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HIGHLIGHT

Update on alpha-1 antitrypsin deficiency

HRCT and fibrosing interstitial lung diseases

Pneumonia following prolonged mechanical ventilation

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

1 dia inteiro
de controle de sintomas[3,4]

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

Recomenda-se duas doses (jatos) em cada narina uma vez ao dia[6]

Referências: *Corticosteroide tópico nasal - 1. Meltzer EO. Ann Allergy Asthma Immunol 2007; 98: 12-21. - 2. Patel P et al. ENT J. 2008; 87: 340-353. - 3. Meltzer EO et al. Ann Allergy Asthma Immunol 2007; 98: 175-181. - 4. Ratner PH et al. J Allergy Clin Immunol 2006; 118: 1142-1148. - 5. Chervinsky P et al. Ann Allergy Asthma Immunol 2007; 99: 69-76. - 6. Bula do Produto Omnaris, Data de acesso das informações: 2019.

OMNARIS® (ciclesonida) 1.1618.0265 INDICAÇÕES: Omnaris® é indicado para o tratamento de sintomas de rinite alérgica intermitente ou persistente, incluindo congestão nasal, coriza, prurido e espirros. CONTRAINDICAÇÕES: Omnaris® é contraindicado em pacientes com hipersensibilidade a qualquer dos seus componentes. Omnaris® não deve ser usado no caso de haver uma infecção nasal não-tratada. ADVERTÊNCIAS E PRECAUÇÕES: Raramente podem ocorrer reações imediatas de hipersensibilidade ou dermatite de contato após a administração de corticosteroides intranasais. Os pacientes com reação de hipersensibilidade conhecida a outros preparados de corticosteroides devem tomar cuidado quando usarem spray nasal de ciclesonida, pois pode ocorrer reação cruzada com outros corticosteroides. Pacientes em tratamento com medicamentos supressores do sistema imune são mais suscetíveis a infecções do que os indivíduos sadios. Varicela e sarampo, por exemplo, podem ter um curso mais grave ou até mesmo fatal em crianças ou adultos usuários de corticosteroides. Em crianças ou adultos que não tenham tido estas doenças ou não tenham sido adequadamente imunizadas, deve-se tomar cuidado particular para evitar sua exposição. Em caso de exposição a varicela ou a sarampo, o paciente deve procurar orientação médica adequada para tratamento profilático. Os corticosteroides intranasais devem ser administrados com cuidado principalmente a pacientes com infecções por tuberculose ativa ou inativa do trato respiratório, com infecções fúngicas ou bacterianas, locais ou sistêmicas, com infecções virais ou parasitárias sistêmicas ou com *Herpes simplex* ocular devido ao potencial de piora dessas infecções. Efeitos nasais locais: Ocorreram casos raros de perfuração do septo nasal em pacientes que administraram ciclesonida pela via intranasal. Por causa do efeito inibitório dos corticosteroides sobre a cicatrização de ferimentos, pacientes que tenham tido recentes úlceras no septo nasal ou sofrido cirurgia nasal ou trauma nasal não devem usar um corticosteroide nasal até que tenha ocorrido a cicatrização. Em estudos clínicos com Omnaris®, foi raro o desenvolvimento de infecções localizadas por *Candida albicans* no nariz e na faringe. Quando tal infecção surge, ela pode exigir tratamento com terapia local apropriada e descontinuação de Omnaris®. Portanto, pacientes em tratamento com Omnaris® por vários meses ou por um período mais longo devem ser examinados periodicamente quanto à evidência de infecção por *Candida* ou outros sinais de efeitos adversos sobre a mucosa nasal. Efeitos sistêmicos: Doses de Omnaris® maiores que as recomendadas devem ser evitadas. Quando usados em doses excessivas, efeitos corticoides sistêmicos podem ocorrer, como hipercorticismo e supressão adrenal, retardo de crescimento em crianças e adolescentes, diminuição na densidade mineral dos ossos, catarata e glaucoma. Se tais alterações ocorrerem, a dose de Omnaris® deve ser descontinuada devagar, consistente com os procedimentos aceitos para a descontinuação de terapia corticoide