary hypertension, increasing the risk for heart and cerebrovascular disease.[39]

The present study has several limitations. The use of sedative medications was not included as an exclusion criterion and its use could accentuate a hypoxemia present during sleep. However, as the study design was not concerned with diagnosing the cause of nocturnal hypoxemia, but its consequence (significant left ventricular hypertrophy), the cause of severe hypoxemia, whether isolated night hypoxemia, apnea sleep, or chronic use of sedatives (since they are usually chronic medications) would not matter. The result would still be nocturnal hypoxemia, which, if significant, would produce an increase in ventricular mass. In addition, as the study has a relatively small sample size and cross-sectional character, it is necessary to carry out new prospective studies with larger samples that include participants with different severities of COPD to confirm the results found, and to verify the applicability of the evaluation of these parameters of left ventricular hypertrophy in daily clinical practice.

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ORIGINAL ARTICLE

Which is the best protocol and cut-off point in the *4-metre gait speed test* to discriminate exercise capacity in COPD?

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Study carried out in the Laboratório de Pesquisa em Fisioterapia Pulmonar, Departamento de Fisioterapia, Centro de Ciências da Saúde, Universidade Estadual de Londrina, Londrina (PR) Brasil.

ABSTRACT

Objective: To determine the discriminative capacity and cut-off point of different 4-metre gait speed test (4MGS) protocols in identifying preserved or reduced exercise capacity using the six-minute walk test (6MWT) in patients with Chronic Obstructive Pulmonary Disease (COPD); also, to compare 4MGS protocols and characteristics of individuals according to the best cut-off point. **Methods:** We evaluated fifty-six patients with COPD, all of which were submitted to the assessment of anthropometric characteristics, pulmonary function (spirometry) and functional exercise capacity (6MWT and four protocols of the 4MGS). In the 4MGS test, patients were instructed to walk at normal pace and at maximum speed in a 4 meters course (4MGS 4m - usual pace and at maximum) and 8 meters course (4MGS 8m - usual pace and at maximum). **Results:** Only the 4MGS 4m-maximum protocol was able to identify preserved exercise capacity in the 6MWT (AUC=0.70) with moderate correlation between them (r=0.52; P=0<0.0001). The cut-off point found in the 4MGS 4m-maximum was 1.27 m/s. Patients with preserved exercise capacity (4MGS 4m-maximum ≥1.27m/s) walker greater distances on the 6MWT in %pred (91±2 *vs* 76±3; P<0.0001). In the other comparisons involving gender, BMI, FEV1% pred and GOLD index there were no significant differences between the groups. In addition, the agreement of individuals classified as preserved and reduced exercise capacity in the 6MWT and 4MGS 4m-maximum was significant (P = 0.008). **Conclusion:** The 4MGS 4m-maximum test can be used to discriminate preserved exercise capacity in patients with COPD and correlates with the 6MWT.

Keywords: Chronic Obstructive Pulmonary Disease; Velocity measurement; Gait.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is defined as "[...] a common, preventable and treatable disease, characterized by persistent respiratory symptoms and limited airflow, due to airway abnormalities caused by significant exposure to harmful particles or gases"[1]. In addition to airflow obstruction, COPD can also be characterized by deconditioning and physical inactivity.[2,3] Skeletal muscle dysfunction is an extrapulmonary characteristic of the disease, related to the decreased functional capacity for exercise and consequently to physical inactivity. Physical inactivity leads to physical deconditioning and is considered a risk factor for exacerbations and early mortality.[4-6] Therefore, the assessment of exercise capacity in patients with COPD is necessary for both the research field and clinical practice.[7]

Functional exercise capacity can be validated through field tests such as a six-minute walk test (6MWT).[7] The 6MWT is a simple, safe, low-cost test, easy to apply, and reproducible,[7,8] in which the patient is instructed to walk the longest distance possible in a 30-meter flat corridor in six minutes.[8] This test enables us to evaluate global responses and integrated different systems involved during the exercise.[9] Also, a percentage of the predicted value below 82% is indicative of reduced exercise capacity in these patients.[10]

Although the 6MWT is considered a practical and simple test, it requires space (e.g. a 30-meter corridor), time (e.g. two tests with a 30-minute interval are needed) and trained personnel to apply the test.[7] Thus, alternative tests such as the 4-meter gait speed test (4MGS) have been used in patients with COPD to assess functional capacity.[11-14] In 4MGS, the patient must walk 4 meters at the speed requested to measure gait speed. Recent studies have shown an association between gait speed and exercise capacity in patients with COPD.[14,15] The 4MGS is considered a simple, reliable test that requires a small

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space, is a low-cost, easy test to apply and quick to perform.[12-14,16,17]

This test uses different protocols. The most frequently used are the 4MGS-4meter and the 4MGS-8meter, in which the patient is instructed to walk at his usual or maximum speed, crossing corridors of 4 and 8 meters.[12-14] However, differences between these protocols are yet unknown in terms of which of the 4MGS test protocols have the greatest discriminative power, and which cut-off value is capable of identifying patients with preserved or reduced exercise capacity assessed using the 6MWT.

The study aimed to verify the discriminatory power and cut-off point of the 4MGS protocols to identify the preserved or reduced exercise capacity in the 6MWT in patients with COPD; and to compare 4MGS protocols and the characteristics of the individuals according to the best cut-off point found.

METHODS

This is a cross-sectional study with a convenience sample of patients diagnosed with COPD, who were evaluated at the *Laboratório de Pesquisa em Fisioterapia Pulmonar* (LFIP) at the *Universidade Estadual de Londrina*, Londrina, PR, Brazil. All patients were under initial evaluation for inclusion in a pulmonary rehabilitation program unrelated to this study.

The Research Ethics Committee Involving Human Beings of the institution approved the study under CEP/UEL 080/2014. All participants signed an informed consent form.

The study included patients diagnosed with COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[1] with clinical stability, absence of comorbidities that could influence the performance of the tests and have not participated in physical training programs in the past twelve months. Individuals who for some reason were unable to complete all assessments were excluded from the study.

All patients underwent an anthropometric, pulmonary function and functional exercise capacity assessment. The anthropometric assessment was performed to better characterize the sample. Thus, the scale and stadiometer measured the weight and height (Ítaca Com. Equip. LTDA, model MIC2/BA, São Paulo - SP), determining the body mass index (BMI).

A portable spirometer (Spiropalm®; COSMED, Italy) was used for the lung function assessment. The technique was performed according to the guidelines of the American Thoracic Society/European Respiratory Society,[18] determining the forced expiration volume in the first second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC index. We used the reference values proposed for the Brazilian population by Pereira et al.[19]

Patients were also assessed for their functional exercise capacity through the 6-minute walk test (6MWT) and four different protocols of the 4-meter gait speed test (4MGS). The 6MWT was performed according to internationally recommended standards, in which patients were instructed to walk the longest distance possible in a 30-meter corridor for six minutes.[7] Two tests were performed with an interval of at least 30 minutes between them and the longest walking distance was used for analysis. We used reference values described by Britto et al.,[20] specific to the Brazilian population.

We used the calculation of the lower limit to classify individuals with preserved and reduced exercise capacity in the 6MWT. This calculation is performed by subtracting the product from 1.645 by the standard error of estimating the total distance equation predicted by the reference equation.[21]

In the 4MGS test, patients were instructed to walk at their usual pace and at maximum speed over 4 and 8 meters. The tests followed the protocols of Karpman et al.[12,13] and Kon et al.[14] In the 4MGS-4 meter protocol, the patient was instructed to walk 4 meters, at his usual pace and at maximum speed in a 4-meter corridor bounded by two cones. The stopwatch was started from the patient's first movement and was interrupted when the patient crossed the second cone.[14] In the 4MGS-8 meters, the individual was instructed to walk 4 meters at a usual pace and at fast speed but in a course of 8 meters: besides the 4 meters, the course had 2 meters of acceleration and 2 meters of a slowdown. However, the counting occurred only in the central 4 meters, discarding the initial 2 meters and the final 2 meters.[12,13] For each test, two repetitions were performed, and the test with the shortest execution time was used for analysis.

Statistical analysis

The Statistical Package for the Social Sciences software, version 20.0 (SPSS Inc., Chicago, IL, USA) and the GraphPad Prism, version 6.0 (GraphPad Software Inc., La Jolla, CA, USA) performed statistical analyzes. We also used the Shapiro-Wilk test for the analysis of the normality of the data. Results were described as mean and standard deviation or median and interquartile range 25-75% according to the data distribution. Also, we used the Pearson or Spearman correlation coefficient to verify the relationship between the 6MWT and the 4MGS protocols. The unpaired t-test or Mann-Whitney test compared the individuals with high and low performance on the 6MWT. The comparison of the 4MGS protocols was performed using the paired t-test or Wilcoxon test. For effect size analysis, we used the average of the difference in speed of the two protocols by the standard deviation of one of the protocols. The ROC Curve verified the discriminatory power of the 4MGS in identifying a preserved or reduced exercise capacity in the 6MWT and therefore, finding a cut-off point. The Chi-square test compared the proportion of individuals classified with preserved and reduced exercise capacity in the 4MGS and the 6MWT. Kappa verified the agreement of classification in the 6MWT and 4MGS, and the level of statistical significance was established as $P < 0.05$.

The sample power of this study was calculated according to the correlation results obtained between the 6MWT and the 4MGS test 4 meters maximum of r = 0.52. Considering an alpha = 0.05 and a sample of 56 individuals, we obtained 99% power. The analysis was performed in the GPower software (Franz Faul, Universitat Kiel, Germany).

RESULTS

The study included 58 patients; however, two were excluded for not having completed all the proposed tests. Therefore, the data of 56 patients were considered for the analyzes, and Table 1 described general characteristics.

When the 4MGS protocols were compared, there was a difference between the tests performed on different corridor sizes, one with 4 meters distance and the other with 8 meters. The individuals walked at a higher speed in the 8-meter course, both at maximum speed and at the usual pace (Table 2). The effect size analysis found that when comparing the 4MGS protocols of usual pace and at maximum speed, the values obtained were 0.24 and 0.22, respectively. Also, a moderate correlation of the 6MWT distance with the 4MGS protocols 4 meters Maximum and 4MGS 8 meters Maximum was verified (r = 0.52 and r = 0.58, respectively; P <0.0001 for both). A weak correlation was found between the 4MGS protocols 4 meters Usual (r = 0.33; P = 0.01) and 4MGS 8 meters Usual (r = 0.25; P = 0.05) and the 6MWT distance (Figure 1).

In the discriminative analysis, only the 4MGS 4 meters Maximum protocol identified the preserved exercise capacity in the 6MWT (AUC = 0.70) (Figure 2). However, none of the 4MGS protocols discriminated against a reduced exercise capacity in the 6MWT.

The cut-off point found in the 4MGS 4 meters Maximum was 1.27 m/s with a sensitivity of 0.750 and specificity of 0.625. When comparing the characteristics of the individuals according to the cut-off point found, patients with preserved exercise capacity (4MGS 4 meters Maximum ≥1.27m/s) were younger (65 [60-72] years old vs 72 [69-77] years old; P = 0.0016) and reached a greater distance covered in the 6MWT in absolute values (485 ± 56 meters vs 395 ± 65 meters; P <0.0001) and in the predicted% of the 6MWT (91 ± 2 vs 76 ± 3; P <0.0001). When comparing gender, BMI, FEV1% predicted and GOLD, no significant differences were observed between groups. Additionally, the agreement of individuals classified with preserved and reduced exercise capacity in the 6MWT and 4MGS 4 meters Maximum was significant (P = 0.008). Similarly, there was a greater proportion of individuals (83%) classified with 4MGS 4 meters Maximum ≥ 1.27 m/s as having exercise capacity preserved also by the 6MWT than in individuals classified (50%) as 4MGS 4 meters Maximum <1.27 m/s (P = 0.01) (Figure 3).

Table 1. General characteristics of individuals with COPD.

Variables	N = 56
Gender (M/F)	29/27
Age (years old)	68 ± 8
BMI (Kg/m^2)	26 ± 5
FEV_1 (liters)	1.25 ± 0.44
%FEV_1 (%predicted)	50 ± 18
FEV_1/FVC	55 [45-63]
GOLD (I/II/III/IV)	1/32/16/7
6MWT (m)	452 ± 73
% 6MWT (%predicted)	85 ± 15
4MGS 4 Meters Maximum (m/s)	1.36 ± 0.24
4MGS 4 Meters Usual (m/s)	1.06 ± 0.23
4MGS 8 Meters Maximum (m/s)	1.68 ± 0.31
4MGS 8 Meters Usual (m/s)	1.29 ± 0.24

DISCUSSION

In this study, a cut-off point of 1.27 m/s was found in the 4MGS 4 meters Maximum test to discriminate preserved exercise capacity in the 6MWT. When comparing the characteristics of patients who had a speed above or below 1.27 m/s in the 4MGS 4 meters Maximum, those who had exercise capacity preserved by the 4MGS had a greater distance in the 6MWT in predicted %. In patients who presented walking speed above the cut-off point, 83% also had exercise capacity preserved by the 6MWT. When comparing the protocols, the individuals have a higher gait speed in the protocols performed in 8-meter corridors.

The 4MGS is considered an attractive test for clinical practice because it is simple, requires a small space, is inexpensive and easy to apply, and, therefore, it is used as an alternative and more practical way to assess functional capacity.[12-14,16,17] Several protocols are available in the literature, including in the study by Kon et al.,[14] who used the 4-meter protocol with a specific characteristic: walking a 4-meter course with the usual walking speed. Karpman et al.[12,13] proposed the 4-meter walking protocol on an 8-meter course, with usual pace and at maximum speed. The 8-meter protocol features an acceleration zone of 2 meters, an area of 4 meters for timing, and a deceleration zone of 2 meters. In other studies, much more differentiated protocols are found, as in the study by Andersson et al.[22] In their study, patients were instructed to walk in a 30-meter corridor. First, they walked the course at a self-selected pace, and after a 2-minute rest period, they walked at maximum walking speed. Thus, the patients had a higher speed in the 4MGS performed in 8-meter corridors. This better performance in a larger corridor, both at usual pace and at maximum

Table 2. Comparison of 4-meter gait speed test protocols.

	4MGS 4 meters	4MGS 8 meters	*P*
Usual (m/s)	1.06 ± 0.23	1.29 ± 0.24	<0.0001
Maximum (m/s)	1.36 ± 0.24	1.68 ± 0.31	<0.0001

4MGS: 4-meter gait speed; *P*: p-value.

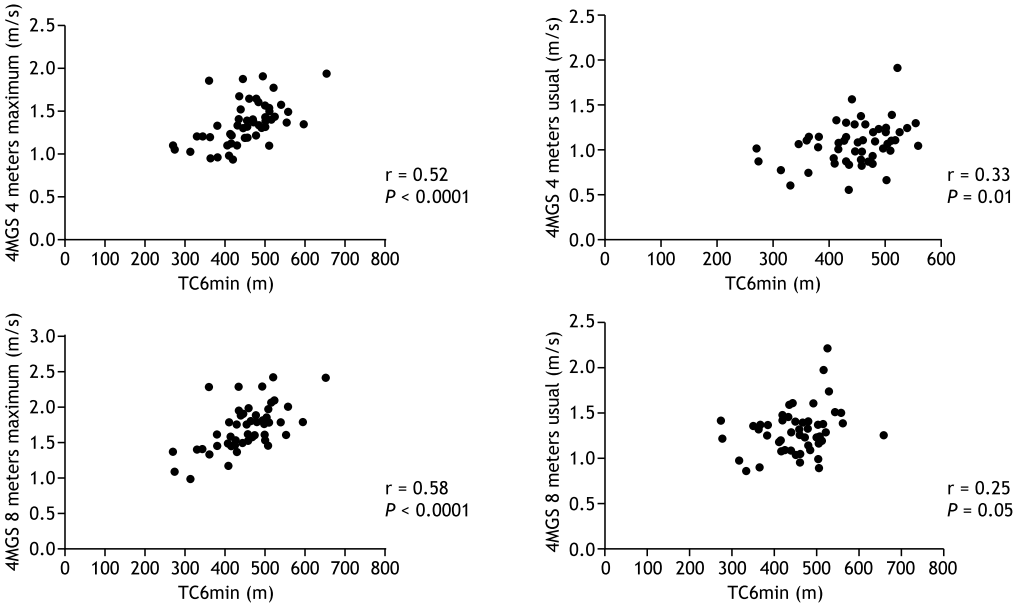

Figure 1. Correlation between the protocols of the 4-meter gait speed test (4MGS) and the six-minute walk test (6MWT). *P*: p-value; r: correlation coefficient.

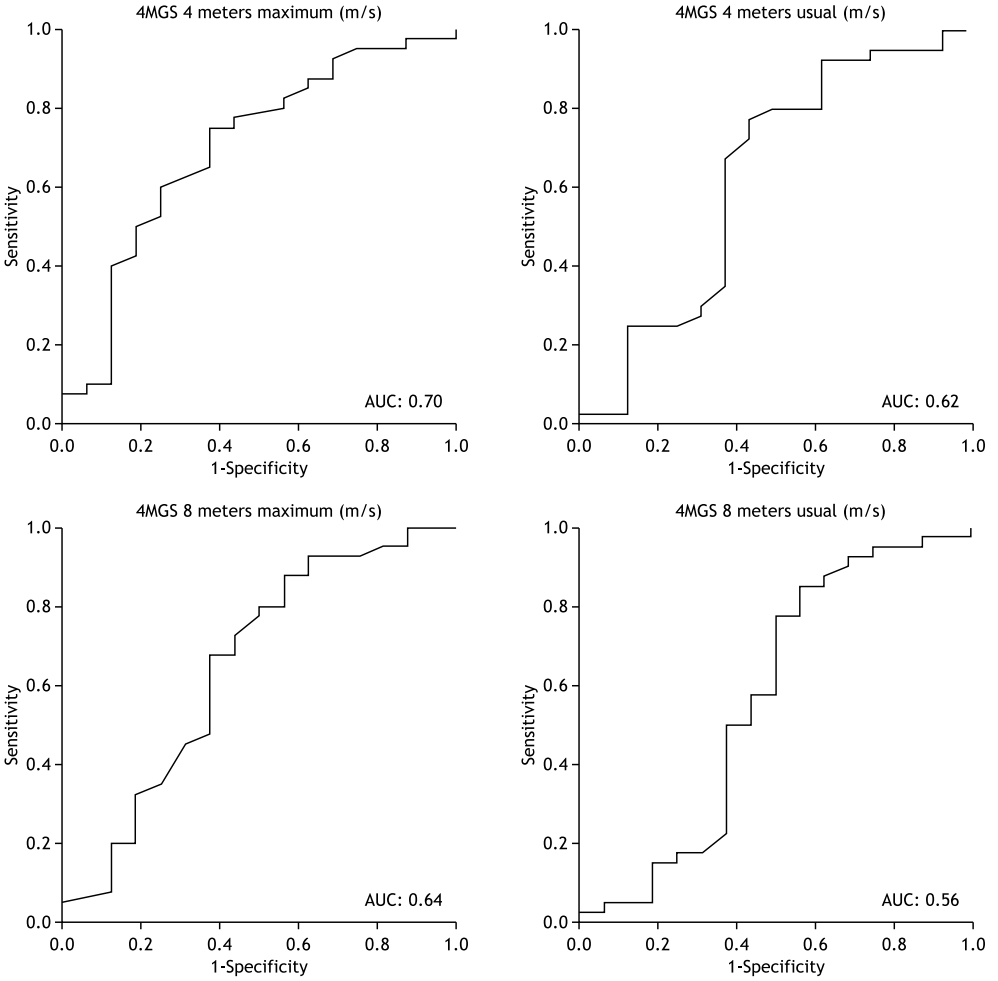

Figure 2. ROC curves of the different protocols of the 4-meter gait speed (4MGS) in meters per second (m/s) to identify preserved exercise capacity in the six-minute walk test. AUC: area under the ROC curve.

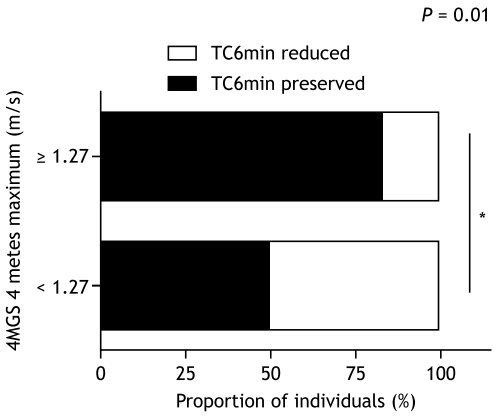

Figure 3. Comparison of the proportion of individuals with preserved exercise capacity in the six-minute walk test (6MWT) who walked at a speed greater or equal and less than 1.27m/s in the 4-meter gait speed of 4 meters - maximum speed (4MGS 4 meters maximum). *P*: p-value; *: *P*=0.01.

speed, can be explained by the zone of acceleration and deceleration that the protocol proposes. Timing starts when the individual is already moving and stops, without having to slow down, as there are still two meters (deceleration zone) to be walked.[13]

Among the variables studied, the 4MGS 4 meters and 8 meters Maximum showed a moderate correlation with the 6MWT. These findings corroborate other studies on the same topic. Karpman et al.[13] showed that gait speed is associated with exercise capacity (6MWT), and established that the correlation between gait speed at usual pace and at maximum speeds and 6MWT was high, regardless of the protocol (usual or maximum) (r = 0.77; r = 0.80, respectively; P <0.001). DePew et al.[15] also determined that 4MGS at the usual pace is significantly associated with the 6MWT (r = 0.70; P <0.001). Finally, Kon et al.[14] also related the 4MGS at the usual pace with exercise capacity measured differently, using the Incremental Shuttle Walking Test, and found a positive and significant correlation between both tests (r = 0.78; P <0.001).

Regarding the discriminative capacity of the 4MGS functional test, the maximum 4-meter protocol was the only one capable of identifying preserved exercise capacity in the 6MWT (AUC = 0.70). A possible explanation for this result may be due to the maximum speed being the one that best correlates with the exercise capacity since the 6MWT patients are encouraged to reach the longest distance possible. The Maximum 8-meter protocol had a lower discriminative capacity, which may be due to disregarding acceleration and deceleration. This difference may have occurred, as this aspect is not considered in the 6MWT since patients perform this acceleration and deceleration when turning the cones during the test. This study also found, in a novel way, the cut-off point in the 4MGS of 1.27m/s as identifying preserved exercise capacity by the 6MWT. Therefore, it is possible to use this speed obtained through a test simple as the 4MGS to screen those with preserved exercise capacity.

A limitation of this study is the convenience sample and the shortage of patients with a mild degree of airflow obstruction (GOLD I), which may compromise the external validity of the results for this population. However, individuals with a mild degree of the disease are prone to be asymptomatic and often do not seek treatment. Therefore, future studies are needed to investigate aspects of the 4MGS in these patients and for the cut-off point found in this study to be tested on other samples. Our findings can be used in future studies to screen patients with preserved exercise capacity more quickly and simply.

We concluded that the walking speed of 1.27 m/s obtained through the 4MGS 4 meters Max test identified a preserved exercise capacity in the 6MWT in patients with COPD. The 4MGS 4 meters maximum is correlated with the distance covered in the 6MWT.

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ORIGINAL ARTICLE

Evaluation of the association of adherence to long-term home oxygen therapy and clinical markers and five-year mortality in patients with Chronic obstructive pulmonary disease

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ABSTRACT

Objective: Assess the relationship between adherence to long-term oxygen therapy (LTOT) with mortality in patients with chronic obstructive pulmonary disease (COPD) and chronic respiratory failure and their clinical features. **Methods:** Longitudinal retrospective analysis of 254 patients with COPD and chronic respiratory failure from 2008 to 2016. At baseline, we evaluated the diagnosis, spirometry values, arterial blood gas analysis, blood count, pulse oximetry, body composition and health questionnaires (dyspnea, quality of life, anxiety and depression). For referred adherence analysis to LTOT we included 199 patients, divided according to prescription of oxygen**:** 12h/day (G1), 15h/day (G2) and 24h/day (G3). The cause of death and dates were studied over the five-year period. **Results:** In five years we identified 124 deaths (62.3%). No significant difference was found in mortality between the adherence groups (p=0.75) nor did we find differences in the clinical parameters evaluated. LTOT prescription was not associated with mortality (p=0.07). In Cox regression analysis, there was no association between mortality and non-adherence to LTOT (HR**:** 0.75; IC95%: 0.21-2.70). The risk of mortality was increased in G3 compared with G1 (HR: 7.16; IC 95%: 1.44-35.38) and in those with a higher depression score (HR: 1.35; IC: 1.14-1.59). **Conclusion:** No association was found between LTOT adherence and mortality in patients with COPD and respiratory failure. There were no clinical differences between the adherence groups.

Keywords: Chronic obstructive pulmonary disease; Oxygen therapy; Cooperation and treatment adherence; Morbidity and mortality indicators.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by progressive airflow obstruction due to the inhalation of toxic particles or gases, especially smoking, and is not fully reversible.[1] The most serious cases are characterized by chronic respiratory failure, with indication for supplementation of long-term oxygen therapy (LTOT), as it improves quality of life, physical exercise capacity, cardiac output, pulmonary mechanics and reduces hospitalizations due to exacerbations and mortality.[2,3]

LTOT indications include when arterial oxygen pressure (PaO_2) <55 mmHg or pulse oximetry (SpO_2) ≤ 88%. In patients with PaO_2 between 56 and 59 mmHg but with clinical repercussions such as polycythemia (hematocrit ≥ 55%) or cor pulmonale, LTOT is also indicated to decrease the progression of hypoxemia damage.[4]

However, the literature describes markers of worse prognosis that are related to low or high $PaCO_2$, low PaO_2, presence of anemia and greater dyspnea symptoms.[5,6] In addition, a study of 14,000 patients showed that mortality was higher in the group that received an LTOT indication during hospitalization compared to an outpatient indication.[7]

In Brazil, data on survival and its related factors are still scarce. A study carried out in São Paulo showed a 15% survival rate after four years of follow-up, as well as observing a lower survival rate for women compared to men.[8] Another study with 118 patients showed survival of 75.9% in the first year and found an association of lower survival in those with greater severity of hypoxemia and dyspnea.[5]

On the other hand, a characteristic that can influence the prognostic markers of these patients is adherence to LTOT. Studies show that there is wide variation in

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the adherence rate, from 31 to 70%.[9-11] Factors associated with low adherence include age, low education, polypharmacy, few symptoms, active smoking, failure in the doctor-patient relationship and lack of follow-up.[12] Other difficulties are carrying the equipment, social stigma, lack of perceived benefit, fear of side effects, forgetfulness, discomfort, shyness and fear of dependence.[13-16]

In this context, few Brazilian studies have evaluated the influence of adherence to LTOT use on mortality, symptoms and disease evolution. Therefore, the aim of this study was to assess the association between adherence to LTOT use and clinical characteristics, quality of life and mortality after five years of follow-up in patients with very severe COPD.

METHODS

This retrospective longitudinal study evaluated all the medical records of the oxygen therapy outpatient clinic at "Hospital das Clínicas" of the "Faculdade de Medicina de Botucatu" - UNESP between June 2008 and January 2016 (data obtained from the research "Prognostic indicators in patients treated with long-term home oxygen therapy") same service.

Patients diagnosed with COPD and clinical stability (absence of exacerbation three months before the initial evaluation), who agreed with the research conditions, were included. The COPD diagnosis was realized according to the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[4] Exclusion criteria were: other respiratory diseases, cancer and diagnosis for myocardial infarction four months before the start of the study.

As a routine of the service, in the first consultation, all patients are evaluated regarding demographic characteristics, medical diagnoses, indication and titration of oxygen and time of daily use. The flow is prescribed according to the oxygen titration at rest. In patients without severe hypoxemia at rest, but with effort desaturation, we indicated the use of oxygen therapy during efforts and at night 12h/day (Group G1/intermittent). Patients with severe hypoxemia, but who tolerate some period without oxygen supplementation, were prescribed 15 hours/day (Group G2). Patients with the worst clinical condition were prescribed 24 hours/day (Group G3).

After six months, patients were assessed for quality of life, anxiety and depression and dyspnea scores. Complete blood count, blood gas analysis and anthropometric evaluation were also collected. In addition, adherence to LTOT supplementation treatment is assessed. All patients were evaluated every six months for the maintenance of the LTOT indication, as well as their titration.

Pulse oximetry was obtained by a portable oximeter. Arterial gases were collected with the patient breathing room air. Spirometry was performed using a computerized system according to criteria established by the American Thoracic Society.[17] The forced expiratory volume in the first second (FEV_1), the forced vital capacity (FVC) and the FEV_1/FVC ratio were determined before and after the administration of inhaled salbutamol.

Clinical evaluation, height and weight were evaluated and measured by a stadiometer. The body mass index (BMI) was calculated applying the relationship between weight in kilograms (kg) and height in meters squared (m^2).

Quality of life was assessed by the Saint's George Respiratory Questionnaire (SGRQ), considering the total score, which corresponds to the sum of three domains: symptoms, impact and activity.[18] Dyspnea intensity was assessed by the Baseline Dyspnea Index (BDI) and also by the Modified Medical Research Council (MMRC) dyspnea index, which rank dyspnea in relation to the performance of day-to-day activities.[19,20] The hospital anxiety and depression scale (HADS) was used, consisting of seven items aimed at assessing anxiety (HADS-A) and seven for depression (HADS-D).[21]

Anemia was considered when women had hemoglobin <12 g/dL or hematocrit <35% and for men when hemoglobin <13 g/dL or hematocrit <40%.[22] We considered polycythemia when hematocrit> 55%.

Adherence to treatment was assessed during a medical consultation every six months throughout the follow-up. To consider adherence to the study protocol, data were considered after six months of using LTOT . Patients who adopted flow and number of hours according to medical prescription were considered adherent to the treatment. Adequate assessment of cause and date of death were assessed by medical records, family documents and the obituary system. This study was approved by the Research Ethics Committee of "Faculdade de Medicina de Botucatu" (60430116.2.0000.5411).

The comparative statistical analysis between continuous variables with normal distribution was expressed as mean values and standard deviation using the Student's t test. Mann-Whitney analysis was used to compare non-parametric continuous variables. For multiple group comparisons, ANOVA test followed by Tukey test was used. The proportions test was performed using the X^2 test. To assess adherence and survival time, a Kaplan Meier curve was used, followed by Log Rank Test analysis and a Cox proportional hazard multiple regression model was constructed to assess the clinical characteristics associated with follow-up time and mortality. The level of significance was 5%.

RESULTS

425 patient records were evaluated, 66 of whom were excluded with interstitial lung disease and 79 with pulmonary arterial hypertension.

From the 280 patients included, 26 missed follow-up. Table 1 shows the characteristics of the remaining 254 patients, of whom 124 (48.8%) died during the five-year follow-up. Both groups showed similar age, sex and active smoking status. Patients who died

Table 1. Patient characteristics, separated by life status at the end of the study.

	Survivors	Deaths	p
N= Number	130	124	
Gender (Female/Male)	74/56	59/65	0.17
Average follow-up time (days)	1377.4 ± 1051.8	1168.2 ± 989.8	0.10
Active smoking (%)	18 (13.8)	22 (17.7)	0.49
Age (years)	67.12 ± 9.94	68.4 ± 10.07	0.32
FEV_1 (L)	0.93 ± 0.31	0.98 ± 0.44	0.26
FEV_1 (%)	39.6 ± 13.1	42.7 ± 16.7	0.10
FVC (L)	1.89 ± 5.6	2.03 ± 0.74	0.08
FVC (%)	61.8 ± 16.6	68.7 ± 22.2	0.05
FEV_1/FVC	0.50 ± 0.09	0.48 ± 0.11	0.31
$PaCO_2$ (mmHg)	42.8 ± 6.8	42.4 ± 8.9	0.7
PaO_2 (mmHg)	56.2 ± 8.9	53.4 ± 9.9	0.02
SGRQ (%) Symptoms	49.35 ± 22.1	56.3 ± 21.9	0.031
Activity	64.22 ± 22.31	65.9 ± 23.7	0.59
Impact	37.8 ± 17.6	37.96 ± 20.2	0.95
Total	46.8 ± 18.9	51.7 ± 15.7	0.07
Anxiety	4.7 ± 4.1	6.11 ± 4.96	0.05
Depression	3.56 ± 4.02	5.6 ± 5.3	0.07
BDI	5.75 ± 2.7	4.38 ± 3.1	0.56
BMI (kg/m^2)	26.2 ± 6.4	24.08 ± 6.5	0.13
Ht (%)	45.8 ± 7.4	44.73 ± 6.9	0.32

FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; BMI: Body Mass Index; PaO_2: partial pressure of oxygen in arterial gas; $PaCO_2$: partial pressure of carbon dioxide in arterial gas; SGRQ: Saint George's Hospital Questionnaire on Respiratory Illness; Anxiety and Depression: values of the Hospital Anxiety and Depression Scale; BDI: Baseline Dyspnea Index; BMI: Body Mass Index; Ht: hematocrit. "Student t" test, level of significance: 5% ($p<0.05$).

had a worse baseline PaO_2 compared to survivors (53.4 ± 9.9 vs 56.2 ± 8.9mmHg, p=0.02). When we evaluated the SGRQ quality of life questionnaire, we observed a statistically significant difference in the score of the symptom domain, that is, those who died had greater impairment from symptoms compared to survivors (56.3 ± 21.9 vs 49.35 ± 22, 1%, p=0.03). The same statistical difference between the groups was not observed when assessed by the BDI dyspnea index (p=0.56). We also observed no difference between the groups for severity of spirometry, the mean values of hematocrit, BMI or the scores of anxiety and depression.

The average follow-up time was 2.8 years (1.14 - 4.8 years). Respiratory failure was the main cause of death (46.8%), followed by cardiovascular disease (12.1%), neoplasia (8.8%), and other causes (8%). The cause of death was not identified in 22.6%.

To assess adherence and mortality, those who did not have information about the prescription and those who were not using LTOT due to active smoking were excluded. Thus, 199 patients were separated between adherent and non-adherent in each LTOT prescription group (Table 2). The G1 group showed 27.16% non-adherent individuals, G2 26.66% and G3 25.86%, with no statistically significant difference between the adherent and non-adherent groups according to the type of LTOT prescription (p=0. 61). We did not identify any statistically significant difference when comparing the mortality rate in relation to the type of LTOT prescription (G1: 36.36%, G2: 56.14%, G3: 44.68%, p=0.07) (Table 2). When comparing the groups, we identified that the patients in the G3 group experienced greater impairment from airway obstruction, gas exchange and quality of life and more intense dyspnea (Table 2).

We did not identify statistically significant differences in age, BMI, PaO_2, $PaCO_2$, FEV_1, hematocrit, hemoglobin, quality of life, dyspnea index or patients' anxiety and depression in relation to adherence to LTOT (Table 3).

Regarding mortality after five years, among adherents, we observed 79 (54.86%) live patients and 65 (45.13%) deaths. Among non-adherents, 26 remaining alive (50.98%) and 25 (49.01%) deaths (p=0.75).

Regarding survival according to LTOT adherence, we found that there was no statistically significant difference between groups (Log Rank Test: p=0.80) (Figure 1).

We also did not identify any difference in mortality according to the type of LTOT prescription (Log Rank Test: p=0.22) (Figure 2).

When Cox multiple regression was analyzed, we identified that patients with a 24-hour LTOT indication had a higher risk of mortality over time when compared to those with a 12-hour indication (HR: 7.16; 95% CI: 1, 45-35.4). The variation in the depression score also presented a risk of mortality (HR: 1.35; 95% CI: 1.14-1.59) (Table 4).

Table 2. Relation between LTOT prescription and adherence, mortality and clinical characteristics.

Status	G1 (12h)	G2 (>15h)	G3 (24h)	p
Adherent (%)	59 (72.83)	44 (73.33)	43 (74.13)	0.61
Non-adherent (%)	22 (27.16)	16 (26.66)	15 (25.86)	
Alive (%)	49 (63.63)	25 (43.85)	26 (55.31)	0.07
Deaths (%)	28 (36.36)	32 (56.14)	21 (44.68)	
Age (y)	69.6 ± 9.2	67.4 ± 10.2	66.1 ± 11.9	0.25
PaO_2 (mmHg)	62.8 ± 5.7a	52.5 ± 7.4b	45.6 ± 6.9c	<0.001
$PaCO_2$ (mmHg)	40.0 ± 5.5a	42.4 ± 9.0a	45.8 ± 9.2b	<0.001
SpO_2	91.7 ± 3.7a	85.8 ± 6.7b	79.4 ± 8.3c	<0.01
FVC (L)	2.02 ± 0.69a	2.01 ± 0.58a	1.69 ± 0.50b	0.002
FVC (%)	65.7 ± 20.1	66.4 ± 18.7	60.6 ± 19.9	0.175
FEV_1 (L)	0.96 ± 0.39a	0.98 ± 0.37a	0.82 ± 0.27b	0.021
FEV_1 (%)	40.9 ± 15.6	41.0 ± 14.5	37.9 ± 14.0	0.382
FEV_1/FVC	0.47 ± 0.09	0.48 ± 0.10	0.49 ± 0.11	0.425
HT (%)	43.6 ± 7.1a	44.6 ± 5.9ab	46.9 ± 5.9b	0.027
HB (g/dL)	14.3 ± 1.9	14.7 ± 1.9	15.2 ± 1.9	0.049
Symptoms	46.5 ± 18.0	54.0 ± 22.9	60.4 ± 21.5	0.054
Activity	63.3 ± 20.5	67.0 ± 26.2	74.9 ± 16.2	0.122
Impact	34.6 ± 17.6a	38.8 ± 19.9ab	48.5 ± 16.8b	0.034
Total	45.7 ± 15.2a	49.4 ± 20.0ab	58.5 ± 16.1b	0.038
MMRC	1.88 ± 0.87a	2.29 ± 1.16ab	2.61 ± 1.03b	0.029
BDI	6.27 ± 2.2a	4.84 ± 2.54a	3.96 ± 2.71b	<0.001
Anxiety	4.95 ± 4.32	6.41 ± 4.94	4.85 ± 3.94	0.171
Depression	3.83 ± 4.63	5.43 ± 4.76	4.47 ± 4.72	0.152

G1: patients with a 12-hour oxygen prescription per day; G2: patients with a 15-hour oxygen prescription per day; G3: patients with a 24-hour oxygen prescription; PaO_2: partial pressure of oxygen in arterial gas; $PaCO_2$: partial pressure of carbon dioxide in arterial gas; SpO_2: pulse oximetry; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; HT: hematocrit; HB: hemoglobin; MMRC: Modified Medical Research Council dyspnea index; BDI: Baseline Dyspnea Index. X^2 test to compare proportions. Significance level: 5% (p=0.05). For the comparison of the means between the groups, the ANOVA test was used, followed by the Tukey test for the pair comparisons. Different letters (a, b, c) mean statistically significant differences between the groups, with p<0.05.

Table 3. Adherence in relation to clinical characteristics.

	Adherent N=146	Non-adherent N=53	p
Age (years)	67.6 ± 10.6	67.4 ± 9.3	0.90
BMI (kg/m²)	24.7 ± 6.3	26.7 ± 6.6	0.05
PaO_2 (mmHg)	55.2 ± 9.6	53.3 ± 9.3	0.21
$PaCO_2$ (mmHg)	42.2 ± 7.8	43.8 ± 8.5	0.22
FEV_1 (L)	0.94 ± 0.36	1.01 ± 0.44	0.26
FEV_1 (%)	40.7 ± 14.4	42.6 ± 18.3	0.34
FVC (L)	1.92 ± 0.62	2.02 ± 0.74	0.36
FVC (%)	64.7 ± 18.8	2.02 ± 0.74	0.34
FEV_1/FVC	0.49 ± 0.11	0.49 ± 0.09	0.69
Hematocrit (%)	44.9 ± 6.8	46.0 ± 8.7	0.42
Hemoglobin (g/dL)	14.8 ± 2.2	14.8 ± 2.1	0.92
Total SGRQ (%)	48.0 ± 18.7	45.9 ± 16.1	0.53
Dyspnea - MMRC (0-4)	2.20 ± 1.2	2.0 ± 1.0	0.26
HADS-anxiety (0-21)	5.35 ± 4.4	5.21 ± 4.8	0.86
HADS-depression (0-21)	4.48 ± 4.8	3.34 ± 4.0	0.41

N= number of patients; BMI: Body Mass Index; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; SGRQ: Saint George's Hospital Questionnaire on Respiratory Illness; MMRC: Modified Medical Research Council dyspnea index; HADS: Hospital Anxiety and Depression Scale. Student's "t" test, significance level: 5% (p<0.05).

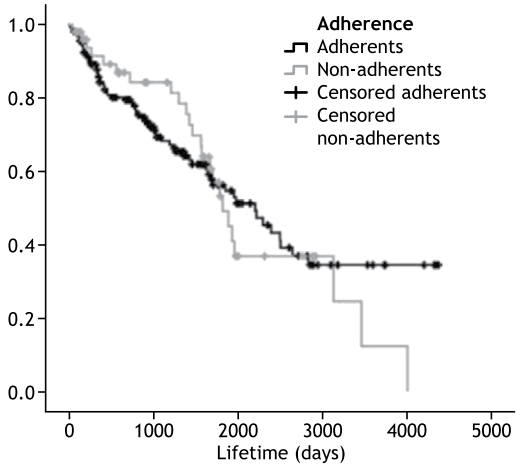

Figure 1. Kaplan Meier curve of survival time according LTOT adherence.

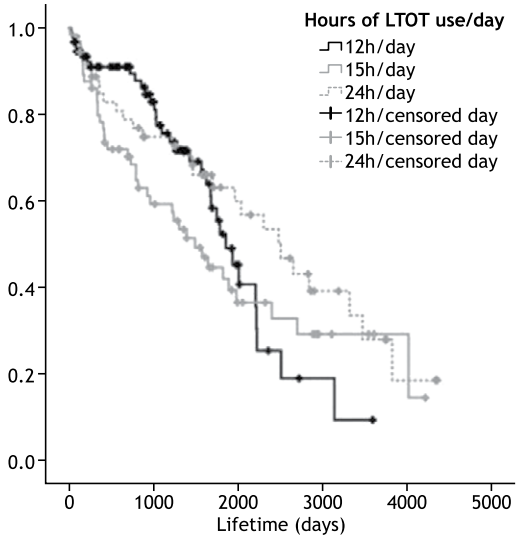

Figure 2. Kaplan Meier curve in survival time according to the type of LTOT prescription.

DISCUSSION

The findings of the present study show that adherence to LTOT was not associated with mortality, nor did we identify clinical differences between groups. Prescribing hours of LTOT use has also not been shown to be associated with LTOT adherence.

The adherence found in the present study was higher than that described in the scientific literature, which ranges from 31 to 70%.[9-11] This may be associated with our service offering multidisciplinary treatment for care of LTOT dependents, in addition to medical assistance, individualized guidance by social service professionals, nutritionist, physiotherapist and nurse and home visits. In fact, a recent study shows that the role of nurses in the management of LTOT is essential for the follow-up of these patients, showing the importance of multiprofessional care for patients who have multi-comorbidities in respiratory diseases.[23]

However, the method used to assess adherence to treatment is subjective because it does not directly assess how great the patient's adherence is. In a review article by Bourbeau and Bartlett[12] the interview was the most used means in studies to assess adherence in COPD patients, due to the ease of application. Other forms of assessment exist, such as electronic devices capable of measuring oxygen therapy, providing more reliable data, but they are expensive and subject to technical malfunction.[24]

We can speculate whether the modification of the pharmacological treatment of COPD over the past few years has not also changed survival of patients with hypoxemia, as adherence to oxygen therapy did not improve survival and also did not show better clinical characteristics in this sample. In this regard, we asked whether changes in survival in patients with hypoxemia and who are adherent to the LTOT treatment, can really benefit from the large studies of the 1980s of the last century. It is possible that adherence to drug treatments involving inhalation devices has a greater impact on survival even in those with hypoxemia.

Table 4. Analysis of regression of survival time and adherence and LTOT prescriptions by Cox regression model.

	p	HR	IC 95%
Age years)	0.19	1.03	0.98-1.09
BMI (kg/m²)	0.08	0.90	0.80-1.01
PaO2 (mmHg)	0.05	0.90	0.82-1.00
FEV_1 (L)	0.64	0.99	0.95-1.02
12h/day (reference)	--	--	--
15h/day	0.13	5.92	0.57-60.7
24h/day	0.01	7.16	1.44-35.4
Non-adherence	0.66	0.75	0.21-2.70
Total SGRQ	0.44	1.02	0.96-1.08
Hematocrit (%)	0.63	0.98	0.91-1.05
BDI	0.22	1.24	0.87-1.77
Depression	<0.001	1.34	1.14-1.59
Anxiety	0.09	0.85	0.71-1.02

BMI: Body Mass Index; PaO2: partial pressure of oxygen; FEV_1: forced expiratory volume in the first second; 12-24h/day: time in hours of oxygen therapy per day; SGRQ: Saint George's Hospital Questionnaire on Respiratory Illness; BDI: Baseline Dyspnea Index; Depression and Anxiety: scores on the Hospital Anxiety and Depression Scale; HR: Hazard Ratio; 95% CI: 95% confidence interval. Statistically significant difference of p values <0.05.

This assumption still needs to be confirmed by other clinical studies.

Although adherence is not related to the mortality rate, which was still high and in agreement with previous studies on the topic,[6,8,25] these very serious patients, who already have failure of the compensatory mechanisms responsible for adequate oxygenation, are at increased risk of mortality. In addition, the symptoms in these very severe patients show greater impact than those of lesser severity. The present study identified that the quality of life of patients who died, suffered greater impact due to symptoms, compared to those who survived, pointing to this parameter as a possible marker of worse prognosis. A Brazilian study with 118 patients showed that more intense dyspnea was related to mortality.[5] Another study with 142 patients with respiratory failure also showed that hypoxemia and dyspnea were determinants for the highest risk of mortality.[6] This finding points to the importance of a detailed assessment of the intensity of dyspnea and the impact of the disease on the patient's quality of life.