oral. Gravidez e lactação: A experiência com corticosteroides orais desde a sua introdução demonstra que, pelo fato de haver um aumento natural na produção de corticosteroides durante a gestação, a maioria das mulheres precisará de uma dose exógena de corticosteroide menor. Muitas nem precisarão de tratamento com corticosteroides durante a gestação. Categoria C de Risco na Gravidez – não existem estudos clínicos bem controlados em gestantes. Tal como acontece com outros corticosteroides, a ciclesonida deve ser administrada durante a gravidez somente se o benefício potencial para a mãe justificar o risco potencial para a mãe, o feto ou o bebê. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica ou do cirurgião-dentista. Não se sabe se a ciclesonida é excretada no leite humano. Entretanto, outros corticosteroides são excretados no leite humano. Deve-se tomar cuidado se Omnaris® for administrado a lactantes. Omnaris® só deve ser administrado quando o benefício para a mãe que estiver amamentando for considerado maior que o risco potencial para a mãe e/ou criança. Efeitos não-teratogênicos: Pode ocorrer hipoadrenalismo em bebês nascidos de mães que tenham recebido corticosteroides durante a gestação. Pacientes pediátricos: Estudos clínicos controlados demonstraram que os corticosteroides intranasais podem causar redução na velocidade de crescimento de pacientes pediátricos. Os potenciais efeitos sobre o crescimento do tratamento prolongado devem ser ponderados com os benefícios clínicos obtidos e a disponibilidade de tratamentos seguros e efetivos alternativos aos corticosteroides. Pacientes idosos: Os estudos clínicos de Omnaris® não incluíram um número suficiente de indivíduos com 65 anos de idade ou mais para determinar se eles respondem de maneira diferente dos indivíduos mais jovens. Em geral, a seleção da dose para um paciente idoso deve ser cuidadosa, normalmente começando na extremidade inferior da faixa de dosagem, considerando a maior frequência de diminuição da função hepática, renal ou cardíaca e de doenças concomitantes ou aplicação de outras terapias. INTERAÇÕES MEDICAMENTOSAS: Em um estudo de interação medicamentosa, a coadministração de ciclesonida inalada por via oral e de cetoconazol oral, um potente inibidor do citocromo P450 3A4, aumentou a exposição (AUC) da des-ciclesonida em aproximadamente 3,6 vezes no equilíbrio dinâmico (*steady state*), enquanto os níveis de ciclesonida permaneceram inalterados. Portanto, cetoconazol deve ser administrado com cuidado com ciclesonida intranasal. Não se verificaram interações de Omnaris® com a alimentação. POSOLOGIA: Para crianças acima de seis anos de idade e adultos recomendam-se duas doses (jatos) em cada narina uma vez ao dia (50 mcg por jato; total 200 mcg por dia). Não se devem aplicar mais de duas doses (jatos) em cada narina diariamente. Omnaris® deve ser administrado exclusivamente pela via intranasal. A dose máxima diária recomendada é de 200 mcg por dia. A duração do tratamento dependerá da resposta ao uso da medicação e deve ser estabelecida pelo médico. REAÇÕES ADVERSAS: As reações adversas mais comuns que podem ocorrer durante o uso prolongado de Omnaris® são dor de cabeça, sangramento no nariz e infecções das vias aéreas superiores. Reações comuns (> 1/100 e < 1/10): Respiratórias – sangramento do nariz (8,4%), irritação da mucosa do nariz (4,3%); Sistema nervoso – dor de cabeça (1,6%). Reações incomuns (> 1/1.000 e < 1/100): Gastrintestinais – boca seca (0,2%), dispepsia (0,2%); Infecções – candidíase (0,2%), rinite (0,2%); Respiratórias – ressecamento nasal (0,4%), dor na garganta (0,4%), secreção nasal (0,3%,), irritação na garganta (0,2%); Outras – transtorno do paladar (0,2%), aumento do número de leucócitos (0,3%). Reações com frequência não conhecida (frequência não pode ser estimada a partir dos dados disponíveis): Perfuração do septo nasal. VENDA SOB PRESCRIÇÃO MÉDICA.

Contraindicações: Omnaris® é contraindicado em pacientes com hipersensibilidade a qualquer dos seus componentes. Omnaris® não deve ser usado no caso de haver uma infecção nasal não-tratada. **Interações medicamentosas:** Em um estudo de interação medicamentosa, a coadministração de ciclesonida inalada por via oral e de cetoconazol oral, um potente inibidor do citocromo P450 3A4, aumentou a exposição (AUC) da des-ciclesonida em aproximadamente 3,6 vezes no equilíbrio dinâmico (steady state), enquanto os níveis de ciclesonida permaneceram inalterados. Portanto, cetoconazol deve ser administrado com cuidado com ciclesonida intranasal.

COVIS PHARMA

Material exclusivo de uso do representante comercial
para promoção junto a profissionais de saúde habilitados
a prescrever e/ou dispensar medicamentos.
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World Pulmonary Hypertension Day: reflections and planning

Jaqueline Sonoe Ota-Arakaki[1], Frederico Thadeu Assis Figueiredo Campos[2], Rogério Souza[3]

Every year on May 5, there is a worldwide campaign on pulmonary hypertension (PH). The primary goal of this global initiative is to increase awareness and understanding of diseases related to increased pressure in the pulmonary circulation, which remain underdiagnosed and have high morbidity and mortality. Over the last 20 years, there have been notable scientific advances in the field of pulmonary vascular diseases, especially in relation to pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension, with the development of several therapeutic options and strategies. Such advances have resulted in improved quality of life and survival in patients with these serious diseases.

The time is ripe for a critical analysis of the situation in Brazil regarding everything that concerns this group of diseases, from the generation of knowledge in the field to the impact of our initiatives on patient care.

BRAZILIAN THORACIC ASSOCIATION PULMONARY CIRCULATION COMMITTEE

The *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) Pulmonary Circulation Committee was founded in 1996 on the initiative of Professor Sérgio Saldanha Menna-Barreto and has been, over the years, involved in continuing education and in the development of guidelines or recommendations for the management of PAH[1] and chronic thromboembolic pulmonary hypertension.[2] An update on the recommendations for the management of PAH is being planned by the current committee.

Our performance in public health policies still faces many challenges, especially in the preparation, together with the Brazilian National Ministry of Health, of *protocolos clínicos e diretrizes terapêuticas* (PCDT, clinical protocols and therapeutic guidelines) for PH. The last PCDT for PH was released in 2014. Such PCDT also depend on the incorporation of new technologies into the *Sistema Único de Saúde* (SUS, Brazilian Unified Health Care System) by the Brazilian National Commission for the Incorporation of Technologies into the SUS. Currently, there are 16 drugs approved for the treatment of PAH in different countries, but only 4 of these drugs are available for use within the SUS in Brazil. Access to combination therapy is heterogeneous in the different states of the country.

REFERRAL CENTERS

The first referral centers for the treatment of PH emerged as a result of lung transplant programs that were being created in Brazil. Patients with PH began to be referred to these transplant centers, making the organization of specific care for this clinical condition necessary. The evolution towards the construction of dedicated PH treatment centers was natural after that and was certainly encouraged by the emergence of therapeutic options years later.

In 1998, with the establishment of the University of São Paulo (USP) referral center, the first internship in diseases of pulmonary circulation was incorporated into the mandatory curriculum for a pulmonary medicine residency program. Subsequently, specific areas of study on pulmonary circulation were incorporated into graduate programs at both USP and the Federal University of São Paulo, and the training of physicians who would later establish referral centers in other regions of the country began.