The presence of anxiety and depression can be associated with adherence or mortality,[26] but that was not observed in the present study. In addition, anxiety can influence the intensity of the sensation of dyspnea. A Turkish study evaluated 54 patients with COPD grade IV and use of LTOT, finding that 63% suffered major depression. Depression was proportionally more frequent in patients who did not adhere correctly to LTOT (90.6%) compared to adherents (22.7%). This suggests that depression can affect adherence to treatment and the prognosis of the disease.[26]

The other clinical parameters evaluated in the study were also not associated with adherence to LTOT. Similarly, a study by Hernandez et al.[11] demonstrated that there was no relationship between poor adherence and disease severity (blood gas analysis, spirometry or Charlson's comorbidity index). However, the same study identified characteristics associated with non-adherent patients: greater use of health services, less assessments of disease severity (lung function, symptoms and comorbidities), more physical activity, less dependence, less fragility and better quality of life. Another French study of 930 patients found that 31.9% of patients reduced the duration of oxygen use because they believed that the therapy was ineffective.[27]

Our study did not identify the influence of adherence to LTOT on mortality, but we found that patients who needed to use 24h/day had a higher risk of mortality when compared to those who use 12h/day. However, by comparing groups, we observed that patients who need 24h/day present more severe COPD, which is associated with a higher risk of mortality. In the scientific literature, a recent study by Ahmadi et al.[28] with 2,249 patients with severe COPD, found no difference between the use of 15 to 16 h/day compared to use for more than 15 h/day.

The present study has limitations such as a failure to assess hospitalizations and exacerbations that may have influenced adherence and, consequently, mortality. Thus, other studies that take into account the influence of these variables must be carried out. The patients' follow-up time was also short, and cannot be definitive for longer periods. We did not identify any great variation in quality of life between adherent and non-adherent groups, which demonstrates the need to increase the sample size so that we can in fact confirm the null hypothesis of the study.

In conclusion, the present study showed that adherence to LTOT and the type of prescription were not associated with mortality rates. The clinical characteristics of the patients were not associated with adherence to LTOT and a high mortality rate was identified in patients with COPD using LTOT in five years.

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ORIGINAL ARTICLE

Influence of pulmonary rehabilitation in patients with COPD exacerbator phenotype

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ABSTRACT

Objective: To verify if there are differences in Chronic Obstructive Pulmonary Disease (COPD) patient exacerbator and non-exacerbator phenotypes undergoing a Pulmonary Rehabilitation Program (PRP). **Methods:** A real life retrospective study included outpatients with COPD from public primary care who completed a 12-weeks PRP, three times a week. All were assessed before and after PRP using the six-minute walk test (6MWT), the modified Medical Research Council (mMRC) dyspnea index, quality of life and Body-mass Index, airflow Obstruction, Dyspnea and Exercise (BODE index). **Results:** A total of 151 patients were analyzed and mean age was 65.0 ± 8.1 years and mean Forced Expiratory Volume (FEV) 1% of predicted was 39.8 ± 15.9. The predominant gender was male (66.9%). Of these patients 31 (20.5%) were exacerbator phenotype There was a significant improvement in the mean distance in the 6MWT in both groups, with the largest change observed in the exacerbator group [mΔ (95% CI): 84.9 (57.1-112.6) vs. 48.6 (37-60.2) p= 0.018]. Significant reduction in dyspnea on the mMRC scale occurred in both groups, with the highest intensity in the exacerbator group [mΔ (95% CI): - 0.8 (-1.11 to 0.51) vs. -1.6 (-2.20 to -1.13) p = 0.006]. Improvement in the BODE index occurred in both groups, but the mean variation was also significantly greater in the exacerbator group [mΔ (95% CI): -1.44 (-2.17 to -0.70) p= 0.045]. **Conclusion:** Patients with COPD exacerbator phenotype had a greater magnitude of response to PRP (36 meters) when compared to non-exacerbator phenotype regardless the severity of airflow obstruction, also showing improvement in prognosis measured by the BODE index.

Keywords: Chronic obstructive pulmonary disease; Phenotype; Rehabilitation.

INTRODUCTION

The natural history of Chronic Obstructive Pulmonary Disease (COPD) is punctuated by exacerbations, especially in patients with moderate to severe airflow obstruction. These exacerbation events are characterized by a change in the intensity of respiratory symptoms, which may require switches of regularly used medication. An exacerbator is defined as a patient diagnosed with COPD who has presented two or more exacerbations in the past year or at least one exacerbation requiring hospitalization.[1] These exacerbations must be separated by at least four weeks from the end of the treatment of the last exacerbation or six weeks from the beginning of the event.[2] A recent study[3] tracking more than two thousand COPD patients showed that the best predictor of an exacerbation was the history of exacerbations in the previous year.

Pulmonary Rehabilitation (PR) is a comprehensive intervention based on thorough patient assessment, followed by specific therapies that include, but are not limited to, physical training, education and changing of attitudes, which are designed to improve patients' physical and psychological condition with Chronic Respiratory Diseases (CRDs), in addition to promoting long-term adherence to health-improving behaviors.[4] Since exacerbations have a negative and significant impact on quality of life, disease progression, mortality and health treatment costs, pulmonary rehabilitation has been recommended as a more comprehensive strategy, in addition to pharmacological treatment.[1]

Currently, pharmacological management of patients with COPD is based on phenotypes, and the exacerbator phenotype poses a bigger therapeutic challenge as it presents greater morbidity and higher mortality.[5] Among all therapeutic strategies to reduce exacerbations and hospitalizations, there is still a gap in the understanding of the role of PR.[6-8] Since the studies that address PRP do not have an approach based on phenotypes, as all COPD patients have an indication for this type of treatment, the aim of the present study was to verify whether COPD patients with exacerbator and non-exacerbator phenotypes respond differently when treated in a Pulmonary Rehabilitation Program (PRP).

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METHODS

A real-life retrospective study was undertaken with COPD patients from the public outpatient primary care network from March 2005 to December 2018, whose clinical data were collected at the time of evaluation by physicians and other professional members of the PRP. Patients were followed for a period of twelve weeks, when they finished the Program and were reassessed by all professionals. The PRP is an extension project serving patients in the pulmonology and in primary care outpatient clinics of the municipality of Novo Hamburgo, in the state of Rio Grande do Sul (RS) since 2002. The study protocol was approved by the Ethics Committee of the University where the study was developed and all participants signed a Free and Informed Consent Form (ICF).

The COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) standards, using patients' clinical history, physical examination and confirmation of airflow obstruction measured by means of the ratio of Forced Expiratory Volume in one second (FEV1) with respect to Forced Vital Capacity (FVC) under 70 after the use of a bronchodilator.[1] A patient with a COPD diagnosis was considered an exacerbator if they had two or more exacerbations in the previous year or one exacerbation requiring hospitalization.[1] In order to minimize systematic bias, no patient was included for treatment during exacerbation, and those patients who did not complete PRP were also excluded from the analysis even if they presented all the clinical information necessary for diagnosis and baseline data.

Patients were asked about their degree of dyspnea according to the certified version of the modified Medical Research Council (mMRC) dyspnea scale for COPD patients, whose score comprises five levels ranging from zero to four in accordance with the different activities that lead to shortness of breath: 0: no dyspnea, except after strenuous exercise; 1: shortness of breath when walking quickly on level ground or climbing a gentle slope; 2: walks more slowly than a person of the same age on level ground due to shortness of breath, or needs to stop to catch their breath; 3: stops to catch their breath after walking one block (90 to 120 m) or after a few minutes on level ground; 4: too dyspneic to leave the house or dyspneic when dressing up.[9]

The following variables were considered for calculation of the Body-mass Index, airflow Obstruction, Dyspnea and Exercise (BODE index): Body Mass Index (BMI); forced expiratory volume in one second, as a percentage of predicted values (FEV1% predicted); mMRC score and the distance covered in the Six-Minute Walk Test (6MWT). The score was considered according to the results obtained for the four variables (0-3 for FEV1; 0-3 for mMRC; 0-3 for DPTC6 and 0-1 for BMI),[3] with the total score ranging from 0 to 10 (higher scores indicate greater severity).[10]

To assess quality of life, the Saint George Hospital Quality of Life Questionnaire (SGRQ) was used. This questionnaire comprises three domains: symptoms, activities, and impact, plus total. The questionnaires, containing objective questions, were handed to patients, who were asked to read, interpret and mark the answers. Values above 10% reflected an altered quality of life in a given domain. Reductions equal to or greater than 4% after an intervention, in any domain or in the total sum of points, indicated a clinically significant improvement in the patients' quality of life.[11]

The 6MWT was performed according to the American Thoracic Society (ATS) criteria,[12] and the following variables were monitored during the test: Heart Rate (HR) and peripheral oxygen saturation (SpO2), using a Morrya model 1001 oximeter (Ipiranga - São Paulo State, Brazil). The Borg CR-10 Scale was used to measure the sensation of dyspnea at the beginning and end of the 6MWT. The test was carried out on a level corridor, with previously demarcated distances of 10 m. The entire corridor measured 50 m, and the distance traveled by the patient was measured at the end. The patient's height was checked using a Cardiomed wall stadiometer and weight was measured using a Welmy scale (Santa Bárbara do Oeste, São Paulo State, Brazil). With these data, the BMI was calculated using the weight divided by height squared. Application of SGRQ and 6MWT before and after PRP was performed on different days. A reference equation developed for the Brazilian population was used to calculate the predicted value of the distance covered during the 6MWT.[13]

The PRP consisted of a multidisciplinary program, lasting three months, during which patients received medical, psychological, nutritional and physical training applied by a physiotherapist and physical educator. Patients performed warm-ups, aerobic exercises, exercises to gain muscle strength and stretches. Warm-up: functional diagonals were performed for upper limbs and lower limbs. Aerobic exercises were performed on a Moviment brand treadmill (Pompeia, São Paulo State, Brazil), with progressive training time varying between 5 and 30 minutes of walking, and speed variation according to the patient's subjective perception of effort and HR. Strength training for upper and lower limbs, on the other hand, was performed on weight training equipment (high pulley, extensor, supine position and dorsal chair) of the Tech Press brand (São Paulo, Brazil) at intensities varying between 50 and 80% of the maximum load, obtained in the Maximum Load Test performed by the physical educator and, at the end of the exercises, patients stretched the main muscle groups involved in the training.

Sample size was calculated using G*Power for Windows, version 3.1.9.2 software (Franz Faul, Universitat Kiel, Germany). A minimum of 29 individuals in each group was needed to make up the study sample in order to detect a minimum difference of 30 meters in the 6MWT (effect size equal to 0.75) between groups after PRP, adopting $\alpha = 5\%$ and test power $(1-\beta)$ equal to 80%.

Data processing and analysis were performed using the Statistical Package for the Social Sciences (SPSS)

software version 21.0. Descriptive analysis consisted of means, standard deviations, medians, percentiles and proportions. The Shapiro-Wilk and Levene tests, respectively, were used to verify compliance with the assumptions of data normality and homogeneity of variances between groups. Fisher's exact test was used in order to verify the association between categorical variables. Continuous variables were compared by Student's *t* test for independent samples. Continuous variables of repeated measurements were analyzed using Generalized Estimation Equations (GEE). Statistical significance was set at $p < 0.05$.

RESULTS

Out of a total of 367 patients enrolled in the PRP, 151 patients diagnosed with COPD who completed the Program were included retrospectively in the study and had their pre- and post-rehabilitation data analyzed (Figure 1). Of the 151 patients who completed the three months of PRP, the majority (79.5%) were considered as belonging to a non-exacerbator phenotype. The mean age of the patients was 65 ± 8.1 years and, of these, the majority were men (66.9%). The average BMI was 25.4 ± 4.8 kg / m-$_2$. As shown in Table 1, the groups showed similar results with regard to lung function. However, in FEV1% of predicted, the group of patients considered as exacerbating had a significantly lower average (41.1 ± 16.3 vs. 34.3 ± 13.1; $p < 0.05$). The 6MWT variables, level of dyspnea and BODE index, as well as smoking burden, were not different between groups. Exacerbation average was 0.8 ± 1.4, with the non-exacerbator group having an average of 0.2 ± 0.4 and the exacerbator group an average of 3.2 ± 1.8. The drug treatment used is described in both groups.

The results regarding distance walked, dyspnea index, prognosis and quality of life had a statistically significant

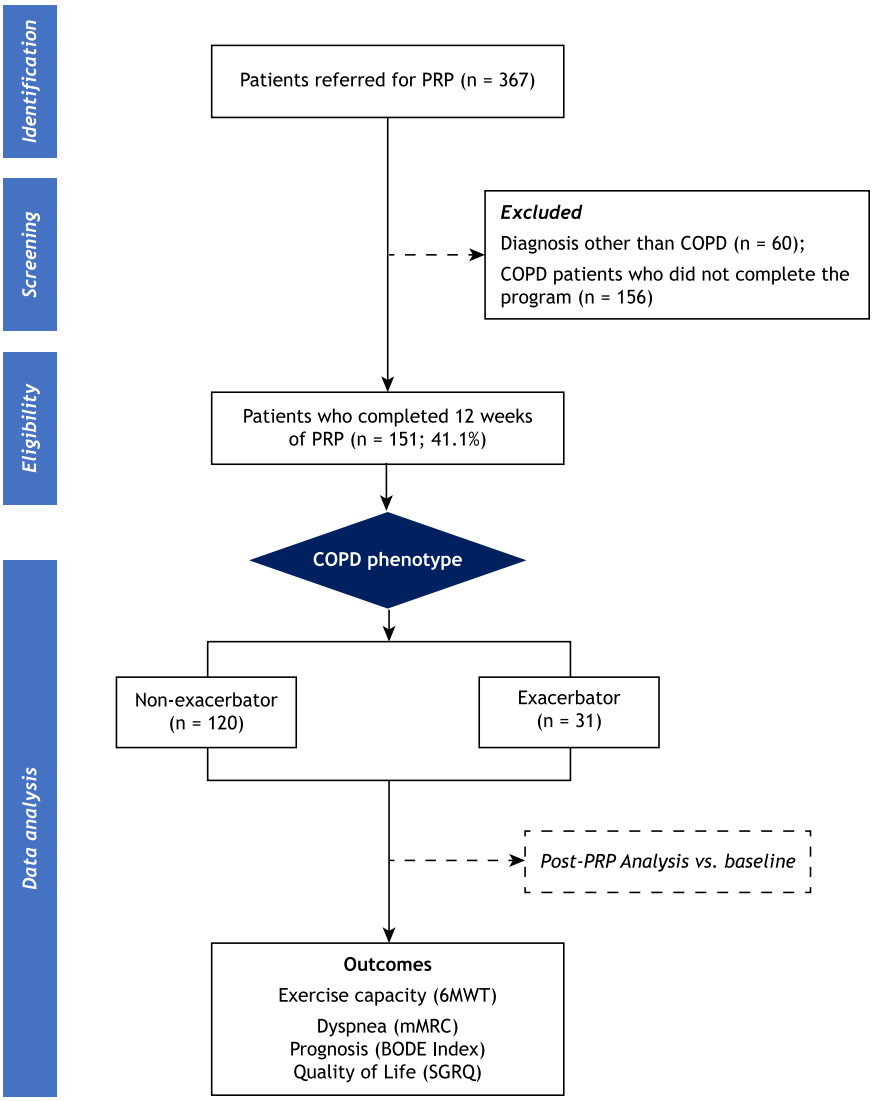

Figure 1. Flowchart of inclusion of patients in the study. 6MWT: Six-Minute Walk Test; mMRC: *modified Medical Research Council* (Dyspnea Scale); SGRQ: *Saint George's Respiratory Questionnaire*. COPD (Chronic Obstructive Pulmonary Disease), PRP (Pulmonary Rehabilitation Program).

Table 1. Baseline characteristics of 151 patients diagnosed with COPD undergoing a pulmonary rehabilitation program.

Variable	All (n = 151)	Non exacerbator (n = 120)	Exacerbator (n = 31)
Age, years	65.0 ± 8.1	65.1 ± 8.4	64.9 ± 6.8
BMI, kg/m^{-2}	25.4 ± 4.8	25.3 ± 4.6	25.7 ± 5.5
Gender			
Male	101 (66.9)	79 (65.8)	22 (71)
Female	50 (33.1)	41 (34.2)	9 (29)
Lung Function			
FVC, L	2.29 ± 0.88	2.29 ± 0.91	2.26 ± 0.81
FVC, % of predicted	64.7 ± 19.5	64.9 ± 20.1	63.6 ± 17.4
FEV_1, L	1.12 ± 0.55	1.15 ± 0.57	1.0 ± 0.47
FEV_1, % of predicted	39.8 ± 15.9	41.1 ± 16.3	34.3 ± 13.1*
FEV_1/ FVC	49.1 ± 13.8	50.0 ± 13.4	45.3 ± 14.9
Six-Minute Walk Test (6MWT)			
6MWD baseline (m)	392.4 ± 96.7	396.4 ± 94.9	376.1 ± 103.9
Distance predicted (m)[a]	543.5 ± 33	543.1 ± 33.4	545.4 ± 31
mMRC (0-4)	2.13 ± 1.32	2.11 ± 1.31	2.19 ± 1.36
BODE Index (0-10)	3.5 ± 1.8	3.3 ± 1.8	4.3 ± 1.5
Packs/year, mean (25-75)	35 (16-75)	35 (18-74)	42.5 (1-83)
Number of exacerbations in last year	0.8 ± 1.4	0.2 ± 0.4	3.2 ± 1.8**
Spirometric classification, GOLD			
Mild	1 (0.7)	1(0.8)	0 (0)
Moderate	39 (25.8)	33 (27.5)	6 (15.4)
Severe	61 (40.4)	50 (41.7)	11 (35.5)
Very severe	50 (33.1)	36 (30)	14 (45.2)
Medication treatment			
LABA	20 (13.2)	14 (11.7)	6 (19.4)
LAMA	31 (20.5)	25 (20.8)	6 (19.4)
LABA + ICS	46 (30.5)	38 (31.7)	8 (25.8)
LABA + ICS + LAMA	23 (15.2)	18 (15)	5 (16.1)

Values are expressed as means, standard deviations (except for smoking load, expressed as average and 25 and 75 percentiles) and proportions; BMI: Body Mass Index; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second; L: Liters 6MWT: Six-Minute Walk Test; 6MWD: Distance covered in the six-minute walk test; mMRC: *modified Medical Research Council*; LABA: *Long-Acting Beta$_2$ Agonists*; LAMA: *Long-Acting Muscarinic Antagonists*; ICS: *Inhaled Corticosteroids*. GOLD: Global Initiative for Chronic Obstructive Lung Disease. [a]Predicted distance m= 622. 461 − (1.846 × Age in years) + (61.503 × Gender $_{men = 1;\ women = 0}$); GEE: Generalized Estimating Equations; Bonferroni correction; Fisher's exact test for categorical variables and Independent Student's *t* test for continuous variables; *p<0.05; **p<0.001 between exacerbators and non-exacerbators.

improvement in both groups when comparing numbers before and after, as shown in Table 2. Regarding the exercise capacity assessed through the 6MWT before and after the PRP, the non-exacerbator and exacerbator groups significantly increased the distance covered, which also occurred with dyspnea assessed by means of the mMRC. Both groups improved their prognosis of the disease as assessed by means of the BODE index. The results of the Quality of Life assessment also showed significant benefits after PRP in both the non-exacerbator and exacerbator groups (p <0.0001).

Table 3 shows the variation in exercise capacity, dyspnea, quality of life and prognosis measured by the BODE index between the two groups. Figure 2 shows the comparison of the distance covered in the 6MWT before and after PRP, according to the disease exacerbation phenotype and adjusted for baseline lung function (FEV1%).

The average variation in the reduction of the BODE index and dyspnea was significantly greater in the exacerbating group when compared to the non-exacerbating group. Variation in the various sectors of the quality of life questionnaire did not differ significantly between groups, despite being measured intra-group.

DISCUSSION

Our study showed that PRP improved exercise capacity, dyspnea, quality of life and prognosis for this group of patients diagnosed with COPD. More importantly, it demonstrated that the improvement in exercise capacity, assessed through the absolute distance covered and that predicted in the 6MWT, was significantly greater in exacerbators than in non-exacerbators, even after adjustment for FEV1%, as shown in Figure 2. It is also worth noting that both groups reached distances much longer than those considered clinically

Table 2. Exercise capacity (submaximal), dyspnea, prognostic index and quality of life in 151 patients diagnosed with COPD undergoing a pulmonary rehabilitation program.

Variable	Non-exacerbator		Exacerbator	
	Baseline	Post-PRP	Baseline	Post-PRP
6MWD (m)	396.4±94.9	445.0±99.0*	376.1±103.9	461±94.2*
% of predicted[a]	73.0±17.0	82.0±17.0*	69.0±18.0	84.0±16.0*
mMRC (0-4)	1.9±1.3	1.1±1.1*	2.9±1.1	1.3±1.4*
BODE Index (0-10)	3.3±1.8	2.7±1.9**	4.3±1.5	2.9±1.5**
SGRQ Symptoms	46.8±20.3	32.6±18*	52.9±20.9	34.9±21.1*
SGRQ Activities	65.8±23.1	52.1±23.1*	76.9±21.7	57.5±21.8*
SGRQ Impact	32.9±18.9	20±15.4*	40.7±18.7	24.5±18.5*
SGRQ Total	46.3±16.9	32.7±16.3*	54.0±16.0	36.3±18.1*

6MWD: Distance covered in the six-minute walk test; mMRC: *modified Medical Research Council* (Dyspnea Scale); SGRQ: *Saint George's Respiratory Questionnaire*. [a]Predicted distance m= 622. 461 – (1.846 × Age in years) + (61.503 × Gender $_{males = 1}$; $_{females = 0}$); Generalized Estimating Equations (GEE); Bonferroni adjustment; *p<0.0001 of baseline; **p<0.01 of baseline.

Table 3. Variation in exercise capacity, dyspnea, prognostic index and quality of life in 151 COPD patients undergoing a pulmonary rehabilitation program.

Variable	Alteration of baseline (Δ)			
	Non-exacerbator	Exacerbator	Wald	p
6MWD (m)	48.6 (37.0 to 60.2)	84.9 (57.1 to 112.6)	5.57	*0.018**
% of predicted[a]	8.9 (6.7 to 11.0)	15.4 (10.1 to 20.7)	5.51	*0.019**
% of change	14.8 (10.7 to 18.9)	29.5 (13.3 to 45.6)	2.98	*0.084*
mMRC (0-4)	- 0.8 (-1.11 to - 0.51)	-1.6 (-2.20 to -1.13)	7.49	*0.006**
BODE Index (0-10)	- 0.61(-0.94 to - 0.28)	-1.44 (-2.17 to -0.70)	4.03	*0.045**
SGRQ Symptoms	-14.2 (-18.2 to -10.2)	-18.0 (-27.0 to -9.0)	0.57	*0.450*
SGRQ Activities	-13.7 (-18.2 to -9.2)	-19.3 (-28.5 to -10.2)	1.17	*0.279*
SGRQ Impact	-13.0 (-16.0 to -9.9)	-16.1 (-23.1 to -9.1)	0.65	*0.419*
SGRQ Total	-13.6 (-10.8 to -16.5)	-17.7 (-10.9 to -24.5)to	1.14	*0.285*

Values expressed as means and 95% Wald Confidence Intervals. Six-Minute Walk Test; 6MWD: Distance covered in the six-minute walk test; mMRC: *modified Medical Research Council* (Dyspnea Scale); SGRQ: *Saint George's Respiratory Questionnaire*. [a]Predicted distance m= 622. 461 – (1.846 × Age in years) + (61.503 × Gender $_{males = 1}$; $_{females = 0}$); Generalized Estimating Equations (GEE); Bonferroni adjustment: *p<0.05 between groups.

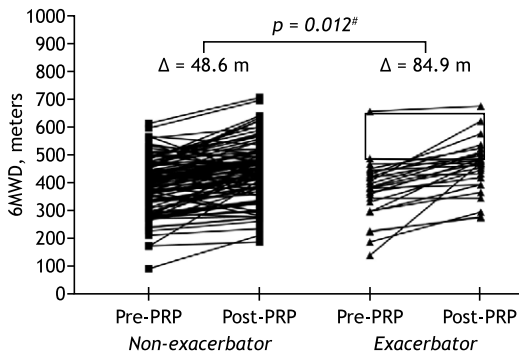

Figure 2. Comparison of submaximal exercise capacity (6MWD), before and after pulmonary rehabilitation program (PRP), according to the phenotype for disease exacerbation, adjusted for baseline lung function (FEV1,%).

significant, which are of 25 to 35 meters,[4] with the group of non-exacerbator patients walking on average 48.6 meters after rehabilitation and the exacerbator ones, an average of 84.9 meters, i.e. 36.3 meters more than non-exacerbators.

In patients with COPD, the severity of the disease and the prognosis are not determined solely by changes in lung function. In individuals with mild or moderate disease, exercise capacity and daily life activities are often altered, which impacts negatively on quality of life. Thus, in addition to the drug treatment used to improve dyspnea, lung function and reduce the number of exacerbations,[14] PRP has been advocated as a non-pharmacological strategy to be used,[15] and in this group of exacerbator patients it has shown to be much more beneficial when compared with the benefit for patients with a non-exacerbator phenotype.

When analyzing the behavior of the dyspnea index measured by the mMRC, a significant improvement was observed in both groups, along with a greater magnitude in the group of patients of the exacerbator phenotype (-0.8 vs. -1.6; p <0.006). Dyspnea is certainly the main symptom and the most limiting factor in this disease, especially for patients' day-to-day activities or during physical exercise. This symptom usually improves significantly with aerobic physical training, but the mechanism is still not well understood. Lower pulmonary ventilation in identical work rates and also in oxygen consumption, signaling a lower hyperinflation, would not fully explain the improvement obtained.[15]

Quality of life as assessed by the Saint George questionnaire improved in both groups in levels well

above the 4 percentage points recognized as the clinically significant minimum difference. Most studies highlight the improvement in quality of life as the major benefit of pulmonary rehabilitation,[4,15,16] which was also observed in our study in both groups. However, when comparing the quality of life between patients with COPD of the exacerbator and non-exacerbator phenotypes, no statistically significant difference was observed.

Studies connecting pulmonary rehabilitation with exacerbations have focused on the ability of this intervention to reduce the number of occurrences, emergency-room visits and hospitalizations. While a study with two hundred patients showed that pulmonary rehabilitation reduced hospitalizations related to breathing difficulties over one year, with a 50% drop in hospitalization time,[17] another study with sixty patients showed more exacerbations in the control group, but saw no difference in number of hospitalizations per patient.[18]

A meta-analysis showed that, although randomized controlled trials suggested that PRPs reduced subsequent admissions, the results of cohort studies did not corroborate this benefit. The authors argued that the heterogeneous nature of the patients included in the various observational studies and the diversity of protocols used by the different PRPs could justify these findings.[19] In view of this response from different studies regarding use of PRP to reduce exacerbations, which is still controversial, advantages obtained in other parameters, such as exercise capacity and improvement in quality of life, support its prescription.

To date, few studies have been concerned with analyzing the response to pulmonary rehabilitation in the different COPD phenotypes. Studying 73 patients with COPD from mild to very severe, Jenkins et al.[20] showed that fewer exacerbator patients completed the PRP when compared to non-exacerbators (45% vs. 69%), and that the effects between groups were similar. A prospective and multicenter study[21] that aimed at studying the response to PRP in different COPD phenotypes included 364 patients in six centers, divided between patients with obstruction of airways and patients with destruction of the parenchyma. It found that both benefited from the treatment, with no difference between the groups. Our study differs from the previous ones in that it included only patients who had completed the PRP, and also in that they were classified as exacerbator and non-exacerbator and not as airway disease and lung parenchyma destruction patients. It is known that exacerbations are independent predictors of mortality in patients with COPD, increasing the chance of death by almost five times,[22] and this phenotypic dichotomization could provide more relevant information, as demonstrated in our study.

Besides its value as a predictor of hospitalization and mortality in COPD patients participating in a PRP,[23] in our study the BODE index was significantly lowered after treatment in the group of exacerbator patients when compared to non-exacerbator patients. In spite of the absence of follow-up data on the number of exacerbations and even hospitalizations after completion of rehabilitation, this index clearly shows a better prognosis when compared to the situation before rehabilitation.

Our study, however, has some limitations. The first is its retrospective design, although the data analyzed were collected in a prospective and standardized manner, as they are used in the final report to be sent to the attending physician. Another limitation was the fact that the transitional dyspnea index was not used, although it could better assess dyspnea after interventions than mMRC. However, this is a real-life study that corroborates the benefit of PRP for all COPD patients, and particularly for those with an exacerbator phenotype.

In conclusion, patients with a diagnosis of COPD and an exacerbator phenotype benefited the most from PRP, walking an average of 36 meters more in the 6MWT when compared to the non-exacerbator one. This benefit is also corroborated by the greater reduction of dyspnea and the improvement in prognosis as measured by the BODE index. Prospective cohort studies will be needed to further confirm these findings.

AUTHOR CONTRIBUTIONS

Ivo Bohn Júnior. Participated in the preparation of the study, data collection, data analysis and wrote the article. Cassia Cinara da Costa participated in the study design, data collection and revised the article. Rafael Machado de Souza participated in the study design, data collection and revised the article. Álvaro Huber dos Santos participated in the data analysis and revised the article. Paulo José Zimermann Teixeira participated in the preparation of the study, data collection, data analysis and revised the article.

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ORIGINAL ARTICLE

Portuguese translation and validation of the Patient Generated Index instrument for patients with Chronic Obstructive Pulmonary Disease: individualized quality of life assessment

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ABSTRACT

Objective: To translate, adapt and validate the Patient Generated Index (PGI) for Brazilians with chronic obstructive pulmonary disease (COPD). **Methods:** 50 volunteers with COPD, mostly men (74%), with 73.1 ± 8.9 years of age, FEV1 of 52.3 ± 14.5% of predicted and FEV1 / FVC of 56.2 ± 8.6% of predicted responded to PGI, to the Saint George Respiratory Questionnaire (SGRQ) and to perform Glittre Activities of Daily Living test (Glittre ADL). After 1-2 weeks, PGI was again applied for the analysis of relative and absolute reliability. **Results:** The translation occurred without changes in the questionnaire. The score obtained in PGI had weak correlation with the SGRQ total score ($r = -0.44$, $p < 0.001$) and with the impact domain ($r = -0.40$, $p < 0.05$), presented a moderate correlation with the symptoms domain of the SGRQ ($r = -0.55$, $p < 0.001$) and weak correlation with the activity domain ($r = -0.31$, $p < 0.05$). A weak correlation was observed between PGI and Glittre ADL ($r = -0.30$; $p < 0.05$). It was observed high reliability among the measures of PGI (ICCr = 0.94). **Conclusion:** This study shows that the Brazilian version of PGI is a reliable and valid instrument to measure health-related quality of life (HRQL) in patients with COPD. It is a new and individualized form of evaluation of COPD patient-centered quality of life.

Keywords: Quality of life; Chronic obstructive pulmonary disease; Reproducibility of results and translations.

INTRODUCTION

The study of health-related quality of life (HRQoL) in individuals with chronic obstructive pulmonary disease (COPD) has traditionally been carried out using structured questionnaires such as the *Saint George's Respiratory Questionnaire* (SGRQ),[1] the *Chronic Respiratory Questionnaire* (CRQ),[2] and the *Airways Questionnaire 20* (AQ20).[3] Such questionnaires are structured in domains and each one, has questions that specifically address an area that is known to be affected by COPD. Although extremely useful in clinical practice, structured questionnaires do not allow stipulating the relevance or importance of a particular factor or domain in an individualized way. Thus, tools that enable patient-centered assessment can provide additional information on the importance of a particular aspect of HRQoL, as well as infer which components of the International Classification of Functionality and Disability (ICF) could be most affected.

Given the patient-centered approach, Ruta et al.[4] developed the questionnaire ***Patient Generated Index* (PGI)**, which uses an innovative approach to measure HRQoL and can be adapted to different diseases and/or treatment conditions.[4] Patients are directed to define the most important areas of their lives that are affected by the disease, reporting the degree of importance for each area and classifying them in terms of relevance.[5]

This instrument is valid, reliable and responsive in several health conditions[4-7] however, to date, there are no versions translated into Portuguese and its application in COPD patients is not known. Therefore, the main objective of the present study was to carry out the cross-cultural adaptation of the PGI to the Portuguese language spoken

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in Brazil and to evaluate the validity in a population of individuals with COPD. As a secondary objective, to analyze the content of the PGI responses regarding the components of the ICF.

METHODS

It is a study of cross-cultural adaptation and analysis of measurement properties, which was carried out in two phases: translation into Portuguese and cross-cultural adaptation of the PGI instrument; and analysis of psychometric properties for patients with COPD. The convergent analysis was performed using the Glittre ADL test and the competitor with the Saint George's Respiratory Questionnaire (SGRQ). The study was approved by the Research Ethics Committee of the Federal University of Vales do Jequitinhonha e Mucuri (UFVJM) (CAAE n. 73581917.4.0000.5108), and all participants signed the Free and Informed Consent Form (TCLE). The study was conducted from May 2017 to March 2019.

The methodology for translation and cross-cultural adaptation was based on

Guillemin et al.[8] The use of the instrument was authorized by the author who recommended the version of the PGI used for the disease-specific adaptation of the version developed by Camfield and Ruta.[9]

The translation of the questionnaire was carried out by two independent bilingual translators, fluent in English and native speakers in Portuguese. After the reconciliation in which a third translator proposed a final translation, the version was then back-translated into English, by 2 independent translators, bilingual native speakers of English and fluent in Portuguese. Both back-translations were sent to the author of the original instrument for consideration. Since no divergences were found between the original and translated versions, the pre-test stage started in individuals with COPD.

In the Portuguese version, the name and abbreviation of the instrument in English were maintained to facilitate its recognition (Figure 1).

Participants were recruited at a University Physiotherapy School Clinic, doctors' offices and hospitals in the city. The study inclusion criterion was the clinical diagnosis of COPD confirmed by spirometry.[10] The exclusion criteria were: illiterate individuals or those unable to understand the questionnaire or follow the instructions, cognitive impairment, clinical instability in the month before the evaluation, presence of severe or limiting disease and individuals unable to perform any of the evaluations. To characterize the sample, participants underwent spirometry (Pony Graphic, Cosmed, Rome, Italy), following the Guidelines for Lung Function

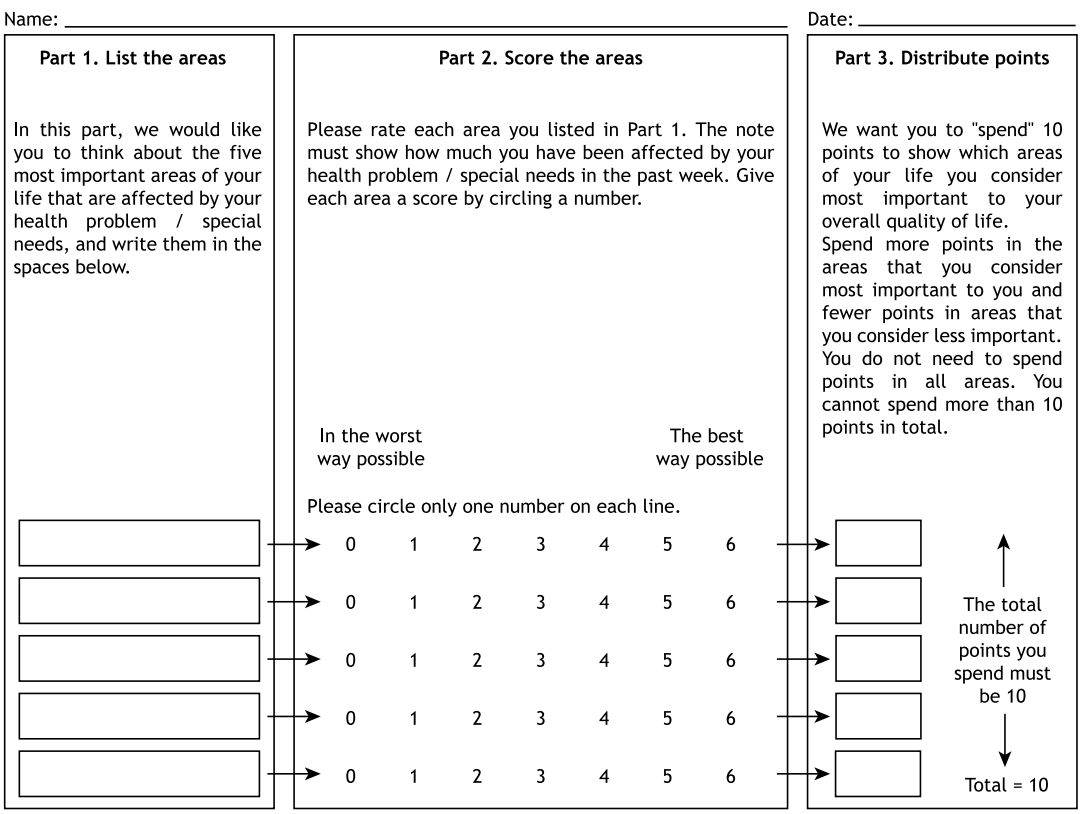

Figure 1. Final version of the PGI in Portuguese.

Tests.[11] Anthropometric measurements were recorded. The strategy for PGI validation included convergent validity with the SGRQ questionnaire and divergent validity with the Glittre ADL functional test and analysis of test-retest reliability and absolute reliability, by calculating the Standard Error of the Measure (EPM) and the Minimum Detectable Difference (MDD). The pre-test sample consisted of 5 individuals who completed the PGI (translated and back-translated version), with no misinterpretation of the text; this version was used in the study.

Fifty individuals[12] diagnosed with COPD composed the sample for validation of the instrument. 7-14 days after the first assessment and application of the PGI, the patients responded to the PGI again. PGI and SGRQ were applied in the form of an interview, and the same researcher conducted all the interviews.

Patient-Generated Index (PGI) is completed in three stages: (1) individuals identify, at most, the five most important areas of their life affected by COPD, (2) then assess how much each area has been affected by the disease using a scale of 0 to 6, where 0 is the worst imaginable and 6 exactly as they would like it to be; (3) in the final stage, individuals distributed 10 points seeking to reflect their relative importance, that is, giving more points for the most important areas in their life and fewer points for the less important areas identified in step 1. All 10 points must be distributed.[9] The calculation of the total PGI score is given according to Figure 2.

SGRQ is a questionnaire structured in 76 items, where each item has a certain score and the assessment of the quality of life is divided into the domains: symptoms, activity and psychosocial impact of respiratory disease. The final result is the sum of the scores of the items in each domain, generating a score, which ranges from 0 (without reducing the quality of life) to 100 (maximum quality of life reduction); considering the percentage reached by the patient regarding the maximum score and the total score obtained for that domain, in addition to the percentage of this maximum.[13]

Glittre ADL was carried out in a 10-meter corridor, bounded on one side by a chair and on the other by a bookcase. The volunteer started the test sitting on the chair, carrying a backpack containing a weight of 2.5 kg for women or 5 kg for men. The marking of the time spent for the execution, using a stopwatch, was started immediately after the individual was notified of the start of the test. The volunteer was instructed to walk the corridor through a three-step staircase located in the middle of the corridor and towards the bookcase. On the shelf there were three weights of 1 kg each, located on a shelf adjusted to the height of one's shoulder girdle. The individual was instructed to transfer the weights to a lower shelf, adjusted to the height of his pelvic girdle and then to the floor. Then, he/she should return the weights to the same shelves and the highest shelf and return the route until he/she sits back on the chair. The test execution time was recorded using a stopwatch. The volunteer had to do this route five times, in the shortest time possible, without running.[14]

The analysis of PGI responses was based on the linking process according to the methodology proposed by Cieza et al.[15] These are ten rules for linking the domains or issues addressed in an instrument and the ICF. To analyze the content of the responses rules 5 (Identify and document the categorization of response

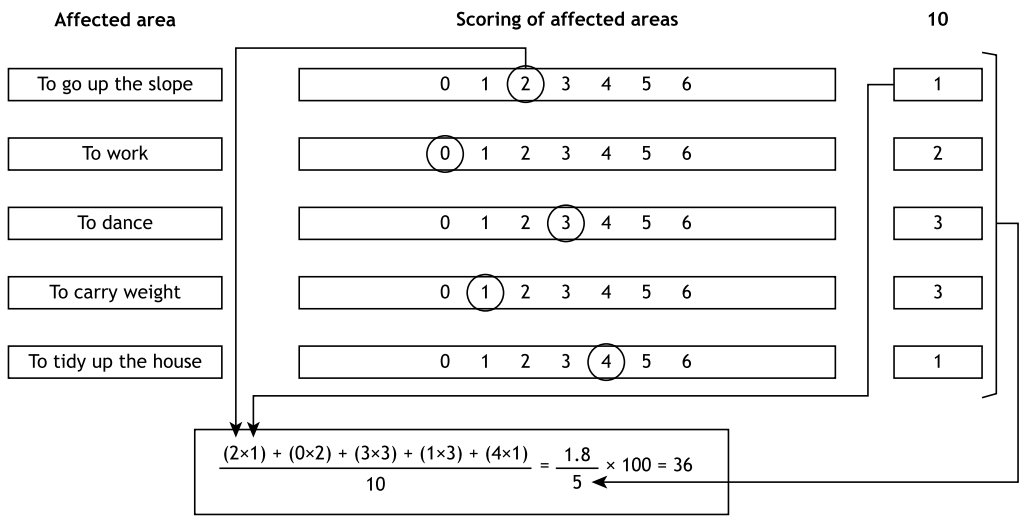

Figure 2. Score of the PGI questionnaire. The PGI score is calculated by multiplying the classification score in phase 2 by the proportion of the 10 points allocated in phase 3 for each area, adding the results and dividing them by 10. To generate a scale score of 100, divide the result obtained by the number of areas identified in phase 1 and multiplies by 100, with Zero being the worst possible HRQoL and 100 being the best HRQoL.

options) and 6 (Link the main, relevant and/or additional concepts to the most accurate category of the ICF) were applied since the PGI is a patient-centered instrument. Two independent researchers proceeded to link the responses to the ICF concepts; a third researcher with experience in using the ICF[15] resolved potential divergences.

For statistical analysis, the program IBM SPSS Statistics, version 20.0 (IBM Corporation, Armonk, NY, USA) was used. The normality of the data was assessed by the Shapiro-Wilk test. The validity analysis was performed using Spearman's correlation coefficients. Coefficients between 0 and 0.25 showed a negligible correlation; 0.25 and 0.50 weak correlation; 0.50 and 0.75 moderate correlation; and> 0.75 strong correlation.[16] Test-retest reliability was analyzed using the intraclass correlation coefficient (ICCr), alpha model, two-way random effects (model alpha, 2-way random-effects model) and agreement using the Bland-Altman diagram. High reliability was considered when ICCr ≥ 0.90. Absolute reliability was assessed by EPM and MDD, according to the equations described below.[17] EPM was estimated by the equation: EPM = DP * √ (1-r), in which DP represents the standard deviation of the sample and r the ICCr. MDD was estimated using the formula: MDC_{indiv} = EPM * 1,65 *√2, where 1.65 represents the z-score of the 90% confidence interval and √2 represents the number of errors associated with the repeated measure. The comparison between the two tests was performed using the paired Wilcoxon test. Statistical significance was considered when p <0.05 in all analyzes.

RESULTS

The Portuguese translation of the PGI instrument was carried out, obtaining a version without major adaptations. Of 52 individuals evaluated, two individuals were excluded: one for having a hypertensive peak before starting Glittre ADL and the other for not being able to perform it (balance deficit). Fifty COPD patients made up the final sample. The sample characteristics are shown in Table 1. The mean PGI score was 43.5 ± 15.0 points. The 50 patients listed 229 areas, on the first day of PGI administration, which were grouped into 28 categories; the five most cited categories were walking fast, climbing a slope/ladder, working, lifting weights and dancing. Additional material can be found in the Supplementary Material (Chart S1 and Table S1).

The score obtained in the PGI had a weak correlation with the total score of the SGRQ (r = −0.44; p <0.001) and with the impact domain (r = −0.40; p <0.05); moderate correlation with the symptoms domain (r = −0.55; p <0.001); and weak correlation with the activities domain (r = −0.31; p <0.05). Weak correlation was found with Glittre ADL (r = -0.30; p <0.05).

When classifying the categories cited according to the ICF, we found that most of the patients' responses comprised the activities and participation domains, with the activities domain being the predominant one (126 responses) (Table S1). The results presented in Figure 3 point to 229 responses distributed in 28 categories after the content analysis (Chart S1), which were distributed in 20 items for the activities and participation component (d), one item for environmental factors and two items for personal factors. No response included domains of the body functions and structures component.[18]

Seven domains of the activity and participation component were mentioned in the participants' responses: mobility, self-care, home life, interpersonal interactions and relationships, main areas of life and community, social and civic life. The mobility domain stood out with eight items affected among individuals with COPD.

There was no statistically significant difference between the 1st and 2nd measurements of the PGI (95% CI −1.6-2.1); p = 0.788. Excellent test-retest reliability was observed ICCr = 0.94 (IC 95%: 0.91-0.97). EPM and MDD for PGI were 4.7 and 10.8, respectively. The Bland-Altman diagram showed agreement between measures 1 and 2 of the PGI, with Bias = 0.3 (Figure 4).

Table 1. Sample characteristics (n= 50).*

Age (years)	73.14 ± 8.96
BMI (Kg/m²)	24.13 ± 3.60
FVC (L)	2.85 ± 0.60
FVC% of predicted	72.50 ± 14.94
FEV_1 (L)	1.75 ± 0.63
FEV_1% of predicted	52.99 ± 14.50
FEV_1/FVC %	56.18 ± 8.63
GOLD, stages II-III-IV, n (%)	
II	38 (76)
III	6 (12)
IV	6 (12)
Schooling in years, n (%)	
0 to 4 years	12 (24)
5 to 9 years	22 (44)
More than 9 years	16 (32)
PGI (Day 1)	43,50 ± 14,95
PGI (Day 2)	42,25 ± 14,47
Total SRGQ	45.56 ± 14.53
Activity	55.83 ± 17.72
Impact	38.19 ± 15.61
Symptoms	49.33 ± 19.18
Glittre ADL (min)	06.25 ± 1.89

BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; FEV_1/FVC: the relationship between forced expiratory volume in the first second and forced vital capacity; PGI: *Patient-Generated Index*; SGRQ: *Saint George Respiratory Questionnaire*; Glittre ADL: *Glittre Activities of Daily Living*. *Data presented as mean ± standard deviation, except where indicated.

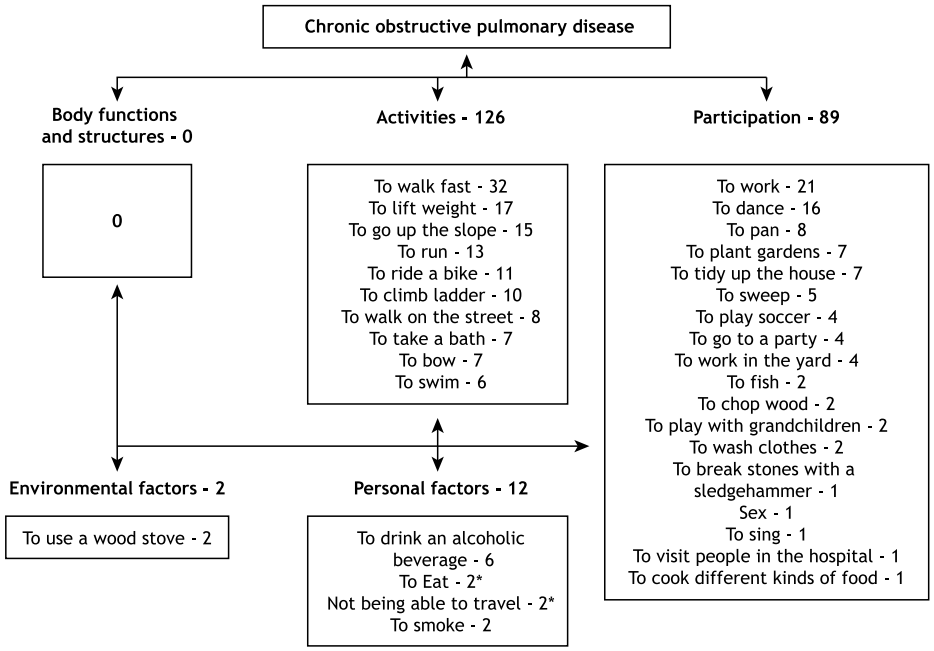

Figure 3. Categories cited by patients in response to PGI classified according to the ICF. *Items that are not classified in the ICF.

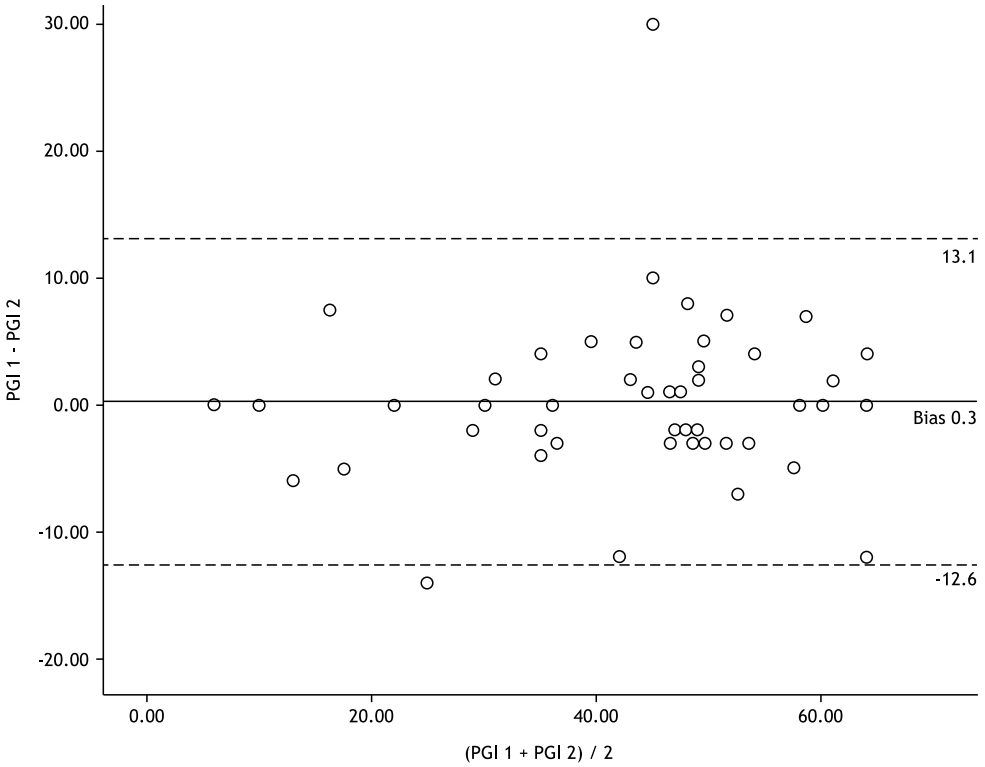

Figure 4. Bland-Altman graph plot of test-retest reliability. (PGI 1: PGI Day 01; PGI 2:PGI Day 2).

DISCUSSION

This study presents the translation into Portuguese and validation of the PGI questionnaire for patients with COPD. Despite cultural differences between Brazil and England, the Brazilian version of the PGI questionnaire did not require major adaptations. This is probably because PGI is a simple and conceptually universal instrument.

To our knowledge, this is the first study that prepared a Brazilian version of the PGI questionnaire, which has already been adapted and validated in countries such as the United States[19-21] and Canada[5,22,23] and the cross-cultural adaptation was made to Norway.[24] Besides, a modified version of the PGI has been validated in Ethiopia, Thailand and Bangladesh, covering Bengali, Thai, Amharic and Oromo.[9]

As it is a questionnaire that is framed within a specific disease, the PGI has validation for several diseases such as low back pain,[4] multiple sclerosis,[20] cancer,[25] arthritis,[26] atopic dermatitis,[7] HIV[27] among others. However, this is the first study reporting the validation of PGI for a population with COPD.

Convergent and concurrent validation for COPD was performed through the correlation analysis of PGI with Glittre ADL and SGRQ, validated tools for assessing HRQoL and functional performance in patients with COPD.[11] Although the PGI obtained a weak correlation with the impact and activity domain of the SGRQ, and with the total score, the symptoms domain showed a moderate correlation with the PGI. When we standardized PGI responses according to the ICF, we obtained a higher prevalence of responses in the activities domain. This result can be explained by the differences in the questionnaire characteristics. While in the structured questionnaire (SGRQ), the weight of a given item is predetermined, in patient-centered questionnaires (PGI) the individual is the one who assigns the weight to a specific item on his HRQoL.

The moderate relationship observed with the symptoms domain of the SGRQ with the PGI suggests an influence of changes in the structure and function of the body on the components of ICF activity and participation. Besides, the PGI data allow us to infer that the influence of symptoms on HRQoL is due to its outcomes in the individual's activity and participation and not due to the symptoms themselves. Thus, the PGI appears as a complementary tool to the structured questionnaires useful for assessing HRQoL, especially regarding aspects related to the ICF activity and participation domains. These items are often not easily detected in structured questionnaires, which makes PGI a strong ally in the more detailed and globalized complementary assessment of individuals with COPD. As an example, we name the most cited areas in the PGI that do not constitute daily life activities (DLA) such as, dancing, cycling, swimming, playing football, drinking alcoholic beverages and going to parties. These activities had a direct impact on the quality of life assessed by the PGI of these patients, sometimes being more cited than the symptoms.

Previous studies have also demonstrated low to moderate correlations of PGI with generic[5,9,23,28] or specific[5,29] quality of life instruments. This demonstrates the peculiarity of the PGI, where, differently from what occurs with structured questionnaires, the individual is invited to describe and score the items that, in his point of view, have greater meaning and relevance in his quality of life; while, in structured instruments, the items to be scored are previously described.

Although we have not identified any other study that correlates PGI with a functional test, we chose to use Glittre ADL. The choice was made because it is a test that mimics activities of daily living. Skumlien et al.,[14] observed a moderate correlation between SGRQ and Glittre ADL only in the activity domain. In our study, we identified a weak correlation between PGI and Glittre ADL. Considering that PGI is a generic questionnaire, this weak correlation suggests that there may be a compromise in the performance of ADL by the individual, which could affect the HRQoL of patients with COPD, but other factors may also be determinants.

PGI is based on the assumption that health problems affect individuals and their quality of life differently and, therefore, are better defined by the patient individually. This study sought to identify in which aspects COPD affects HRQoL, and to what extent PGI can provide information not addressed by a specific HRQoL instrument.

Patients determined 229 areas of their lives that, in some way, were affected by COPD. These 229 areas were grouped into 28 categories. By comparing the PGI response categories with the SGRQ items, we were able to identify that many of the areas identified by COPD patients (16 of the 28 categories) were covered by the SGRQ. The nine categories most cited in the PGI assessment (walking fast, climbing uphill / stairs, working, lifting weights, dancing, doing heavy work, running, tidying up and cycling) were included directly among the items of the SGRQ.

Some of the remaining categories could be contemplated indirectly by some items, such as singing, an area identified by a patient, which could perhaps be identified in the item "I feel short of breath when I speak". However, interestingly, singing for this patient weighted 30% in the total PGI score, while the item "I have no air when I speak", had zero weight in the SGRQ score, which can demonstrate the greater sensitivity of the PGI. We also identified areas such as sex, "mood for cooking different foods", drinking an alcoholic beverage, using a wood stove, "to visit people in the hospital" and even to smoke, which were mentioned as having an impact on the HRQoL of these patients, but are not covered by the SGRQ.

Thus, we consider that the PGI may be able to exclude issues that are not of direct interest to the individual and can capture areas of life that are important from an individual point of view, which are not usually represented in the structured HRQOL tools.

Our study demonstrated high test-retest reliability of the PGI, with an ICCr value within the minimum acceptable for the reliability of clinical tests.[17] Similar levels of reliability have been found in other studies with comparable versions and populations.[23,28,29] For clinical practice, there is a 68% probability that repeated measurement of the PGI is within 1 Standard Error of the Measure (EPM), or 4.7 points, and a

96% probability of being within 2 EPM or 9.4 points. The EPM value was used to calculate the Minimum Detectable Difference (MDD), which is clinically applied to differentiate a real change from a change related to the individual measurement variation. Thus, variations of 10.8 points in the PGI indicate clinically relevant variations in patients with COPD. No other study was found that have assessed the absolute reliability of PGI.

Our results suggest that PGI can be considered an instrument with the potential for being used in clinical practice as a complementary instrument in the assessment of patients with COPD, which would allow individualized strategies for its treatment.

As limitations of our study, we highlight that our sample was mostly composed 76% (38) by individuals classified as GOLD II, which could limit the external validity of the study. Also, the PGI was applied in the region of Diamantina, Minas Gerais, a region with a human development index (HDI) below the national average. We also emphasize the strong culture of mining and the common presence of the wood stove at homes, which justify the answers found in the PGI. Another limitation is that the time spent by patients to answer the instrument was not recorded, however roughly speaking, we saw that it takes around 10 minutes.

In summary, this study shows that the Brazilian version of PGI is a reliable and valid instrument for measuring HRQoL in patients with COPD; able to highlight areas that are not captured by generic instruments, and can be applied in a complementary way to traditional instruments for assessing HRQoL in COPD.

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SUPPLEMENTARY MATERIAL

Supplementary material accompanies this paper.

Chart S1. PGI responses according to ICF.

Table S1. Categories cited by patients in response to PGI and the number of times they were cited.

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ORIGINAL ARTICLE

Lung transplant in patients with familial pulmonary fibrosis

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ABSTRACT

Objective: Familial pulmonary fibrosis (FPF) is defined as an idiopathic interstitial lung disease affecting two or more members of the same family; poor outcome with high risk of death and chronic lung allograft dysfunction (CLAD) after lung transplant has been reported in these patients. The present study aimed to compare the short- and long-term outcome of lung transplants in patients with FPF and patients transplanted because of other interstitial lung diseases. **Method:** Clinical pre- and post-transplant data from 83 consecutive patients with pulmonary fibrosis who underwent lung transplant at our centre were collected retrospectively. Patients were divided into those with familial (n=9 FPF group) and those with non-familial pulmonary fibrosis (n=74 controls). **Results:** The FPF group was composed of 4 females and 5 males; 44.5% were ex-smokers. The majority presented their CT scan and pathology evidence of usual interstitial pneumonia. Patients with FPF had significantly lower pre-transplant levels of haemoglobin and haematocrit. No other differences in pre- and post-transplant characteristics were observed concerning controls. The clinical post-operative course was similar in the two groups. No significant difference in one-year CLAD-free survival and overall survival was observed. **Conclusion:** The post-transplant course of patients with FPF was similar to patients with non-familial pulmonary fibrosis, although more patients with FPF had pre-transplant anaemia. Short- and long-term outcome was comparable in both groups. Lung transplant proved to be a valid option for patients with FPF as it was for patients with other types of pulmonary fibrosis.

Keywords: Pulmonary fibrosis; Lung transplantation; Therapeutics.

INTRODUCTION

Lung transplant (LTX) is a justified treatment option for selected patients with end-stage lung disease.[1] Although new treatments and prognostic biomarkers are available, patients with idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), or cystic fibrosis (CF) are still those who obtain the most benefit.[2-7]

Familial pulmonary fibrosis (FPF) is defined as an idiopathic interstitial lung disease affecting two or more members of the same family.[8] Since the first cases described in the 1950s, interest in FPF has increased but there are still uncertainties regarding its definition and classification.[8-12] Its age of onset is earlier than for idiopathic pulmonary fibrosis (IPF) and it can present with different radiology and pathology pictures.[13,14] Several gene variants have been associated with the onset of FPF: variants in genes encoding for the telomerase complex seem to have a major role.[15] In carriers of these variants, FPF may also have extrapulmonary manifestations, including non-specific blood disorders (anaemia and thrombocytopenia), immune alterations (ANA), liver cirrhosis, enteropathies, osteoporosis, increased risk of skin and blood tumours and early grey syndrome.[16] In carriers of variants in genes encoding the telomerase complex, LTX outcome has been reported to be poor with high rates of blood, renal and gastrointestinal complications, and increased risk of death and CLAD.[17-20]

The present study aimed to compare the short- and long-term outcomes of lung transplants in patients with familial pulmonary fibrosis, irrespective of genetic alterations, and patients undergoing LTX because of other interstitial lung diseases, at a single lung transplant centre.

METHODS

In this study, we included patients with pulmonary fibrotic disorders who underwent lung transplant from 2002 to 2019 at Siena University Hospital, Italy (Azienda Ospedaliera Universitaria Senese). Patients were divided into two groups: those with familial pulmonary fibrosis (n=9) (FPF group) and those with non-familial pulmonary

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fibrosis (n=74) (PF or control group). The research was approved by the local ethical committee (Azienda Ospedaliera Universitaria Senese, protocol OSS_REOS n° 12908). All participants gave their written informed consent to the study.

Our definition of FPF was an idiopathic diffuse parenchymal lung disease affecting two or more members of the same primary biological family.[8] The PF group was composed of patients with idiopathic interstitial pnaumonias (IIPs), hypersensitivity pneumonitis, and other forms of pulmonary fibrosis.

We collected pre- and post-operative data retrospectively from the medical records, including baseline respiratory diagnosis, comorbidities, BMI, time on a waiting list, and need for bridging extra-corporeal membrane oxygenation (ECMO) before transplantation.

The intra-operative data concerned the type of transplant (single or bilateral), graft ischemia time, severe intra-operative arterial hypotension, need for blood transfusion, and need for intra-operative ECMO (in cases of poor hemodynamic control and low oxygenation during the operation, veno-arterial ECMO with central cannulation was performed). The post-operative data included invasive ventilation time, need for post-operative ECMO, primary graft dysfunction (PGD) at 72 hours, need for and time of inhaled nitric oxide (NO) therapy, need for tracheostomy, acute cellular rejection (ACR) episodes, duration of intensive care, total in-hospital time and one-year survival after transplant.

In a subgroup of 40 patients with PF and 6 with FPF, we measured the following blood parameters at baseline (before surgery) and post-operatively on days 7, 14, 30, 90, 180 and 365: white blood cell count (WBC), haemoglobin (HB), haematocrit (HCT), mean corpuscle volume (MCV), platelets (PLT), C-reactive protein (CRP) and lactate dehydrogenase (LDH).

All patients received corticosteroid therapy with 125 mg methylprednisolone before graft re-perfusion, followed by 375 mg on day 0 and 1 mg/kg from day 1, with subsequent 20% reductions every 2 days. Induction therapy was included in our protocol as from 2009 but was not administered to all patients, as decided by the surgeon. Therapy was based on basiliximab (20 mg at days 0 and 4) or thymoglobulin (ATG) (1.5 mg/kg/day for 2-5 days). Calcineurin inhibitors were administered between days 3 and 5: tacrolimus (trough level 10–15 ng/ml) or cyclosporine (trough level 250–300 ng/ml). Cyclosporine was used predominantly until 2007; tacrolimus subsequently. Depending on clinical condition, azathioprine 100 mg/day or mycophenolate mofetil 1 gr/day was administered between post-operative days 7 and 10. Since 2007 mycophenolate mofetil has replaced azathioprine in the base regime for all patients.

The statistical analysis was conducted with GraphPad Prism v 6.0 for Macintosh; non-parametric tests were used and differences with $p<0.05$ were considered significant. The difference between the two groups was studied by the Mann-Whitney test, analysis of the variance with the Kruskal-Wallis test, and differences in prevalence on contingency tables with the Fisher or Chi-square test. All data were expressed as mean ± standard deviation, unless otherwise stated. Survival analysis was based on Kaplan-Meyer curves and Cox regression.

RESULTS

From 2002 to 2019, 160 patients underwent lung transplant at our Transplant Centre (63 females, 97 males, age at transplant 51.4 ± 12.2 years old, 88 bilateral transplants, 72 single transplants). Basal diagnoses were: pulmonary fibrosis 52%, CF 19.3%, COPD 20%, other diagnosis 8.7%.

Patients with pulmonary fibrosis (n=83) were included in the present study; 9 had familial pulmonary fibrosis (age 54.1 ± 7.1 years, 4 females) (FPF group), and 74 non-familial pulmonary fibrosis (age 57.2 ± 7.4 years, 17 females) (PF group). Forty-nine of the 74 patients in the PF group were diagnosed with IPF, 7 with connective tissue disease-associated pulmonary fibrosis, 6 with hypersensitivity pneumonitis (HP), 4 with non-specific interstitial pneumonia (NSIP), 2 with post-GVHD (graft-versus-host-disease) pulmonary fibrosis after bone marrow transplant and 6 with unclassifiable pulmonary fibrosis.

The FPF group was composed of 4 females and 5 males; 44.5% were ex-smokers. At pre-transplant chest-high-resolution CT scan (HRCT), 6 patients had a usual interstitial pneumonia (UIP) pattern; two cases also had emphysema, with significant ground-glass pattern in one and mediastinal lymphoadenomegaly in the other. In one patient the UIP pattern was associated with pleuroparenchymal fibroelastosis in the upper lobes (case no. 6). In the remaining 3 cases, the HRCT pattern was compatible with NSIP; one also had paraseptal emphysema.

HRCT pattern corroborated pathology findings in 7/9 FPF patients. In the two discordant cases, HRCT showed an NSIP pattern while pathology revealed a UIP pattern in one, whereas in the other HRCT showed a UIP pattern combined with pulmonary emphysema, while the pathology report indicated alterations compatible with NSIP (Table 1). In one case (patient no. 9) chest HRCT showed mediastinal lymphoadenomegaly associated with UIP pattern, and the pathology report indicated a neoplastic lesion compatible with adenocarcinoma in right upper lobe in a context of dense fibrosis with UIP pattern and right hylar lymph node metastasis. This patient died of lung cancer 314 days after transplant.

In three patients, the pre-transplant evaluation showed mild to moderate anaemia; in two cases macrocytosis was concomitant, while none of the patients showed leukopenia or thrombocytopenia. No patients had liver disease, early grey syndrome, or other alterations compatible with short telomerase syndromes.

No other differences in pre- and post-transplant characteristics were observed between groups. The clinical post-operative course was similar in both groups (Tables 2 and 3).

Patients with FPF underwent bilateral transplants more often than patients with PF (77.7% vs. 30.1%, p=0.0081). Regarding immunosuppressant therapy, patients with FPF more frequently underwent induction therapy (basiliximab or thymoglobulin) and were more frequently treated with tacrolimus instead of cyclosporine, compared to patients with PF (77.7% vs. 36.9%, p=0.02; 88.8% vs. 45.2%, p=0.02, respectively) (Table 3).

Analysis of blood parameters showed that patients with FPF had significantly lower pre-transplant levels of HB and HTC (p=0.03 and p=0.01, respectively). Levels of HB were lower at post-operative day 180 (p=0.05), while levels of HCT were reduced at day 365 (borderline significant p=0.07). At day 180, FPF patients showed higher white blood cell counts (p=0.03) (Table 4). No difference in platelet count between groups was observed during follow-up.

Table 1. Demographic, clinical, HRCT, and pathology findings of FPF patients.

	Sex	Blood group	Age (years)	Smoking (packs/year)	HRCT pattern	Pathology pattern	Comorbidities	Number of relatives with fibrosis
Case 1	F	A-	59	NO	NSIP with micronodules	NSIP	No	4
Case 2	F	AB-	46	NO	NSIP and pulmonary emphysema	NSIP	Osteoporosis	4
Case 3	M	A+	50	20	UIP	UIP	Arterial hypertension, Osteoporosis	3
Case 4	F	A+	48	NO	UIP, intralobular ground glass and paraseptal emphysema	NSIP	Osteoporosis	3
Case 5	F	0+	44	NO	NSIP	UIP	Diabetes, Dyslipidaemia, Osteoporosis	2
Case 6	M	0+	55	20	UIP and pleuroparenchymal fibroelastosis	UIP	Arterial hypertension, Osteoporosis	2
Case 7	M	0+	60	22	UIP and pulmonary emphysema	NSIP	Arterial hypertension	2
Case 8	M	0+	65	30	UIP	UIP	Dyslipidaemia	2
Case 9	M	0+	56	20	UIP and lymph node enlargement	UIP and ADK	No	3

F: female gender; M: male gender; HRCT: high resolution computed tomography; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia; ADK: adenocarcinoma.

Table 2. Pre-operative characteristics of FPF and PF patients.

	FPF	PF	Significance
Number	9	73	
Age (years)	54.14 ± 7.116	57.23 ± 7.439	0.2409
Male sex	5 (55.55%)	56 (76.71%)	0.2243
Smoking history	6 (66.66%)	35 (47.95%)	0.4821
BMI (kg/m2)	23.39 ± 4.167	26.00 ± 4.338	0.0913
Comorbidities			
• Diabetes	1 (11.11%)	30 (41.10%)	0.1429
• Arterial hypertension	3 (33.33%)	42 (57.53%)	0.2871
• Hypercholesterolemia	2 (22.22%)	36 (48.31%)	0.1660
• Osteoporosis	5 (55.55%)	46 (63.01%)	0.7238
• Pre-LTX malignancies	0 (0%)	4 (5.4%)	>0.9999
Time on waiting list (days)	194.2 195.2	221.6 214.7	0.7171
pre-LTX ECMO (bridging)	1 (11.11%)	2 (2.74%)	0.2977

LTX: lung transplantation: FPF: familial pulmonary fibrosis; PF: pulmonary fibrosis; BMI: body mass index; ECMO: extracorporeal membrane oxygenation.

Table 3. Post-operative data of FPF and PF patients.

	FPF	PF	Significance
LTX procedure			
• Single LTX	2 (22.22%)	51 (69.86%)	0.0081*
• Bilateral LTX	7 (77.77%)	22 (30.14%)	
Ischemia Time			
• 1st Lung (minutes)	246.8±52.69	270.7± 111.9	0.5548
• 2nd Lung (for bilateral LTX) (minutes)	374.9±85.43	437.3±220.1	0.4773
Induction therapy (basiliximab or thymoglobulin)	7 (77.77%)	27 (36.99%)	0.0296*
CNI therapy			
• Cyclosporine	1 (11.11%)	40 (54.79%)	0.0291*
• Tacrolimus	8 (88.88%)	33 (45.21%)	
Azathioprine/mycophenolate mophetil	7 (77.77%)	47 (64.38%)	0.7113
Severe hypotension/hemodynamic decompensation	2 (22.22%)	14 (19.18%)	>0.9999
Vasoactive amines (hours)	64.00±41.57	93.74±144.6	0.5431
Blood transfusion	4 (44.44%)	29 (39.73%)	>0.9999
IMV > 96 hours	4 (44.44%)	36 (49.31%)	>0.9999
Tracheostomy	1 (11.11%)	18	0.6772
NO inhalation (hours)	42.00±34.47	78.25±92.20	0.2480
Intra-operative ECMO	2 (22.22%)	13	0.6662
Post-operative ECMO	0	7	>0.9999
PGD at 72 hours			
• All Grades	7 (77.77%)	55	>0.9999
• Grade 1	1 (11.11%)	13	>0.9999
• Grade 2	4 (44.44%)	24	0.6950
• Grade 3	2 (22.22%)	16	>0.9999
ACR			
• 1 episode of ACR	5 (55.5%)	36 (49.3%)	0.3868
• ≥ 2 episodes of ACR	0 (0%)	11 (15%)	0.6006
ICU stay (days)	16.89±10.65	19.48±19.62	0.6993
Total in-hospital stay (days)	42.22±18.16	42.68±26.21	0.9596
Overall survival			
• 1 year	66.6%	58.4%	0.7067
• 3 years	41.6%	45.4%	
• 5 years	41.6%	43.4%	
Overall survival according to LTX type (single/bilateral)			
• 1 year	37.5% / 50%	58.6% / 69.2%	0.2689 / 0.6774
• 3 years	12.5% / 50%	36.0% / 65.1%	
• 5 years	12.5% / 50%	36.0% / 65.1%	
CLAD-free survival			
• 1 year	87.5%	73.8%	0.1883
• 3 years	72.9%	44.3%	
• 5 years	72.9%	39.4%	
CLAD-free survival according to LTX type (single/bilateral)			
• 1 year	100% / 62.5%	83.3% / 68.2%	0.5326 / 0.1837
• 3 years	100% / 62.5%	42.5% / 48.3%	
• 5 years	100% / 62.5%	34.7% / 41.5%	

LTX: lung transplantation; FPF: familial pulmonary fibrosis; PF: pulmonary fibrosis; CNI: calcineurin inhibitor; NO: nitric oxide; IMV: invasive mechanical ventilation; ECMO: extracorporeal membrane oxygenation; ACR: acute cellular rejection; PGD: primary graft dysfunction; ICU: intensive care unit; CLAD: chronic lung allograft dysfunction. *statistically significant.

Table 4. Pre- and post-transplant blood parameters and acute-phase proteins in FPF and PF patients.

	Basal (pre-LTX)			Day 7			Day 14			Day 30		
	PF (n 6)	FPF (n 40)	p	PF (n 6)	FPF (n 39)	p	PF (n 6)	FPF (n 36)	p	PF (n 6)	FPF (n 34)	p
WBC	12.66 ± 4.19	13.09 ± 4.35	0.81	11.73 ± 4.11	10.09 ± 2.61	0.37	13.58 ± 7.42	11.15 ± 6.54	0.32	8.26 ± 3.95	9.90 ± 8.00	0.95
HB	14.3 ± 1.7	11.8 ± 2.9	0.03*	9.6 ± 1.2	9.7 ± 0.8	0.77	10.0 ± 1.2	9.9 ± 1.2	0.73	10.5 ± 1.4	10.7 ± 1.3	0.63
HCT	43.3 ± 4.9	35.6 ± 7.7	00.1*	29.6 ± 3.6	30.3 ± 1.8	0.55	29.8 ± 4.6	30.3 ± 3.9	0.97	31.8 ± 3.9	32.5 ± 4.0	0.64
MCV	90.8 ± 3.9	93.5 ± 9.7	0.86	91.2 ± 4.6	93.1 ± 4.8	0.42	90.3 ± 4.0	91.0 ± 4.0	0.79	91.5 ± 3.6	91.6 ± 4.2	0.882
PLT	212.0 ± 64.4	272.2 ± 84.6	0.09	127.7 ± 70.4	132.2 ± 57.7	0.72	171.4 ± 98.2	239.5 ± 110.7	0.19	192.5 ± 87.1	277.0 ± 214.4	0.62
CRP	1.07 ± 1.25	2.01 ± 1.87	0.54	4.12 ± 4.91	12.33 ± 9.29	0.17	6.09 ± 10.03	3.11 ± 2.69	0.76	2.49 ± 3.86	1.04 ± 1.42	0.17
LDH	376.7 ± 150.3	340.6 ± 140.0	0.60	836.9 ± 165.7	344.5 ± 42.2	0.23	686.0 ± 640.7	541.3 ± 227.5	0.90	371.0 ± 171.8	323.6 ± 140.4	0.53
	Day 90			Day 180			Day 365					
	PF (n 6)	FPF (n 29)	p	PF (n 4)	FPF (n 27)	p	PF (n 4)	FPF (n 25)	p			
WBC	7.87 ± 3.24	9.14 ± 3.16	0.21	7.29 ± 2.10	11.00 ± 2.07	0.03*	7.03 ± 2.36	10.11 ± 5.96	0.42			
HB	11.4 ± 1.4	11.6 ± 0.7	0.88	12.1 ± 1.2	10.5 ± 0.9	0.05*	11.9 ± 1.4	9.9 ± 1.8	0.14			
HCT	34.9 ± 4.2	35.3 ± 2.4	0.91	37.2 ± 3.5	33.2 ± 2.9	0.07	36.8 ± 3.9	31.3 ± 5.3	0.07*			
MCV	93.3 ± 5.0	97.3 ± 7.5	0.24	93.5 ± 5.9	94.9 ± 4.8	0.98	91.2 ± 9.1	90.8 ± 10.9	0.99			
PLT	199.8 ± 57.1	224.6 ± 94.5	0.81	209.5 ± 58.2	226.7 ± 105.0	0.99	188.3 ± 65.4	321.0 ± 183.8	0.41			
PCR	1.04 ± 1.42	1.19 ± 1.40	0.83	0.67 ± 1.28	0.87 ± 118	0.93	2.4 ± 8.2	0.07 ± 0.03	0.25			
LDH	289.1 ± 124.3	280.5 ± 113.1	0.97	282.1 ± 89.5	340.7 ± 294.0	0.41	243.3± 62.6	232.5 ± 40.3	0.94			

FPF: familial pulmonary fibrosis; PF: pulmonary fibrosis; WBC: white blood cells; HB: haemoglobin; HCT: haematocrit; MCV: mean corpuscle volume; PLT: platelet; CRP: C reactive protein; LDH: lactate dehydrogenase; n: number; p: statistical significance; * statistically significant.

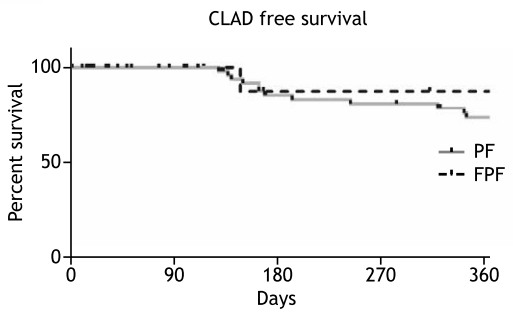

Figure 1. CLAD-free survival at 1 year based on Kaplan-Meyer curves in FPF and PF patients.

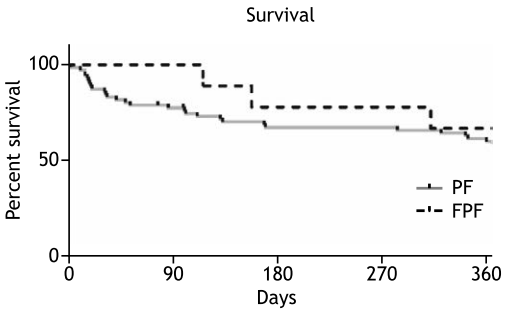

Figure 2. 1-year survival analysis based on Kaplan-Meyer curves FPF and PF patients.

No significant difference in one-year CLAD-free survival was observed. While FPF patients showed a better outcome, the difference was not significant (CLAD one-year survival FPF group 87.5%, PF 73.8%) (Figure 1). Likewise, survival analysis at 1 year did not show significant differences between groups (66.7% FPF, 58.4% PF) (Figure 2). 1, 3, and 5-years survival and CLAD-free survival data, also stratified for single/bilateral LTX, are reported in Table 3.

DISCUSSION

Lung transplant is a viable therapeutic option in patients with end-stage lung disease and vascular lung disease unresponsive to medical or surgical therapy or in patients for whom no therapy is available.[1] Patients with pulmonary fibrosis, CF, and COPD are those most likely to benefit, although the long-term outcome in cases of IPF is reportedly poorer than in cases with other indications.[21] In the USA, since the advent of the Lung Allocation Score (a composite score based on various clinical and physiological parameters predicting life expectancy in the waiting list), IPF has become the first indication for transplant.[22] However, mortality on the waiting list is still a major issue for these patients.[23]

Some patients with pulmonary fibrosis may have one or more family members with interstitial lung disease. In these cases, the definition of familial pulmonary fibrosis (FPF) has been proposed.[8] Radiological and clinical manifestations vary widely, as do evolution and prognosis.[8-14] FPF has a vertical transmission, suggesting autosomal dominant inheritance with incomplete penetrance (i.e. not everyone with the genetic variant develops the disease).[15] Several genetic variants have been documented, but nearly 80% of cases are unknown. Most of the known variants of concern genes encoding the telomerase complex.[15,16] Here we compared clinical features and short- and long-term outcomes of patients with FPF and of patients with other interstitial lung diseases (PF or control group) who underwent lung transplants at our centre.

The baseline demographic and clinical features of our populations were homogeneous. Our cohort did not show the demographic differences commonly reported between patients with FPF and patients with sporadic IPF (younger age, the same prevalence in males and females, less exposure to smoking).[8-14] This was probably because the group of patients with sporadic pulmonary fibrosis was selected for transplant, where age below 65 years old, for example, is a fundamental prerequisite for the waiting list. As regards gender, the PF group also included diseases other than IPF (e.g. connective tissue disease, hypersensitivity pneumonitis) where gender distribution is not always in favour of males.

Several pathologies and HRCT presentation patterns have been reported in FPF patients, the UIP pattern being the most frequent.[13] However, aspects of NSIP, COP, centrilobular nodulation, and unclassified pulmonary fibrosis are not uncommon.[8-14] In our cases, HRCT scans showed a UIP pattern in most patients (66.7%) and pathology data were congruous, showing UIP alterations in 55.5% of patients. Radiology and pathology findings were discordant in two cases; similar data of CT and pathology accordance have been reported.[24,25]

One patient was diagnosed with lung cancer from the pathology report on the native lungs and made a very poor post-operative course. Despite chemotherapy, the patient died about a year later. Diagnosis of lung cancer after transplant has been reported by others and evolution in these cases can be very aggressive.[26] Accurate pre-transplant screening for chest cancer is important, especially in patients with pulmonary fibrosis. There is a strong association between PF and lung cancer and a higher incidence than in the general population and other lung diseases.[21] Nevertheless, post-transplant solid-organ malignancies in lung transplant recipients is a major issue; in particular, skin and lung cancers demonstrated a higher incidence rate.[27]

About pre-LTX malignancies, our centre requires 5 years disease-free interval before listing for LTX. In the

present study, the incidence of pre-LTX malignancies was not different between groups. In the FPF group, no patients had pre-LTX tumors, while in the PF two patients had a history of a haematological disease for which underwent bone marrow transplantation and subsequently developed chronic pulmonary graft-versus-host-disease (GVHD) and so got to LTX, one patient had colorectal cancer (pT1, N0, M0) 6 years before LTX and another undergone abdominal surgery for a gastrointestinal stromal tumor (GIST) that was considered a benign lesion.

Regarding intra- and post-operative variables, patients with FPF and PF received similar treatment and we did not observe different short- and long-term outcomes. The only differences were the type of transplant and immunosuppressant therapy. Patients with FPF underwent bilateral LTX, received induction therapy, and first-line immunosuppressant therapy was based on tacrolimus more frequently than in PF patients. These differences reflect the different eras in which patients underwent a transplant in our centre. Indeed, induction therapy, tacrolimus instead of cyclosporine, and bilateral transplant are in line with our more recent clinical activity, in parallel with the literature and with experience acquired by our team.[28,29] In our PF cohort, the use of basiliximab showed to be associated with a better outcome in terms of overall survival and CLAD-free survival (p=0.05, HR=0.503 (0.247-1.027) and p=0.003, HR=0.165 (0.050-0.543), respectively). Most patients with FPF were transplanted since 2009 when our protocol had already undergone substantial changes (only one patient was transplanted previously, in 2006), so 7 of the 9 FPF patients were treated with basiliximab and received bilateral LTX. Cox regression analysis did not demonstrate a significant association of gender, age, LTX type procedure (single/bilateral), use of basiliximab, and tacrolimus instead of cyclosporine with overall survival and CLAD-free survival in this group (data not shown). ACR is a recognized risk factor for CLAD development however, in our cohorts, we could not demonstrate this association (p=0.123, HR=2.158 in PF patients, and p=0.848, HR=1.266 in FPF patients respectively).

Blood and liver anomalies have been reported in patients with FPF. In particular, anaemia, thrombocytopenia, and in some cases, leukopenia have been observed in patients with short telomere syndrome, mainly linked to variants in genes encoding the telomerase complex.[15,16] A negative effect of immunosuppressant therapies has been reported in IPF patients with short telomere. In 2018, patients with this syndrome from the PANTHER-IPF and ACE-IPF studies and an independent observational cohort study from the University of Texas Southwestern Medical Center (UTSW), exposed to triple prednisone/azathioprine/N-acetylcysteine therapy, showed an increased risk of mortality, post-transplant complications, hospitalization and a greater reduction in forced vital capacity (FVC).[29] Lung transplant patients with short telomere are also reported to have a poorer outcome with high rates of blood, renal and gastrointestinal complications, impaired immunity to CMV, and increased risk of death and CLAD.[17-20,30,31] In 2018, the Leuven group reported positive outcomes in a case series of multiple solid organ transplants in patients with telomeropathy.[32]

In our cohort, three patients showed mild-moderate anaemia before transplant, with macrocytosis in two cases, while no patient showed leukopenia, thrombocytopenia, liver anomalies, or other manifestations of short telomere syndromes, including early grey syndrome. Unfortunately, we did not consider genetic variants because the genetic analysis was only available for three patients and was found negative in all three (genes for surfact C and A2, ABCA3, TERT, and TERC were tested).

Compared to the PF group, our FPF patients showed a significant reduction in pre-transplant values of haemoglobin and haematocrit. These differences were no longer significant in the early post-transplant phase but reappeared 6 and 12 months later. This is probably due to the effect of post-operative blood and platelet transfusions, which while not significantly different between groups, could have mitigated blood parameter differences. The hypothesis that these patients could be a carrier of some genetic mutations resulting in telomere abnormalities is interesting; however, since no genetic analysis was available, no definite conclusion can be made.

The long-term outcome of our PF patients was in line with the literature[21] and no differences between FPF and PF groups were found. Time to CLAD development did not differ between groups and one, three and five-year survival was similar. Literature is controversial on long term outcome in FPF and patients with genetic mutations; some studies reported lung transplant may still be viable and offer reasonable survival to patients with FPF, despite major complications,[17,18] while some other studies observed worse survival and shorter time to onset of chronic lung allograft dysfunction in patients with telomere abnormalities.[19,20]

The present study has several limitations, notably the small statistical sample, the fact that the study was retrospective, concerned a single institution and genetic analysis was not available. The number of patients enrolled is small because FPF is rare, even if our centre has earned a name for particular attention to these patients.

In conclusion, our study offers further evidence that lung transplant is just as valid a therapeutic option for patients with familial pulmonary fibrosis as it is for patients with sporadic pulmonary fibrosis. Baseline characteristics were similar and the risk of blood complications was not different, although more patients with FPF may have pre-transplant anaemia.

Short- and long-term outcomes were comparable in patients with familial and non-familial pulmonary fibrosis, confirming that despite major complications, a lung transplant may still be viable and offer reasonable survival to patients with FPF.

Further studies, considering specific genetic variants and involving multicentre cohorts, are needed for better evaluation of lung transplant candidates with familial pulmonary fibrosis and a better appreciation of long-term outcomes.

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ORIGINAL ARTICLE

Noninvasive ventilation in a pediatric ICU: factors associated with failure

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ABSTRACT

Objective: Evaluate the efficacy of Noninvasive Mechanical Ventilation (NIV) in preventing Endotracheal Intubation (ETI) in a heterogeneous pediatric population and identify predictive factors associated with NIV failure in Pediatric Intensive Care Unit (PICU). **Methods:** Prospective non-randomized clinical trial conducted with patients aged 0-10 years, hospitalized in a PICU with NIV indication, who presented acute or chronic respiratory failure. Demographic data and clinical and cardiorespiratory parameters were evaluated, and patients who did not progress to ETI in 48 h after withdrawal of NIV were classified as "success group", whereas those who progressed to ETI were included in the "failure group". Multivariate logistic regression was performed to identify the predictive factors of failure to prevent ETI. **Results:** Fifty-two patients, 27 (51.9%) males, with median age of 6 (1-120) months were included in the study. When evaluating the effectiveness of NIV, 36 (69.2%) patients were successful, with no need for ETI. After analyzing the predictive factors associated with failure, patients with tachypnea after 2 h of NIV were 4.8 times more likely to require ETI in 48 h. Regardless of outcome, heart (p<0.001) and respiratory (p<0.001) rates decreased and oxygen saturation (p<0.001) increased after 2 h of NIV. **Conclusion:** We concluded that use of NIV was effective in the studied population, with significant improvement in cardiorespiratory parameters after 2 h of NIV, and that tachypnea was a predictive factor of failure to prevent ETI.

Keywords: Noninvasive ventilation; Intensive care units; Children, Pediatric; Artificial ventilation.

INTRODUCTION

Noninvasive mechanical ventilation (NIV) is defined as a ventilatory support that does not require endotracheal intubation (ETI) or tracheostomy.[1-3] It is used through an interface with the aim of promoting adequate ventilation, reducing respiratory work, preventing respiratory muscle fatigue, increasing alveolar ventilation and improving gas exchange, thus preventing intubation and promoting, in some cases, early extubation.[1-3] The use of NIV can also decrease complications associated with the use of invasive mechanical ventilation and, consequently, the morbidity and mortality rates associated with the latter.[2,3]

Currently, NIV is considered an alternative ventilatory support in Pediatric Intensive Care Unit (PICU), with good acceptability and high success rates, being indicated in the presence of acute or chronic respiratory disorders, neuromuscular diseases, central nervous system disorders and obstructive sleep apnea, as well as in the postoperative and post-extubation periods and in early extubation.[1-7] The use of NIV in adults is widely established and recommended; however, due to the great variability of low quality studies, heterogeneity of diseases found in PICU, and the low availability of trained professionals, it is important to conduct new studies addressing the use of NIV in pediatrics.[4,8-10]

There has been an increase in the success rates of the use of NIV in various diseases over time.[7-9] In the beginning, these rates ranged from 5 to 40% and, currently, they can reach 80%.[7-9] NIV has been increasingly used both in our institution and in other centers that utilize it in the pediatric population, and we hypothesize that its success rates, defined as to prevent ETI, vary between 60 and 80% according to the literature.[7-9] However, it is necessary to carry out complementary studies in multi-professional centers in order to improve and disseminate knowledge on the subject, in addition to establishing protocols for the application of NIV.[4,8-14]

Thus, the objective of this study was to evaluate the effectiveness of NIV in preventing ETI in a heterogeneous population of pediatric patients and identify the predictive factors associated with its failure in a PICU at the *Clinical Hospital* (CH) of the *University of Campinas* (Unicamp).

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METHODS

A prospective non-randomized clinical trial was carried out with infants, preschoolers, and schoolchildren aged 0-10 years, of both genders, admitted to the PICU of CH - Unicamp between November 2015 and December 2016.

Upon consensus among the professionals working in the PICU, the following inclusion criteria were adopted for all patients with indication for NIV: presence of type I and II acute respiratory failure (ARF), chronic respiratory failure (CRF) with signs of exacerbation and signs of respiratory distress (RD) as a rescue technique against dyspnea, tachypnea and use of accessory muscles, as well as being or in the post-extubation period. Other factors for indicating NIV were presence of hypoxemia and/or PaO_2/FIO_2 ratio <300 and/or hypercapnia with pH >7.20 and/or $PaCO_2$ >45 mmHg in patients with acute diseases and $PaCO_2$ >60 mmHg in diseases chronic diseases.[2]

The same factor considered for contraindication of NIV were used as exclusion criteria, namely, hemodynamic instability, arrhythmia, Glasgow Coma Scale (GCS) score adapted for the pediatric population <10, presence of facial or airway deformity injuries, previous trauma and/or craniofacial surgery, undrained pneumothorax, active bleeding in the upper gastrointestinal tract, and/or cardiorespiratory arrest.

As hemodynamic instability, the following symptoms were considered: altered level of consciousness, filiform pulses, important tachycardia, skin pallor, sweating, slow or extremely fast capillary filling, arterial hypotension, and oliguria.

The choice of ventilation mode between Continuous Positive Airway Pressure (CPAP) or Bilevel Positive Airway Pressure (BiPAP) was based on the patient's clinical condition, and included respiratory work, presence of signs of RD, gas exchange, and tolerance to the selected ventilation mode. BiPAP was the initial ventilation mode for children with signs of RD and/or with hypercapnia in gas exchange, whereas CPAP was the ventilation mode initially used for patients with signs of mild-to-moderate RD and without hypercapnia in gas exchange. Initial Expiratory Positive Airway Pressure (EPAP) between 5-7 cmH_2O was used in CPAP, whereas Inspiratory Positive Airway Pressure (IPAP) between 8-12 cmH2O with EPAP between 5-7 cmH_2O were applied in BiPAP (see Figure 1).

Figure 1 shows a flowchart with information on the indications and contraindications for NIV in the present study, in addition to the protocol established for the therapeutic follow-up of patients.