In 2004, institutions that already had dedicated PH patient care units held their first meeting: USP *Hospital das Clínicas* and Heart Institute; Federal University of São Paulo *Hospital São Paulo*; State University at Campinas *Hospital de Clínicas*; São Paulo Hospital for State Civil Servants; Dante Pazzanese Hospital; Federal University of Rio de Janeiro *Hospital do Fundão*; Federal University of Rio Grande do Sul *Hospital das Clínicas*; Santa Casa Sisters of Mercy Hospital of Porto Alegre; Júlia Kubitschek Hospital of the Hospital Foundation of the State of Minas Gerais, in Belo Horizonte; and University of Pernambuco PROCAPE. Currently, there is at least one referral center in most Brazilian state capitals and in the Federal District of Brasília. However, lung transplantation, thromboendarterectomy, and pulmonary angioplasty are therapeutic modalities that are performed in a few centers only.

RESEARCH AND INTERNATIONALIZATION

Brazil has gained a prominent position in research on different forms of PH over the last 20 years, both in terms of pathophysiology studies and in terms of clinical and epidemiological studies.

There are several examples of the participation of Brazil in this scenario. Perhaps the most striking example is with regard to schistosomiasis-associated PAH. Most of the existing knowledge about this condition, which is one of the most prevalent causes of PAH in the world, comes from our country. From the studies of Professor Chaves in the 1950s and 1960s to the present day, research in Brazil has characterized this form of PAH from a clinical, functional, hemodynamic, radiological, and

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epidemiological standpoint.[3-7] Groups with different expertise have been created in the country, exploring more specific areas of knowledge about diseases of pulmonary circulation and creating an environment very conducive to collaboration.

In addition, the establishment of different referral centers in various regions of Brazil has made it possible to expand not only access to existing therapeutic alternatives, but also national participation in several clinical studies for the development of such alternatives, including our country in the global clinical research scenario in a very significant way. The first national clinical trial of drugs to treat PAH began in 2002, and participation in international multicenter clinical trials began as early as in 2003. Since then, virtually all new drugs have been developed with the participation of national researchers, not only through the inclusion of a significant number of patients in highly relevant clinical trials,[8,9] but also through the development of several of the protocols for those. Therefore, our country has objectively contributed to the world having 16 drugs currently approved for the treatment of PAH.

Our country, represented by Professor Rogério Souza, has also had outstanding participation in different world symposiums on PH, initially as a listener in 1998, as part of the working groups in 2003 and 2008, in the coordination of groups in 2013, and in the general coordination of the 2018 world symposium.[10-12]

CHALLENGES

Brazilian physicians and researchers in the field of pulmonary circulation have contributed markedly in various fronts of action, providing better health care for patients and increasing the available scientific knowledge. Nevertheless, the challenges are great. It is necessary to establish more integrated health care research networks, sharing data and initiatives that make it possible to extend PH patient care to all regions of the country and to carry out a greater number of studies that represent all the existing diversity. To that end, it is urgent that unified databases be created and public policies for diagnosis and treatment be developed on the basis of the latest information on diagnostic strategies and therapeutic options. The SBPT, which has been prominent since the inception of the field of pulmonary circulation in Brazil, plays a fundamental role as a guide and motivator for the joint efforts of all pulmonologists working for the benefit of patients with different forms of PH in this new moment.

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The challenge of diagnosing interstitial lung disease by HRCT: state of the art and future perspectives

Gaetano Rea[1], Marialuisa Bocchino[2]

Chest HRCT is the gold standard for the recognition of lung alteration patterns underlying interstitial lung diseases (ILDs) and those entities with potential for fibrotic evolution. In the era of antifibrotic therapies, the central role of imaging to achieve early diagnosis and prognosis is unquestionable. The diagnostic accuracy of chest HRCT is indeed sufficiently high to detect even subclinical alterations that occur in ILDs at an early stage. Any alteration is a component of a puzzle that should be carefully analyzed and revised over time by combining additional elements. The capacity of the skillful mind of the observer to interpret their meaning and insert them into a specific pattern will reduce, within the appropriate clinical context, the range of possible disease entities.