After the child's adaptation to NIV, pressures were adjusted according to the clinical evaluation and reassessed throughout the process. The following signs or parameters were monitored: RD, respiratory rate (RR), heart rate (HR), tidal volume (TV) between 6-8 ml/Kg according to the child's real weight or weight inferred by the parents, as well as patient tolerance to NIV. In both cases, the initial fraction of inspired oxygen (FiO_2) was 50%, which was adjusted to maintain peripheral oxygen saturation (SpO_2) between 92-95%. Flow sensitivity was adjusted between 0.5-1 L/min, with an apnea alarm set between 10-15 s[2].

Noninvasive machanical ventilation was performed using the following mechanical ventilators: RTC E360Br (Newport Medical Instruments, Brazil), MV Drager EVITA 4 (Dräger Medical AG & Co. KGaA, Germany), and BiPAP® Focus™ (Respironics Inc., California, USA).

The choice of the interface between the Philips Respironics Wisp nasal mask (Philips Medical Systems Ltda., Brazil) or the Babyflow® System - nasal mask or cannula (Dräger Medical GmbH, Germany) was based on the size, age and shape of each patient's face, aiming to minimize air leakage and provide the best comfort and patient-mask adaptation (Figure 2).

For assessing continuity, making adjustments, or interrupting NIV, cardiorespiratory parameters such as HR, RR, SpO_2, presence of signs of RD, TV (6-8 ml/kg), and arterial blood gas (ABG) before and after 2 h of NIV placement were evaluated. In addition, information on sex and diagnostic hypotheses was collected.

Subsequently, patients were classified according to efficacy of NIV use into "success group" -patients who did not progress to ETI or required it in 48 h after withdrawal of NIV and the "failure group" -patients who needed ETI.

Throughout the study, patients were continuously monitored every two hours using oximeters, thermometers, electrocardiograms, HR, RR, TV and systemic blood pressure monitors, pulmonary auscultation, ABG analysis, GCS adapted for pediatric population, presence of signs of RD, abdominal distention and lesions on the face, adequate humidification of the system, and leakage of the interface.

The following criteria were considered for interrupting NIV with immediate need for ETI:[2] FiO_2 >60%; progressive increase in ventilatory parameters; continuous dependence on NIV after 24 h, with no tolerance to remain short periods outside the device; no improvement in gas exchange (hypercapnia with major respiratory acidosis and/or severe hypoxemia, with PaO_2/FiO_2 ratio <100 in the first 2 h); GCS adapted for pediatric population <10; patient intolerance or agitation with the use of NIV.

Data obtained were processed using the SPSS 16.0 for Windows (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL; USA).

Statistical descriptive analysis was performed with categorical variables expressed in absolute and relative frequencies and continuous variables expressed in mean, standard deviation, median, minimum and maximum.

Unadjusted Odds Ratio (OR) values, 95% CI, and *p*-value were determined for "failure to prevent ETI" in relation to each predictor variable by Univariate Logistic Regression (Enter method). Cardiorespiratory parameters was classified for each age, with RR in eupnea and tachypnea and HR in sinus rhythm and

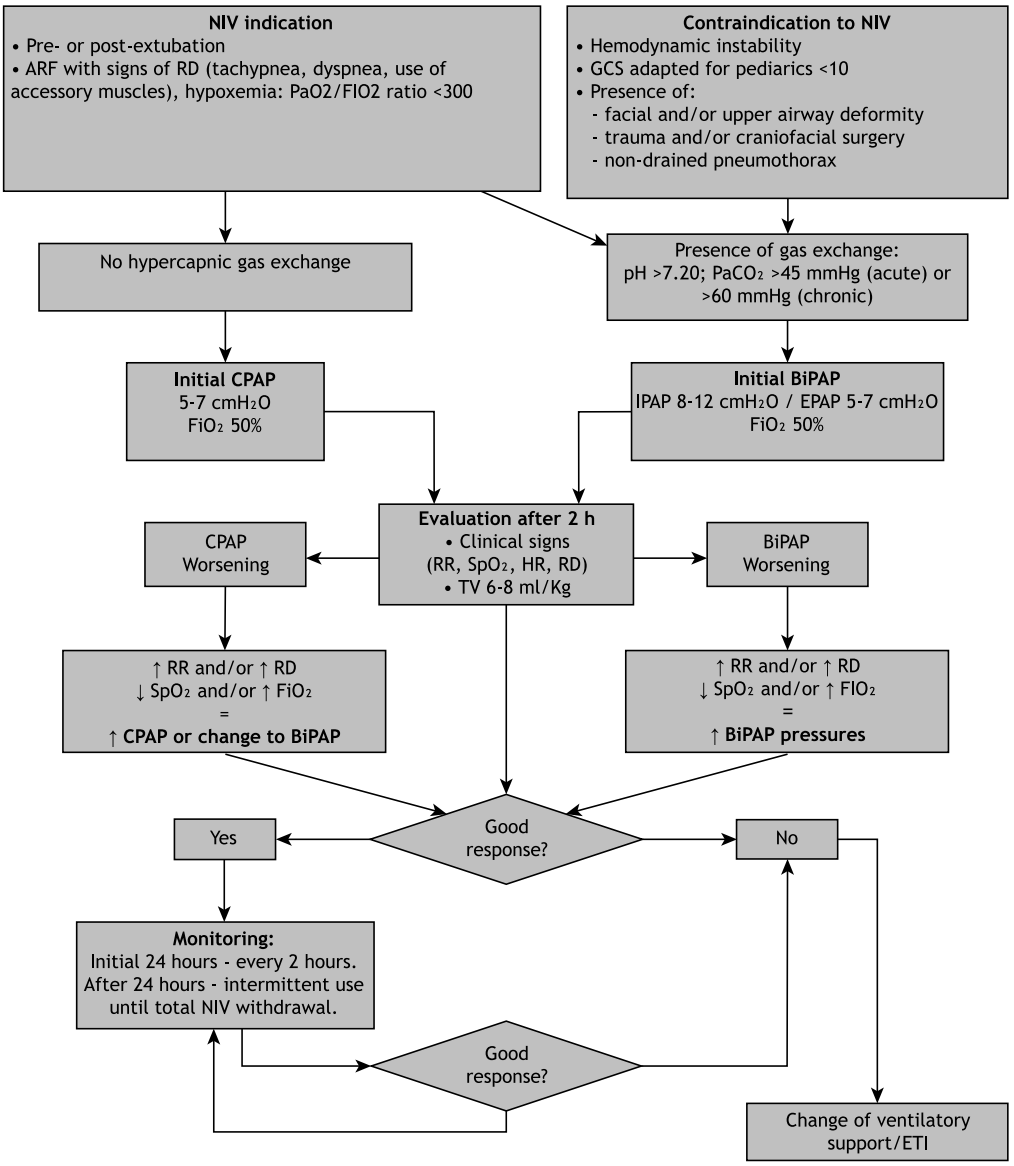

Figure 1. Flowchart of indications, contraindications, and therapeutic follow-up throughout the study. NIV: non-invasive mechanical ventilation; ARF: acute respiratory failure; PaO_2: arterial oxygen pressure; FIO_2: fraction of inspired oxygen; $PaCO_2$: blood pressure carbon dioxide; GCS: Glasgow Coma Scale; RD: respiratory distress; CPAP: Continous Positive Airway; BiPAP: Bi-level Positive Airway Pressure; IPAP: Pressure Inspiratory Positive Airway Pressure; EPAP: Pressure Expiratory Positive Airway Pressure; RR: respiratory rate; HR: heart rate; SpO_2: peripheral oxygen saturation; TV: tidal volume; ET: orotracheal tube.

tachycardia, according to the normality values found in the literature.[15]

Subsequently, the predictor variables with $p<0.200$ in the univariate analysis were selected to compose the multivariate logistic model. The Forward Selection (Wald) method was used with 0.05 and 0.01 inclusion and exclusion *p*-value steps, respectively.

Comparison between the means of the two paired groups was performed by the Student's *t*-test for parametric samples and the Wilcoxon test for non-parametric samples. A significance level of 5% ($p<0.05$) was adopted for statistical analyses.

This study was submitted and approved by the Research Ethics Committee of the College of Medical Sciences of Unicamp under protocol no. 1.313.165. All parents and/or legal guardians signed the Free and Informed Consent Form (FICF) prior to study commencement and those whose children were photographed signed a term allowing the use of the images.

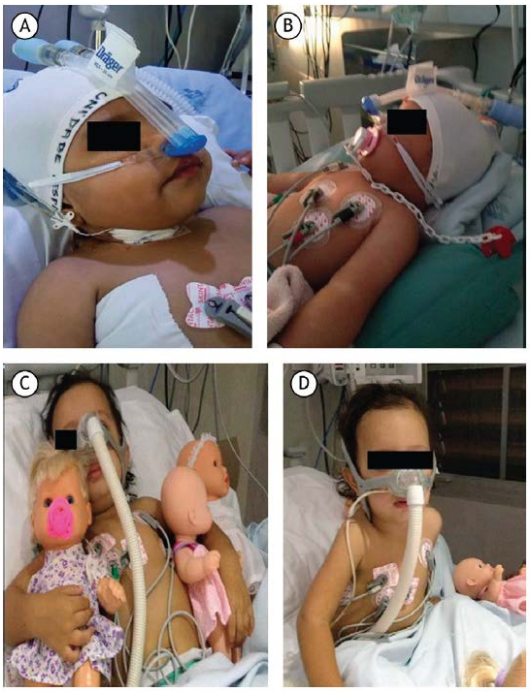

Figure 2. Patients with appropriate interfaces for the age and shape of the face. A: infant in CPAP with nasal cannula; B: infant in BiPAP with unventilated nasal mask; C and D: child in BiPAP with ventilated nasal mask.

RESULTS

The initial study sample comprised 532 infants, preschoolers and schoolchildren admitted to the PICU of CH-Unicamp between November 2015 and December 2016. After application of the inclusion and exclusion criteria, 52 patients were selected to participate in the study.

The study sample consisted of 52 patients, 27 (51.9%) males, with median age of 6 (1-120) months. Among them, there were 41 (78.8%) infants including preterms according to chronological age, four (7.7%) preschoolers, and seven (13.5%) schoolchildren.

All participants presented some type of respiratory failure with indication of NIV. The basic diseases that led to PICU admission were acute viral bronchiolitis (AVB), (19 patients; 36.5%) and pneumonia (9 patients; 7.3%). Some children presented associated comorbidities such as 3 (5.8%) with history of prematurity with bronchopulmonary dysplasia, 4 (7.7%) with cystic fibrosis,3 (5.8%) with laryngitis, 1 (1.9%) with asthma and 8 (15.4%) with basic diagnoses of non-respiratory origin such as Down Syndrome, traumatic brain injury, epilepsy and septic shock, and progressed to NIV as a result of type I ARF.

No adverse effects associated with the use of NIV, such as skin or mucosal lesions due to interface pressure, abdominal distension or eye irritation, were observed throughout the study period.

When assessing the effectiveness of using NIV, 36 (69.2%) patients were successful and 16 (30.8%) failed with need for ETI, 12 of them due to the presence of hemodynamic instability such as decreased SpO_2, RD, tachycardia or tachypnea, two because of decreased level of consciousness with absence of respiratory drive; one as a result of cardiopulmonary arrest; one due to poor adaptation and acceptance to the NIV interface. These signs were identified within the first two hours of NIV placement.

Table 1 shows the demographic and clinical characteristics of the participants in addition to the NIV parameters.

After analyzing the variables that represented predictive factors of "failure to prevent ETI", patients with signs of RD after 2 h of NIV were 3.79 times more likely to require ETI in 48 h (OR: 3.79; 95% CI, 1.10-13.03; p=0.035). In addition, patients with presence of tachypnea after 2 h of NIV were 4.80 times more likely to require ETI in 48 h (OR: 4.80; 95% CI, 1.12-20.48 ; =0.034) (Table 2).

Analysis of the multivariate logistic regression, with inclusion of the predictor (presence of RD and altered RR after 2 h of NIV) and confounding (history of previous mechanical ventilation, type of ARF, pH <7.35, $PaCO_2$ >45 mmHg, and altered initial SpO_2) variables, only RR remained in the multivariate model (OR: 4.80; 95% CI, 1.12-20.48; p=0.034). Therefore, patients with tachypnea after 2 h of NIV present 4.80 fold chance of requiring EDI in 48 h.

Table 1. Demographic and clinical characteristics and initial NIV and cardiorespiratory parameters of the patients included in the study.

	Total (N = 52)
Gestational age	**N (%)**
Preterm	19 (36.5)
Term	33 (63.5)
ARF	**N (%)**
Type I	27 (51.9)
Type II	25 (48.1)
Previous MV	**N (%)**
Yes	23 (44.2)
No	29 (55.8)
Modality	**N (%)**
CPAP	17 (32.7)
BiPAP	35 (67.3)
Initial RD	**N (%)**
Yes	38 (73.1)
No	14 (26.9)
Days in NIV	**Median (min-max)**
Success group	2 (2-6)
Failure group	1 (0-1)

N: Number of cases; %: Relative percentage of cases; min: Minimum; max: Maximum; MV: History of previous mechanical ventilation; ARF: Acute respiratory failure; RD: Presence of respiratory distress; NIV: Noninvasive ventilation.

Table 2. Univariate logistic regression with the predictive variables for failure to prevent ETI in 48 h after placement of NIV.

	Failure Group		p	OR	95% CI
	N (%)	Total			
Gender					
Male	8 (29.6)	27	0.853	0.89	0.27-2.91
Female	8 (32.0)	25		1.00	
Gestational age					
Preterm	7 (36.8)	19	0.473	1.55	0.46-5.20
Term	9 (27.3)	33		1.00	
Current age					
Infant	11 (26.8)	41	0.241	0.44	0.11-1.73
Pre-schooler and schoolchildren	5 (45.5)	11		1.00	
Previous MV					
Yes	10 (43.5)	23	0.082	2.95	0.87-9.98
No	6 (20.7)	29		1.00	
ARF					
Type I	6 (22.2)	27	0.170	0.43	0.13-1.44
Type II	10 (40.0)	25		1.00	
Modality					
CPAP	4 (23.5)	17		1.00	
BiPAP	12 (34.3)	35	0.433	1.70	0.45-6.35
Initial RD					
Yes	13 (34.2)	38	0.380	1.91	0.45-8.06
No	3 (21.4)	14		1.00	
Initial RR					
Eupnea	9 (31.0)	29		1.00	
Tachypnea	7 (30.4)	23	0.963	0.97	0.30-3.18
Initial HR					
Sinus rhythm	6 (31.6)	19		1.00	
Tachycardia	10 (30.3)	33	0.924	0.94	0.28-3.19
Initial SpO_2					
>92%	11 (25.6)	43		1.00	
≤92%	5 (55.6)	9	0.088	3.64	0.83-16.01
pH gasometria inicial					
<7.35	5 (55.6)	9	0.144	0.300	0.06-1.51
7.35-7.45	6 (27.3)	22		1.00	
>7.45	4 (26.7)	15	0.967	1.03	0.23-4.53
Initial $PaCO_2$					
<35 mmHg	2 (16.7)	12	0.290	0.40	0.73-2.18
35-45 mmHg	10 (33.3)	30		1.00	
>45 mmHg	3 (75.0)	4	0.141	6.00	0.55-65.29
RD after 2 h					
Yes	10 (47.6)	21	0.035	3.79	1.10-13.03
No	6 (19.4)	31		1.00	
RR after 2 h					
Eupnea	10 (23.8)	42		1.00	
Tachypnea	6 (60.0)	10	0.034	4.80	1.12-20.48
HR after 2 h					
Sinus rhythm	11 (33.3)	33		1.00	
Tachycardia	5 (26.3)	19	0.598	0.71	0.20-2.50
SpO_2 after 2 h					
>92%	14 (28.0)	50		1.00	
≤92%	2 (100.0)	2	0.999	-	-

N: Number of cases; %: Relative percentage of cases; OR: Odds ratio; 95% CI: 95% confidence interval; MV: History of previous mechanical ventilation; ARF: Acute respiratory failure; CPAP: Continuous Positive Airway Pressure; BiPAP: Bilevel Positive Airway Pressure; RD: Presence of respiratory distress; RR: Respiratory rate; HR: heart rate; SpO_2: Peripheral oxygen saturation.

Table 3. Comparison of heart rate, respiratory rate, and peripheral oxygen saturation before and two hours after NIV placement.

	Moment	Average	SD	Minimum	Median	Maximum	p
HR	Before NIV	151.35	28.24	83	153	220	<0.001[a]
(bpm)	After NIV	135.57	24.65	83	137	185	
RR	Before NIV	49.58	17.40	20	50	87	<0.001[a]
(ipm)	After NIV	38.96	12.92	15	38	78	
SpO_2	Before NIV	96.42	4.35	87	98	100	<0.001[b]
(%)	After NIV	98.25	3.02	82	99	100	

SD: Standard deviation; HR: Heart rate; bpm: Beats per minute; RR: Respiratory rate; ipm: Incursions per minute; SpO_2: Peripheral oxygen saturation; NIV: Noninvasive ventilation. Statistical Tests: [a]Paired Student's *t*-Test; [b]Wilcoxon Test. p-value <0.05 with statistical significance.

Table 3 shows the comparison of cardiorespiratory values (HR, RR and SpO_2) before placement and after 2 h of NIV for all study participants. Significant differences were observed in all parameters analyzed, with increased values of HR, RR and SpO_2 after placement of NIV.

No statistically significant differences were observed between the failure and success groups when comparing variation in HR, RR and SpO_2 pre- and post-NIV placement.

DISCUSSION

To date, there are no Brazilian studies that have developed and applied an NIV protocol to infants, preschoolers and/or schoolchildren hospitalized in PICU to evaluate prevention of ETI, NIV success rate, and predictive factors of NIV failure. The present study identified a success rate of 69.2% with significant improvement in cardiorespiratory parameters 2 h after placement of NIV, and that tachypnea was a predictive factor of failure and an indication for ETI.

Use of NIV in the pediatric age group has been significantly increasing worldwide;[16,17] however, in a systematic review, Castro-Codesal et al. concluded that, despite the fact that most of the existing studies have low methodological quality, 73% of them have reported benefits regarding its use7. Therefore, NIV is an important therapeutic resource in pediatrics.[2,18]

Presence of respiratory failure was the indication criterion for the use of NIV in this study, and preventing the clinical worsening of patients with ARF is an important goal to be established, since it is considered the main cause of cardiorespiratory arrest in the pediatric age group, and is estimated that over 2 million children progress to death due to ARF every year.[18,19]

In ARF due to AVB, NIV presents recommendation A, since it assists with the upkeep of airways, improves expiratory flow and lung compliance, enables adequate gas exchange, decreases partial pressure of carbon dioxide ($PaCO_2$) and, thereby, minimizes the patient's ventilatory effort and signs of RD.[2,20]

Noninvasive mechanical ventilation provides early improvement in most patients with hypercapnic ARF, with some studies associating low GCS scores, absence of cough, poor adherence to NIV, and presence of bronchiectasis and pneumonia as predictive factors for late failure and consequent intubation.[21] In adults, Holanda et al., carried out a study with the objective of determining the efficacy of noninvasive positive pressure ventilation (NIPPV) in ARF and observed success in 62% of the evaluated patients. In addition, they concluded that failure in NIPPV is associated with high mortality, especially in more severe patients who do not respond as expected to its use.[12]

Presence of reintubation is often associated with increased morbidity, hospital costs and risks of hospital readmissions; therefore, knowledge of the predictive factors associated with extubation failure should be investigated.[22] In this study, patients with presence of tachypnea after 2 h of NIV were 4.8 times more likely to require ETI in 48 h. In a longitudinal study conducted with children admitted to PICU, the need for mechanical ventilatory support and Comfort sedation scale score <26 were factors associated with extubation failure.[22]

Tachypnea in the pediatric population indicates presence of respiratory difficulty or dysfunction, which is present in the conditions of hypoxia and hypercapnia and is one of the most frequently found in emergency services.[23] Persistence of tachypnea, even after placement of NIV, indicates greater severity of the disease, and suggests a failure of this resource and the need for ETI.

Improvement in cardiorespiratory parameters with the use of NIV is due to the presence of positive pressure in the airways, which can be achieved using one or two pressure levels, CPAP and BiPAP, respectively. NIV can improve oxygenation, functional residual capacity, ventilation/perfusion ratio, gas exchange, lung compliance, cardiac output, fatigue, and respiratory work, in addition to assisting with reducing collapsed areas.[2,6,24,25]

The use of NIV is increasingly frequent in PICU in type 1 and 2 ARF and in neuromuscular disorders; however, in order for NIV to be successful, it is necessary to have adequate equipment, patient acceptance, and a trained and prepared multi-professional team.[26-30] Moreover, it is emphasized that NIV should be considered an option for early treatment in children at risk for acute

respiratory distress syndrome (ARDS), provided that it is performed in an appropriate environment and monitored by a specialized multidisciplinary team 24 hours.[27-31]

As study limitations, we can mention that, despite the large number of patients evaluated, the number of participants who met the inclusion and exclusion criteria was substantially small, as it is a reference service, with wide variability in age range and clinical situation. Thus, we were able to evaluate the use of NIV in several diseases, such as AVB, cystic fibrosis, bronchopulmonary dysplasia, Down syndrome, among others. We would also like to point out that, despite the statistically significant differences found in the HR and SpO_2 values pre- and post-NIV placement, these values are not clinically significant.

Another limitation regards the diversity of sizes and shapes of the participants' faces, which hindered the adjustment and adequate adaptation of the interfaces and, consequently, caused failure in the use of NIV. Mortamet et al. conducted a review in order to describe the different types of interfaces for the pediatric age group in acute conditions and concluded that, despite the increased use of NIV and the availability of interfaces, there are no recommendations for choosing the most appropriate interface in this population.[32]

The choice of the ideal NIV interface is still considered challenging, since its adjustment to the child's face must be carried out in appropriately aiming to minimize air escape and leakage, ensure stability, and prevent interface moving and displacements, thus maximizing synchronization between patient and ventilator and increasing the chance of success.[32]

Finally, this study evaluated the response to NIV after 2 h of its placement; however, we suggest that further research be carried out to assess whether response in the cardiorespiratory parameters can occur in a shorter or longer time compared with that observed in the present study, as well as to identify the best period for conducting NIV response assessments.

The 2-hour period after placement of NIV is reported within the concept of "golden two hours", which is described as essential in monitoring patients.[3] Children treated with NIV require very careful observation during the first 2 h, because they need continuous reassessment to verify the indication of maintenance or interruption of its use, thus avoiding delaying intubation in cases of non-improvement of the condition.[3]

Furthermore, periodic assessment of ABG, despite being mentioned in the literature, presents difficulties to be carried out in practice, a situation that is quite often observed in our service. There is indication for first ABG measurement within the first 30 min of NIV, and every hour thereafter. Nevertheless, in most cases, it is decided to monitor vital signs and maintain the patient without painful components, which can cause confusion in the data collected.[3]

We emphasize that there is a precariousness of studies addressing the use of NIV in South America and a systematic review found only five studies in this region.[7] Thus, we emphasize the importance of carrying out this study with the application of NIV in the pediatric population in a Brazilian, reference, multidisciplinary, public hospital, since the results can provide more information on this type of ventilatory support for our population in the different diseases studied.

We conclude that the use of NIV was effective in infants, preschoolers and schoolchildren admitted to PICU with a success rate of 69.2%, and that presence of tachypnea after NIV placement is a predictive factor of failure to prevent ETI. In addition, when using the "golden two hours" concept, we consider this time safe to assess the success or failure of NIV, thus avoiding unfavorable consequences for the patient.

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ORIGINAL ARTICLE

Clinical and epidemiological characteristics of *M. kansasii* pulmonary infections from Rio de Janeiro, Brazil, between 2006 and 2016

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ABSTRACT

Objective: To evaluate clinical, tomographic, and microbiological characteristics of pulmonary disease caused by *M. kansasii* (MKPD) in patients treated at an outpatient unit from 2006-2016. **Methods:** We studied thirty eight patients, and analyzed socio-demographic, clinical-radiological, laboratory, and therapeutic characteristics. **Results:** The mean age was 64 years (SD = 10.6; IIQ = 57-72; median = 65.0), and 22 (57.9%) male patients. Pulmonary comorbidity was present in 89.5% of the patients. The most frequent comorbidity was bronchiectasis (78.9%). Previous treatment for pulmonary tuberculosis (PTB) was found in 65.9%. The most used therapeutic regimen was rifampicin, isoniazid and ethambutol (44.7%). Chest tomography (CT) showed bronchiectasis (94.1%), architectural distortion (76.5%), septum thickening (67.6%), and cavities (64.7%). Disease was bilateral in 85.2%. We observed 10.7% resistance to rifampicin, 67.9% resistance to ethambutol, and sensitivity to clarithromycin. **Conclusion:** In patients with structural lung disease, it is important to search for NTM, the main differential diagnosis with PTB. Chest CT showed different patterns that overlapped with structural disease caused by PTB or other lung diseases. We observed resistance to ethambutol, a drug component of the recommended regimen.

Keywords: Nontuberculous mycobacteria; *Mycobacterium kansasii*; Epidemiology; Treatment.

INTRODUCTION

Historically, pulmonary mycobacteria infections in humans were caused almost exclusively by *Mycobacterium tuberculosis* (Mtb).[1] Initially, non-tuberculous mycobacteria (NTM) were regarded only as environment organisms with limited clinical relevance, obfuscated by *M. tuberculosis*.[2] The AIDS pandemic highlighted the widespread disease caused by *M. avium* and *M. intracellulare* as opportunistic germs, which has caught the attention of the medical community.[2] NTM can be found in soil, in treated or untreated waters, often forming biofilms, sewage, animal surfaces and aerosols generated in the environment.[3,4] The latter is the most frequent source of infection for man, especially disease involving the respiratory system, as described in 94% of NTM cases.[4] Although the most accepted paradigm for transmission continues to be the inhalation of environmentally generated aerosols, mostly from shower,[3-5] conflicting reports suggest that transmission may occur from person to person.[4,6]

Mycobacterium kansasii (MK) is one of the six most isolated NTM species worldwide. Central Europe is a common geographical location of MK.[7] Its presence may be related to distribution systems of treated water and highly urbanized areas.[7,8] Disease presents as apical fibro-cavitary pulmonary disease with great similarity to pulmonary tuberculosis. Other less frequent form is nodular with bronchiectasis.[7]

The four major categories of people susceptible to NTM infection described include:[9] 1) Patients with structural involvement of the pulmonary parenchyma, such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, of pulmonary tuberculosis (PTB) sequelae, bronchiectasis; 2) Patients on immunobiological use, neoplasia, organ transplants; 3) People infected with HIV, who are more prone to disease disseminated by NTM, 4) Genetic diseases with mutation in pathways such as interferon gamma and interleukin 12. Another important group would be postmenopausal women,

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non-smokers with characteristic phenotype including low weight, scoliosis, pectus excavatum and mitral valve prolapse.[9]

In the last two decades, developed countries saw an increase in prevalence of disease caused by NTM and a decrease in tuberculosis incidence. TB control, population aging, the HIV epidemic and the development of new laboratory techniques allowed the isolation and identification of new species of mycobacteria in material from the respiratory tree.[10,11]

In Brazil, the prevalence of pulmonary infections due to NTM (NTMPD) was unknown until the implementation of a surveillance system (SITETB).[12] In Brazilian series with cases of NTMPD, the frequency of *M. kansasii* disease ranged from 16.0 to 33.9%, according to the region studied.[13-15] Between 2014 to 2017 in our country, NTM infections due to *Avium* Complex were more prevalent. However, in Rio de Janeiro State, the disease was mainly due to MK.[12] With the predominance of MK infection in Rio de Janeiro State, this study aims to present an analysis of MK pulmonary diseases (MKPD) in patients attended at our outpatient clinic. Variables studied were demographic aspects, clinical and laboratory characteristics, therapeutic regimens, and treatment outcomes.

METHODS

This is a descriptive study, analyzing medical records from patients having diagnosis of pulmonary disease caused by *M. kansasii*, between January 2006 and December 2016. The study was carried out in an outpatient unit for the treatment of drug-resistant TB and NTM. Patients were referred from different regions of the Rio de Janeiro State (Professor Hélio Fraga Reference Centre (CRPHF/ENSP/FIOCRUZ). The study included patients with growth and identification of *M. kansasii* in two sputum samples, or a bronchoalveolar lavage sample.[16]

We analyzed demographic, clinical-radiological, laboratorial, and therapeutic characteristics including: gender, age, housing municipality, pulmonary and non-pulmonary comorbidities, respiratory symptoms (cough, sputum, hemoptysis, chest pain, dyspnea) and systemic symptoms (fever, sweating, weight loss), number of PTB treatments, previous treatment for MK, clinical specimen, culture conversion, sensitivity test (ST), outcome (favorable, unfavorable, abandonment, death), chest radiography (presence of cavity, unilateral or bilateral), high resolution computed tomography (HRCT) of the lung. HRCT exams had documentation of the sequential cuts of the parenchyma, mediastinum, and high-resolution windows without administration of venous contrast medium. Abnormalities were analyzed according to Fleischner Society[17] classification and the Brazilian guideline on descriptors terminology and patterns of chest CT.[18] The following variables were used: presence or absence of atelectasis, bubble, cavity, emphysema, opacity, septal thickening, bronchiectasis, air trapping, architectural distortion, centrilobular nodular pattern/budding tree, consolidation, pleural alteration, lymph nodes and others.

Data were analyzed with the statistical software "R". Descriptive analysis of continuous variables, the mean, median and interquartile range (IQR), and standard deviation (SD), were obtained as measures of central tendency and dispersion. Percentage values were calculated for categorical variables. Fisher test was done to evaluate the associations between the relevant categorical variables: a) presence of previous TB treatment with gender, age, symptoms, comorbidities, outcomes, type and location of the lesion on HRCT, and ST; b) gender with comorbidities, location and type of lesion on HRCT.

Study was approved by the Ethics and Research Committee of Clementino Fraga Filho Hospital of the Rio de Janeiro Federal University (HUCFF/UFRJ) under number 213/08.

RESULTS

Thirty-eight patients with a microbiological diagnosis of MKPD who fulfilled the criteria defined by the American Thoracic Society (ATS) were included.[16] There were 22 (57.9%) male patients. Mean age was 64 years (SD = 10.63, IQR = 57-72, median = 65). Minimum age was 39 years and 86.9% were 50 years or older (Table 1). Patients came from the metropolitan region of Rio de Janeiro. Of these, 26 (68.42%) were referred from Rio de Janeiro municipality and 12 patients (31.58%) came from Baixada Fluminense (districts adjacent to Rio de Janeiro City) (Table 1).

All patients had some type of comorbidity. These were subdivided into pulmonary and non-pulmonary comorbidities. Pulmonary comorbidity was present in 34 (89.5%), the most frequent condition being bronchiectasis (78.9%), chronic obstructive pulmonary disease (COPD) (55.3%), asthma (15.8%), and silicosis (5.3%) (Table 1). Smoking report was present in 60.5% patients. The most frequent non-pulmonary comorbidities were gastroesophageal reflux in 23.7% (Table 1). The most frequent symptoms were divided into three groups: respiratory, systemic and both. Most patients (94.7%) had respiratory symptoms, and 44.7% had respiratory and systemic symptoms. No patient had systemic symptoms only. Respiratory and systemic symptoms were cough (89.5%), sputum (86.8%), dyspnea (55.3%), chest pain (34.2%), hemoptysis (31.6%), weight loss (34.2%), fever (23.7%) and sweating (10.5%). (Table 1)

Most patients reported previous treatment for pulmonary tuberculosis (PTB) or were undergoing treatment. Of these, 25 (65.9%) patients reported previous treatment for pulmonary tuberculosis. The mean previous treatments was 1.7 (median = 2.0, SD = 0.79, IIQ = 1.0-2.0). Two patients previously treated MKPD. Twenty-seven (71.1%) patients were using a therapeutic regimen to treat suspected pulmonary PTB when diagnosed with MKPD. Regarding the therapeutic regimens used, 17 (44.7%) patients used rifampicin (R), isoniazid (H)

Table 1. Clinical and demographic characteristics, patients with MKPD, Rio de Janeiro, 2006-2016 (N = 38).

	N (%)		N (%)
Gender		*Previous treatments*	
Male	22 (57.9)	MK previous treatment	2 (5.3)
Female	16 (42.1)	TB previous treatment	25 (65.8)
Age (years)		On TB treatment	27 (71.1)
30 to 49	4 (10.5)	*Comorbidities*	
50 to 60	9 (23.7)	*Pulmonary comorbidity*	
61 to 70	12 (3.6)	Bronchiectasis	30 (78.9)
71 to 80	12 (31.6)	Smoking	23 (60.5)
> 80	1 (2.6)	COPD	21 (55.3)
Place of residence		Asthma	6 (15.8)
Northern Zone	16 (42.1)	Silicosis	2 (5.3)
Baixada Fluminense	13 (34.2)	*Other comorbidity*	
West Zone	5 (13.2)	GER	9 (23.7)
South Zone	3 (7.9)	Diabetes	4 (10.5)
Centre	1 (2.6)	Alcoholism	5 (13.2)
Respiratory symptoms		Hepatitis	5 (13.2)
Cough	34 (89.5)	Immunosuppressive use	4 (10.5)
Expectoration	33 (86.8)	Drug addiction	1 (2.6)
Dyspnea	21 (55.3)	HIV infection	1 (2.6)
Hemoptysis	12 (31.6)	*Clinical specimen*	
Thoracic pain	13 (34.2)	Sputum	26 (68.4
Weight loss	13 (34.2)	BAL	12 (31.6
Systemic symptoms		*Thorax X-ray*	
Fever	9 (23.7)	Cavitary bilateral	18 (47.4)
Sweating	4 (10.5)	Cavitary unilateral	11 (28.9)
Respiratory symptoms		Non-cavitary bilateral	6 (15.8)
Yes	36 (94.6)	Non-cavitary unilateral	2 (5.3)
No	2 (5.3)	Normal	1 (2.6)
Systemic symptoms		*Cavities X-ray*	
Yes	17 (44.7)	Yes	29 (76.3)
No	21 (55.3)		
Both symptoms			
Yes	17 (44.7)		
No	21 (55.3)		

MKPD: *Mycobacterium kansasii* pulmonary Disease; N: Case number; TB; tuberculosis; COPD: Chronic Obstructive Pulmonary Disease; BAL: Bronchoalveolar lavage; HIV: Human Immunodeficiency Virus; GER: Gastroesophageal Reflux; MK: *M. kansasii*.

and ethambutol (E). Of these, seven (18.4%) patients used rifampicin, isoniazid (H) and clarithromycin (CLA) and seven (18.4%) patients used RHE and clarithromycin (Table 2).

Regarding the outcomes, after discharge from the treatment, we had two recurrences (5.3%); two deaths (5.3%) due to hemoptysis following discontinuation of the treatment regimen; and three (7.9%) patients discontinued treatment.

We collected two sputum samples from 26 patients (68.4%), and bronchoalveolar lavage in 12 patients (31.6%). The mean time for culture conversion was 75 days (median = 62). Twenty-eight sensitivity tests were performed (Table 2). Only three (10.7%) showed resistance to rifampicin, 19 (67.9%) tests detected resistance to ethambutol, and all tests were sensitive to clarithromycin, moxifloxacin and amikacin.

All patients underwent chest radiography. Eighteen (47.4%) patients showed bilateral cavitary lesion (BC), 11 (28.9%) unilateral cavitary lesion (UC), six (15.8%) bilateral non-cavitary lesion, and (5.3%) had unilateral non-cavitary lesion (UNC), and one (2.6%) with normal radiography. It is noteworthy that 29 (76.3%) patients presented with cavities.

Thirty-four CT scans were analyzed focusing on the frequency of the lesions observed and the location of the lesions in the lung. Lesions were preferentially located in the upper lobes (LSD: 94.1% and LSE: 85.3%). (Table 3) In the upper right lobe the segments most affected were posterior segment (88.2%), apical segment (82.4%) and anterior segment (67.6%). In the upper left lobe: apicoposterior segment (76.5%), lingula (76.5%), and anterior segment (58.8%). In order of frequency, the lesions found

Table 2. Sensitivity test result (N=38).

Drug	Tested		Not tested (%)
	Resistant (%)	Sensitive (%)	
Clarithromycin	0	26 (100)	12 (31.6)
Rifampicin	3 (10.7)	25 (89.3)	10 (26.3)
Amikacin	0	26 (100)	12 (31.6)
Ciprofloxacin	17 (65.4)	9 (34.6)	12 (31.6)
Ethambutol	19 (67.9)	9 (32.1)	10 (26.3)
Moxifloxacin	0	26 (100)	12 (31.6)
Trimethoprim-sulfamethoxazole	25 (96.2)	1 (3.8)	12 (31.6)
Linezolid	1 (4.5)	21 (95.5)	16 (42.1)

Table 3. Location of lesions on HRCT (N = 34).

	N (%)
Right lung	33 (97.1)
Upper right lobe	32 (94.1%)
Anterior	23 (67.6)
Apical	28 (82.4)
Posterior	30 (88.2)
Middle lobe	19 (55.9%)
Medial	18 (52.9)
Lateral	18 (52.9)
Right lower lobe	23 (67.6%)
Superior	18 (52.9)
Anterior	17 (50.0)
Medial	14 (41.2)
Lateral	17 (50.0)
Posterior	17 (50.0)
Left lung	30 (88.2)
left upper lobe	29 (85.3%)
Anterior	20 (58.8)
Apicoposterior	26 (76.5)
Lingula	26 (76.5)
left lower lobe	21 (61.8%)
Superior	17 (50.0)
Anteromedial	17 (50.0)
Lateral	17 (50.0)
Posterior	18 (52.9)
Bilateral disease	29 (85.2)
Right lung disease (exclusive)	4 (11.8)
Left lung disease (exclusive)	1(3.0)

Table 4. Frequency of lesions at the HRCT scan (N = 34).

Lesion type	N (%)
Bronchiectasis	32 (94.1)
Architectural distortion	26 (76.5)
Septal thickening	23 (67.6)
Cavity	22 (64.7)
Opacity	21 (61.8)
Centrallobular nodules / budding tree	20 (58.8)
Atelectasis	16 (52.9)
Emphysema	13 (38.2)
Air trapping	10 (29.4)
Bubble	7 (20.6)
Pleural changes	6 (17.6)
Lymph node enlargement	3 (8.8)

HRCT: Higth Resolution Computed Tomography.

were bronchiectasis (94.1%), architectural distortion (76.5%), septal thickening (67.6%), cavities (64.7%), opacity (61.8%) and centrilobular nodules / budding tree (58.8%) (Table 4).

We observed no significant association among most categorical variables studied (Table 5). The data suggest association between previous treatment of PTB and pleural changes in tomography (p-value = 0.06, borderline). There is a statistically significant association between patient gender and presence middle lobe lesion on HRCT (p=0.017). No association was found between prior schedules for Tb and ethambutol resistance.

DISCUSSION

We observed a predominance of males (57.9%) with a mean age of 64 years, as found by others.[19-23] We assume that the predominance of males found in various publications may be related to habits such as smoking, prevalence of pulmonary comorbidities such as COPD and previous PTB treatments, more common in males. Lung infection caused by MK occurred mainly in the elderly, as found by Bakula et al. (2018), contrasting with studies from previous years in which patients were 10 to 20 years younger.[19-21] The most advanced mean age may be related to the greater longevity of the general population and associated comorbidities. In our population, there may be a delay in diagnosis due to the TB burden, and clinical and radiological similarity between them.

Most patients had pulmonary comorbidities. Bronchiectasis was the most frequent finding, with a higher occurrence than that reported by others.[8,19-23] Since the diagnosis of infection is late, pulmonary lesions are more severe on radiology. Prevalence of COPD is high and may be related to the tobacco load found (60.5%). Other authors also report distinct prevalence of COPD and smoking.[8,19-23] There are publications that associate MK infection with the sequelae of PTB in regions endemic for this disease.[8] At the time of diagnosis of MK, 65.8% patients were previously PTB treated, and 71% of them were on medication for TB. Recent Polish publication also mentions that half of the patients had a history of

Table 5. Fisher's test, variables with p-value <0.10.

Gender	N(%) Male	N(%) Female	p-value
HRCT - middle lobe damage			0.017
Yes	7 (36.8)	12 (63.2)	
No	12 (80.0)	3 (20.0)	
Previous TB treatment			0.098
Yes	17 (68.0)	8 (32.0)	
No	5 (38.5)	8 (61.5)	
Previous TB treatment			
Systemic symptoms			0.086
Yes	14 (82.3)	3 (17.7)	
No	11 (52.4)	10 (47.6)	
Both symptoms			0.086
Yes	14 (82.3)	3 (17.7)	
No	11 (52.4)	10 (47.6)	
HRCT- nodules / budding tree			0.080
Yes	15 (75.0)	5 (25.0)	
No	6 (42.9)	8 (57.1)	
HRCT-Pleural changes			0.062
Yes	6 (100.0)	0	
No	15 (53.6)	13 (46.4)	
Rifampicin resistance (N=28)			0.037
Resistant	0	3 (100.0)	
Sensitive	18 (72.0)	7 (28.0)	

p-value: significance probability; TB: Tuberculosis; HRCT: High Resolution Computed Tomography.

previous PTB treatment.[8] Past PTB and MK infection is observed less markedly in other studies, in which PTB prevalence was lower.[19-22]

The high frequency of previous treatments for PTB in cases of MKPD might be related to the high prevalence of PTB in Rio de Janeiro, clinical and radiological similarity between the two diseases, and finally, and the lack of diagnostic resources and trained personnel to diagnose NTMPD. Probably, several cases of NTMPD are treated with schedules employed in TB treatment.

The most frequent non-pulmonary comorbidity was gastroesophageal reflux, an illness that may be related to the pathophysiology of bronchiectasis. We found only one study that cites gastroesophageal reflux as a comorbidity.[8] In a cohort studying the etiology of bronchiectasis, GER was found in only 2.0%. The most common associated diseases with bronchiectasis were the post-infectious cause (PTB and pneumonia).[24] Predominant respiratory symptom was cough with expectoration. In several publications, the most frequent symptom was cough.[19-21,23] Hemoptysis is mentioned in all series studied with varying frequencies, probably caused by erosion of the bronchial vessel present in the cavities.[8,19-22] Systemic symptoms are present in almost half of the patients in sample.

Literature describes two main tomographic patterns of NTM-related lesions: fibrocavities (tuberculosis-like) mainly located in the upper lobes, and nodular/ bronchiectasis.[16] We observed predominance of bilateral lung involvement, with predilection for lesions by the upper lobes, especially the right upper lobe similar to that found by Takahashi.[25] Late diagnosis that occurs in MKPD is possibly due to radiological similarity with PTB, and may explain the strong bilateral involvement found in our study. The high frequency of bronchiectasis with predilection for upper lobes and architectural distortion found may also be related to pulmonary sequelae caused by previous PTB treatments. NTM and MTb are classified as mandatory aerobic, and the high concentration of oxygen in the apices favors MK to be preferentially in this location. Our patients with MKPD showed predominance of cavities and the pattern of involvement of small and large airways, characterized by bronchiectasis and changes due to filling of bronchioles.

Even with high exposure to previous PTB treatments, we found no significant resistance to rifampicin. More than half of the patients were resistant to ethambutol. The higher resistance to ethambutol observed in MKPD may have genetic determinants similar to that occurring in TB. Other studies are needed to point out specific mutations or mechanisms that confer resistance to drugs in MK infection.[8] More than half of the patients used therapeutic regimens containing ethambutol. The combination of drugs in regimens containing rifampicin ensures

successful treatment of MK infection.[26] Despite the higher resistance attributed to ethambutol, patient's outcome was successful.

Presumably, due to the small sample studied, few associations were found. It is worth mentioning the presence of an association between gender and middle lobe lesion on HRCT. Studies that are more robust are needed to better elucidate this finding.

As the investigation was carried out with data from medical records, information bias may have occurred. The study was retrospective; therefore, some information may not have been recorded, like comorbidities and tests results. Even though it is a descriptive study, we must be attentive to the external validity since patients studied come from a population with a high TB burden. The small sample size probably influenced the few associations found between the variables.

We found MKPD in older patients with pulmonary comorbidities. We should be aware of NTM disease in patients with more advanced age with respiratory symptoms. Almost all patients had symptoms, mainly cough. Lesions present in radiology are like those found in tuberculosis, making radiological findings often indistinguishable. Most patients presented sensitivity to rifampicin, which makes possible the use of this drug in the treatment schemes and guarantee the therapeutic success.

Due to the high incidence of PTB in our state, the clinical and radiological similarity that we find between TB and pulmonary infection by MK, the late diagnosis of the disease is common, and consequently functional and structural pulmonary compromises are frequent.

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EBUS-TBNA versus surgical mediastinoscopy for mediastinal lymph node staging in potentially operable non-small cell lung cancer: a systematic review and meta-analysis

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

ABSTRACT

Objective: Lung cancer (LC) is one of the leading causes of death worldwide. Accurate mediastinal staging is mandatory in order to assess prognosis and to select patients for surgical treatment. EBUS-TBNA is a minimally invasive procedure that allows sampling of mediastinal lymph nodes (LNs). Some studies have suggested that EBUS-TBNA is preferable to surgical mediastinoscopy for mediastinal staging of LC. The objective of this systematic review and meta-analysis was to compare EBUS-TBNA and mediastinoscopy in terms of their effectiveness for mediastinal LN staging in potentially operable non-small cell lung cancer (NSCLC). **Methods:** This was a systematic review and meta-analysis, in which we searched various databases. We included studies comparing the accuracy of EBUS-TBNA with that of mediastinoscopy for mediastinal LN staging in patients with NSCLC. In the meta-analysis, we calculated sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios. We also analyzed the risk difference for the reported complications associated with each procedure. **Results:** The search identified 4,201 articles, 5 of which (with a combined total of 532 patients) were selected for inclusion in the meta-analysis. There were no statistically significant differences between EBUS-TBNA and mediastinoscopy in terms of the sensitivity (81% vs. 75%), specificity (100% for both), positive likelihood ratio (101.03 vs. 95.70), or negative likelihood ratio (0.21 vs. 0.23). The area under the summary ROC curve was 0.9881 and 0.9895 for EBUS-TBNA and mediastinoscopy, respectively. Although the number of complications was higher for mediastinoscopy, the difference was not significant (risk difference: −0.03; 95% CI: −0.07 to 0.01; I^2 = 76%). **Conclusions:** EBUS-TBNA and mediastinoscopy produced similar results for mediastinal staging of NSCLC. EBUS-TBNA can be the procedure of first choice for LN staging in patients with NSCLC.