The review article by Torres et al.,[1] published in the present issue of the *Jornal Brasileiro de Pneumologia*, emphasizes the role of chest HRCT in the diagnostic workup of ILDs. The first aspect that deserves attention is the methodology, which requires adequate procedural and technical parameters. They include the placing of the patient in the prone position, acquisition at maximal inspiration, volumetric image acquisition, thin-slice reconstruction (1.00-1.25 mm), use of a high resolution reconstruction filter, and adoption of the shortest rotation time and the highest pitch to reduce acquisition time and movement-related artifacts. Among these, volumetric image acquisition is fundamental to differentiate traction bronchiectasis from honeycombing, which is crucial to diagnose or rule out idiopathic pulmonary fibrosis (IPF).[2,3] In addition, multiplanar image reconstruction of the entire lung, which enables the evaluation of distribution and extent of interstitial abnormalities, can be exclusively obtained with volumetric CT. Integrated image acquisition in the prone position helps differentiate very early reticulation in the lower subpleural regions from gravity-induced nonpathological increase in lung density (lung dependent). Finally, thin-slice, volumetric image CT acquired at end-expiration further improves the diagnostic reliability of small airway diseases.

The authors[1] correctly describe the tomographic features commonly found in fibrosing ILDs and analyze in detail those signs that differentiate the imaging pattern of IPF from that associated with other fibrosing ILDs. On the basis of the most recent international guidelines on the diagnosis of IPF,[2] the authors[1] discuss the new CT classification for IPF in four patterns: UIP, probable UIP, indeterminate for UIP, and alternative diagnosis. There is a certain tendency to consider the first two patterns as only one, because traction bronchiectasis and honeycombing have the same prognostic value regarding the profusion of fibroblastic foci on histology.[4] Indeed, in the appropriate clinical context and in the absence of elements suggestive of other ILDs, the sole CT imaging pattern of probable UIP is highly consistent with the diagnosis of IPF, according to the Fleischner Society.[3] Conversely, the indeterminate for UIP and alternative diagnosis patterns, although not indicative of IPF, do not exclude a histological UIP pattern. CT imaging in these scenarios represents a crucial component of the diagnostic workup, because it facilitates the identification of the best site where to perform biopsy, increasing sampling performance. This means that the combination of radiology with histology is essential, along with clinical information, in the diagnostic workflow of ILDs. Finally, for those patients whose diagnosis remains indeterminate despite all efforts, clinical behavior and disease progression will guide the decision-making process. This is in line with a study[5] recommending that a multidisciplinary team (MDT) discusses about atypical cases in order to achieve a "working diagnosis"; a procedure that can achieve high confidence levels (> 70%). The MDT is perceived as the gold standard for diagnosis of ILDs other than IPF, including a broad panel of entities ranging from ILDs with autoimmunity features to chronic hypersensitivity pneumonia and nonspecific interstitial pneumonia.[6] The lack of classification and standardized diagnostic criteria for some of these entities is still a diagnostic challenge, mainly because a non-negligible proportion of cases of inflammation-mediated ILDs may evolve to fibrosis.