Keywords: Lung neoplasms/diagnosis; Neoplasm staging; Mediastinal neoplasms/diagnosis; Endoscopic ultrasound-guided fine needle aspiration; Mediastinoscopy.

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide.[1] For patients diagnosed with lung cancer, the five-year survival rate is 17.7%, and 50% of such patients present with mediastinal metastasis at diagnosis.[2,3]

In patients with non-small cell lung cancer (NSCLC) and no distant metastases, the most important prognostic information is neoplastic involvement of the mediastinal lymph nodes (LNs). Therefore, accurate mediastinal staging is mandatory in order to assess prognosis and enable treatment planning. Patients with mediastinal LN metastasis (N2/N3 disease) should be considered candidates for multimodal treatment, which might or might not include surgery.[3,4]

The use of CT and PET/CT has improved radiological staging of the mediastinum. However, both have limited sensitivity and specificity.[3-5] Invasive mediastinal staging is recommended for all patients with potentially resectable NSCLC, except for those with bulky disease and no metastases, as well as those with a peripheral clinical stage IA tumor (with no LN involvement on CT or PET/CT), the radiological staging of which is usually sufficient.[6]

Among the methods for surgical staging of NSCLC, surgical mediastinal staging by mediastinoscopy was the gold standard until a few years ago.[7] Although mediastinoscopy provides accurate staging, the costs and risks inherent to the method make it less than ideal.[8-11]

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The introduction of endoscopy-based techniques, such as EBUS-TBNA and endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), revolutionized the approach to lung cancer staging, and these techniques are recommended as the first choice for invasive staging.[6] Numerous LN stations that are important in the setting of lung cancer staging can be accessed with EBUS-TBNA and EUS-FNA.[12]

Most of the systematic reviews available have compared the combined use of endoscopic methods (EBUS-TBNA and EUS-FNA) with that of mediastinoscopy, and few of those reviews have distinguished between the data collected by each endoscopic method.[13,14]

With EBUS-TBNA, real-time biopsy samples can be obtained from mediastinal, hilar, and interlobar LNs, which are relevant stations in lung cancer staging, whereas EUS-FNA is unable to access all of the relevant LN stations on the right side. However, unlike EBUS-TBNA, EUS-FNA enables access to lower paraesophageal, infradiaphragmatic, and retroperitoneal LNs, the latter two having a lesser clinical impact on the therapeutic strategy.[15]

Dong et al.,[16] in a meta-analysis, evaluated the efficacy of EBUS-TBNA for staging mediastinal LNs in cases of NSCLC. However, none of the studies selected compared EBUS-TBNA with mediastinoscopy. In most of the selected studies, mediastinoscopy was not employed in the LN staging.

A meta-analysis conducted by Gu et al.[17] evaluated the efficacy of EBUS-TBNA in LN staging. Eleven studies were selected, of which 5 (45%) also included the diagnostic investigation of lymphadenopathy and 4 (35%) did not compare EBUS-TBNA with mediastinoscopy. In addition, some studies that carried out that comparison provided no information about how many patients underwent mediastinoscopy.

Other studies compared patients who underwent EBUS-TBNA with those who underwent mediastinoscopy. In a meta-analysis, Ge et al.[18] selected studies that used EBUS-TBNA or mediastinoscopy for NSCLC staging. Of the 17 studies selected, only 3 actually compared the two methods in their sample of patients.

Because most of the available studies and meta-analyses have shown that the accuracy of the combined use of EBUS-TBNA and EUS-FNA for mediastinal staging in patients with potentially operable NSCLC is equivalent to that of the use of mediastinoscopy,[19,20] the question that remains is whether EBUS-TBNA alone would have a similar diagnostic yield.

METHODS

The present systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations[21] and was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42016046522).

Eligibility criteria

The studies selected consisted of prospective randomized and nonrandomized clinical trials evaluating the diagnostic efficacy of EBUS-TBNA and that of mediastinoscopy for mediastinal LN staging in patients with potentially operable NSCLC. This meta-analysis included only studies that directly or indirectly provided all the data necessary to calculate the sensitivity, specificity, positive likelihood ratio (LR+), and negative likelihood ratio (LR−). Studies that evaluated the combined use of EUS-FNA and EBUS-TBNA, providing no separate data for EBUS-TBNA, were excluded. We imposed no restrictions regarding the language or year of publication.

The studies selected included patients diagnosed with potentially resectable NSCLC, as defined by radiological criteria, without distant metastasis, and without evidence of bulky disease. There were no limitations regarding patient characteristics such as gender, age, and presence of comorbidities.

The types of interventions studied were EBUS-TBNA and mediastinoscopy. The standard for comparing the two methods was the result of tumor resection surgery, based on systematic mediastinal LN sampling or dissection.

The outcome measures were the sensitivity, specificity, LR+, and LR− for mediastinal LN staging. In addition, the complication rate for each procedure was analyzed.

Information sources and search strategy

Systematic searches were conducted in the MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Elton Bryson Stephens Company (EBSCO), LILACS, Brazilian Virtual Library of Health, and Scopus databases, the date ranges being set to from the inception of the indices through February 12, 2018. We also performed gray literature searches, which included references in the articles selected and in those within the collection of the library of the University of São Paulo. Specific search strategies were used for each database: MEDLINE—("Pulmonary Neoplasms" OR "Neoplasms, Lung" OR "Lung Neoplasm" OR "Neoplasm Lung" OR "Neoplasms Pulmonary" OR "Neoplasm, Pulmonary" OR "Pulmonary Neoplasm" OR "Lung Cancer" OR "Cancer Lung" OR "Cancers Lung" OR "Lung Cancers" OR "Pulmonary Cancer" OR "Cancer Pulmonary" OR "Cancers Pulmonary" OR "Pulmonary Cancers" OR "Cancer of the Lung" OR "Cancer of Lung" OR "Non small cell cancer" OR "Non small cell carcinoma") AND ("EBUS-TBNA" OR "Endobronchial Ultrasound" OR "Endobronchial ultrasound-guided transbronchial needle aspiration") AND ("Mediastinoscopies" OR "Mediastinoscopic Surgical Procedures" OR "Mediastinoscopic Surgical Procedure" OR "Procedure, Mediastinoscopic Surgical" OR "Procedures, Mediastinoscopic Surgical" OR "Surgical Procedure, Mediastinoscopic" OR "Surgery, Mediastinoscopic" OR "Surgical Procedures, Mediastinoscopic" OR "Mediastinoscopic Surgery"

OR "Mediastinoscopic Surgeries" OR "Surgeries, Mediastinoscopic" OR "Surgery"); and Cochrane Central Register of Controlled Trials, EMBASE, EBSCO, LILACS, Brazilian Virtual Library of Health, and Scopus—("Lung Cancer" OR "Pulmonary Neoplasms" OR "Lung Neoplasm" OR "Cancer Lung" OR "Pulmonary Cancer") AND ("EBUS-TBNA" OR "Endobronchial Ultrasound" OR "Endobronchial ultrasound-guided transbronchial needle aspiration") AND ("Mediastinoscopy" OR "Surgery").

Study selection

Studies were selected in a standardized way by two independent specialists. The articles were initially selected by title and abstract. For the meta-analysis, each study was then included or excluded on the basis of a full-text evaluation. Abstract-only and retrospective studies were not included in the systematic review.

Data collection and data items

Absolute numbers were collected directly from the text and separated into true positives, true negatives, false positives, and false negatives. Only studies containing all the necessary data and meeting the criteria applied in the meta-analysis were included. Only published data were considered. The same positivity criteria for the methods used in the selected studies were considered. The interventions compared were EBUS-TBNA and mediastinoscopy, both followed by surgical resection and systematic LN sampling or dissection. The total number of complications reported was also considered in the analysis.

Risk of bias

Two independent reviewers analyzed the quality of the studies using predefined criteria. We used the revised version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) to assess the risk of bias and applicability concerns in patient selection, as well as to assess the risk of bias in the flow and timing of tests.[22] Homogeneous prospective randomized studies were considered eligible. The risk of bias and applicability concerns was considered high when the selected patients were not under suspicion of having NSCLC or had a confirmed diagnosis of NSCLC. Crossover studies in which EBUS-TBNA was followed by mediastinoscopy were considered eligible. In addition, if the interval between tests was short, the risk of bias was assumed to be low.

Synthesis of results and analysis

Quantitative analyses were conducted with the software Review Manager, version 5.3 (RevMan 5; Cochrane Collaboration, Oxford, England). The meta-analysis was carried out using the Meta-Disc program, version 1.4 (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain).[23] The sensitivity, specificity, LR+, and LR− are presented in forest plots. Summary ROC (sROC) curves were constructed, and the areas under the curves were estimated. All of the variables were analyzed by patient. Heterogeneity was assessed by calculating the I^2 coefficient. The Mantel-Haenszel fixed-effect model was used in the meta-analysis. The DerSimonian-Laird random-effects model was used for calculation in cases of high heterogeneity between studies (I^2 > 50%). The Moses-Littenberg linear model was used in the construction of the sROC curves.

Complications were classified as major or minor adverse intraprocedural events. Major complications were death; lidocaine intoxication requiring special intervention; respiratory failure requiring interventions other than oxygen administration; tracheal, nerve, or vessel injury; parenchymal lesions adjacent to major airways; pneumonia; mediastinitis; pericarditis; other infectious complications; fever lasting longer than 24 h; pneumothorax requiring bed rest or thoracic drainage; prolonged bronchospasm; hemorrhage not responsive to the topical application of adrenaline or cold saline, thus requiring further intervention; and vocal cord paralysis. Minor complications were hemorrhage other than that described above; temporary laryngospasm; bronchospasm; desaturations during the procedure; and fever lasting up to 24 h.[24,25]

The total numbers of complications associated with each procedure were considered for analysis as dichotomous data in a forest plot. The risk difference was determined using the Mantel-Haenszel fixed-effects model. In the case of high heterogeneity, a sensitivity analysis was performed in order to identify outlier studies.

Primary and secondary outcomes

The primary outcome of the present systematic review and meta-analysis was to determine the accuracy of EBUS-TBNA for mediastinal LN staging in patients with potentially operable NSCLC. The secondary outcomes were used in order to compare the effectiveness of EBUS-TBNA with that of mediastinoscopy.

RESULTS

The searches of the literature resulted in 1,423 records in MEDLINE and 2,778 in the other databases. Therefore, a total of 4,201 records were eligible for inclusion in this systematic review. After an initial selection, 30 articles were included for full-text evaluation. Eight comparative prospective studies were selected for the systematic review.[26-33] One clinical trial was included despite the combined use of EBUS and EUS, because it provided separate data on EBUS for the analysis.[31] Two randomized controlled clinical trials were excluded because it was impossible to obtain separate data on EBUS-TBNA for the analysis.[29,33] Another clinical trial was excluded because it was not clear whether the study design was retrospective or prospective.[32] One clinical trial reported all data in a per-lesion analysis form, thus rendering it unfeasible to calculate separate values for true positives, false positives, true negatives, and false negatives, as would

be possible in a per-patient analysis.[30] For the purpose of the meta-analysis, 5 studies were considered for the analysis of complications,[26-28,30,31] although only 4 included diagnostic outcomes (Figure 1).[26-28,31]

Among the studies selected for data extraction and analysis, there were 5 prospective sequential clinical studies, all of which were included in the meta-analysis. Those 5 studies included patients diagnosed with potentially resectable NSCLC, as defined by radiological criteria, without distant metastasis, and without evidence of bulky disease. In 4 of the studies included, sensitivity and specificity were presented as fractions. The characteristics of the studies are presented in Table 1.

Risk of bias

We evaluated the studies by qualitative analysis in accordance with the QUADAS-2 criteria (Table 2). The majority of the articles were considered to have a low risk of bias in all domains.

Results in individual studies

Four studies used per-patient analysis. The sensitivity of EBUS-TBNA and mediastinoscopy was 81% (95% CI: 75-86%, I^2 = 46.5%) and 75% (95% CI: 69-81%; I^2 = 84.7%), respectively (Figure 2). The specificity of EBUS-TBNA and mediastinoscopy was 100% for both (95% CI: 99-100%; I^2 = 0.0%). The LR+ for EBUS-TBNA and mediastinoscopy was 101.03 (95% CI: 25.71-397.04; I^2 = 0.0%) and 95.70 (95% CI: 23.94-382.58; I^2 = 0.0%), respectively. The LR− for EBUS-TBNA and mediastinoscopy was 0.21 (95% CI: 0.16-0.28; I^2 = 44.5%) and 0.23 (95% CI: 0.11-0.47; I^2 = 83.5%), respectively (Figure 3). No statistically significant differences were found between the methods regarding the sensitivity, specificity, LR+, or LR−. The area under the sROC curve was 0.9881 for EBUS-TBNA (Figure 4) and 0.9895 for mediastinoscopy (Figure 5).

The total number of complications was higher in the mediastinoscopy group. Nevertheless, no significant difference was found in the meta-analysis (risk difference: −0.03, 95% CI: −0.07 to 0.01; I^2 = 76%; Figure 6). A random-effects model was used because of the high heterogeneity, which persisted even after the exclusion of outliers.

DISCUSSION

Accurate staging of potentially operable NSCLC is mandatory to determine the prognosis and define

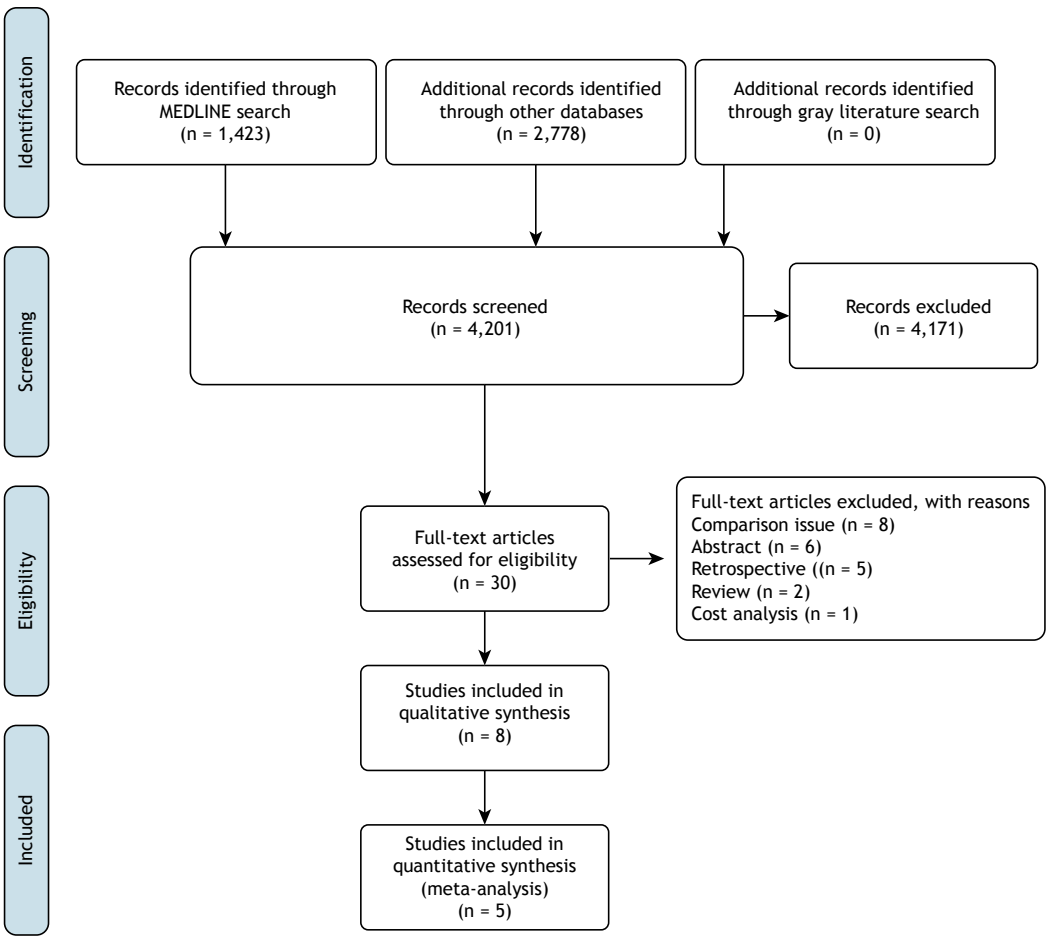

Figure 1. Flow chart of the article selection process.

Table 1. Characteristics of the studies selected that were included or excluded in the meta-analysis.

Study	Patient (n)	Gold standard	Interval	Study design	Inclusion criteria	Test method
Included						
Ernst et al.[30]	60	Surgical staging	Sequential approach or tests performed within a 1-week interval	Prospective crossover	Suspected NSCLC, potentially resectable	EBUS-TBNA vs. cervical mediastinoscopy
Yasufuku et al.[28]	153	Surgical staging	Sequential approach	Prospective crossover	Confirmed or suspected NSCLC	EBUS-TBNA vs. cervical mediastinoscopy
Zhang et al.[27]	26	Surgical staging and mediastinoscopy	Sequential approach	Prospective crossover	Confirmed or suspected NSCLC	EBUS + TBNA vs. transcervical video-assisted mediastinoscopy
Liberman et al.[31]	166	Surgical staging and mediastinoscopy	Sequential approach	Prospective crossover	Potentially resectable NSCLC	EBUS vs. EUS vs. EBUS + EUS vs. SMS (cervical mediastinoscopy and anterior mediastinostomy if necessary)
Um et al.[26]	127	Surgical staging and mediastinoscopy	Tests performed within a 3-week interval	Prospective crossover	Potentially resectable NSCLC	EBUS-TBNA vs. mediastinoscopy (cervical and VAM)
Excluded						
Annema et al.[29]	241	Surgical staging	Unclear	RCT	Potentially resectable NSCLC	Surgical staging vs. endosonography (combined EBUS-TBNA and EUS-FNA) and surgical staging
Sharples et al.[33]	241	Surgical staging	Unclear	RCT	Confirmed or suspected NSCLC, potentially resectable	Surgical staging vs. endosonography (combined EBUS-TBNA and EUS-FNA) and surgical staging
Dziedzic et al.[32]	1,841	Surgical staging	Sequential approach or unclear	Retrospective chart review	Suspected or proven NSCLC	EBUS-TBNA vs. cervical mediastinoscopy

NSCLC: non-small cell lung cancer; EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; EUS-FNA: endoscopic ultrasound with fine needle aspiration; SMS: surgical mediastinal staging (by mediastinoscopy); VAM: video-assisted mediastinoscopy; and RCT: randomized clinical trial.

Table 2. Risk of bias in individual studies.

Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Ernst et al.[30]	Low	Low	Low	Low	Low	Low	Low
Yasufuku et al.[28]	Low	Low	Low	Low	Low	Low	Low
Zhang et al.[27]	Low	Low	Low	Low	Low	Low	Low
Liberman et al.[31]	Low	Low	Low	Low	Low	Low	Low
Um et al.[26]	Low	Low	Low	High	Low	Low	Low

the appropriate treatment. Although CT and PET/CT are frequently used for primary screening, these methods cannot establish the presence of malignancy and definitive tissue diagnosis with EBUS-TBNA or mediastinoscopy is required in order to confirm the results.[6,7]

Yasufuku et al.[28] reported no significant differences between EBUS-TBNA and mediastinoscopy in the

staging of mediastinal LNs in NSCLC. When performed by experienced specialists, EBUS-TBNA can replace mediastinoscopy for accurate mediastinal staging of potentially resectable lung cancer.

A few meta-analyses have been carried out over the last decade to determine the effectiveness of EBUS-TBNA in the staging of LNs in NSCLC. In a meta-analysis, Ge et al.[18] compared video-assisted mediastinoscopy (VAM) and EBUS-TBNA for mediastinal staging and included two different groups. The first group included 10 studies with a collective total of 999 patients who underwent EBUS-TBNA, although only 2 of the studies compared EBUS-TBNA with mediastinoscopy. The second group included 7 studies with a collective total of 915 patients who underwent VAM (without EBUS-TBNA). The pooled sensitivities of VAM and EBUS-TBNA were not significantly different. However, a greater number of procedural complications and fewer false negatives were found in the VAM group than in the EBUS-TBNA group. The two techniques exhibited equally high diagnostic accuracy for the mediastinal staging of lung cancer.[18]

The present meta-analysis selected only studies in which patients underwent EBUS-TBNA followed by mediastinoscopy and in which, if there was no evidence of N2 or N3 disease, patients underwent surgical resection of the tumor and systematic nodal sampling or dissection.[26-28,31] In most of the studies, patients underwent the two procedures sequentially.[27,28,31] In one clinical trial, patients underwent the two procedures within a one-week interval.[28] In another study, patients underwent the two procedures within a three-week interval, which constituted a flow and timing bias.[26]

The European Society of Gastrointestinal Endoscopy, in cooperation with the European Respiratory Society and the European Society of Thoracic Surgeons, published a guideline[34] suggesting that the combined use of EBUS-TBNA and EUS-FNA is preferred over the use of either procedure alone (grade C recommendation). However, if combining EBUS-TBNA and EUS-FNA is not an option, EBUS-TBNA alone is acceptable (also a grade C recommendation).

Various meta-analyses have reported on the performance of EBUS-TBNA/EUS-FNA in the mediastinal staging of lung cancer. Sehgal et al.[20] compared endosonography (EBUS-TBNA and EUS-FNA) with mediastinoscopy for lung cancer staging. Of the 5 studies selected, only 2 showed separate results for EBUS-TBNA. The ability of endoscopic ultrasound (EBUS-TBNA and EUS-FNA) to sample multiple stations with a sensitivity and negative predictive value higher than that of mediastinoscopy makes it the first choice for invasive staging.[20] The present meta-analysis selected studies that compared EBUS-TBNA with mediastinoscopy.[26-28] There was only 1 study that evaluated the combined use of EBUS and EUS, although that study provided separate data for EBUS.[31]

The paraesophageal and infradiaphragmatic LNs (stations 8 and 9), which are inaccessible by EBUS-TBNA, can be accessed with EUS-FNA. To analyze the impact of these stations on LN staging, a multicenter study evaluated data from 1,421 surgical resections in patients with NSCLC. In the sample as a whole, 736

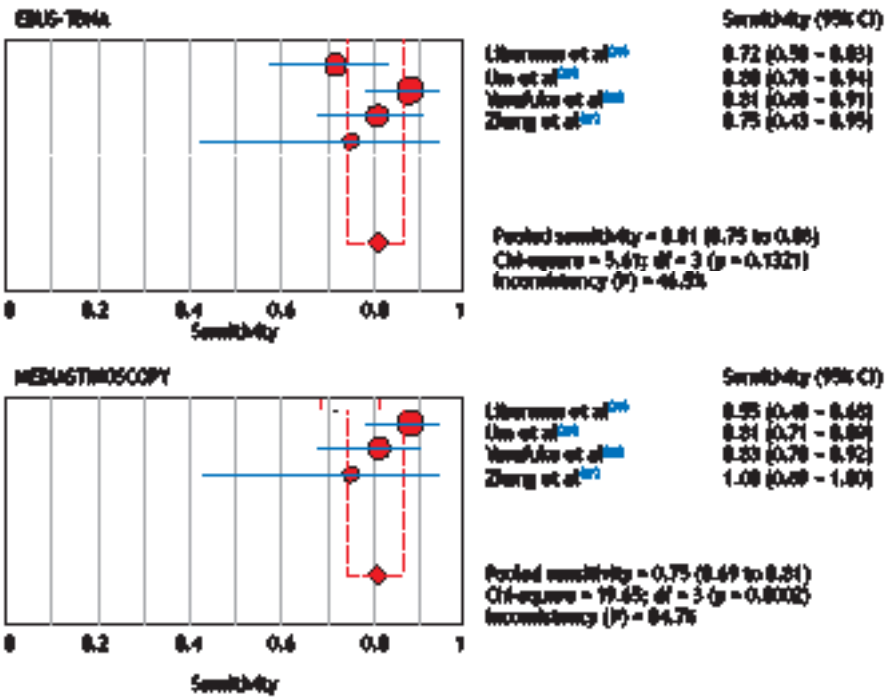

Figure 2. Sensitivity of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy. df: degree(s) of freedom.

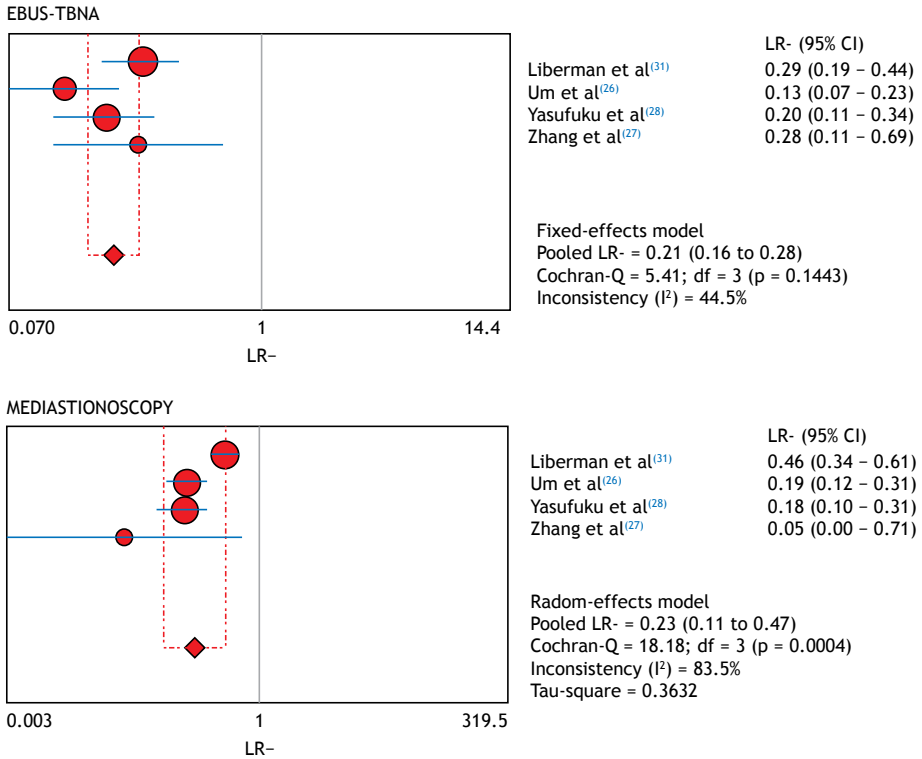

Figure 3. Negative likelihood ratio (LR−) of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy. df: degree(s) of freedom.

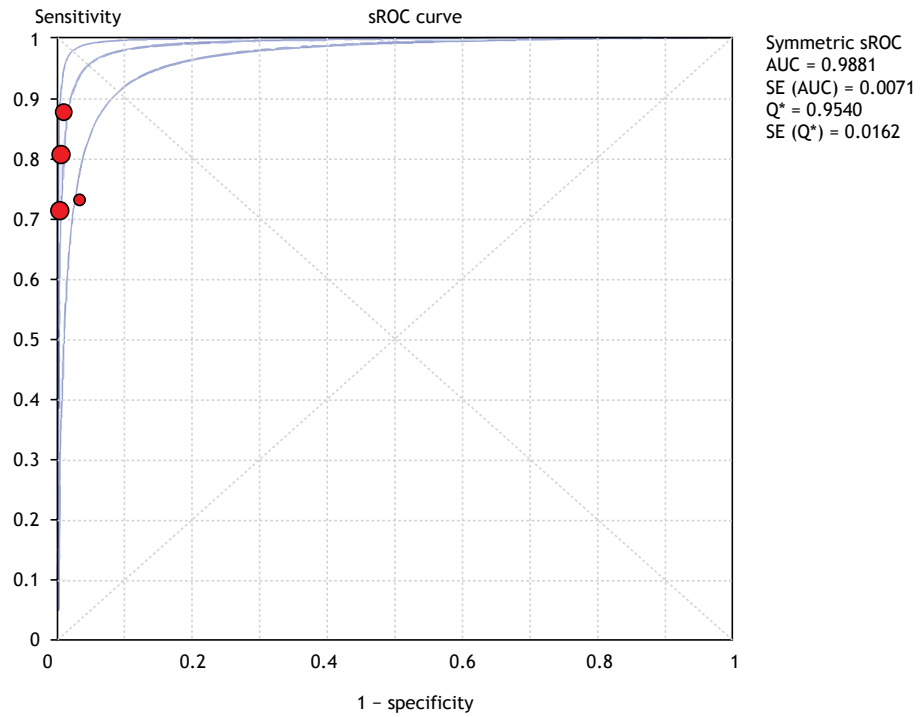

Figure 4. Summary ROC (sROC) curve for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). AUC: area under the curve; and Q*: the point at which sensitivity and specificity are equal, which is the point on the curve closest to the upper left corner.

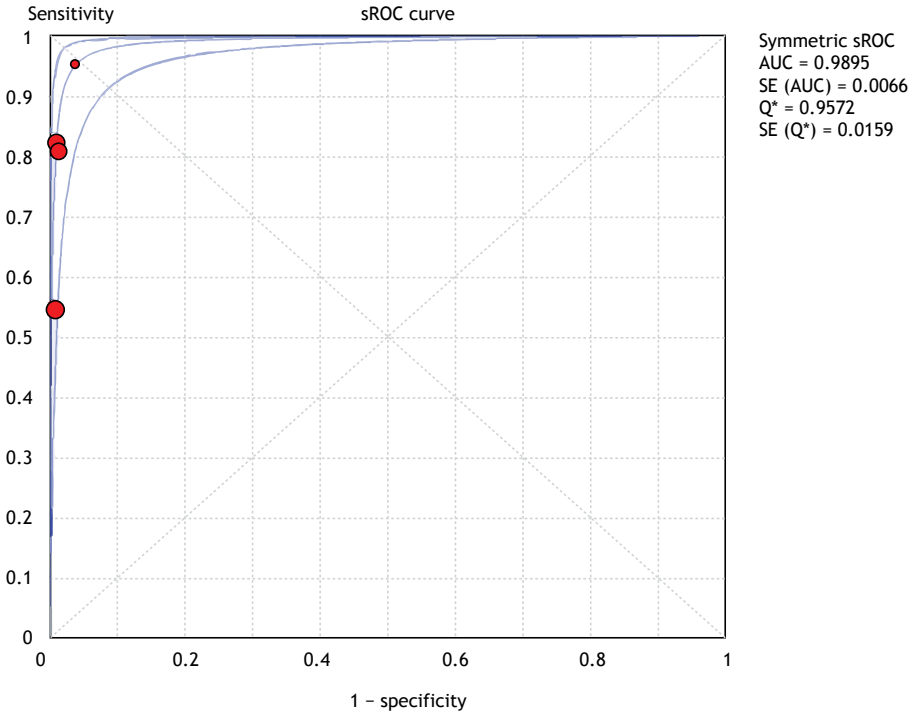

Figure 5. Summary ROC (sROC) curve for mediastinoscopy. AUC: area under the curve; and Q*: the point at which sensitivity and specificity are equal, which is the point on the curve closest to the upper left corner.

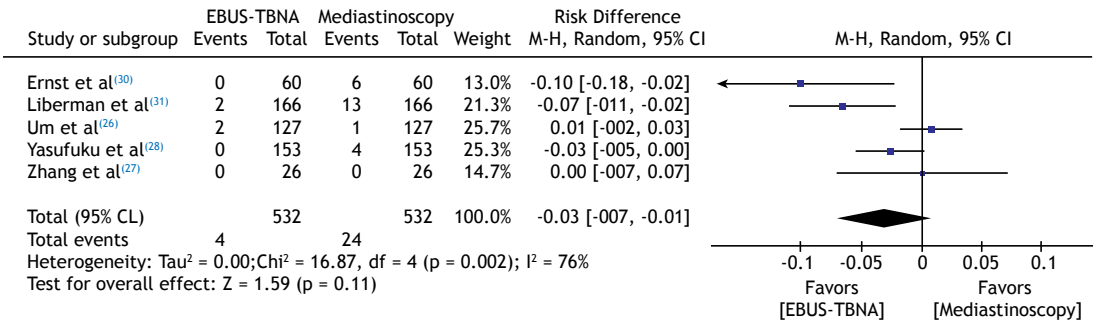

Figure 6. Adverse events (complications) during endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and during mediastinoscopy. M-H: Mantel-Haenszel; and df: degree(s) of freedom.

patients (52%) underwent sampling of LN stations 8 and 9, and only 12 (1.6%) of those patients had metastatic LNs only in these stations, no statistically significant difference in survival being found between those 12 patients and the other 724.[15] In the present systematic review, we sought evidence that EBUS-TBNA is the only procedure capable of effectively performing mediastinal LN staging in patients with NSCLC.

Our results showed no significant differences in sensitivity or specificity between EBUS-TBNA and mediastinoscopy. However, in 1 of the studies selected, it was concluded that EBUS-TBNA could replace mediastinoscopy, given the similarity of the results obtained with the two procedures (91%; $\kappa = 0.8$),[28] whereas the authors of another clinical trial concluded that the results obtained with EBUS-TBNA were superior to those obtained with mediastinoscopy.[31]

EBUS-TBNA cannot replace mediastinoscopy in all scenarios. Czarnecka-Kujawa et al.,[35] in a cost-effectiveness study, compared various modalities of mediastinal staging for NSCLC and found that invasive mediastinal staging is unlikely to be cost-effective in clinical N0 patients if the probability of N2 is smaller than 2.5%. However, EBUS-TBNA is the only staging modality that is cost-effective in patients with a probability of mediastinal metastasis ranging between 2.5% and 57%. In patients with negative EBUS-TBNA results and a probability of N2 > 57%, confirmatory mediastinoscopy should be considered.[35]

Mediastinoscopy has long been considered to be the gold standard for NSCLC staging. It has a sensitivity of 83% and a negative predictive value of 90%.[6] The drawback of mediastinoscopy is its complication rate, which ranges from 1.7% to 2.5%.[12]

The current literature supports the idea that EBUS-TBNA is a safe, minimally invasive procedure. Asano et al.,[36] investigating 7,345 patients who underwent EBUS-TBNA at 210 centers, reported a complication rate of 1.23% (95% CI: 0.97-1.48%). The most frequent complications were hemorrhage, in 50 patients (0.68%); infectious complications, in 14 (0.19%); and pneumothorax, in 2 (0.03%).

Verdial et al.[25] investigated 30,570 patients—15,097 (49%) underwent EBUS-TBNA, and 15,473 (51%) underwent mediastinoscopy. The authors reported that severe adverse events, such as pneumothorax, hemothorax, airway/vascular injuries, and death, were rare and were similar in the EBUS-TBNA and mediastinoscopy groups (0.3% vs. 0.4%; p = 0.189). However, the rate of major vessel injuries was lower in the EBUS-TBNA group than in the mediastinoscopy group (1.4% vs. 2.2%; p < 0.001), as was the rate of vocal cord paralysis (0.02% vs. 0.1%; p = 0.003). EBUS-TBNA was associated with a lower adjusted risk of severe adverse events (OR = 0.42; 95% CI: 0.32-0.55) and of vocal cord paralysis (OR = 0.57; 95% CI: 0.54-0.60).[25]

In the present systematic review, the complication rate for EBUS-TBNA was lower than was that for mediastinoscopy, although the difference was not statistically significant. Adverse events associated with EBUS-TBNA and with the surgical procedure were analyzed in 5 studies.[27-31] No deaths or major adverse events were associated with EBUS-TBNA or mediastinoscopy. The most common adverse events were minor bleeding, in 16 patients; postoperative wound infection, in 3; and left-sided recurrent nerve injury, in 3.

One study,[31] involving 166 patients, showed a greater number of major and minor intraprocedural adverse events associated with EBUS-TBNA and mediastinoscopy. Major adverse events during mediastinoscopy occurred in 2.4% of the patients (tracheal injury requiring muscle flap coverage, external jugular vein injury requiring vessel ligation, left-sided recurrent nerve injury resulting in vocal cord paralysis, and left-sided vocal cord paresis that lasted four months), whereas major adverse events during EBUS-TBNA occurred in 1.2% of the patients (left mainstem bronchus laceration requiring surgical repair and massive hemoptysis controlled with endoscopic interventions). No minor adverse events occurred during EBUS-TBNA, whereas, during mediastinoscopy, there was minor bleeding, in 7 patients; bradycardia, in 1; and arrhythmia, in 1.

Some differences among the selected studies came to light during our analysis. An important factor that might have contributed to higher heterogeneity of complications associated with mediastinoscopy is the fact that 1 study[27] had a sample size that was small in comparison with those of the other studies included (26 patients vs. > 100 patients). In addition, the study with the largest patient sample showed the highest number of complications.[31] A significant difference might have been detected if we had included more studies or studies with larger sample sizes, which could have reduced the degree of heterogeneity. Another issue is the variability among the various centers regarding technical aspects, patient selection, and follow-up periods. For instance, Zhang et al.[27] reported no complications, although the duration of the follow-up period was unclear. However, Liberman et al.[31] provided a very precise description of the follow-up period and of the strategy to detect complications after patient discharge, which contributed to the detection of a greater number of complications. Those authors performed a secondary fixed-effects analysis considering only major complications , which showed low heterogeneity (I^2 = 24%) and no significant differences (risk difference = −0.01; 95% CI: −0.02 to 0.00).

High heterogeneity in EBUS-TBNA results was present in some of the analyses and might be due to the individual experience of the examiner, the number of needle passes, and the expertise of the pathologist. Other aspects not addressed in the present systematic review were the combined use of EBUS-TBNA and EUS-FNA for LN staging, rapid on-site evaluation, and the use of elastography.

One of the advantages of EBUS-TBNA over mediastinoscopy is its ability to provide concomitant accurate lung cancer diagnosis and mediastinal staging during the same procedure if the lesion is central or if mediastinal or hilar LN involvement is suspected. Cytology specimens obtained by EBUS-TBNA are also sufficient to provide accurate histopathological diagnosis, allowing molecular testing (diagnostic yield of 95%) and staging of lung cancer. Therefore, EBUS-TBNA reduces the time to treatment decision when compared with other conventional diagnostic and staging techniques.[37]

In the present systematic review, the complication rate associated with EBUS-TBNA was lower than was that associated with mediastinoscopy, although there was no statistically significant difference. The strength of this systematic review includes the broad search for prospective studies. The limitation is the small number of articles included. Nevertheless, the studies included were of satisfactory quality, and the risk of bias can be considered low. The features of the studies and the sample sizes resulted in a certain degree of heterogeneity. It would be interesting to have more randomized trials comparing these interventions in the future.

In conclusion, EBUS-TBNA and mediastinoscopy achieved similar results for the mediastinal staging of lung cancer. EBUS-TBNA showed a performance and a safety profile that are good enough to replace mediastinoscopy altogether in the mediastinal staging for patients with potentially resectable NSCLC.

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REVIEW ARTICLE

Diaphragmatic ultrasound: a review of its methodological aspects and clinical uses

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ABSTRACT

The diaphragm is the main muscle of respiration, acting continuously and uninterruptedly to sustain the task of breathing. Diaphragmatic dysfunction can occur secondary to numerous pathological conditions and is usually underdiagnosed in clinical practice because of its nonspecific presentation. Although several techniques have been used in evaluating diaphragmatic function, the diagnosis of diaphragmatic dysfunction is still problematic. Diaphragmatic ultrasound has gained importance because of its many advantages, including the fact that it is noninvasive, does not expose patients to radiation, is widely available, provides immediate results, is highly accurate, and is repeatable at the bedside. Various authors have described ultrasound techniques to assess diaphragmatic excursion and diaphragm thickening in the zone of apposition. Recent studies have proposed standardization of the methods. This article reviews the usefulness of ultrasound for the evaluation of diaphragmatic function, addressing the details of the technique, the main findings, and the clinical applications.

Keywords: Ultrasonography; Diaphragm/diagnostic imaging; Respiratory muscles; Critical Illness; Respiratory tract diseases; Neuromuscular diseases.

INTRODUCTION

The respiratory muscles, which comprise the diaphragm, the intercostal muscles, the abdominal muscles, and the accessory muscles (including the sternocleidomastoid and scalene muscles), provide the driving force for ventilation.[1,2] The diaphragm is the main muscle of respiration. Anatomically, it is a dome-shaped structure and is divided into two parts: the central tendon and the peripheral muscular portion. Functionally, the muscular portion is itself divided into two parts[1-4]: the crural portion, which is medial and arises from the lumbar vertebrae (L2-L4) and associated ligaments; and the larger costal portion, which is lateral and is in apposition to the inner aspect of the six lower ribs, constituting the region of apposition to the rib cage, known as the zone of apposition (ZOA). During quiet breathing, diaphragmatic contraction has several effects: the central dome lowers because of contraction of the muscle fibers of the ZOA, leading to a decrease in pleural pressure; the lowering of the central dome increases abdominal pressure, leading to the outward movement of the anterior abdominal wall; and the muscle fibers of the costal part of the diaphragm lift the lower rib cage (insertional force) causing forward (pump-handle) and outward (bucket-handle) movements. As a result, during contraction, the diaphragm moves caudally, increasing the craniocaudal dimension of the thoracic cavity, thus generating negative intrathoracic pressure to inflate the lungs.[1-5]

The diaphragm is innervated by the phrenic nerves that arise from the nerve roots at C3 through C5.[5] To trigger a spontaneous breath, the inspiratory muscles have to receive adequate output from the brain centers and must have anatomical and phrenic nerve integrity.[6] Diaphragmatic function can be affected by diseases that injure the diaphragm itself or by conditions that affect the neuromuscular axis (brain centers, phrenic nerve, or neuromuscular transmission).[6] To maintain continuous, rhythmic, uninterrupted breathing, the diaphragm muscle fibers must be resistant to fatigue. In the adult human diaphragm, approximately 55% of the muscle fibers are type I (slow-twitch fibers that have high fatigue resistance), whereas 21% are type IIA (fast-twitch oxidative fibers that have intermediate fatigue resistance) and 24% are type IIB (fast-twitch glycolytic fibers that have low fatigue resistance).[3]

Diaphragmatic dysfunction (DD) is defined as a loss of muscle force that may be partial (weakness) or complete (paralysis), leading to reduced inspiratory capacity and impaired respiratory muscle endurance.[4] Diaphragmatic weakness or paralysis can involve one or both hemidiaphragms.[7] Because of its nonspecific presentation, DD is underdiagnosed in clinical practice.[6] Unilateral DD is often asymptomatic and diagnosed only

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as an incidental finding. In rare cases, patients with unilateral DD complain of dyspnea that is intensified in the supine position. However, patients with bilateral DD or those with unilateral DD and underlying lung disease can present with not only dyspnea on exertion but also sleep-disordered breathing, decreased exercise performance, and impaired quality of life.[6] The suspicion of DD is typically raised when diaphragm elevation is seen on a chest X-ray ordered to investigate dyspnea or another respiratory symptom.[4,6] Once suspected, DD can be investigated by a variety of tests that are selected based on their availability, usefulness, and invasiveness. A brief description of the tests, other than ultrasound, that are used in the evaluation of diaphragmatic function is provided described in the Supplementary Material.

DIAPHRAGMATIC ULTRASOUND

Technical aspects

Diaphragmatic ultrasound is a useful technique to evaluate the anatomy and function of the diaphragm, specifically diaphragmatic excursion and thickening. Table 1 describes some characteristics of the technique.[8-22] The equipment needed to perform diaphragmatic ultrasound is uncomplicated and is widely available at medical facilities. The ultrasound system should be equipped with a 2.5-5.0 MHz convex transducer and a 7.5-10.0 MHz linear transducer. A brief description of ultrasound transducers and imaging techniques can be found elsewhere,[23] and Figure 1 illustrates some aspects of those techniques. Because of the portability of ultrasound equipment, diaphragmatic ultrasound can be easily performed as an outpatient procedure or at the bedside in the ward, ICU, or emergency department. Because there is less variability and greater reproducibility in the supine position, that is the preferred positioning for diaphragmatic ultrasound.

Echographic appearance of the diaphragm

On ultrasound, the diaphragm can be explored through two acoustic windows: over the subcostal area (SCA), as depicted in Figures 2 and 3; and over the ZOA, as depicted in Figure 4. Through the SCA window, ultrasound shows the diaphragm as a deeply located curved structure that separates the thorax from the abdomen (Figure 2B).[8,9,24] Through the ZOA window, the diaphragm is identifiable as a three-layer structure (Figure 4),[25] consisting of one hypoechoic inner muscle layer surrounded by two hyperechoic outer membranes (the peritoneum and pleura).[24-27] During diaphragmatic contraction in healthy individuals, ultrasound through the SCA window shows the diaphragm descending in the craniocaudal direction (i.e., toward the transducer),[8,9,24] whereas ultrasound through the ZOA window shows the shortening and thickening of the muscle.[27,28] Therefore, ultrasound allows the measurement of diaphragmatic mobility and thickness. To quantify diaphragmatic mobility and thickening in an objective manner, at least three images should be evaluated and the values should be averaged.[8,24,25,29]

Diaphragmatic mobility

Diaphragmatic mobility is measured by visualizing the hemidiaphragms via the anterior subcostal view (the preferred method), posterior subcostal view, or subxiphoid view, in the two-dimensional (B) mode or in the one-dimensional (M) mode.[8,9] Regardless of the technique chosen, diaphragmatic mobility is measured at three time points (Figure 2D): during quiet breathing; during deep breathing at maximal inspiration, and during voluntary sniffing.

The posterior subcostal view (Figure S1 in the Supplementary Material) is usually employed with the patient in a sitting position. A low-frequency convex transducer is placed over the posterior subcostal region, which is assessed in the right or left sagittal planes and in B mode, and the operator looks for the individual hemidiaphragms through the hepatic or spleen window.[30] The amplitude of craniocaudal diaphragmatic mobility is then measured in M mode. Because it requires that specific patient positioning, the posterior subcostal view is usually unfeasible in patients who are critically ill or are on mechanical ventilation (MV).