The timing of chest HRCT in the follow-up of patients is still an issue of debate because there is no consensus. It does enable the differentiation between nonfibrotic and fibrotic ILDs; among the latter, it allows differentiation between forms with a slow progression and those with a rapid progression. In particular, Torres et al.[1] underscore the importance of chest HRCT in the follow-up of progressive forms of fibrosing ILDs, characterized by episodes of acute exacerbation and disease acceleration, in which superimposed ground-glass opacities on the fibrotic background may assume a different value.[7] Currently, the attention paid to the identification of interstitial lung abnormalities (ILAs) is also a topic of interest. ILAs present with early, subclinical, and limited interstitial radiological findings. Initially ascribed to senescence or aging, ILAs are incidentally found in most cases and are relatively common in elderly smokers/former smokers in the absence of a clinically relevant condition.[8] In this setting, chest HRCT is the only available diagnostic tool that distinguishes nonfibrotic from fibrotic ILAs. This differentiation has prognostic implications as fibrotic ILAs

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can evolve to pulmonary fibrosis over a few years of monitoring in up to 40% of the cases.

CT imaging is an evolving field of application and study. There is an increasing need to improve diagnostic performance by integrating visual interpretation with quantification of tissue damage. The advancement of technology has made this objective easier to achieve. Both open-source and commercially available tools have been generated to improve patient profiling and prognosis stratification, providing mathematical and statistical data.[9,10] Artificial intelligence for human support is an emerging possibility that is expected with hope. Fibrotic ILDs represent a highly complex sector of medicine that requires integration of specific and in-depth knowledge, as well as close interaction among different (and complementary) professionals. Nintedanib and pirfenidone have been currently used for IPF treatment, but emerging evidence suggests that they can also be used as a reliable strategy to counteract non-IPF progressive fibrotic ILDs.[11,12]

The radiologist is an irreplaceable component of the MDT. Chest HRCT is of fundamental importance in the natural history of ILDs, including early diagnosis, severity assessment, prognosis stratification, disease progression, and prompt identification of any short- and long-term complications.

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New insights into pneumonia in patients on prolonged mechanical ventilation: need for a new paradigm addressing dysbiosis

Jordi Rello[1,2,3], Jacques Schrenzel[4], Alexandre M Tejo[5]

Ventilator-associated pneumonia (VAP) is related to poor outcomes and is most commonly treated with the use of antibiotic therapy in ICUs. The Infectious Diseases Society of America defined VAP as a new lung infiltrate of infectious origin occurring ≥ 48 h after endotracheal intubation.[1] Systemic antibiotic use may increase the risk of VAP by depleting commensal microorganisms and selecting gram-negative bacteria that may have multiple mechanisms of resistance. Traditional endotracheal aspirate cultures are unspecific and lead to widespread use of antimicrobial agents. As an alternative to systemic antibiotics, aerosolization has been suggested,[2] despite the current lack of evidence of reduction in mortality or in the number of days on mechanical ventilation (MV).[3]

In the present issue of the *Jornal Brasileiro de Pneumologia*, Núñez et al.[4] address the occurrence of VAP in tracheostomized patients on prolonged MV (median = 56 days). The authors reported 30-day and 90-day mortality rates of 30.0% and 63.7%, respectively. The SOFA score and the use of vasoactive drugs were significantly associated with 30-day mortality, whereas advanced age, SOFA score, use of vasoactive drugs and COPD were associated with 90-day mortality.[4] *Pseudomonas aeruginosa* was confirmed as the major pathogen isolated, especially in COPD patients. Interestingly, although *Acinetobacter baumannii* was isolated from microbiological cultures from various patients,[4] this was not associated with mortality, suggesting that patients die of pneumonia as an ultimate event rather than as a consequence.

The reason why most episodes of VAP develop within the first 10 days of MV is thought-provoking. Recent metagenomic technologies offer the potential to better the understanding of the interaction among the respiratory microbiota, immune response, and underlying conditions of individuals. Such advances call into question the traditional view of the pathogenesis of pneumonia—that is, the view that pneumonia is caused by a single organism and is a consequence of microaspiration. Metagenomic studies have revealed that other bacteria (anaerobes or "uncultivable" organisms) are frequently associated with the putative major pathogen[5] and, as a new concept, that the development of VAP is a combination of dysbiosis and failure of the host immune response. Because ARDS and VAP are associated with different respiratory microbiomes, a better understanding of this interplay should be of value for ARDS and VAP management strategies. Pathogens are introduced into a pre-existing complex microbial community, which facilitates or hinders pathogen growth and ultimately determines infection. A better understanding of the microbiota using metagenomics is required in order to improve treatment and for effective prevention of VAP.[6] The microbiome has a critical role in immune activation and host defense in patients on prolonged MV.