The subxiphoid view is particularly useful in children and slender adults. A low-frequency convex transducer is placed below the xiphoid process in a transverse orientation, angled cranially and dorsally toward the posterior hemidiaphragms.[31] In B mode, the right and left hemidiaphragms can both be seen, allowing a qualitative comparison of their excursion.[32] In M mode, the excursion of each hemidiaphragm can be measured objectively.

Testa at al.[9] presented a detailed description of the use of the anterior subcostal view. In brief, a low-frequency convex transducer is placed over the anterior SCA, between the midclavicular and anterior axillary lines (Figure 2A). The right and left hemidiaphragms can be evaluated via the liver and spleen windows, respectively. In B mode, transverse scanning is performed, looking across the liver for the inferior vena cava on the right of the screen and the gallbladder in the middle of the screen. The right hemidiaphragm appears as a thick, curving, hyperechoic line (Figures 2B and 2D). The transducer is directed medially, cranially, and dorsally, so that the ultrasound beam reaches the posterior third of the right hemidiaphragm.[8,9] The transducer is held firmly in place, and the patient is asked to engage in quiet breathing, deep breathing, and voluntary sniffing (Figure 2D and, in the Supplementary Material, Video S1). In M mode, the M-mode line is positioned as perpendicular as possible, to obtain maximum excursion (Figures 2C and 2D).[8,9,24] The amplitude of the diaphragmatic excursion is measured by placing calipers at the bottom and top of the diaphragmatic inspiratory slope (Figures 2C and 2D).

Table 1. Diaphragmatic ultrasound.

Advantages	
Safety	- Noninvasive - Does not expose patients to ionizing radiation[8]
Feasibility	- Can be performed in less than 15 min,[9] even in approximately 5 min[8] - Bedside assessment, does not require transportation of the patient - Possibility of several repetitions
Availability	- Requires only basic, usually ubiquitous, ultrasound equipment
Accuracy	- High temporal resolution,[8,9] high reproducibility, and high accuracy, with intraclass correlation coefficients ranging from 0.876 to 0.999 for intraobserver agreement and from 0.56 to 0.989 for interobserver agreement[10-18] - Has high interobserver and intraobserver agreement,[8] for diaphragmatic excursion[9] and thickness[10] - Is superior to fluoroscopy for the diagnosis of diaphragmatic dysfunction[19]
Disadvantages	
Availability	- Despite requiring only basic ultrasound equipment, it is not available at all facilities. - Physicians trained in the technique must be on staff.
Accuracy	- The left hemidiaphragm may be difficult to visualize, particularly in obese patients.[20] - Diaphragmatic excursion depends on the maximal voluntary inspiratory effort of patients and is influenced by the position of the subject.[21] - Diaphragmatic excursion is affected by the abdominal contents and pressure, which limit diaphragm displacement.[22]

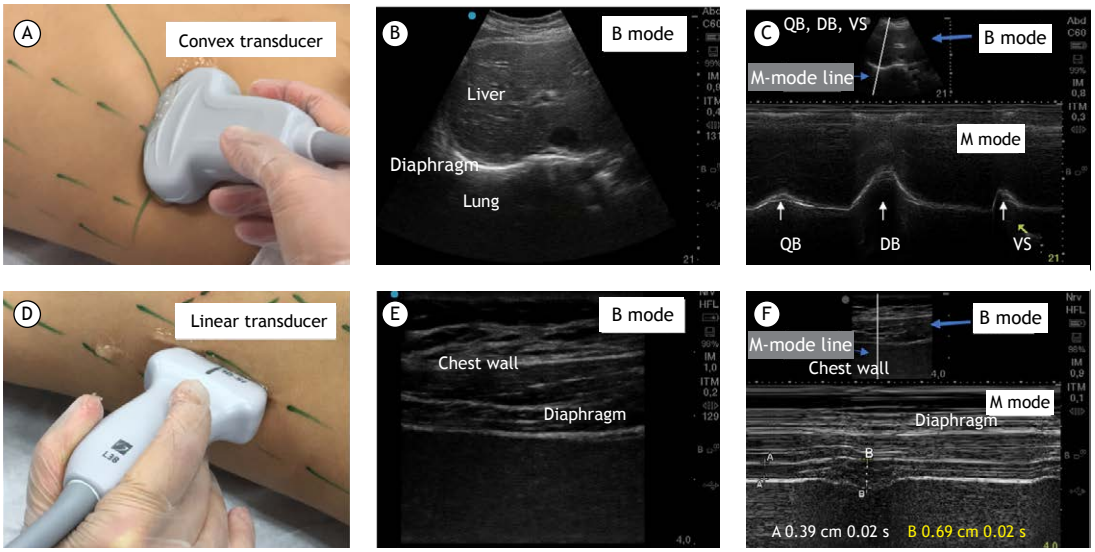

Figure 1. A convex transducer (A) uses a lower frequency, allowing a deep penetration and a wide field of view. In a convex transducer, the crystals are embedded along a curved shape (A). The ultrasound beams emitted from the lateral aspects of the transducer lead to decreased lateral resolution and a pie-shaped image on the screen (B and top of C). Convex transducers are primarily used for abdominal scans due to their wider and deeper view. A linear transducer (D) emits a beam with a high frequency (6-12 MHz), providing better resolution and less penetration, making it ideal for imaging superficial structures. The crystals are aligned in a linear fashion within a flat head and produce sound waves in a straight line. The image produced is rectangular in shape (E) with high lateral resolution. The imaging modes are demonstrated in B, C, E, and F. The diaphragm is seen in B mode, also known as real-time imaging (B and E). B-mode ultrasound presents a two-dimensional slice of a three-dimensional structure, rendering a cross-sectional view. The diaphragm is seen in M mode (C and F), which displays the motion of a given structure over time through the placement of a vertical (exploratory, M-mode) line in the directed plane of the transducer, during quiet breathing (QB), deep breathing (DB), and voluntary sniff (VS). The M-mode line is anchored at the top and center of the screen, although its orientation and direction can be adjusted laterally. On the screen, the motion of the structure is plotted along the y-axis, and time is plotted along the x-axis, in seconds. M-mode ultrasound allows high time resolution.

There are regional differences in mobility between the parts of the diaphragm.[33] The middle and posterior portions of the diaphragm show the greatest craniocaudal excursion during spontaneous breathing.[33] In B-mode ultrasound, it is fundamental to be aware of the direction of diaphragmatic excursion, whether toward the transducer (descending = normal) or away from it (paradoxical = abnormal).

Quantifying left hemidiaphragm mobility can be problematic because of the smaller acoustic window of the spleen and the interposition of gas in the stomach. When left diaphragmatic paralysis is suspected, there

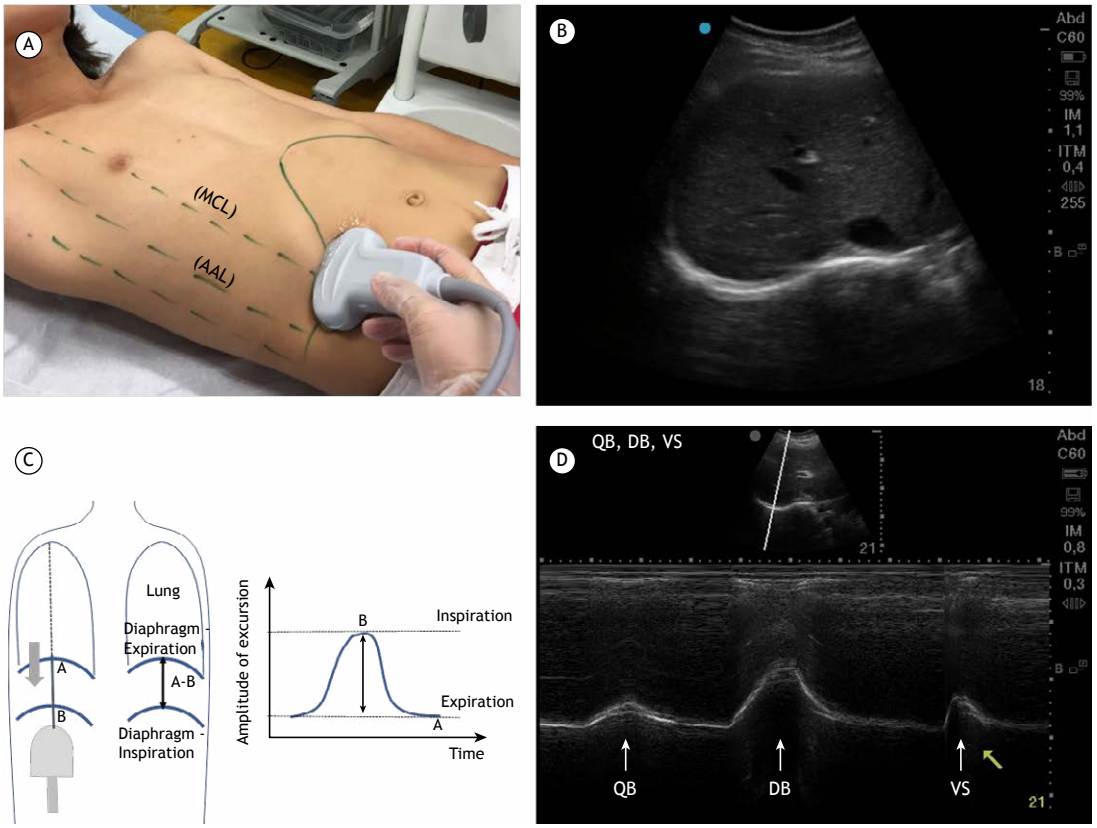

Figure 2. In A, measuring the excursion of right hemidiaphragm using the anterior subcostal view with the convex probe positioned below the costal margin between the midclavicular line (MCL) and anterior axillary line (AAL). In B, ultrasound appearance of the right hemidiaphragm in the subcostal region between the MCL and AAL. In C, schematic representation of the measurement of diaphragmatic excursion: on the left, placement of the probe in the subcostal region to display the diaphragm in B mode and placement of the exploratory line demonstrating excursion from expiration to inspiration (points A-B). In D, measurement of diaphragmatic excursion in M mode. The top of the figure depicts the normal right diaphragm in B mode, and the bottom portion depicts M-mode ultrasound of the diaphragmatic excursion during quiet breathing (QB), deep breathing (DB), and voluntary sniff (VS).

are strategies that can facilitate the observation and measurement of diaphragmatic excursion (Figure S2 in the Supplementary Material).

The diagnosis of DD can be made through ultrasound measurement of diaphragmatic mobility. Diaphragmatic paralysis can be diagnosed by identifying the absence of mobility during quiet breathing and deep breathing, together with paradoxical motion during deep breathing or voluntary sniffing (Figures 3C and 3D).[34,35] Diaphragmatic weakness can be diagnosed by identifying reduced mobility during deep breathing, with or without paradoxical motion during voluntary sniffing (Figure 3D).[8,36]

Diaphragm thickness and thickening fraction

To assess atrophy and contraction of the diaphragm, it is necessary to evaluate diaphragm thickness (Tdi) and the thickening fraction (TF), respectively.[26,28] A high frequency (7-13 MHz) linear transducer is placed over the ZOA, between the eighth and ninth intercostal spaces, usually 0.5-2.0 cm below the costophrenic angle, between the anterior axillary and midaxillary lines (Figure 4A).[24,25,29] At a depth of 1.5-3 cm, the diaphragm is identified as the hypoechoic inner muscular layer bounded by two hyperechoic membranes (Figure 4B), namely those of the pleura (superficial line) and peritoneum (deeper line).[25-27] Tdi is measured from the center of the pleural line to the center of the peritoneal line, at end-expiration (Tdi-exp) (Figure 4B), then at end-inspiration (Tdi-insp), in B mode and M mode (Figure 4C and, in the Supplementary Material, Video S2). The TF is calculated as follows:

$$TF = \frac{Tdi\text{-}insp - Tdi\text{-}exp}{Tdi\text{-}exp} \times 100$$

The diagnosis of DD can be made by measuring Tdi with ultrasound. A chronically paralyzed diaphragm is thin, atrophic, and does not thicken during inspiration.[26] However, in acute or subacute diaphragmatic paralysis, the Tdi may be normal but the thickening capacity will be decreased.[37,38] Table 2 shows a variety of studies that used diaphragmatic ultrasound to measure diaphragmatic mobility and thickness in healthy subjects.[8-10,25,27,29,33,36,39]

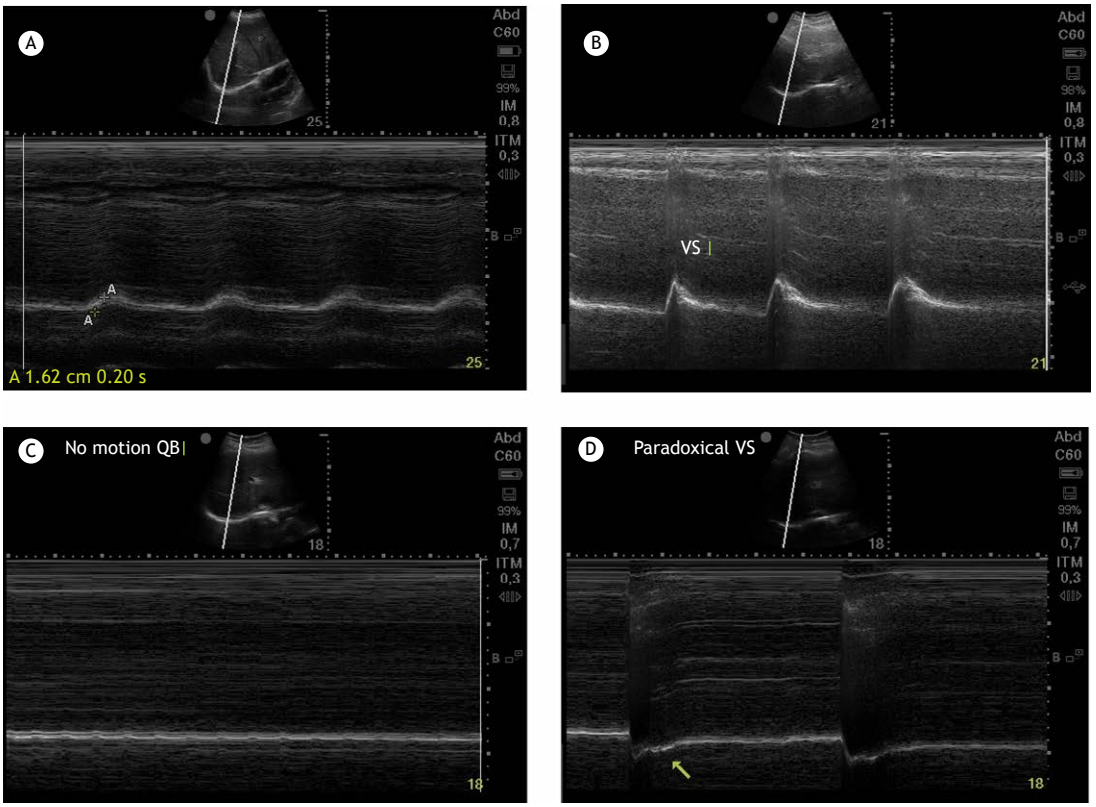

Figure 3. Measurement of diaphragmatic excursion. At the top of all of the panels, we can see images in B mode showing the position of the probe, whereas at the bottom of each panel, the M-mode images show the diaphragmatic excursion (A and B), lack of excursion (C), and paradoxical excursion (D). Panel A depicts diaphragmatic excursion during quiet breathing (QB), and panel B shows diaphragmatic excursion during a voluntary sniff (VS). Panels C and D depict the trace of a paralyzed diaphragm. In C, diaphragmatic excursion is absent during QB. Panel D shows paradoxical motion during VS.

CLINICAL USES OF DIAPHRAGMATIC ULTRASOUND

Critical care

Critically ill patients are especially vulnerable to DD, because of a number of potentially myotoxic factors.[40,41] In critically ill patients, DD is highly prevalent, even at the beginning of ICU admission,[42] especially in patients with respiratory failure who require MV.[40,43] Studies have shown that DD is associated with adverse outcomes, such as weaning failure,[13,40,43] prolonged MV,[44] prolonged ICU stay,[40] and increased mortality.[40,42,44,45]

Diaphragmatic function is rarely monitored in critically ill patients, mainly because it is difficult to employ the tools required in order to do so. Recently, diaphragmatic ultrasound has contributed significantly to the assessment of diaphragmatic function in critical care settings.[12,13,16,18,43,46] One study suggested a rational approach to the use of diaphragmatic ultrasound in critical care, for a variety of purposes[47]: to diagnose DD; to assess the work of breathing; to identify atrophy of the diaphragm; and to predict weaning outcomes.

Diaphragmatic ultrasound can be used in order to diagnose DD at admission or during MV, provided that no neuromuscular blockers are being used and that the ventilator is triggered by patient effort (assisted modes). Abnormal diaphragmatic mobility (reduced, absent, or paradoxical movement) can be indicative of DD.[48] Diaphragmatic excursion < 10 mm is the criterion most often used in order to diagnose DD in critically ill patients.[13,49] Diaphragmatic ultrasound-diagnosed DD is associated with adverse outcomes (longer MV and weaning times, as well as higher mortality). Lu et al.[50] reported the prevalence of DD to be 34% among patients on MV for prolonged periods. Lerolle et al.[14] demonstrated that diaphragmatic excursion < 25 mm (during a best excursion maneuver) accurately identified DD in patients on MV for prolonged periods after cardiac surgery.

The work of breathing can also be assessed with diaphragmatic ultrasound. Recent studies have shown that the TF correlates with the diaphragmatic pressure-time product and the esophageal pressure-time product.[16,17]

Another application of diaphragmatic ultrasound is in the identification of atrophy of the diaphragm through the measurement of Tdi-exp.[15,18,51,52] In a previous

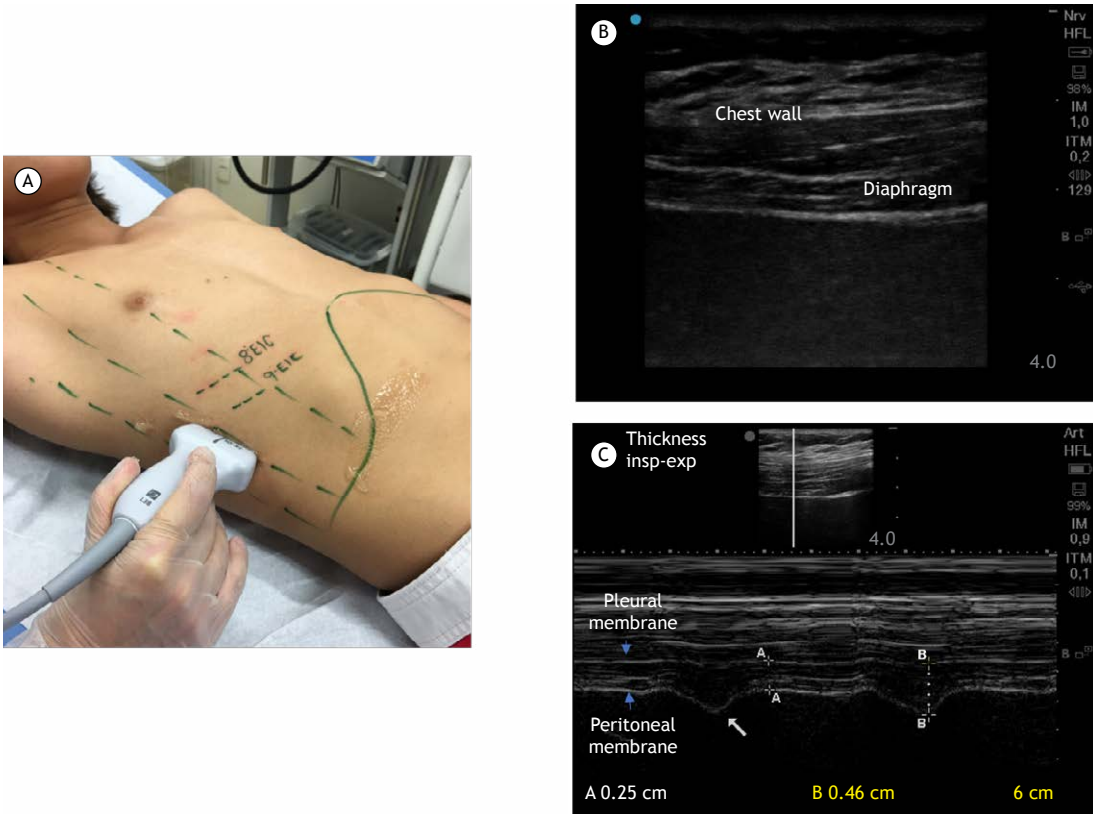

Figure 4. In A, measuring the thickness of right hemidiaphragm through the placement of the linear transducer over the zone of apposition (ZOA) at the ninth intercostal space, between the anterior axillary and midaxillary lines. In B, ultrasound appearance of the left hemidiaphragm at the ZOA between the ninth and tenth intercostal spaces, during quiet breathing, at functional residual capacity. In C, measurement of diaphragm thickness: the top of the figure displays the ZOA of a normal diaphragm, in B mode; and the bottom portion shows, in M mode, the diaphragm thickness at end-expiration (exp), or distance A-A, and diaphragm thickness at end-inspiration (insp), or distance B-B.

study, Tdi-exp was found to decrease 6.0-7.5% per day on MV and the level of ventilator support showed a linear relationship with the incidence of atrophy of the diaphragm.[18]

Diaphragmatic ultrasound can also be used in order to predict the weaning outcome. During spontaneous breathing trials, diaphragmatic excursion cutoff values of < 14 mm[53,54] and < 11 mm[13] have both been found to be predictive of weaning failure, as have TF values of < 20%,[43] < 30%,[46] and < 36%.[11]

The usefulness of diaphragmatic ultrasound in predicting weaning outcomes continues to be extensively explored and debated. However, there is considerable heterogeneity across studies, due to the following methodological aspects: the definition of weaning failure employed; the inclusion criteria (e.g., the timing of diaphragmatic ultrasound during the spontaneous breathing test); the diaphragmatic ultrasound technique chosen; the positioning of the patient; differences among patient populations; the diaphragmatic ultrasound parameters evaluated to predict weaning (diaphragmatic excursion, the TF, or the combination of several parameters). That marked heterogeneity among studies makes it difficult to draw general conclusions on the usefulness of diaphragmatic ultrasound in predicting weaning outcomes, which could explain the lack of guidelines. Recent, high-quality studies, including a systematic review,[47] three meta-analyses,[55-57] and a narrative review,[58] have synthesized the available knowledge on this subject. Although a complete review of all such studies is beyond the scope of the present report, there is compelling evidence that diaphragmatic ultrasound is a feasible, promising technique for use in critical care, especially in patients with respiratory failure.[12,13,16,18,43,45,46,52] However, there are still conflicting results regarding the efficiency of the technique in predicting weaning outcomes.[59,60] Table 3 summarizes the relevant studies on this topic.[12-15,18,40,43-46,48-50,52-54,61-64]

Diaphragmatic paralysis

In patients with bilateral diaphragmatic paralysis, inspiration is achieved by the contraction of inspiratory intercostal and accessory muscles, which lowers the pleural pressure and expands the rib cage. During inspiration, the paralyzed diaphragm moves cranially and does not thicken.[4] Diaphragmatic ultrasound has been explored as a tool to diagnose diaphragmatic paralysis.

Table 2. Diaphragmatic ultrasound to measure diaphragmatic mobility and thickness in healthy subjects.

Reference	n	Patient positioning Probe placement Probe orientation	Measure	Reference values
Harris et al.[33]	50	Supine Subcostal MCL and longitudinal	Mobility DB	Anterior third: 4.0 ± 1.6 cm Middle and posterior third: 4.8 ± 1.6 cm 4.0 ± 1.2 cm (F); 5.4 ± 1.7 cm (M)
Gerscovich et al.[36]	23	Supine Longitudinal semi-coronal Subcostal or low intercostal between MCL and MAL	Mobility QB	Right hemidiaphragm - QB: 1.5 cm; DB: 5.7 cm; VS: 1.7 cm Left hemidiaphragm - QB: 1.6 cm; DB: 6.7 cm; VS: 1.8 cm
Kantarci et al.[39]	160	Supine Coronal plane Low anterior intercostal, subcostal, or both	Mobility DB	DB Right: 4.7 ± 1.0 (F) vs. 5.3 ± 1.1 cm (M) Left: 4.8 ± 0.3 (F) vs. 5.4 ± 1.3 cm (F)
Boussuges et al.[8]	210	Standing Right subcostal between MCL and AAL Left lower intercostal spaces or subcostal, between AAL and MAL	Mobility QB DB	QB - Right: 1.6 ± 0.3 cm (F); 1.8 ± 0.3 cm (M) - Left: 1.6 ± 0.4 cm (F); 1.8 ± 0.4 cm (M) DB - Right: 5.7 ± 1.0 cm (F); 7.0 ± 1.1 cm (M) - Left: 6.4 ± 1.0 cm (F); 7.5 ± 0.9 cm (M) VS - Right: 2.6 ± 0.5 cm (F); 2.9 ± 0.6 cm (M) - Left: 2.7 ± 0.5 cm (F); 3.1 ± 0.6 cm (M)
Testa et al.[9]	40	Supine, semi-recumbent 45° Subcostal anterior at MCL Probe is orientated transversely and directed cranially	Mobility QB DB	QB - Experienced operator: 1.8 ± 0.8 cm - Inexperienced operator 2.2 ± 0.9 cm DB - Experienced operator 6.9 ± 1.4 cm - Inexperienced operator 7.9 ± 1.3 cm
Ueki et al.[27]	13	Sitting ZOA	Thickness	Tdi-exp: 1.7 ± 0.2 mm Tdi-insp: 4.5 ± 0.9 mm
Baldwin et al.[10]	13	Semi-recumbent 45° ZOA, ninth intercostal space	Thickness Tdi-exp	Tdi-exp: 1.7 [1.1-3.0] mm
Boon et al.[25]	150	Supine eighth or ninth intercostal space, immediately anterior to the AAL	Thickness Tdi-exp Thickening ratio	Tdi-exp: 2.7 ± 1 mm (F); 3.8 ± 1.5 mm (M) - LLN Tdi-exp: 1.4-1.7 mm - LLN thickening ratio: 1.2-1.3%
Carrillo-Esper et al.[29]	109	Supine ZOA, at FRC	Thickness Tdi-exp	Tdi-exp: 1.6 ± 0.4 mm 1.4 ± 0.3 mm (F); 1.9 ± 0.4 mm(M)
Cardenas et al.[24]	64	Semi-recumbent 45° Mobility: right anterior, subcostal region Diaphragm thickness: ZOA between AAL and MAL, at FRC and at TLC	Mobility QB DB Thickness Tdi-exp Tdi-insp TF	Mobility QB: 1.5 ± 0.4 cm DB: 6.41 ± 1.02 cm (F); 7.79 ± 0.82 cm (M) LLN DB mobility: 4.37 cm (F); 6.15 cm (M) Tdi-exp: 1.9 ± 0.3 mm (M) LLN at FRC: 1.2 mm (F); 1.3 mm (M) Tdi-insp: 4.81 ± 0.95 mm (F); 5.6 ± 0.9 mm (M) TF: 169 ± 43% (F); 204 ± 61% (M)

MCL: midclavicular line; DB: deep breathing; F: female; M: male; MAL: midaxillary line; QB: quiet breathing; VS: voluntary sniff; AAL: anterior axillary line; ZOA: zone of apposition; Tdi-exp: diaphragm thickness at end-expiration; Tdi-insp: diaphragm thickness at end-inspiration; LLN: lower limit of normal; FRC: functional residual capacity; and TF: thickening fraction.

Gottesman et al.[26] measured the Tdi in 30 subjects (5 with bilateral diaphragmatic paralysis, 7 with unilateral diaphragmatic paralysis, 3 with inspiratory weakness, and 15 who were healthy). The Tdi-exp and Tdi-insp were measured. The TF was also calculated. The authors showed that, in patients with unilateral paralysis, the Tdi-exp and TF were significantly lower for the paralyzed hemidiaphragm than for the normal hemidiaphragm and for the hemidiaphragms of healthy volunteers, and that only patients with diaphragmatic paralysis had a Tdi-exp < 20 mm and a TF < 20%.[26] The authors concluded that diaphragmatic ultrasound can be used in order to diagnose diaphragmatic paralysis by identifying the characteristic lack of thickening. It is of note that the TF of the paralyzed hemidiaphragms showed negative values (mean, −8 ±

Table 3. Relevant studies about the use of diaphragmatic ultrasound in critical care.

Authors	n	Setting	Measurement	Cutoff/Correlate
Predicting weaning outcome – TF				
DiNino et al.[46]	63	Medical ICU	TF during SBT (PSV [5] or T tube)	Cutoff for TF: > 30%
Jung et al.[43]	33	Medical and Surgical ICU	TF during SBT (PSV [5] or T tube) Only patients with ICUAW	Cutoff for TF: > 20%
Dres et al.[40]	76	Medical ICU	TF during SBT on PSV	Cutoff for TF: > 29%
Blumhof et al.[61]	56	Medical ICU	TF during SBT on PSV (5,10, and 15)	Cutoff for TF: > 20%
Farghaly et al.[62]	54	Respiratory ICU	TF during SBT on PSV (8)	Cutoff for TF: > 34%
Dres et al.[63]	76	Medical ICU	TF and PtrStim a few minutes before SBT SBT on PSV (7), ZEEP	Cutoff for TF: > 25.8% PtrStim > 7.2 cm
Predicting weaning outcome – DE				
Jiang et al.[53]	55	Medical ICU	DE during SBT on PSV or T tube	Cutoff for DE: 1.1 cm
Kim et al.[13]	82	Medical ICU	DE during SBT on PSV or T tube	Cutoff for DE: 1.0 cm
Spadaro et al.[54]	51	Medical ICU	DE during SBT (not clear)	Cutoff for DE: 1.4 cm
Dres et al.[40]	76	Medical ICU	DE during SBT on PSV	Cutoff for DE: 0.95 cm
Farghaly et al.[62]	54	Respiratory ICU	DE during SBT on PSV	Cutoff for DE: 1.05 cm
Assessing atrophy during MV				
Grosu et al.[52]	7	Medical ICU	Tdi-exp measured daily since intubation	Tdi-exp ⇓ 6%/day of MV
Goligher et al.[12]	107	Medical ICU	Tdi-exp and TF measured daily since intubation until 72 h of MV -Tdi-exp ⇓ = Tdi-exp reduction > 10% - Tdi-exp ⇑ = Tdi-exp increase > 10%	Tdi-exp in 44%; Tdi-exp ⇑ in 12% Low TF correlated with ⇓ in Tdi-exp High TF correlated with ⇑ in Tdi-exp. TF ⇓ with ⇑ driving pressure and CMV
Schepens et al.[15]	54	Medical ICU	Tdi-exp measured during first 24 h of MV, and daily after	Tdi-exp ⇓ ≈32% at the nadir MV duration associated with atrophy
Zambon et al.[18]	40	Medical ICU	Tdi-exp measured daily since intubation during SB or CPAP High PSV (5-12) Low PSV (> 12): CMV	Tdi-exp ⇓ ≈7.5%/day on CMV Tdi-exp ⇓ ≈5,3%/day on high PSV Tdi-exp ⇓ ≈1.5%/day at low PSV Tdi-exp ⇑ ≈2.3%/day in SB/CPAP
Goligher et al.[64]	211	Medical ICU	Tdi-exp and TF measured daily since intubation until 72h of MV Inspiratory effort → TF Tdi-exp ⇓ = Tdi-exp reduction > 10% Tdi-exp ⇑ = Tdi-exp increase > 10%	Tdi-exp ⇓ in 41%; Tdi-exp in 24% Tdi-exp ⇓ associated with ⇑ MV, ICU admission and ⇑ risk of complications Tdi-exp ⇑ predicted ⇑ MV ⇓ Tdi-exp correlated with low inspiratory effort ⇑ Tdi-exp was related to excessive effort TF (15-30%) → shortest duration of MV
Assessing DD				
Lerolle et al.[14]	28	Adult cardiac ICU	DE, Pdi, and Gilbert index Severe DD = best DE < 25 cm MV > 7 days	Best DE < 25 correlated with Gilbert index < 0
Kim et al.[13]	82	Medical ICU	During SBT on PSV or T tube MV > 48 h	DD in 24 (29%) DE < 1.0 cm predicted weaning outcome

TF: thickening fraction; PSV: pressure-support ventilation (numbers in parentheses/brackets are cmH_2O); SBT: spontaneous breathing trial; ICUAW: ICU-acquired weakness; PtrStim: tracheal pressure in response to phrenic nerve stimulation; ZEEP: zero end-expiratory pressure; DE: diaphragmatic excursion; Tdi-exp: diaphragm thickness at end-expiration; MV: mechanical ventilation; CMV: controlled mechanical ventilation; SB: spontaneous breathing; CPAP: continuous positive airway pressure; DD: diaphragmatic dysfunction; Pdi: transdiaphragmatic pressure; ARF: acute respiratory failure; ACV: assist-control ventilation; and LOS: length of stay.

Table 3. Continued...

Authors	n	Setting	Measurement	Cutoff/Correlate
Valette et al.[48]	10	Medical ICU	DE during unassisted breathing DD = paradoxical or absent excursion, or DE < 1.0 cm	DD in 10 patients High mortality rate (60%) of patients with DD and ARF
Mariani et al.[49]	34	Medical ICU	DE during SBT on T tube DD = DE <1.0 cm MV > 7 days and SBT eligible	DD in 13 (38%) Bilateral DD in 8 Unilateral (left/right side) DD = 3/2
Lu et al.[50]	41	Medical ICU	TF during SBT on PSV only patients with prolonged MV DD = TF < 20%	DD prevalence in 14 (34.1%). DE < 1.0 cm predicted weaning outcome
Dubé et al.[45]	112	Medical ICU	PtrStim, TF and DE measured during first < 24 h of MV or during ACV or at switch to PSV DD = PtrStim <11 cmH_2O	TF and DE correlated with PtrStim at switch to PSV, but not at initiation of MV TF < 29% identified DD TF < 29% was associated with ⇑ ICU-LOS, ⇑ MV duration, and ⇑ mortality

TF: thickening fraction; PSV: pressure-support ventilation (numbers in parentheses/brackets are cmH_2O); SBT: spontaneous breathing trial; ICUAW: ICU-acquired weakness; PtrStim: tracheal pressure in response to phrenic nerve stimulation; ZEEP: zero end-expiratory pressure; DE: diaphragmatic excursion; Tdi-exp: diaphragm thickness at end-expiration; MV: mechanical ventilation; CMV: controlled mechanical ventilation; SB: spontaneous breathing; CPAP: continuous positive airway pressure; DD: diaphragmatic dysfunction; Pdi: transdiaphragmatic pressure; ARF: acute respiratory failure; ACV: assist-control ventilation; and LOS: length of stay.

13% vs. 65 ± 26% for the normal hemidiaphragms). The authors attributed that to the passive stretching of the paralyzed diaphragm, as previously shown in a case report.[37]

In acute diaphragmatic paralysis, the Tdi-exp may be unaltered, because atrophy may not yet have occurred. In addition, recent studies have indicated that Tdi-exp values in healthy individuals are lower than previously thought (lower limit of normal = 1.2 mm in women and 1.3 mm in men).[24]

The measurement of diaphragmatic mobility has also been studied as a means of diagnosing diaphragmatic paralysis. Lloyd et al.[35] described the use of diaphragmatic ultrasound in 10 adult patients referred for evaluation of suspected diaphragmatic paralysis. The paralyzed diaphragm presented a lack of inspiratory (caudal) mobility on M-mode diaphragmatic ultrasound and abnormal paradoxical mobility, particularly during a sniff test. Those findings were recently confirmed by other authors.[7,34] Boussuges et al.[34] assessed diaphragmatic mobility on M-mode during quiet breathing, deep breathing and voluntary sniffing in 26 patients with unilateral diaphragmatic paralysis. In all of the patients evaluated, the authors found abnormal mobility of the paralyzed hemidiaphragm, characterized by immobility or weak paradoxical displacement during quiet breathing; paradoxical mobility during voluntary sniffing; and paradoxical mobility during deep breathing. Caleffi-Pereira et al.[7] assessed diaphragmatic motion and thickness during quiet breathing, deep breathing, and voluntary sniffing in 27 patients with unilateral diaphragmatic paralysis. The authors found that mobility (during quiet breathing and deep breathing), and thickness (Tdi-exp, Tdi-insp and TF) were both significantly lower in the paralyzed hemidiaphragm than in the normal hemidiaphragm. In view of these findings, diaphragmatic paralysis can be diagnosed by identifying a lack of excursion during quiet breathing, deep breathing, and voluntary sniffing or paradoxical excursion during deep breathing and voluntary sniffing. Diaphragmatic weakness is diagnosed by identifying reduced diaphragmatic excursion during quiet breathing and deep breathing, with or without paradoxical motion on sniffing.

Diaphragmatic ultrasound may also be useful in the follow-up of patients with DD. Summerhill et al.[38] studied 16 patients with diaphragmatic paralysis (bilateral in 6 and unilateral in 10), following them for up to 60 months. Diaphragmatic TF was measured initially and during subsequent visits. The authors found that 7 patients recovered their diaphragmatic function (mean recovery time of 14.9 ± 6.1 months), whereas the remaining patients did not. In the postoperative period after cardiac surgery, DD can lead to complications. Lerolle et al.[14] studied 28 patients requiring MV for a prolonged period (> 7 days) after cardiac surgery, evaluating a control group of 20 patients with an uncomplicated postoperative course for comparison. The authors measured the transdiaphragmatic pressure (Pdi) during maximal inspiratory effort and calculated the Gilbert index (the ratio between the amplitude of gastric pressure at peak inspiration to the amplitude of Pdi during inspiration), which evaluates the contribution the diaphragm makes to respiratory pressure swings (a Gilbert index > 0.30 indicates normal diaphragmatic function, whereas a value ≤ 0 indicates severe DD). The authors employed diaphragmatic ultrasound to measure diaphragmatic mobility during maximal inspiratory effort. They found that the Pdi was below

Table 4. Main findings and potential clinical implications of diaphragmatic ultrasound.

Critically ill patients with respiratory failure on mechanical ventilation	
Main findings	**Potential clinical implications**
1. To diagnose DD DE < 1.0 cm[13,48,49] TF < 20-29%[45,50]	DD (DE < 1.0 cm): associated with high mortality rate (60%) in patients with DD and ARF[48]; predicted weaning outcome[13,50]; and DD (TF < 29%) associated with longer ICU LOS, prolonged MV, and increased mortality[45]
2. To assess atrophy of the diaphragm during MV Tdi-exp decreases 6.0-7.5%/day of MV (especially on CMV).[18,28,52] Tdi-exp is > 10% lower in 44% of patients and unchanged in 44%[12]	Atrophy of the diaphragm (Tdi-exp ⇓ > 10%) associated with ⇑ MV[15,64], ⇑ ICU admission, and ⇑ risk of complications[64] Diaphragmatic hypertrophy (Tdi-exp ⇑ > 10%) - associated with increased duration of MV[39]
3. To predict weaning from MV DE < 1.0-1.4 cm[13,40,53,54,62] TF < 20-30%[40,43,46,61-63]	Diaphragmatic ultrasound and weaning prediction DE < 1 cm and TF < 20-30% associated with increased weaning failure
Diaphragmatic paralysis	
Main findings	**Potential clinical implications**
1. Chronic paralysis Atrophy: Tdi-exp < 0.11-0.12 cm (LLN)[7] TF < 20%, even negative[26] DE absent or weak/paradoxical during QB[34,35] DE reduced, absent, or paradoxical during DB and VS[34] 2. Acute or subacute paralysis Unaltered Tdi-exp (Tdi-exp > 0.15 cm) with abnormal TF (TF < 20% or even negative)[37]	If diaphragmatic paralysis is suspected: Reduced, absent, or paradoxical DE supports the diagnosis. Reduced Tdi-exp (< 0,11 cm) and reduced TF (< 20%) supports the diagnosis of chronic diaphragmatic paralysis. Reduced, absent, or paradoxical DE and reduced TF < 20% support the diagnosis of acute/subacute diaphragmatic paralysis (Tdi-exp may be unaltered). Diaphragmatic ultrasound may follow the recovery of diaphragmatic paralysis.[38]
Cystic fibrosis	
Main findings	**Potential clinical implications**
1. Increased Tdi-exp (effect of training of the diaphragm)[67,68] 2. Reduced Tdi-exp in severe pulmonary disease and low fat-free mass[69]	Increased Tdi-exp (due to the effect of training of the diaphragm) or reduced Tdi-exp (due to deleterious effects on respiratory muscle function)
COPD	
Main findings	**Potential clinical implications**
1. Reduced diaphragmatic mobility,[70,71] which was inversely correlated with air trapping[71] and dyspnea(70) and positively correlated with 6MWD[70] 2. Tdi-exp and TF similar to controls[72] 3. Tdi-exp and TF inversely correlated with air-trapping[73] 4. During acute exacerbation of COPD: DD (TF < 20%) was associated with poorer outcomes (NIV failure, longer ICU stay, prolonged MV, need for tracheostomy).[74] DE predicted NIV failure.[76]	Air trapping correlated with reduced diaphragmatic mobility, thickness, and thickening. Reduced diaphragmatic mobility correlated with increased dyspnea on exertion. Reduced TF (< 20%) and mobility during acute exacerbation of COPD correlates with poorer outcomes. DE predicted early NIV failure. DE was greater in NIV successes than in NIV failures.
Interstitial lung diseases	
Main findings	**Potential clinical implications**
1. Reduced DB diaphragmatic mobility correlated with lung function.[78-80] 2. Increased Tdi-exp is an effect of training of the diaphragm.[78,80] 3. Reduced mobility and thickening during DB correlated positively with lung function, exercise tolerance, and HRQoL, correlating negatively with dyspnea.[80]	Lung restriction (reduced lung volumes) reduces diaphragmatic mobility and thickening. Maximal diaphragmatic mobility and thickening is associated with clinically relevant parameters (exercise tolerance, HRQoL and dyspnea).
Neuromuscular disorders	

DD: diaphragmatic dysfunction; DE: diaphragmatic excursion; TF: thickening fraction; ARF: acute respiratory failure; LOS: length of stay; MV: mechanical ventilation; Tdi-exp: diaphragm thickness at end-expiration; CMV: controlled mechanical ventilation; LLN: lower limit of normal; QB: quiet breathing; DB: deep breathing; VS: voluntary sniff; SNIP: sniff nasal inspiratory pressure; NIV: noninvasive ventilation; HRQoL: health-related quality of life; ALS: amyotrophic lateral sclerosis; and V_T: tidal volume.

Table 4. Continued...

Main findings	Potential clinical implications
1. Reduced Tdi-exp and thickening in patients with ALS with vital capacity < 80% predicted[85] and in those with bulbar-onset ALS[86] 2. Thickening with inspiration correlated with SNIP and MEP[84] and lung function[83] 3. Maximal excursion correlated with FVC[87] 4. The Tdi at V_T/Tdi at TLC ratio is indicative of weakness and may predict NIV initiation in ALS[88] 5. Duchenne muscular dystrophy and myotonic dystrophy type 1: Reduced mobility during DB and VS[89] DB excursion correlated with FVC values[89]	Diaphragm thickness and excursion are reduced and correlate with lung function in ALS. Diaphragm thickening may be related to respiratory muscle strength in ALS. The Tdi at V_T/Tdi at TLC ratio may suggest weakness and predict the initiation of NIV in ALS. DB and VS diaphragmatic mobility may be related to SNIP and lung function in Duchenne muscular dystrophy and myotonic dystrophy type 1.

DD: diaphragmatic dysfunction; DE: diaphragmatic excursion; TF: thickening fraction; ARF: acute respiratory failure; LOS: length of stay; MV: mechanical ventilation; Tdi-exp: diaphragm thickness at end-expiration; CMV: controlled mechanical ventilation; LLN: lower limit of normal; QB: quiet breathing; DB: deep breathing; VS: voluntary sniff; SNIP: sniff nasal inspiratory pressure; NIV: noninvasive ventilation; HRQoL: health-related quality of life; ALS: amyotrophic lateral sclerosis; and V_T: tidal volume.

normal in 27 of the 28 patients requiring MV for a prolonged period. In 8 patients, the Gilbert index was ≤ 0, indicating severe DD, and those patients had lower diaphragmatic mobility during maximal inspiratory effort than did the patients with a Gilbert index > 0. In addition, a diaphragmatic excursion during maximal inspiratory effort of < 25 mm during maximal inspiratory effort was found to be an accurate predictor of a Gilbert index ≤ 0 (area under the ROC curve of 0.93, a positive likelihood ratio of 6.7, and a negative likelihood ratio of 0). The diaphragmatic excursion during maximal inspiratory effort was > 25 mm in all of the patients with an uncomplicated course.

Diaphragmatic ultrasound has also been used in order to identify DD after neck dissection.[65] Immediately after neck dissection, only a few (8.9%) of the diaphragms at risk showed immobility, with decreased inspiratory strength that returned to preoperative values after one month. However, at one month after dissection, Tdi decreased, indicating atrophy of the diaphragm.[65]

DIAPHRAGMATIC ULTRASOUND IN RESPIRATORY DISEASES

Diaphragmatic ultrasound has been employed in the evaluation of a variety of respiratory diseases, including asthma, cystic fibrosis, COPD, and interstitial lung disease (ILD). Table 4 summarizes the main findings and potential clinical implications of the use of diaphragmatic ultrasound in patients with respiratory diseases.

Asthma

In 1997, de Bruin et al.[66] addressed the usefulness of diaphragmatic ultrasound in a sample of 9 middle-aged patients with asthma, minor pulmonary hyperinflation, and preserved peripheral muscle strength. The authors found moderately impaired inspiratory muscle strength and slightly increased thickness of the costal diaphragm, indicating muscle hypertrophy.