VAP should be differentiated from ventilator-associated tracheobronchitis,[1] which is more common and represents an intermediate step between airway dysbiosis and VAP development,[2] leading to the overuse of antibiotics, which, in turn, increases the risk of emergence of multidrug resistant pathogens.[5,7,8] In addition, most patients on prolonged MV have already had one or more episodes of infection or relapse caused by the same pathogen. Our group[9] assessed *P. aeruginosa* colonization in patients on MV using pulsed field gel electrophoresis and found that 18% of the individuals had recurrent pneumonia that were not reinfection cases, but relapses caused by the same clone with more resistant phenotypes. It remains to be determined whether this is also true for colonization with *A. baumannii*.

To break the cycle of antibiotic overuse, antimicrobial resistance, and dysbiosis of the host microbiome, a new paradigm is required. Changes in microbiota may be a lung response to chronic disease and may render the host most susceptible to infection. Flanagan et al.[10] were the first to sequence the *16s rRNA* gene from endotracheal aspirate specimens in ventilated patients with *P. aeruginosa* colonization: the most common bacteria belonged to the phyla Firmicutes, Bacteroidetes, and Proteobacteria. Antibiotic therapy reduced microbiota diversity and induced a predominance of *P. aeruginosa*.[10] According to most studies, there is an interaction between bacterial and fungal communities, and modifications in one community affect the other, whereas their interaction with the virome is yet to be elucidated. Although there is no impact on mortality, bronchial colonization by the phylum Ascomyta (*Candida* spp.) is a well-known independent risk factor for *Pseudomonas*-related VAP.[11]

In summary, the traditional paradigm of VAP (that it is a disease caused by a single bacterial pathogen acquired thorugh microaspiration) needs to be replaced by a hypothetical model in which VAP would be associated with dysbiosis. The gut microbiome contributes to protection against opportunistic pathogens. Enriching the microbiota with members of the phylum Proteobacteria, which are considered commensals, increases serum IgA levels.[12]

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Thus, lung dysbiosis combined with gut dysbiosis might induce local immunosuppression and lung dysfunction, facilitating the occurrence of VAP. The role of the Th17 response provoked by segmented filamentous bacteria, which provides protection from staphylococcal pneumonia, seems crucial. These observations are not only of academic interest. Early identification of patients with dysbiosis associated with a higher risk of developing VAP is an unmet clinical need, and this should lead to innovative, targeted preventive strategies.

Whereas whales and dolphins are protected from the consequences of pharyngeal and gut aspiration, both remain susceptible to pneumonia, a common cause of death among cetaceans. The time has come to consider the microbiome-regulated host immunity as a pivotal component of the physiopathology of VAP.

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The not so small role of adjuvant chemotherapy in resected non-small cell lung cancer

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In this retrospective study of 231 patients, Harada and colleagues evaluated real-world data on adjuvant chemotherapy in patients with stage I-IIIA non-small cell lung cancer (NSCLC) who underwent lobectomy or pneumonectomy plus lymph node dissection. The primary end point was overall survival (OS), while the secondary end points were recurrence-free survival (RFS) and safety/feasibility of cisplatin and vinorelbine. Eighty patients received adjuvant chemotherapy, 62 of whom (68%) received a cisplatin-based regimen and 18 (22%), a carboplatin-based regimen. In patients with stage-II NSCLC, adjuvant chemotherapy improved RFS and OS; however, in stage-III patients, only RFS showed statistically significant improvement.