Cystic fibrosis

Considering the fact that chronic respiratory diseases can affect diaphragmatic function, Pinet et al.[67] evaluated patients with cystic fibrosis who had severe respiratory impairment and malnutrition. The authors showed that, although the patients had diaphragmatic weakness, they did not have muscle atrophy; the patients had thicker diaphragms and abdominal muscles than did the control subjects, indicating hypertrophy due to respiratory muscle training. Dufresne et al.[68] underscored those findings, showing that the patients with cystic fibrosis had thicker diaphragms and greater inspiratory muscle strength than did the control subjects. In addition, fat-free mass and airway resistance were found to be independent predictors of Tdi, although systemic inflammation was not, suggesting that in cystic fibrosis, the diaphragmatic training occurred despite the presence of systemic inflammation. However, patients with chronic respiratory diseases may present many factors (e.g., inflammation, altered nutritional status, poor physical conditioning, and corticosteroid use) influencing respiratory muscle function other than training.

Enright et al.[69] studied 40 adults with cystic fibrosis and 30 age-matched healthy subjects. In that study, patients with cystic fibrosis who had severe pulmonary disease and low fat-free mass presented poorer inspiratory muscle function and reduced Tdi-exp when compared with patients with cystic fibrosis with a normal fat-free mass. The patients with cystic fibrosis with normal fat-free mass showed inspiratory muscle function and Tdi-exp values similar to those of age-matched healthy individuals.

COPD

Ultrasound has been used to evaluate the diaphragm in COPD. In a study involving 54 patients with COPD and 20 healthy subjects, Paulin et al.[70] attempted to determine whether diaphragmatic mobility could

influence exercise tolerance and dyspnea. The authors found that patients with COPD had lower diaphragmatic mobility than did the controls. They also found that diaphragmatic mobility correlated positively with the distance covered on the six-minute walk test, whereas it correlated negatively with dyspnea on exertion.

Dos Santos Yamaguti et al.[71] investigated the influence of lung function on diaphragmatic mobility in patients with COPD. The authors found that such patients had reduced diaphragm mobility that was mainly associated with air trapping and was not influenced by inspiratory strength or pulmonary hyperinflation.

Baria et al.[72] evaluated the Tdi-exp and thickening ratio (calculated as the Tdi-insp divided by the Tdi-exp) in 50 patients with COPD and compared that with a database of information on 150 healthy control subjects. The authors found that the values for Tdi-exp and thickening ratio were comparable between the patients and the controls.

Smargiassi et al.[73] evaluated the correlation between Tdi, respiratory function, and body composition in 32 patients with COPD. The authors showed that Tdi at different lung volumes, mainly the Tdi-exp, was related to the fat-free mass. The authors also showed that diaphragm thickening was inversely related to hyperinflation (greater hyperinflation resulting in less diaphragm thickening), postulating that diaphragmatic ultrasound could be useful to assess lung hyperinflation and the loss of fat-free mass in patients with COPD.

Antenora et al.[74] studied 41 patients with COPD with exacerbation, admitted to the ICU for noninvasive ventilation (NIV), and investigated the use of diaphragmatic ultrasound to identify and assess the prevalence of DD (defined as a TF < 20% during spontaneous breathing), to determine its impact on outcomes in those patients. The authors identified DD in 10 patients (24.3%). They demonstrated that DD was associated with corticosteroid use and poorer outcomes, including NIV failure, longer ICU stays, prolonged MV, the need for tracheostomy, and ICU mortality. That study was extended in a recent report by Marchioni et al.,[75] who investigated the outcomes of 75 patients with COPD exacerbation who required NIV and had DD (defined as a TF < 20%). Those authors showed that DD was associated with poorer clinical outcomes, such as NIV failure, prolonged MV, higher tracheostomy rates, and longer ICU stays, as well as higher ICU, in-hospital, and 90-day overall mortality rates.

Cammarota et al.[76] studied 21 patients with COPD admitted to the emergency department for exacerbation and investigated the feasibility of performing diaphragmatic ultrasound to evaluate diaphragmatic excursion, thickness, and TF, before NIV, as well as after the first and second hours of treatment, attempting to determine whether those variables were predictors of early NIV failure. Comparing NIV successes and NIV failures, the authors found that diaphragmatic excursion (although not Tdi-exp and TF) was significantly greater in the former group before NIV ($p = 0.02$), after the first hour of treatment ($p = 0.007$), and after the second hour of treatment ($p = 0.008$). During an acute exacerbation of COPD, diaphragmatic excursion was found to be predictive of early NIV failure.

ILD

There have been few studies using diaphragmatic ultrasound to assess diaphragmatic function in patients with ILD. He et al.[77] evaluated the mobility of the diaphragm during quiet breathing and deep breathing in a mixed sample, comprising patients with combined pulmonary fibrosis and emphysema, patients with idiopathic pulmonary fibrosis, patients with COPD, and healthy controls. Diaphragmatic mobility during quiet breathing and deep breathing was similar between patients with ILD and healthy controls. More recently, Santana et al.[78] reported a reduction in deep breathing diaphragmatic mobility and TF, as well as an increased Tdi-exp in 40 patients with ILD in comparison with matched healthy controls. Additionally, the reduced deep breathing diaphragmatic mobility was associated with lung volumes in ILD. These results were recently confirmed by Boccatonda et al.[79] who showed a reduced deep breathing diaphragmatic mobility and a positive correlation between reduced FVC and diaphragmatic mobility in patients with ILD. In another study, Santana et al.[80] attempted to determine whether diaphragmatic mobility and thickness correlated with clinical and functional parameters (including dyspnea, exercise tolerance, quality of life, and lung function) in patients with ILD. The authors showed that diaphragmatic mobility and thickening during deep breathing correlated positively with lung function, exercise tolerance, and health-related quality of life, whereas both correlated negatively with dyspnea. In addition, the TF was below normal in 70% of the patients with ILD.

NEUROMUSCULAR DISEASES

Neuromuscular diseases (NMD) can affect the inspiratory and expiratory muscles, resulting in weakness and fatigue,[81] and can evolve from mild impairment (mild alveolar hypoventilation and a restrictive pattern of lung function, mainly in the supine position) to chronic respiratory failure.[82] Patients with NMD may be referred to a pulmonologist for respiratory muscle evaluation. The initial tests are spirometry and volitional assessment of global respiratory muscle strength—MIP, MEP, and (sniff nasal inspiratory pressure) SNIP—although those tests have limitations due to reduced patient motivation, cognitive decline, and orofacial muscle weakness, which can cause air leaks that lead to inaccurate tests. Nonvolitional respiratory muscle strength tests are invasive, expensive, and rarely employed. Diaphragmatic ultrasound can be a useful diagnostic tool in patients with NMD.

Among the various types of NMD, diaphragmatic ultrasound has been extensively explored in amyotrophic lateral sclerosis (ALS). Fantini et al.[83] studied 41 patients with ALS, using diaphragmatic ultrasound to measure the Tdi at tidal volume (V_T) and at TLC, calculating the ratio between the two. When that ratio approaches 1, the maximum inspiratory effort becomes unable to further contract the diaphragm starting from V_T, suggesting diaphragmatic weakness. The authors found that the ratio between the Tdi at V_T and the Tdi at TLC was the variable that best correlated with lung function.[83] Pinto et al.[84] studied 42 patients with ALS (25% with bulbar onset), most (76%) without respiratory symptoms and with normal respiratory test results. The authors found that the Tdi-insp showed a significant positive correlation with diaphragm compound muscle action potential and respiratory strength (as quantified by determining the SNIP and MEP),[84] although Tdi was not found to correlate with the pulmonary function test results in the subgroup of patients with bulbar-onset ALS. Hiwatani et al.[85] employed diaphragmatic ultrasound to assess 36 patients with ALS and 19 age-matched healthy controls. The authors found that the Tdi-exp, Tdi-insp, and the thickening ratio were all significantly lower in the patients with a vital capacity < 80% of the predicted value than in those with a vital capacity ≥ 80% of the predicted value and in the healthy controls. The Tdi-exp, Tdi-insp, and thickening ratio were all found to correlate positively with vital capacity and negatively with $PaCO_2$.[85] In a study involving 20 patients with ALS and age-matched healthy controls, Sartucci et al.[86] found that Tdi-exp and TF were lower in the patients. The authors also found that, in the patients with bulbar-onset ALS, lung volumes correlated strongly with Tdi-exp and TF. Carrié et al.[87] investigated the relationships between diaphragmatic mobility and lung volumes in 45 patients with ALS or myotonic dystrophy. The authors found a significant correlation between FVC and diaphragmatic mobility during deep breathing. The authors suggested that the measurement of diaphragmatic mobility could be a reliable tool to identify impaired respiratory function (FVC < 50% of predicted) in patients with ALS or myotonic dystrophy. In a more recent study, Fantini et al.[88] found that, in patients with ALS, a Tdi at V_T/Tdi at TLC ratio > 0.75 (suggesting diaphragmatic weakness) increased the risk of requiring NIV (hazard ratio = 5.6; p = 0.001) and the risk of death (hazard ratio = 3.7; p = 0.0001), inferring that diaphragmatic ultrasound is an accurate method of predicting the need for NIV in ALS.

In a mixed sample of 89 patients with NMD, primarily Duchenne muscular dystrophy and myotonic dystrophy type 1, diaphragmatic mobility during sniff ultrasound was found to be significantly associated with SNIP and to accurately predict FVC < 60% (area under the ROC curve = 0.93; p < 0.0001).[89] In addition, diaphragmatic mobility during voluntary sniffing and deep breathing was found to be lower in the patients with NMD than in a group of healthy controls. Other studies employing diaphragmatic ultrasound have shown that Tdi-exp is lower in patients with myopathy or neuropathy than in healthy individuals.[90,91] In patients with high spinal cord injury and neuropathy, the quantification of diaphragmatic mobility by ultrasound may be a useful tool for the diagnosis of DD.[19,35,36] Table 4 summarizes the main findings and potential clinical implications of the use of diaphragmatic ultrasound in patients with NMD.

LIMITATIONS OF DIAPHRAGMATIC ULTRASOUND

Diaphragmatic ultrasound has some limitations. First, ultrasound systems have inherent resolution limits (usually 0.1 mm) that can correspond to 5-10% of the normal thickness of the diaphragm. In addition, the assessment of the left hemidiaphragm can be problematic. However, taking extra precautions during the diaphragmatic ultrasound examination (e.g., placing the patient in the supine position and rotating the transducer) can help overcome these limitations. Furthermore, because ultrasound is an operator-dependent examination, repeated training can improve accuracy. Diaphragmatic ultrasound has shown good reliability for measuring Tdi (intraclass correlation coefficient = 0.990; 95% CI: 0.918-0.998), as well as for quantifying diaphragmatic excursion (correlation analysis) during quiet breathing (r = 0.95) and deep breathing (r = 0.94).[10,34] Moreover, although diaphragmatic ultrasound has been shown to have a steep learning curve when applied in healthy subjects,[8,9] few studies have evaluated how to develop the appropriate skills. One study, involving a pediatric population, found that 4 h of hands-on diaphragmatic ultrasound training focused on the recognition of normal and abnormal diaphragmatic motion resulted in high concordance between the diaphragmatic ultrasound findings reported by a trainee and those reported by a pediatric intensivist.[92] Another study, involving adult subjects, showed that three to five diaphragmatic ultrasound training sessions, lasting 10-15 min each, enabled learners to identify the diaphragm and measure its thickness.[46] More recently, Garofalo et al.[93] found that a combined approach consisting of a theoretical module followed by practical training is more effective in making learners capable of obtaining accurate diaphragmatic ultrasound measurements. The authors suggested that 25 supervised examinations would be sufficient to achieve adequate diaphragmatic ultrasound skills, analogous to those required to perform bedside lung ultrasound examinations.[94] Although training can ensure adequate diaphragmatic ultrasound skills, it does not imply that learners would successfully perform unsupervised diaphragmatic ultrasound evaluation in the clinical arena, where confounding factors can hinder the diaphragmatic ultrasound assessment.[93] Therefore, diaphragmatic ultrasound should be

performed only by physicians who have been properly trained and are dedicated to clinical care.

Diaphragmatic ultrasound is still not widely used in the assessment of diaphragmatic function in daily practice. That is probably due to a lack of knowledge about diaphragmatic impairment in various clinical contexts, as well as about the usefulness and possible clinical implications of ultrasound in evaluating the diaphragm. An exponentially increasing number of studies of diaphragmatic ultrasound have been published, especially regarding critical care, producing clinically relevant findings that should highlight the usefulness of ultrasound in assessing diaphragmatic function.

FINAL CONSIDERATIONS

Diaphragmatic ultrasound has marked advantages over other techniques used in order to assess diaphragmatic function, such as the fact that it is noninvasive and does not employ ionizing radiation, as well as being feasible, reproducible, repeatable, and affordable. In addition, there is convincing evidence in the literature about the usefulness of ultrasound to assess diaphragmatic function in diverse clinical settings. It is reasonable to suppose that in the near future, the use of diaphragmatic ultrasound by pulmonologists and intensivists will be ubiquitous and that it will have new applications in the diagnosis and monitoring of diseases and interventions, such as rehabilitation.

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AUTHOR CONTRIBUTIONS

PVS, LZC, ALPA, CRRC, and PC contributed to the study conception and design (formal analysis and methodology). PVS and PC contributed to drafting the manuscript. PVS, LZC, ALPA, CRRC, and PC contributed to writing, reviewing, and editing the manuscript. All of the authors approved the final manuscript.

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REVIEW ARTICLE

Upper limb exercise training and activities of daily living in patients with COPD: a systematic review of randomized controlled trials

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ABSTRACT

Objective: To investigate the efficacy of upper limb exercise training (ULExT) in improving the performance of activities of daily living (ADL) that involve the upper limbs (UL) in patients with COPD. **Methods:** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used in this systematic review. PubMed and EBSCOhost databases were searched to identify randomized controlled trials involving adults with COPD who underwent ULExT, compared with those who underwent other types of exercise or no exercise, in order to assess the performance of ADL that involve the UL. The methodological quality of the selected studies was assessed using the Physiotherapy Evidence Database scale. **Results:** Five studies, with a total sample of 173 subjects, met the inclusion criteria. The results of the selected studies showed that ULExT is safe and can significantly improve the performance of ADL that involve the UL in patients with COPD. However, there were inconsistencies in the results, especially regarding the perception of symptoms during ADL. The small number of studies included and their methodological quality do not allow for firm conclusions. **Conclusions:** The findings of this review revealed that ULExT is a safe therapeutic approach and can improve the performance of ADL that involve the UL in patients with COPD, but the results are unclear. Further investigation through well-designed randomized trials is warranted to determine the effectiveness of ULExT in improving the performance of ADL that involve the UL in patients with COPD.

Keywords: Upper extremity; Pulmonary disease, chronic obstructive; Activities of daily living, Exercise therapy.

INTRODUCTION

COPD is a chronic respiratory disease that has high rates of mortality and morbidity.[1] Dyspnea is one of the major symptoms of patients with COPD, limiting their physical activity and affecting their ability to perform activities of daily living (ADL).[2] More specifically, activities that require elevation of upper limbs (UL) over the shoulder height may disrupt normal breathing and cause hyperinflation,[3] which is associated with the occurrence of dyspnea.[2] In such patients, ADL tasks using the UL have been shown to increase metabolic and ventilatory costs, as assessed by the oxygen uptake/maximal oxygen uptake ratio (expressed as a percentage); the minute ventilation/maximal voluntary ventilation ratio (expressed as a percentage); and oxygen pulse. These increments could explain tiredness and be associated with increased perception of dyspnea, which leads to limitation of ADL.[4] In addition, some pathological muscle changes (such as weakness and loss of mass) that might occur in patients with COPD[5] also contribute to the increase in dyspnea and early fatigue.[6,7] For all of these reasons, patients with COPD suffer from shortness of breath during ADL when they use the UL,[8-10] such as when cooking or driving, and they might try to avoid such ADL in order to avoid dyspnea.

Pulmonary rehabilitation programs, including exercise training, have shown to be able to reduce dyspnea and fatigue in patients with COPD and improve their exercise capacity and quality of life.[11] However, recent guidelines for pulmonary rehabilitation are unclear about whether UL exercises should be performed as part of exercise training.[11,12]

Improving the performance of ADL should be one of the most important goals of rehabilitation, because it could affect the ability of patients for self-care. For this reason, the present study undertook a systematic review of randomized controlled trials to investigate whether UL exercise training (ULExT) can improve the performance of ADL in patients with COPD and whether ULExT is safe for such patients.

METHODS

The article selection process was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[13,14]

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in the present systematic review. We searched the following electronic databases (from inception to May of 2019): PubMed and EBSCOhost (CINAHL Plus and SPORTDiscus). The search was limited to literature written in English. The selected keywords were related to COPD ("COPD"; "chronic obstructive pulmonary disease"; "chronic obstructive lung disease"; "chronic obstructive airway disease"; "emphysema"; "chronic airflow limitation"; and "chronic airway obstruction"), UL ("arm"; "upper extremity"; and "upper limb"), exercise ("exercise therapy"; "exercise"; "respiratory rehabilitation"; "pulmonary rehabilitation"; "physical exercise"; "physiotherapy"; "physical therapy"; "training"; "exercise capacity"; "exercise test"; and "exercise endurance"), and symptoms ("dyspnea" and "fatigue"). Articles retrieved were perused for other relevant references.

The search yield was initially screened by two independent reviewers in order to remove duplicates and to assess titles and abstracts of potentially relevant articles. Full-text articles were retrieved when the title or abstract provided insufficient information to determine article inclusion. In cases of disagreement, a consensus was reached by discussion, and, if necessary, a third reviewer made the decision regarding article inclusion/exclusion.

In order to be included in our systematic review, the articles had to meet criteria that were developed following the PICOS—an acronym for **P**opulation of interest, **I**ntervention, **C**omparison, **O**utcome, and **S**tudy design—approach. In the present review, the criteria were as follows: **P** = men and women over 18 years of age, diagnosed with COPD (regardless of severity); **I** = any form of ULExT program; **C** = three types of comparison (ULExT vs. no ULExT; ULExT and lower limb exercise training vs. lower limb exercise training only; and comparison between two types of ULExT); **O** = performance of ADL; and **S** = randomized controlled trials.

It is worth mentioning that the primary outcome of the present review was the performance of ADL that involve the UL. The ability to perform various ADL is influenced by symptoms of dyspnea and fatigue in patients with COPD. For this reason, the perception of these symptoms was a secondary outcome in this review. The safety of ULExT was also a secondary outcome measure, the studies included being screened for reported adverse events related to the exercise program.

A customized Excel workbook was used for data extraction based on a recent systematic review about ULExT in COPD,[15] including methods (study design, total duration of study, details of any run-in period, number of study centers and their location, study setting, withdrawals, and date of study); participants (number, mean age, gender, severity of COPD, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria); interventions (intervention and comparison groups); outcomes (primary and secondary outcomes and reported time points); results of outcome measures; and notes (funding and conflicts of interest).

The quality and the risk of bias of the studies were assessed based on some methodological and statistical criteria (e.g., randomization, blinding, data comparison before and after the intervention and between groups, etc.). The methodological quality of each study was assessed independently by two investigators using the Physiotherapy Evidence Database (PEDro) scale, which is based on the criteria of the Delphi List[16] and is considered to be valid and reliable.[17,18] A study with a PEDro scale score ≥ 7 is considered to have high methodological quality, whereas those with a score between 4 and 6 and those with a score ≤ 3, respectively, are considered to have intermediate and poor methodological quality.

RESULTS

During the initial search in the electronic databases, 201 articles were found. Only five studies met all the aforementioned inclusion criteria and had the data required for investigating the effectiveness of ULExT in patients with COPD (Figure 1).[19-23]

In accordance with the PEDro scale, the methodological quality of the studies was moderate (two studies) to high (three studies), with scores ranging from 4 to 9 (Table 1). All studies referred to the comparison of the outcome measures between the groups. In two of the trials, there was no form of blinding (either for participants or for researchers or examiners).

The total sample size of each study ranged from 22 to 50 patients, with the number of participants per group ranging from 6 to 25. The five studies together involved 173 patients. The majority of the patients in the studies were men. In one of the studies, all of the participants were male.[20] The overall mean age of the participants was 66 years. In one of the studies, sex and age of the patients were unavailable.[19] The characteristics of the participants are presented in Table 2.

Overall, the patients had moderate to very severe COPD as determined by the Global Initiative for Chronic Obstructive Lung Disease criteria.[24] In all studies, having stable COPD was an inclusion criterion, whereas the presence of an exacerbation three weeks to two months prior to the study was considered an exclusion criterion in most of the studies.[20-23]

Of the five studies, four reported that the diagnosis of COPD was based on spirometry results, and one did not specify how COPD was diagnosed.[19] In addition, two of the studies also included the presence of dyspnea or fatigue during ADL as an inclusion criterion.[22,23]

In all of the studies, the samples were divided into groups, of which at least one group followed a ULExT program. Samples were divided into two groups in three studies[21-23] and into three groups in two studies.[19,20] The intervention group performed unsupported arm resistance exercise (i.e., using various weights such

as dumbbells and hand weights) in all studies.[19-23] Control groups performed breathing exercises,[23] respiratory hygiene,[20] or participated in a pulmonary rehabilitation program with no ULExT.[19,21] In one of the studies, the control group performed sham UL exercises which included flexibility exercises and stretching.[22]

The total duration of the training programs ranged from three to eight weeks. In most studies, there were three training sessions per week.[20,22,23] In one study, the total duration of the training program was three weeks (five training sessions per week).[21] In another study, the first week of training consisted of one session daily, followed by two daily sessions during the following weeks.[19] Most of the training programs were supervised; however, participants were supervised "approximately weekly" in one study.[19]

Various parameters were used in order to determine exercise intensity. In strength training programs, exercise intensity was determined by the load of weights (in pounds)[19] and by the number of sets and repetitions.[20-23] In one of the studies, they also used the number of arm motions per exhalation to determine exercise intensity.[19] In all of the studies, there was a gradual increase in exercise intensity taking into consideration the ability of the patients to complete the whole program (sets and repetitions) with no interruption.[19] Exercise intensity was increased based on the absence of dyspnea, fatigue, or muscle pain in three studies.[21-23] Finally, in one of the studies, the training load was adjusted based on a ten-repetition maximum test in the middle of the program period.[20] The characteristics of the training programs are presented in Table 3.

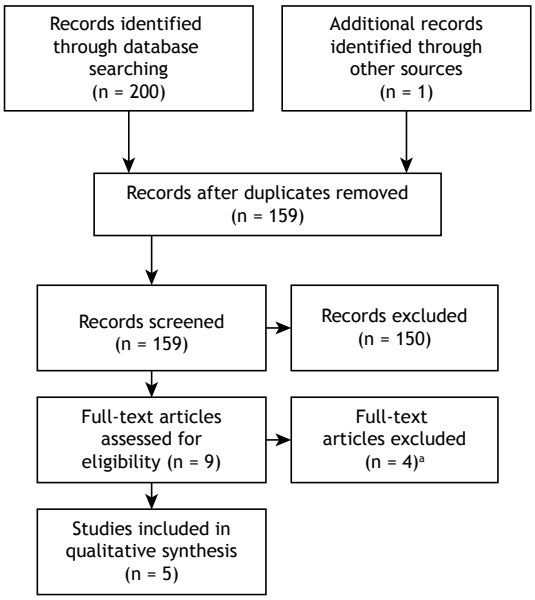

Figure 1. Flowchart of the record selection process. [a]The intervention group performed upper and lower limb exercises, and there was no control group.

Although attrition was reported in four of the studies,[19,20,22,23] noncompliance with the training program was mentioned only in two (1 patient each).[19,22] The reasons for noncompliance and adverse events reported in each study were investigated in order to evaluate the safety of ULExT in patients with COPD. The overall number of dropouts was 35 patients: 2 presented with an exacerbation[22,23] during the training program (which was reported to be unrelated to the training program in 1)[22]; 14 dropped out for medical reasons, 13 of whom unrelated to COPD or to the training program, such as prostate cancer (in 1),[23] and 1 presented with back pain, which was probably related to the training program[19]; 9 dropped out for nonmedical reasons (2 being noncompliant patients); 3 were unable to participate in the final evaluation[23]; and 7 were lost to follow-up (and no further information was available).[20] In addition, 3 complained of pain or severe dyspnea (it was unclear whether or not those complaints were related to the training program; however, none of those patients discontinued the program, which was adapted to their needs).[22]

The performance of ADL that involve the UL was an outcome measure in four studies.[19-21,23] Assessment of the performance of ADL included blackboard erasing,[19-21,23] dishwashing,[19,21,23] shelving groceries or lifting weight,[19-21,23] and changing light bulbs.[21,23] The patients were asked to perform the activities within a given timeframe[20,21,23] or the time needed to complete the ADL tasks was recorded.[19] In one

Table 1. Study methodological quality assessment based on the Physiotherapy Evidence Database scale.

Author	Criterion											
	1	2	3	4	5	6	7	8	9	10	11	Total score
Ries et al.[19]	0	1	0	1	0	0	0	0	0	1	1	4
Marrara et al.[20]	0	1	0	1	0	0	0	0	0	1	1	4
Costi et al.[21]	1	1	1	1	0	0	1	1	1	1	1	8
Janaudis-Ferreira et al.[22]	1	1	1	1	1	0	1	1	1	1	1	9
Calik-Kutukcu et al.[23]	1	1	1	1	0	0	1	1	0	1	1	7

Criteria: 1: eligibility criteria were specified (not included in the total score); 2: random allocation of the participants in groups; 3: allocation was concealed; 4: groups were similar at baseline regarding the most important prognostic indicators; 5: all subjects were blinded; 6: all therapists who administered the therapy were blinded; 7: all assessors who measured at least one key outcome were blinded; 8: measurements of key outcomes were obtained from more than 85% of the subjects initially allocated to groups; 9: data for at least one key outcome were analyzed by "intention to treat"; 10: between-group statistical comparisons were conducted; and 11: point measures and measurements of variability were provided for at least one key outcome.

Table 2. Characteristics of the participants.

Author	Participants (M/F), n	Severity of COPD	Study group (n)
Ries et al.[19]	28 (N/A)[a]	Moderate to very severe	UAE + GR (8) UAE + PNF (9) Control (11)
Marrara et al.[20]	22 (22/0)	Moderate to severe	UAE (8) LE (8) Control (6)
Costi et al.[21]	50 (33/17)[a]	Moderate to very severe	UAE (25) Control (25)
Janaudis-Ferreira et al.[22]	31 (N/A)	Moderate to very severe	ART (13) Control (18)
Calik-Kutukcu et al.[23]	42 (27/15)	Moderate to severe	ART (21) Control (21)

M/F: male/female; UAE: unsupported arm exercise; GR: gravity resistance; PNF: proprioceptive neuromuscular facilitation; LE: leg exercise; and ART: arm resistance training. [a]All of the participants received pulmonary rehabilitation.

Table 3. Characteristics of the exercise training programs.

Author	Type of arm training	Intensity	Frequency	Duration	Additional interventions	Control group
Ries et al.[19]	Arm ergometry & resistance training (hand weights)	GR: 1-2 sets × 10 reps (1-5 lb) PNF: 3 sets × 4-10 reps (1-5 lb)	1-2 × day	6 weeks	Arm ergometry; PR	PR (no upper extremity training)
Marrara et al.[20]	Resistance training (free weights)	3 sets × 10 reps 1st: 50% 10 RM 2nd: 75% 10 RM 3rd: 100% 10 RM	3 × week	6 weeks	UL & LL stretching; bronchial hygiene	Respiratory exercises; bronchial hygiene; stretching
Costi et al.[21]	Resistance training (dumbbells)	3 sets × 10-15 reps 50% 1 RM	5 × week	3 weeks	PR; cycle ergometry; calisthenics; resistance exercise	PR; cycle ergometry; calisthenics; resistance exercise
Janaudis-Ferreira et al.[22]	Resistance training (free weights)	Loads equivalent to 10-12 RM	3 × week	6 weeks	Walking; lower and upper extremity strength training; breathing exercises; self-management education	UL flexibility and stretching exercises
Calik-Kutukcu et al.[23]	Resistance training (free weights)	3 sets × 8-12 reps 40-50% 1 RM	3 × week	8 weeks	Arm ergometry and stretching exercises for warm-up and cool down; breathing exercises	Breathing exercises

GR: gravity resistance, reps: repetitions; PNF: proprioceptive neuromuscular facilitation; PR: pulmonary rehabilitation; RM: repetition maximum; UL: upper limbs; and LL: lower limbs.

study, the Glittre-ADL test[25,26] was also used in order to evaluate the performance of ADL.[23] The Borg scale was used in order to determine the perception of dyspnea or fatigue before, during, and after the simulation tests. Two studies used tools specific for the assessment of UL activities, such as the Milliken ADL Scale[23] and a modified version of the Disabilities of the Arm, Shoulder and Hand Questionnaire,[22] in order to assess ADL. Finally, in one study, patients were asked to rate their perception of dyspnea during the tests using the dyspnea domain of the Chronic Respiratory Disease Questionnaire.[22] In one of the studies, there was a significant decrease in the time taken to complete the ADL test, a greater decrease being seen in the ULExT group undergoing proprioceptive neuromuscular facilitation.[19] In addition, two studies[21,23] that used an ADL test similar to that of the study above[19] showed a significant increase in the number of completed

cycles in the ULExT group compared with the control group[21] or with baseline.[23] Another study evaluated the metabolic response during ADL tests and revealed that the minute ventilation/maximal voluntary ventilation ratio and the oxygen uptake/maximal oxygen uptake ratio decreased during blackboard erasing in the ULExT group.[20] One study showed significant improvement in Milliken ADL Scale scores in the ULExT group.[23] However, no significant changes were found in the Glittre-ADL test results[23] or in Disabilities of the Arm, Shoulder and Hand questionnaire scores.[22]

In three studies, the perception of dyspnea showed no significant changes during UL-related ADL simulation tests.[19,20,23] In only one study did the perception of dyspnea significantly improve in both groups.[21] In another study, there was a significant reduction in the perception of dyspnea during the Glittre-ADL test in the ULExT group.[23] Finally, the perception of dyspnea during ADL tests significantly changed in both groups in one study.[22]

Fatigue during ADL assessment showed no significant changes in two studies.[19,23] Only in one study did arm fatigue show a significant improvement during ADL simulation testing in the intervention group.[21] The results in the ULExT groups are presented in Table 4.

DISCUSSION

The aim of the present systematic review was to investigate the potential effectiveness of ULExT in improving the performance of ADL that involve the upper limbs in patients with COPD. Our results indicate that ULExT is a safe therapeutic approach for these patients. In addition, significant improvements in the performance of ADL that involve the UL were found in the ULExT group compared with baseline[20,23] or compared with the control group.[21] However, ULExT has shown contradictory results in symptom perception during ADL that involve the UL.

ADL, especially activities involving the UL, are compromised in patients with COPD. The results of four of the studies that examined the effect of ULExT in UL-related ADL simulation tests showed that ULExT can provide significant improvements (Table 4).[19-21,23] In one study, there was a significant reduction in the total time taken to complete the ADL tasks.[19] This finding was also seen in two other studies, in which there was a significant increase in the number of cycles completed during the ADL simulation test within a ten-minute timeframe in the ULExT group.[21,23] Finally, in another study, a significant decrease in metabolic and ventilatory demand during blackboard erasing was seen only in the ULExT group.[20]

Although significant improvements were seen in the intervention groups, there were some contradictory findings in some of these studies. In one of the studies, in which there was a significant difference in group-time interaction in the total time taken to complete the ADL tasks, there was no significant effect of group or time factors.[19] This finding can be attributed to the fact that the time taken to complete the ADL test at baseline was longer in the group undergoing proprioceptive neuromuscular facilitation than in the other groups; however, no significant differences were found.[19] In another study, there was a significant increase in the number of cycles performed during the ADL simulation test both in the intervention and control groups.[23]

Symptom perception might explain the improvements in the performance of ADL during the tests. It is well known that the occurrence of symptoms of dyspnea and fatigue might restrict UL activities.[9] One study reported that improved symptom perception correlated with improved performance of ADL.[21] However, in one study, no significant improvement in the perception of dyspnea or fatigue during ADL simulation tests was reported, although the number of cycles completed during the tests significantly increased in the intervention and control groups.[23] This phenomenon might be attributed to the respiratory exercises that both groups performed.[27] It is well known that the use of UL can cause hyperinflation,[3,10] which is associated with the occurrence of dyspnea[2] and dysfunction of intrinsic contractile properties of respiratory muscles.[28] Nevertheless, hyperinflation is not the sole cause of dyspnea. Various studies have clearly shown that dyspnea is a complex symptom and is triggered by many factors, such as emotions, cognition, context, and pathophysiology.[29] According to these findings, it seems logical that arm training and breathing exercises can improve hyperinflation and pulmonary function during UL activities without necessarily improving the perception of dyspnea. This assumption seems to be confirmed in one of the studies included in this review, in which there was a decrease in metabolic and ventilatory demand during blackboard erasing but no significant change in the perception of dyspnea in the ULExT group.[20]

In some cases, ADL were assessed by means of tests or questionnaires. In one study, the Glittre-ADL test was used, but no significant changes were found within or between the groups.[23] This test requires getting out of a chair, walking ten meters, walking up and down a ladder while carrying a weighted backpack, and moving objects in a bookcase.[25,26] The lack of significant results using this test might be because it requires the performance of activities that involve the lower limbs (such as walking); exercises involving the lower limbs were not included in the ULExT in that study.[23] However, activities such as housecleaning and doing laundry showed significant changes according to ADL questionnaire scores.[23] Nevertheless, questionnaires have the disadvantage of providing subjective answers that are not always real.

Although significant improvements were found in some of the studies included in the present review, the aforementioned findings cannot be generalized because of some quantitative and qualitative limitations of those studies. The number of studies included was small (only five), which seems quite insufficient to provide clear results. In addition, according to the PEDro scale, the

Table 4. Results of upper limb exercise training (before and after the intervention or between intervention and control groups).

Author	UL-related ADL simulation test	UL-related ADL questionnaires	Dyspnea during ADL	Fatigue during ADL	ULExT-related AE
Ries et al.[19]	Decrease in the time taken to complete the ADL test*		NS	NS	Back pain (n = 1)
Marrara et al.[20]	Decrease in V_E/MVV and in VO_2/VO_2max during blackboard erasing*		NS		No AE reported
Costi et al.[21]	Increased number of ADL cycles in 10 min*†		Significant decrease*	Significant decrease*†	No AE reported
Janaudis-Ferreira et al.[22]		NS in modified DASH scores	Significant decrease*		Elbow pain (n = 1) Neck pain (n = 1) Severe dyspnea (n = 1)
Calik-Kutukcu et al.[23]	Increase in the number of ADL cycles in 10 min Improvement in MAS housecleaning and laundry integrated scores* NS in the Glittre-ADL test	Improvement in MAS scores*	Significant decrease during the Glittre-ADL test*	NS	No AE reported

UL: upper limbs; ADL: activities of daily living, AE: adverse events; ULExT: upper limb exercise training; NS: not significant;V_E: minute ventilation; MVV: maximal voluntary ventilation; VO_2: oxygen uptake, VO_2max: maximal oxygen uptake, DASH: disabilities of the arm, shoulder and hand (questionnaire); and MAS: Milliken ADL scale. *$p < 0.05$ in the ULExT group before and after the intervention. †$p < 0.05$ between the ULExT group and the control group.

methodological quality of the studies was moderate, in two studies, and high, in three studies, and there was no blinding of researchers in two studies.[19,20] In such cases, their personal beliefs in favor of or against an intervention can alter the results (information bias).[30,31]

In most of the studies included in this review, the sample size was not determined on the basis of a statistical power analysis, and, in some cases, the number of participants in each group was smaller than 11 patients (pilot studies). In addition, the majority of the samples comprised males. The severity of COPD, in accordance with the Global Initiative for Chronic Obstructive Lung Disease criteria, ranged from moderate to very severe; no patients with mild COPD were included in any of the trials.

Apart from the limitations in the methodological design, there were several differences regarding the ULExT among the selected studies, such as the frequency of ULExT sessions (from three times a week to twice daily), total duration of the program (ranging from three to eight weeks), duration of the sessions, type of exercise, and exercise intensity. In addition, the activities proposed to the control groups were different. Another limitation involves the assessment of ADL. Four studies used nonvalidated simulation tests to assess ADL.[19-21,23] Moreover, there were differences in the methods of assessment and in outcome measures to evaluate ADL, the number of ADL tasks being two in one trial,[20] three in another trial,[19] and four in two trials.[21,23] Furthermore, the outcome measure of ADL simulation tests was time, measured in seconds, in one study,[19] or the number of cycles completed in ten minutes, in two studies.[21,23] All of these limitations prevent generalization of the findings of the studies. Because of these discrepancies, a meta-analysis could not be performed.

Three previous systematic reviews investigated ULExT and the ability to perform ADL that involve the UL in patients with COPD.[15,32,33] The number of trials included in the reviews was smaller than was the number of trials in our study, ranging from one to three. The outcome measure was the performance of ADL or symptoms during ADL. One of the three reviews concluded that ULExT should not be recommended,[32] and two concluded that there was no clinical evidence to support the efficacy of ULExT in improving symptoms during ADL,[15,33] one of which reporting a general improvement in dyspnea but not during ADL.[15] The trials included in those reviews[15,32,33] were also included in the present systematic review, with the addition of two other studies. Our review demonstrated that, in four of the five studies included, the performance of ADL that involve the UL in the ULExT group improved significantly compared with baseline[19,20,23] or with the control group.[21] A decrease in the perception of dyspnea during ADL in the ULExT group was reported in three studies,[21-23] whereas a significant decrease in fatigue in the ULExT group, compared with the control group, was reported only in one study.[21]

ULExT can be considered safe for patients with COPD, because no deterioration of the disease or any other severe adverse effects, which could lead to hospitalization or death, have been reported.

A major goal of pulmonary rehabilitation, especially ULExT, is improving the performance of ADL in patients with COPD. The findings of this review revealed

that ULExT is safe and can significantly improve the performance of ADL that involve the UL in such patients. However, the limitations of the selected studies and their contradictory results regarding the symptoms of dyspnea and fatigue during ADL that involve the UL bring uncertainty regarding the results. Further research through well-designed randomized controlled trials is warranted to determine the efficacy of ULExT and the proper parameters for this type of training in patients with COPD.

AUTHOR CONTRIBUTIONS

All authors have contributed to the preparation of the manuscript (study design, interpretation of findings, and drafting, writing, and revising of the manuscript) and have read and approved the final version for submission.

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New CT finding (the target sign) in three patients with COVID-19 pneumonia

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TO THE EDITOR:

In December of 2019, the city of Wuhan, in Hubei province, China, became the epicenter of an outbreak of pneumonia caused by a new coronavirus, which was later designated SARS-Cov-2 by the World Health Organization, the disease caused by SARS-Cov-2 being designated COVID-19. COVID-19 was declared a global public health emergency by the World Health Organization on January 30, 2020.[1] COVID-19 is diagnosed by positive RT-PCR testing on nasopharyngeal aspirates or lower respiratory tract secretions (sputum, tracheal lavage fluid, or bronchoalveolar lavage fluid). However, because RT-PCR results can be delayed or false negative, chest CT has become an important diagnostic aid, being strongly recommended in suspected cases of COVID-19.[2]

The clinical expression of COVID-19 is variable, including mild, moderate, severe, and critical disease. The initial clinical presentation includes fever and flu-like symptoms, which can gradually progress to dyspnea and respiratory failure in 7-14 days.[3]

Chest CT findings are well established and, like the clinical expression of COVID-19, are variable, being consistent with the temporal progression of the disease.[4,5] The most commonly reported CT findings in patients in the early stages of COVID-19 are nodular/patchy, single/multiple ground-glass opacities in a peripheral/peribronchovascular distribution, as well as intralobular/interlobular septal thickening, together with a crazy-paving pattern. In the progressive phase, the number of lesions increases, as does their size and density, generally coexisting with ground-glass opacities, consolidations, and, in some cases, bronchiectasis and atelectasis. In the severe phase, all lung segments are affected, and atelectasis is present. In the healing (or dissipation) phase, cord-like opacities appear, indicating fibrosis. COVID-19 can have a short clinical course, with early imaging findings rapidly progressing to findings consistent with the healing phase of the disease.

Several chest CT scan signs have been described in patients with COVID-19 pneumonia,[6] including the batwing sign, representing bilateral perihilar opacities, the white lung sign, representing diffuse, high-density opacities, the *Rosa roxburghii* sign, representing focal nodular ground-glass opacities, the gypsum sign, representing patchy consolidations of varying density in both lungs, and the reversed halo sign, which is defined as a focal area of ground-glass opacity surrounded by a ring of consolidation and which has been shown to be associated with several infectious and noninfectious diseases,[7] including viral pneumonia.[8]

In three RT-PCR–confirmed COVID-19 patients undergoing HRCT at our facility, ground-glass opacities or peripheral curvilinear consolidative opacities were found in the secondary pulmonary lobule, together with central nodular opacity (corresponding to a perilobular pattern with central involvement in the secondary pulmonary lobule) surrounding the centrilobular arteriole, giving an appearance similar to that of a shooting target.

Patient 1 was a 36-year-old man who was admitted with severe dyspnea. He underwent HRCT 11 days after the onset of symptoms. The findings included ground-glass opacities and target signs in the lower lobes (Figure 1A). Patient 2 was a 43-year-old woman who was admitted with an 8-day history of dry cough and chills. She underwent HRCT 10 days after the onset of symptoms. The findings included bilateral target signs in the lower lobes (Figure 1B). Patient 3 was a 42-year-old woman who was admitted with a 7-day history of productive cough, rhinorrhea, and odynophagia. HRCT findings included target signs in the lower lobes (Figures 1C and 1D).

The finding of perilobular opacity associated with central nodular opacity in the secondary pulmonary lobule on chest CT scans of patients with COVID-19 was first reported in a study published in June of 2020[9] and was designated the target sign. According to the authors of the study,[9] a perilobular pattern and the reversed halo sign are indicative of organizing pneumonia in patients with COVID-19; also according to the authors, in COVID-19 patients presenting with the target sign, the peripheral opacities are suggestive of organizing pneumonia, whereas the central nodular opacity is suggestive of vascular and perivascular inflammation or focal enlargement of the pulmonary artery. We suggest the possibility of organizing pneumonia involving the periphery and the center of the secondary pulmonary lobule, given that organizing pneumonia can present with peribronchovascular involvement.[10]

To our knowledge, the target sign has not been described before in viral or bacterial respiratory infections and could be a hallmark of COVID-19 pneumonia, given the appropriate clinical context. However, in order to determine that, there is a need for studies comparing CT findings of COVID-19 pneumonia with those of other types of pneumonia and those of other diseases that can present with organizing pneumonia.

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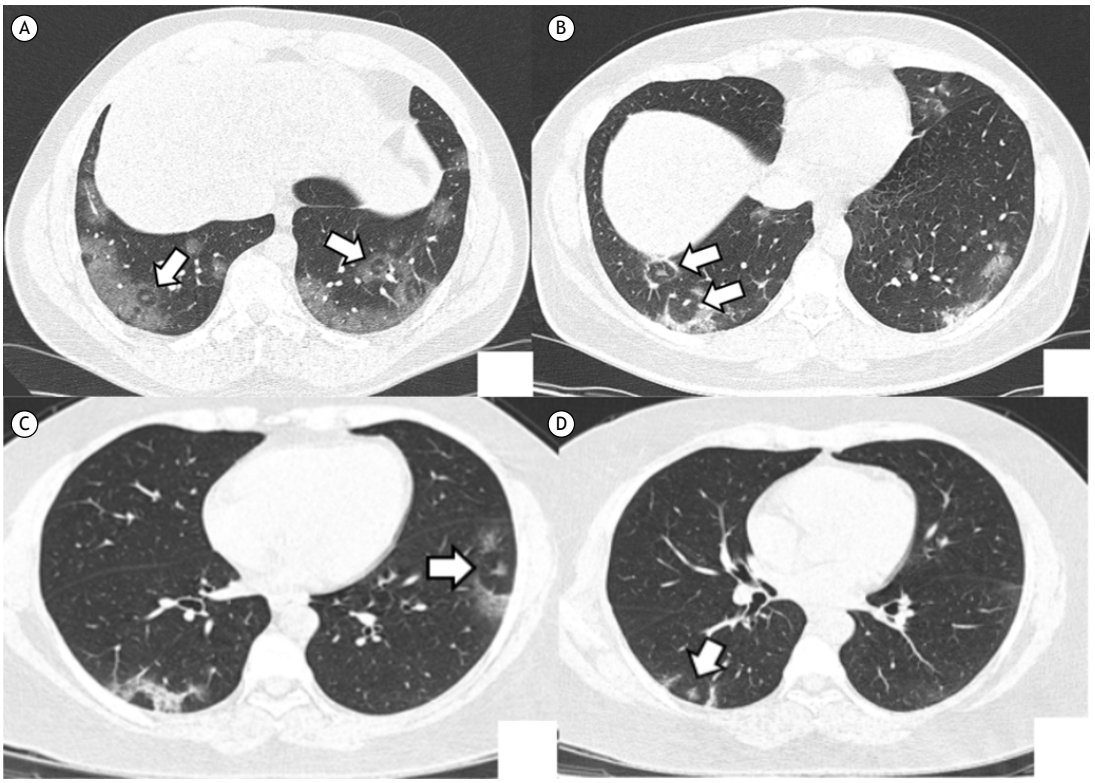

Figure 1. Axial HRCT scans of patients with COVID-19 pneumonia, showing bilateral ground-glass opacities containing lesions at the lung bases (the target sign, arrows).

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Is the CT target sign specific to COVID-19 pneumonia?

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We read with interest the letter to the editor by Martins et al.,[1] who reported the cases of three RT-PCR–confirmed COVID-19 patients presenting with the target sign, a recently described chest CF finding in COVID-19.

In a series of nearly simultaneous studies,[2-5] the target sign has been described as a new CT finding in patients with COVID-19, consisting of central nodular opacity surrounded by a dense peripheral rim. The sign has variously been termed the target sign,[2,4] the "double halo" sign,[3] and the "bullseye" sign.[5] However, the target sign appears to be the most appropriate and widely accepted term to describe it[2,4,6] because of its peculiar appearance, similar to that of a shooting target.

Careful analysis of CT findings in COVID-19 patients presenting with the target sign shows that the sign represents central nodular opacity of variable density (soft-tissue density or ground-glass density), surrounded by a less dense rim (of normal parenchyma or ground-glass opacity), which in turn is surrounded by a denser peripheral rim (of ground-glass density or soft-tissue density). In some cases, multiple concentric ring-like opacities are seen.[6]

A review of the literature[1-6] shows that the densities of the central and peripheral opacities vary across cases; in some cases, the center has soft-tissue density, whereas, in others, it has ground-glass density. One study[5] showed that there can be an "inner ring of air" (corresponding to normal parenchyma) between the central nodular opacity and the dense peripheral rim. This is consistent with some of our own findings (Figures 1A and 1B).

The target sign has been confused with the reversed halo sign (RHS), despite the fact that they can be differentiated by morphological criteria. The RHS is also seen in patients with COVID-19 and is a nonspecific sign, having been shown to be associated with several infectious and noninfectious diseases.[7] It has recently been shown

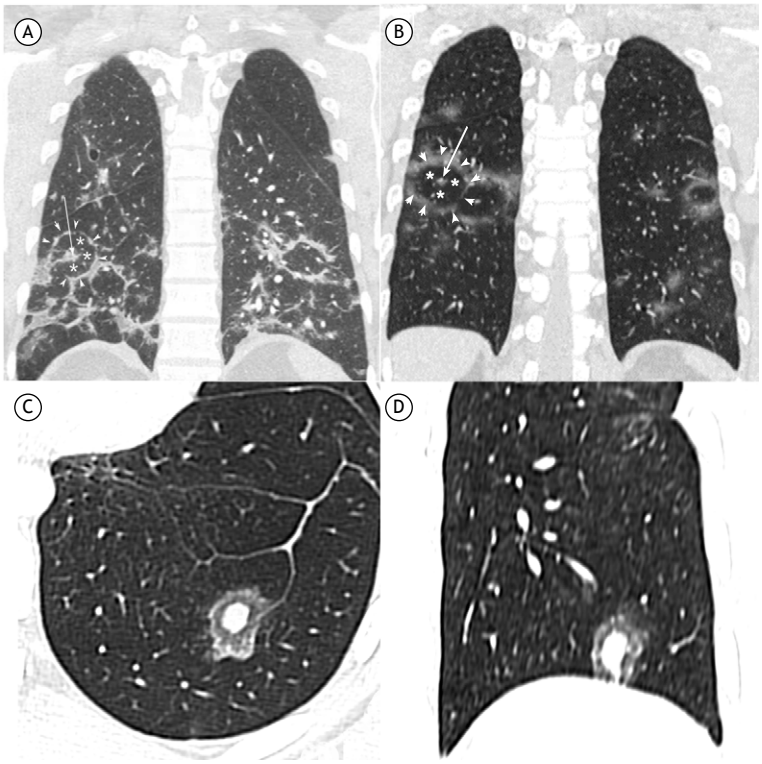

Figure 1. In A and B, coronal CT scans of two different patients with confirmed COVID-19, showing perilobular opacities and imaging findings consistent with the target sign, including central nodular opacity (arrows), a dense peripheral rim (arrowheads), and an inner ring suggestive of normal lung parenchyma (asterisks). In C and D, chest CT scans of a patient with pulmonary osteosarcoma metastasis, showing similar imaging findings, including central nodular opacity surrounded by two concentric ring-like opacities of low density.

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that patients with COVID-19 can present with either an RHS,[8] which is defined as a focal rounded area of ground-glass opacity surrounded by a more or less complete ring of consolidation,[9] or a reticular RHS, which is an RHS with low-attenuation areas within the halo, with or without reticulation, suggestive of pulmonary infarction.[10]

Although for the sake of scientific rigor it is important to differentiate between the two, they both indicate organizing pneumonia in patients with COVID-19.[11]

According to Martins et al.,[1] the target sign has not been described before in viral or bacterial respiratory infections and could be a hallmark of COVID-19 pneumonia in the appropriate clinical context. In order to determine that, there is a need for studies comparing CT findings of COVID-19 pneumonia with those of other types of pneumonia and those of other diseases that can present with organizing pneumonia.[1]

Following this line of reasoning, we report the case of a 16-year-old male patient who presented with a typical target sign on chest CT, with no relation to COVID-19 or organizing pneumonia. The patient was admitted with a tumor in the right femur. The tumor was resected, and the histopathological diagnosis was osteosarcoma. The patient underwent chemotherapy. After 3 months, the disease progressed with multiple nodular opacities in the lungs; one of the opacities was a soft-tissue density nodule located in the left lower lobe and surrounded by two concentric ring-like opacities of low density, characterizing the target sign (Figures 1C and 1D). A new CT scan, performed 2 months later, showed an increase in nodule diameter, as well as the target sign. Diagnostic resection of one of the lesions followed by pathological analysis revealed osteosarcoma metastasis. The lesions progressed, and the patient died 13 months after being diagnosed with a femoral tumor.

Therefore, we sought to show that the target sign is not specific to COVID-19 and can be seen in conditions other than organizing pneumonia, including osteosarcoma metastasis.

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Lung cancer in the era of COVID-19: what can we expect?

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TO THE EDITOR,

In Brazil, lung cancer is the most lethal malignant neoplasm and the third most common type of cancer among males;[1,2] it is also associated with high morbidity and mortality despite recent advances in its treatment. It is estimated that 70% of all cases of lung cancer in the country are diagnosed in an advanced or metastatic stage (stages III and IV, respectively), whereas less than 9% are diagnosed in stage I, a lower proportion than what has been reported for some high-income countries.[3] We know that delays in diagnosing the disease can lead to adverse outcomes (such as rapid progression of the disease and death), which could be partially related to the limited availability of diagnostic procedures such as biopsy (percutaneous or surgical), mediastinoscopies, and bronchoscopies in our public health care system.[4] In recent years, the delay in diagnosis has been one the main challenges faced in the management of lung cancer patients in Brazil.[2]

More recently, the COVID-19 pandemic has imposed new logistical challenges to the Brazilian health care system in dealing with the staggering volume of infected patients who need hospitalization. In an attempt to reduce the spread of the disease, consultations and emergency care were initially limited, which made managing other pathologies a challenging task for physicians and patients. In addition, the immediate suspension of elective and surgical procedures, including various oncological procedures, as well as prioritized reallocation of available financial resources, has contributed to making this the largest public health crisis in recent history.

Population-based studies evaluating the impact of the current pandemic on the clinical oncology practice have registered delays in the management of various types of cancer, including lung cancer,[5-7] which could lead to an increase in the number of avoidable cancer-related deaths in the near future. One of those studies highlighted a special concern in relation to younger patients, in whom the risk of nosocomial infection during hospitalization does not justify any delay in the treatment, even if only for a few weeks.[6] To our knowledge, despite growing concern in the international medical and scientific community on the subject, there have been no studies of this nature conducted in Brazil.

From the epidemiological data available on the information platforms of the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System),[8,9] we made an observational analysis of the number of hospitalizations and interventional diagnostic procedures (percutaneous or surgical lung biopsies and bronchoscopies) related to lung neoplasms (ICD-10 codes C33-C34) performed at outpatient clinics and hospitals between March and May of 2020. For the comparative analysis, we used as a reference the values obtained for the same period in 2019 and the values projected for the current year by linear regression of a time series for the same period in each year from 2016 to 2019 (Figure 1). That analysis revealed that the number of hospitalizations per pulmonary neoplasm (in the trachea, bronchi, or lungs) during the period evaluated in 2020 was 7% smaller than for the same period in 2019 (6,106 vs. 6,601) and differed significantly from the estimated number (6,879; $p = 0.02$). In the same period of comparative analysis, the numbers of lung biopsies and bronchoscopies performed in the SUS diminished 13% (1,219 biopsies in 2020 vs. 1,399 in 2019) and 35% (6,423 bronchoscopies in 2020 vs. 9,952 bronchoscopies in 2019), respectively, the difference in relation to the number of bronchoscopies projected for 2020 being statistically significant ($p = 0.002$). This abrupt decline in the number of bronchoscopies can be explained by the fact that the procedure potentially presents a high risk of contaminating the care staff, which explains the the *Sociedade Brasileira de Pneumologia e Tisiologia* recommendation to suspend elective procedures during March of 2020.

The data presented here should be interpreted with caution, especially given the observational nature of our analysis and the short period of time evaluated. It is unknown how the health care system will deal with the patient flow returning to pre-pandemic levels, especially if we consider the likely overload caused by the backlog of demand for health care appointments. However, these data underscore the urgent need to discuss actions directed toward maintaining a prioritized, organized flow of patients with a suspected or confirmed diagnosis of lung cancer. This would involve not only raising the awareness of the population at risk (mainly heavy smokers) of the need for screening programs but also combating the uncertainty and panic that can impede the proper treatment of some patients during the pandemic. In addition, reliable epidemiological data and scientific evidence should guide the planning of

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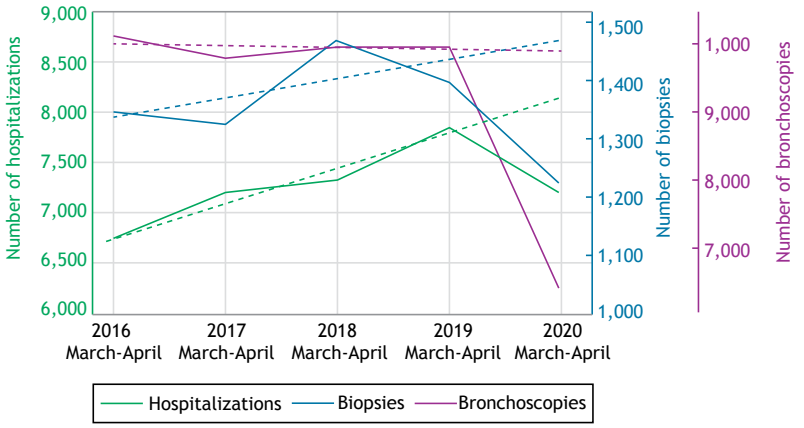

Figure 1. Comparative analysis of the number of hospitalizations related to lung cancer, the number of lung biopsies, and the number of bronchoscopies performed via the Brazilian Unified Health Care System between March and April over the last five years. The dashed lines represent the trends projected by linear regression based on time series for the previous years.

public health programs focused on this new reality. After a larger amount of data has been amassed, it will be necessary to conduct further studies, involving longer clinical follow-up and new mortality correlations.

AUTHOR CONTRIBUTIONS

All of the authors contributed equally to the conception of the study, as well as to the drafting, revision, and approval of the manuscript.

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Lung cancer associated with cystic airspaces: a new radiological presentation of lung cancer

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TO THE EDITOR:

Lung cancer associated with cystic airspaces, also known as cystic or pericystic lung cancer, was once thought to be a rare presentation of lung malignancy; however, in recent years, these forms have become more commonly recognized.[1] This is likely due to the increased availability of contiguous thin-section CT scans of the chest for the follow-up of patients with general respiratory diseases, as well as to the introduction of lung cancer screening programs.[1]

Cystic/pericystic lung cancer is usually diagnosed late, representing as much as 22% of missed lung cancers in screening programs. This is probably due to the low awareness of this morphological subtype among radiologists and clinicians.[1,2] Current guidelines for lung nodule management consider differences between solid and subsolid nodules but fail to provide a management proposal for cystic and pericystic lung cancers.[2]

Cyst wall thickening or nodularity at the interface between normal and fibrotic/emphysematous lung parenchyma, as well as progressive wall thickening or nodularity abutting a cystic airspace, should raise the suspicion of cystic/pericystic lung cancer.[2]

The morphological classification of cystic/pericystic lung cancer was proposed in 2006 and updated in 2015.[3,4] According to the current classification, a type I lesion is a cystic airspace with an exophytic solid component, whereas a type II lesion is a cystic airspace with an endophytic solid component. A type III lesion presents as asymmetrical or circumferential thickening of the cyst wall. A type IV lesion is a multilocular cystic lesion with interposed solid tissue or a ground-glass component (Figure 1).[3-5] Differences among these types, as well as their growth rate, biological behavior, and prognosis, have yet to be determined.

These lesions were previously thought to arise from congenital cysts; however, recent studies have failed to find histopathological evidence to support that theory.[5] Currently, the two most accepted evidence-based theories are that there is a pre-existing cystic airspace in which malignancy develops or that there is formation of a cyst by a "check-valve mechanism" due to a small malignant lesion that only becomes visible after growth.[2,5]

Whatever the initial pathogenesis, the histology of cystic/pericystic lung cancer differs from that of the more commonly known cavitary lung cancer. Cavitation

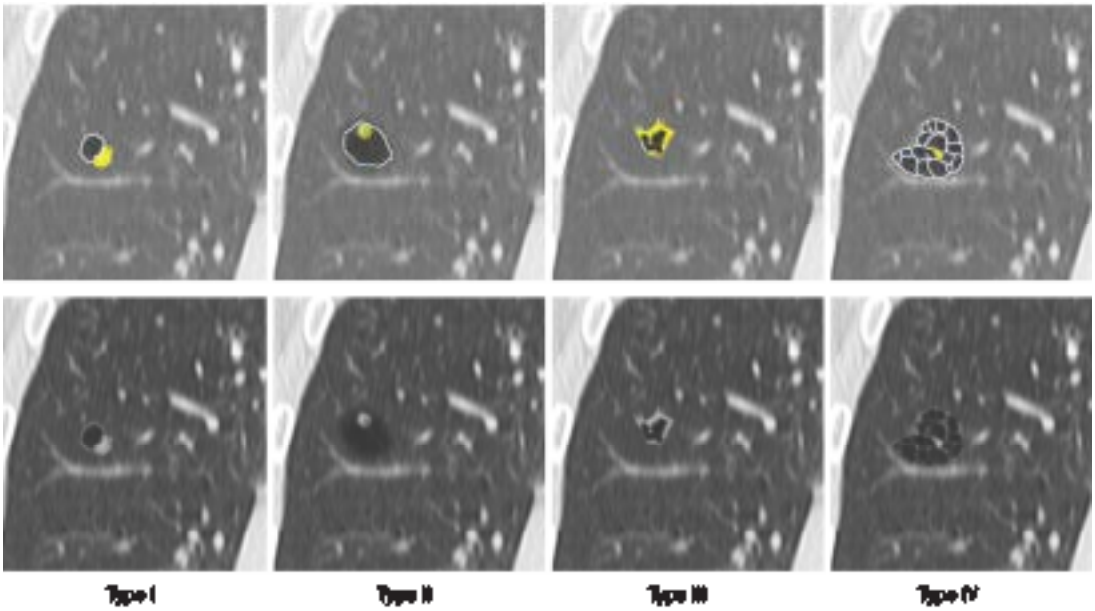

Figure 1. Morphological classification of cystic/pericystic lung lesions. The drawings in the first row of images simulate the different types of cystic/pericystic lung lesions on CT scans: type I—a nodular lesion outside the cyst wall; type II—a nodular lesion inside the cyst wall; type III—cyst wall thickening without a focal nodule; and type IV—a focal nodule within a complex multicystic lesion.

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is usually due to post-treatment necrosis, internal cyst formation, or internal desquamation of tumor cells with subsequent liquefaction.[5] The most common histological type of cavitary lung cancer is non-small cell lung carcinoma, especially squamous cell carcinoma, whereas the most common histological type of cystic/pericystic lung cancer is adenocarcinoma.[2,5]

The delay in diagnosis is due to significant overlap of radiological features between cystic/pericystic malignancies and inflammatory or infectious lesions. Common differential diagnoses include cavitary lesions, such as the ones seen in tuberculosis, squamous cell carcinoma, aspergilloma, and rheumatoid nodules, as well as rare mimickers, such as amyloid nodules and cystic lung metastasis. Cystic/pericystic cancer can be misdiagnosed as a severe form of emphysematous disease, distal airway enlargement, or fibrosis.[5]

When cystic/pericystic malignancy is suspected, histological confirmation and metabolic activity assessment are problematic because of the risk of false-negative results, which represent a potential harm to the patient. 18F-fluorodeoxyglucose positron emission tomography is usually only useful if the solid component of the cystic lesion is larger than 10 mm. Otherwise, the metabolic activity will be wrongly estimated as being mild or even absent. It is difficult to obtain a representative tissue sample from the focal thick wall or small-sized nodular component. In our experience, cystic/pericystic lesions in which positron emission tomography/CT or nondiagnostic biopsy reveals potential pitfalls should be discussed in a multidisciplinary meeting in order to make a decision for follow-up or surgical resection based on the clinical status of the patient and the expertise of the local surgical team.

Here, we sought to increase the awareness of cystic/pericystic lung cancer among radiologists and pulmonologists and highlight the importance of a timely and accurate diagnosis. As we move toward early lung cancer detection and lung cancer screening programs, further studies on these types of lesions are essential to improve knowledge, as well as diagnostic and treatment performance.

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Carinal resection via robotic surgery: a safe approach for selected cases

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TO THE EDITOR:

Tracheal tumors have an annual incidence of less than 0.2/100,000 population and a prevalence in autopsies of only 1 case in every 15,000.[1] They account for only 0.1% of all cancer deaths.[1] Among the histological types of tracheal tumors, the second most common is adenoid cystic carcinoma, which has an incidence of 18-59%. In addition, tracheal adenoid cystic carcinoma has equal gender distribution and is not related to smoking.[2,3] Its symptoms are nonspecific, and the diagnosis is usually delayed.[4] The treatment of choice is surgical resection.[4]

Because tracheal tumors are rare, few institutions have had the opportunity to gain experience regarding this type of neoplasm, and, consequently, treatment is provided exclusively at some specialized health care facilities. Therefore, surgical resection of tracheal tumors continues to be a challenge for the thoracic surgeon. Most procedures are performed via thoracotomy or median sternotomy. Some specialized centers are capable of video-assisted thoracoscopy.

As an alternative for performing this complex surgical procedure, robotic surgery has been shown to be a minimally invasive surgical modality that features several technological advances, such as a three-dimensional view for the surgeon, a greater range of motion of instrumentation, greater precision of movements, and less tissue damage. These advances make surgery safer, more precise, and more efficient. Robotic surgery has the following benefits[5]: shorter postoperative recovery; less postoperative pain; shorter hospital stays; a lower risk of bleeding and infections; smaller incisions; and surgeon-friendly ergonomics.

Here, we present the case of a 70-year-old male patient who presented with an episode of acute myocardial infarction, in his hometown, in February of 2018. During hospitalization, the patient developed hospital-acquired pneumonia. A lesion within the lumen of the carina was identified as an incidental finding on a CT scan of the chest. The patient underwent rigid bronchoscopy with excision of the lesion. The pathology result was adenoid cystic carcinoma.

The patient was then referred to a health care facility in the city of Belo Horizonte, Brazil, where he underwent flexible bronchoscopy, during which a residual exophytic lesion was seen in the carina. The decision was made to use robotic surgery in order to perform carinal resection and mediastinal lymphadenectomy, with carinal reconstruction.

The patient was intubated with a single-lumen endotracheal tube, which was introduced into the left main bronchus under endoscopic guidance. Extracorporeal membrane oxygenation was available if necessary.

The da Vinci Xi robotic system (Intuitive, Sunnyvale, CA, USA) was used. An intercostal nerve block was performed, and four robotic ports were put in place. The optical port was placed in the eighth intercostal space on the right anterior axillary line, whereas the port for the anterior robotic arm was placed in the sixth intercostal space on the right anterior midclavicular line. The ports for the two other robotic arms were placed to form a triangle with the optical port, each being 7 cm from it. The surgery started with lymphadenectomy of the station 7 (subcarinal) mediastinal lymph nodes for visualization of the carina, as well as for dissection and stapling of the azygos vein (Figure 1A). The trachea was released to allow greater freedom of movement so that bronchoplasty could be performed. Bronchotomy was performed in the left main bronchus (Figure 1B), and the neoplastic lesion was identified by direct visualization. Carinal resection with histologically confirmed (frozen section) tumor-free margins was performed. That was followed by tracheal reconstruction and carinal reconstruction with continuous 3-0 polydioxanone barbed sutures (Figures 1C and 1D), together with a bovine pericardial patch and biological glue.

The patient had a favorable course and was discharged on postoperative day 3. Two weeks after discharge, he presented with moderate chest pain. A pneumothorax was identified, and the patient underwent chest tube drainage. Bronchoscopy revealed a bronchopleural microfistula. The decision was made to pursue conservative treatment, consisting of five days with a chest tube in place, and the condition resolved. Clinical and endoscopic follow-up showed adequate bronchial healing. The pathology result was adenoid cystic carcinoma without involvement of mediastinal lymph nodes and with disease-free surgical margins.

Robotic surgery has a series of advantages over other methods: it is minimally invasive, resulting in less pain, shorter hospital stays, and a rapid return to daily activities compared with open surgery; the robotic arms mimic the movements of the human hand, allowing more precise dissection compared with other minimally invasive

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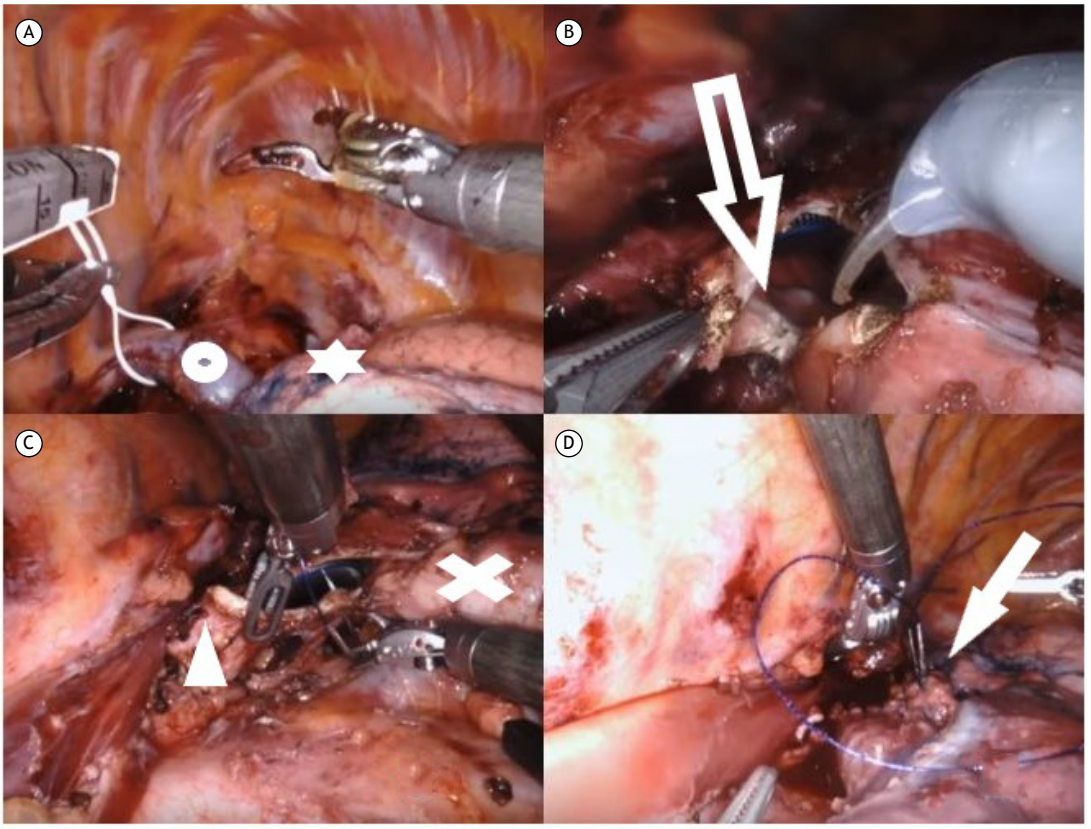

Figure 1. In A, dissection and repair of the azygos vein (circle) for sectioning and visualization of the right upper lobe (star). In B, opening of the main carina for resection of the tracheal tumor (arrow). In C, carinal reconstruction with continuous sutures, with visualization of the right main bronchus (X) and left main bronchus (arrowhead). In D, end of the suture line and the newly constructed carina (arrow).

approaches; the three-dimensional view magnifies the details of the anatomical structures, making surgery safer; and, as demonstrated here, robotic surgery is entirely feasible for carefully selected cases, such as those requiring resection of small tumors without mediastinal invasion.

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Does pulmonary rehabilitation decrease plasma myostatin levels in patients with COPD?

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TO THE EDITOR:

Myostatin, a member of the TGF-β superfamily, is a negative regulator of skeletal muscle development and growth.[1] Muscle and circulating levels of myostatin are increased in patients with COPD.[2-4] Myostatin seems to be a marker for impaired muscle regenerative capacity.[2]

Pulmonary rehabilitation (PR) is a well-established treatment that increases muscle strength and exercise capacity, thus reducing the impact of COPD. Therefore, we hypothesized that myostatin levels would decrease after PR in patients with COPD. In clinical practice, it is easier to assess plasma myostatin than muscle myostatin because the latter requires a muscle biopsy. However, the effect of PR on plasma myostatin levels is unknown. The mechanisms of muscle depletion and muscle changes after PR would be better understood with more knowledge of the effect that PR has on plasma myostatin levels. Therefore, we aimed to investigate the effects of PR on plasma myostatin levels in patients with COPD.

The study included patients with spirometry-confirmed COPD (Global Initiative for Chronic Obstructive Lung Disease stages II to IV) who were clinically stable for at least four weeks prior to the protocol. The additional criteria were being a nonsmoker for ≥ 6 months, having a smoking history ≥ 20 pack-years, and being ≥ 40 years of age. Patients who were using oral corticosteroids were excluded, as were those who had participated in any exercise program in the last year, those who had a lung disease other than COPD, and those with any musculoskeletal or neurological disorder that could compromise their ability to perform any of the PR exercises or study assessments. In a sample of patients without cachexia, Vogiatzis et al.[5] reported a reduction in mRNA expression of myostatin in muscle after endurance training (effect size: 1.28, two-tailed α: 0.05). Therefore, 8 patients would be required in order to achieve a power of 80%. Anticipating patient dropouts and greater variability in plasma myostatin levels, we tripled the sample size (N = 24). The sample size was calculated by using the free statistical software program G*Power, version 3.1.9.2.

Plasma myostatin levels, exercise capacity—as quantified by the six-minute walk test (6MWT) and six-minute walk distance (6MWD),[6]—and the impact of PR on COPD—as determined with the COPD Assessment Test (CAT)[7]—were assessed at baseline, after 24 sessions of PR, and after 48 sessions of PR. Each PR session included aerobic training, lower limb strength training, upper limb resistance training, education, and nutritional orientation. Aerobic training was performed on a treadmill for 30 min (initially at 60% of the average 6MWT speed). The workload was increased progressively in accordance with the patient-reported level of dyspnea (Borg CR10 scale score: 4-6). Lower limb training involved the quadriceps and triceps surae muscles with free weights or using an extension machine (two sets of 10-15 repetitions). Upper limb training was performed in diagonal axes with free weights or elastic bands. Each diagonal was performed in two sets of 2 min each. The first 24 sessions occurred three times a week, the last 24 occurring twice a week. Blood samples were collected and centrifuged, the plasma then being stored at −20°C until analysis. Total plasma myostatin was determined by ELISA (Quantikine® GDF-8/Myostatin Immunoassay kit [DGDF80]; R&D System Inc. Minneapolis, MN, USA) in accordance with the manufacturer instructions. This study was approved by the Human Research Ethics Committee of the Porto Alegre Federal University of Health Sciences, in the city of Porto Alegre, Brazil (Reference no. 836.248).

Data are reported as means ± standard deviations. Correlations were analyzed using Spearman's test. Generalized estimating equation, considering the Gamma model, and Bonferroni post hoc test were used in order to compare the three time points (at baseline, after 24 PR sessions, and after 48 PR sessions) in terms of plasma myostatin levels, 6MWD, and CAT scores. Statistical significance was set at $p < 0.05$. Data were analyzed using the IBM SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA).

At baseline, plasma myostatin levels showed no correlation with age ($r = -0.294$; $p = 0.184$), body mass index ($r = 0.272$; $p = 0.221$), FEV_1 ($r = -0.037$; $p = 0.869$), CAT score ($r = 0.207$; $p = 0.367$), or 6MWD ($r = -0.059$; $p = 0.793$). Of the 24 patients included in the study, 22 (13 males) completed 24 PR sessions. Among those 22 patients, the mean age was 64.8 ± 7.9 years, the mean FEV_1/FVC ratio was 0.48 ± 0.1, the mean FEV_1 was 34.4 ± 13.8% of the predicted value, and the mean body mass index was 27.2 ± 5.1 kg/m^2. Only 16 of the 24 patients completed all 48 PR sessions.

Although exercise capacity and the impact of COPD improved after the first 24 PR sessions, there was no additional improvement after completion of all 48 PR sessions (Figures 1A and 1B). In addition, no significant

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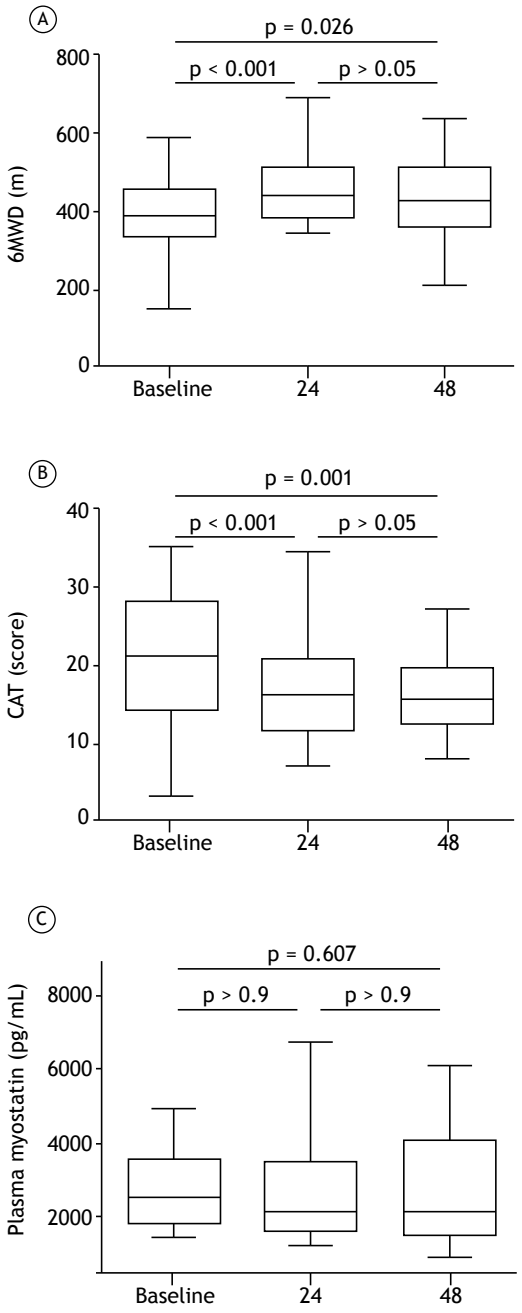

Figure 1. Pulmonary rehabilitation (PR) outcomes. In A, six-minute walk distance (6MWD) at baseline (392.0 ± 92.8 m), after 24 PR sessions (463 ± 82 m), and after 48 PR sessions (442 ± 111 m). In B, COPD Assessment Test (CAT) score at baseline (5.04 ± 1.80), after 24 PR sessions (3.78 ± 0.80), and after 48 PR sessions (3.93 ± 1.10). In C, plasma myostatin levels at baseline (3,346 ± 2,228 pg/mL), immediately before PR session 24 (2,997 ± 2,049 pg/mL), and immediately before PR session 48 (2,813 ± 1,580 pg/mL).

changes in plasma myostatin levels were found after 24 or 48 PR sessions (Figure 1C).

It is known that quadriceps myostatin mRNA expression is inversely correlated with quadriceps strength, 6MWD, physical activity, and quadriceps endurance.[3] However, in the present study, plasma myostatin levels did not correlate with the 6MWD or the CAT score. Plasma myostatin correlates positively with muscle myostatin mRNA expression in healthy controls but not in patients with type 2 diabetes.[8] Whether plasma myostatin reflects muscle myostatin mRNA expression in patients with COPD is yet to be known.

Previous studies have investigated the effect of exercise training on muscle myostatin in patients with COPD.[5,9,10] Lewis et al.[9] found no changes in myostatin mRNA muscle abundance after resistance training, testosterone administration, or a combination of both. Troosters et al.[10] observed that, among patients hospitalized with COPD exacerbation, the levels of myostatin mRNA expression were lower in those who underwent quadriceps resistance training than in those who did not. Conversely, Vogiatzis et al.[5] found that muscle myostatin was downregulated at the mRNA and protein levels after high-intensity cycling training, although only in patients without cachexia. The authors found that mean muscle fiber cross-sectional area increased in the patients with and without cachexia, although the increase was significantly smaller in the former. In addition, patients in both groups showed a decrease in the proportion of type IIB fibers and an increase in the capillary-to-fiber ratio, with no significant differences between the two groups.

Although there is no consensus regarding the effect that exercise training has on muscle myostatin, even less is known about its effect on plasma myostatin. One study reported that plasma myostatin levels decreased by approximately 20% after 10 weeks of high-intensity resistance training in healthy men.[11] To our knowledge, this is the first study to investigate the effect of exercise training on circulating myostatin in patients with COPD. In contrast to previous studies, our study assessed the impact of PR that combines resistance and aerobic exercise.

A crucial caveat in quantifying myostatin is that the current methods fail to distinguish between its active and inactive forms. In fact, myostatin abundance might not necessarily reflect myostatin activity. Whether the proportional relationship between the two forms can change after exercise training remains to be determined. In addition, the abundance of endogenous inhibitors of myostatin or the degree to which they interact with myostatin might be affected by exercise training.

Our study has some limitations. First, because of the lack of a control group, we were unable to investigate the behavior of plasma myostatin in patients with COPD who did not undergo PR. Second, information regarding muscle mRNA expression, muscle strength, and muscle volume would enrich the interpretation of the data. However, information regarding plasma myostatin response to exercise is novel, whereas the determination of plasma myostatin is easier and less invasive than are muscle biopsies in clinical practice.

In summary, although PR improved functional capacity and reduced the impact of COPD in this sample of patients, plasma myostatin levels remained stable. There is a need for further studies investigating the relationship between muscle and plasma myostatin, as well as their interactions with their inhibitors.

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Araujo CLP—research conceptualization, methodology, formal analysis, investigation, resources, data curation, original draft writing, project administration, funding acquisition, and approval of final version. Silva IRV—research methodology, formal analysis, investigation, resources, original draft writing, and approval of final version. Dal Lago P—research conceptualization, methodology, data curation, investigation, resources, original draft writing, review, editing, supervision, project administration, funding acquisition, and approval of final version.

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Bronchial atresia with calcified bronchocele

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A 59-year-old woman presenting with *situs inversus totalis* was admitted for exploration of a dense pulmonary nodule seen on a chest X-ray (Figure 1A). Physical examination and laboratory test findings were unremarkable. CT scans of the chest showed a branching, partially calcified nodular lesion in the left lower lobe with adjacent hypoattenuation (Figures 1B to 1E). The final diagnosis was bronchial atresia, given the absence of a history of infection, the branching of the nodular formation (bronchocele), and the hyperinflation of the adjacent parenchyma.

Bronchial atresia is a congenital abnormality characterized by focal interruption of a lobar, segmental, or subsegmental bronchus, associated peripheral mucus impaction (bronchocele or mucocele) and hyperinflation of the obstructed lung segment. Most adults with this condition are asymptomatic. On chest CT, bronchial atresia is associated with a triad of findings that is pathognomonic for this condition: bronchocele, visible as a branching tubular or ovoid area of increased attenuation; hyperinflation of the obstructed pulmonary segment due to collateral ventilation; and pulmonary hypovascularity. The treatment for asymptomatic patients is conservative.[1,2] Calcified bronchocele in the context of bronchial atresia is an extremely unusual finding.[1]

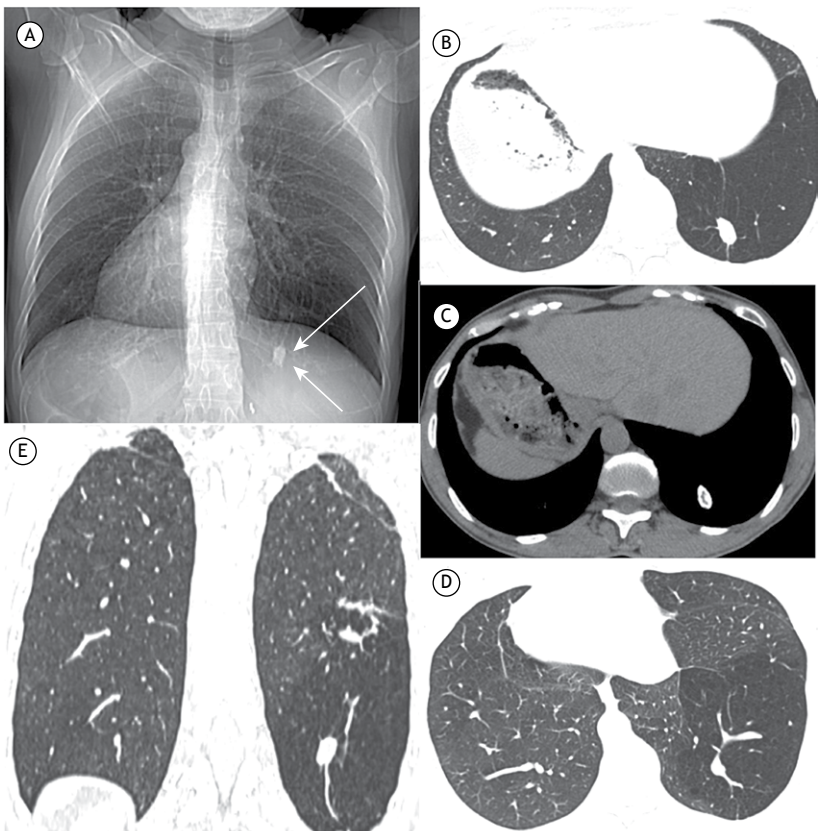

Figure 1. In A, a chest X-ray showing a nodular opacity in the left lower hemithorax (arrows) with adjacent hyperinflation. Axial (in B, C, and D) and coronal (in E) reconstructions of chest CT scans demonstrating a branching, partially calcified lesion in the left lower lobe (bronchocele). The adjacent lung parenchyma was hyperinflated with sparse vascularity. Note that the patient has *situs inversus totalis.*

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

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In an article published in the *Jornal Brasileiro de Pneumologia*, Lapas et al.[1] translated the Sleep Apnea Clinical Score (SACS) into Brazilian Portuguese, adapting it to the cultural context and validating it for use as a method of screening for polysomnography in Brazil, and concluded that this tool can be used to assess the risk of obstructive sleep apnea syndrome in individuals in the country.[1]

The lack of formal objective measures of assessment not only has an indisputable effect on the diagnosis but also leads to uncertainty in treatment and in intervention plans, which can compromise the effectiveness and efficiency of the treatment offered. Aspects such as culture, semantics, technology, content, standards, and concepts are the foundations that enable equivalent comparison at the different levels mentioned. In addition, it is necessary to determine whether the instrument is truly categorical in its proposal.

Certain aspects of the proposed Brazilian-Portuguese version of the SACS should be discussed. Despite the remarkable argumentation of the authors and the fundamental importance of the SACS, equivalence in cultural adaptation requires determining whether equipollence exists in concepts (assessment of the construct of interest in order to determine whether the concepts are relevant in the context to which they are being adapted), items (assessment of the relevance of the items by instrument domain), semantics (ability to transfer meaning from the concepts contained in the original instrument to the adapted version), and operation (comparison between aspects of instrument use in the target and source populations), as well as in measurement (investigation of the instrument's psychometric properties), as described by Reichenheim and Moraes.[2]

Limitations such as the difficulty in comparing results, given the variation of approach in different cultures (which indicates cultural differences and the limited dissemination of the instrument among health care professionals, who, as a rule, work at various health care facilities and have very little time available), and the fact that the methodology used does not mention that examiners need to be trained before using the test can result in biases. The small number of patients (n = 20) should also be taken into account. Beaton et al.[3] show the need to examine psychometric properties, reliability, and validity in order to determine whether the content of the original tool remains unchanged.

It is considered reckless to apply an instrument that has low accuracy and sensitivity, such as the 57.0% (95% CI: 45.8-67.6%) and 45.3% (95% CI: 32.8-58.2%), respectively, determined by Lapas et al.[1] for the Brazilian-Portuguese version of the SACS, because, in the analyses performed, the number of patients who completed the SACS was small (limited demographic data) and because the text does not mention the need to train professionals to apply the important instrument proposed (with consequent understanding of the semantics, culture, technology, concepts, standards, and content of the instrument, as mentioned above).

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Authors' reply

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Obstructive sleep apnea syndrome (OSAS) is a highly prevalent disease, and its proper diagnosis requires overnight polysomnography.[1,2] To inform the decision regarding which patients should be prioritized in referrals for polysomnography, several instruments have been widely used.[2] Obviously, all such instruments have flaws, because if there were a perfect correlation between one such instrument and polysomnography, the latter would become obsolete and could be replaced by the former. Among the most commonly used of such tools is the SACS,[3] which was originally designed to be completed by the patient (without interference from technicians or physicians) and requires the measurement of neck circumference, which should be performed by a trained professional. The SACS consists of three very simple questions: the first aims to determine whether the patient has hypertension; and the other two address whether the patient snores or has respiratory pauses during sleep. The nature and simplicity of the questions facilitated the cultural adaptation. When we tested the translated version in patients, we found that the SACS questions do not involve situations that can be interpreted differently because of cultural peculiarities. The reliability of the SACS was determined through the analysis of internal consistency, and Cronbach's alpha coefficient was calculated to be 0.82 (lower limit of the 95% CI: 0.67), confirming that the translated instrument could be used in patients suspected of having OSAS.

The Brazilian-Portuguese version of the SACS (SACS-BR) that was applied in 86 patients who subsequently underwent polysomnography in a sleep laboratory 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%). These values are in agreement with those found in the assessments made by the authors of the original tool.[3] Neck circumference and the presence of hypertension are independent variables that are highly predictive of the risk of OSAS, and the SACS includes both of those variables in its analysis. Therefore, it is clear that this instrument can have high specificity when the patient has a score ≥ 15. That characteristic was recognized by the authors of the SACS, who consider it to be a tool with a high positive predictive value for the diagnosis of OSAS.[3] However, as mentioned above, of the three questions on the SACS, one asks whether the patient snores and one asks whether the patient has respiratory pauses during sleep. Patients who sleep alone are likely to deny having experienced those symptoms even if they do occur. That contributes to reducing the sensitivity and accuracy of the SACS. That characteristic had been addressed by the authors of the original tool[3] and was again evaluated in the SACS-BR, being thought to be inherent to the tool itself rather than to its translation or adaptation. Therefore, we conclude that the SACS-BR, like the original version of the SACS, has high specificity to select patients who should undergo polysomnography but should be interpreted with caution, especially in individuals who sleep alone, and that only polysomnography data currently inform the diagnosis of OSAS.

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

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

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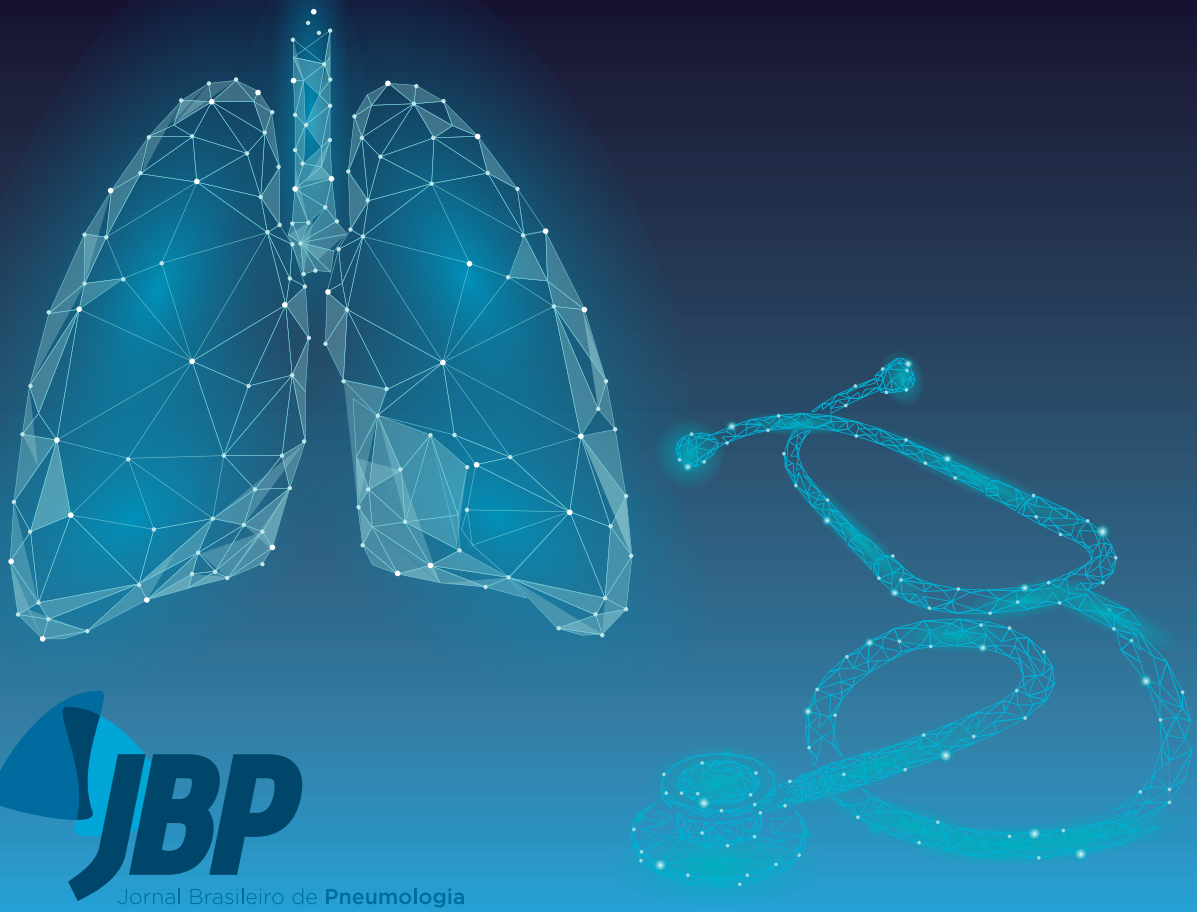

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