We congratulate the authors for this well-conducted and designed retrospective study from a single center in Brazil. It reinforces the significant survival benefit of adjuvant cisplatin-based chemotherapy in patients with resected stage IB-IIIA NSCLC. We are all aware of the extensive body of literature evaluating adjuvant chemotherapy in NSCLC; however, most of the data come from large prospective, randomized clinical trials, where most of the patients enrolled are not reflective of our daily practice.[1-8] Therefore, not infrequently, we extrapolate the results from a very limited and restricted population to a broader and heterogeneous group of patients. In this context, real-world data play an increasing role in health care decisions and help us fill some of the gaps in the literature. Although reports of adverse events in real-world data tend to be less accurate than the close monitoring of randomized trials, the former can still provide an idea of treatment tolerability and toxicity. In the study by Harada *et al*., 89% of the patients receiving cisplatin and vinorelbine had grade 3-4 toxicity, 49% were hospitalized due to toxicity, and 9% died. These numbers are alarming; nevertheless, the sample size was small (n = 62).[9] Multiple studies have evaluated cisplatin combined with vinorelbine versus other cisplatin doublets and found a strikingly lower incidence of febrile neutropenia and neutropenia, with no difference in RFS or OS.[7,8] In the United States, the standard adjuvant regimen is platinum-pemetrexed for non-squamous histology and platinum-docetaxel/gemcitabine for squamous cell histology.

After at least a decade of stagnation, the role of adjuvant treatment in resected NSCLC is finally taking important steps forward. The ADAURA trial recently reported an 80% reduction in the risk of recurrence or death with osimertinib compared to placebo in resected IB-IIIA NSCLC harboring *EGFR*-sensitive mutations.[10] This led to the approval of this third-generation tyrosine kinase inhibitor (TKI) by the Food and Drug Administration (FDA) in the adjuvant setting. The survival data is still immature; however, due to its impressive improvement in DFS and central nervous system DFS compared to placebo, osimertinib quickly became widely adopted in the United States. Continuing to build on biomarker-driven adjuvant therapy, the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) (NCT02194738) is a large National Cancer Institute (NCI) sponsored National Clinical Trials Network (NCTN) initiative to address the role of genomic testing and personalized therapies in the adjuvant treatment of NSCLC. The study is evaluating crizotinib in resected IB-IIIA NSCLC with an *ALK* rearrangement and erlotinib in resected patients with *EGFR*-sensitive mutations. In light of the ADAURA study results, the enrollment in the erlotinib arm was recently suspended. The LIBRETTOO-432 (NCT 04819100) is a phase III study, which will enroll resected patients with IB-IIIA *RET*-fusion positive NSCLC to selpercatinib or placebo. Many more studies are on the way, and hopefully, the treatment paradigm will continue to evolve in the adjuvant setting.

There is a strong rationale for incorporating immunotherapy in early-stage NSCLC, given the breakthrough results with checkpoint inhibitors as monotherapy or combined with cytotoxic therapy in patients with metastatic disease. Immunotherapy has produced durable responses and impressive survival rates in advanced NSCLC. The ANVIL arm of the ALCHEMIST study randomized patients in more than 600 sites in the United States to nivolumab or observation after surgical resection and standard of care adjuvant therapy (chemotherapy if indicated) in resected IB-IIIA NSCLC. Primary end points are DFS and OS.[11] The IMPOWER-010 is a phase III study, which randomized 1280 patients with resected IB-IIIA NSCLC to atezolizumab or best supportive care (BSC) after adjuvant chemotherapy. Atezolizumab showed a significant DFS benefit versus BSC in resected stage II-IIIA, with a more significant benefit in PD-L1 positive tumors.[12] KEYNOTE-091 is another phase III trial randomizing 1177 patients with resected IB-IIIA NSCLC to pembrolizumab or BSC after adjuvant chemotherapy. The primary end point is DFS as well. There are multiple adjuvant immunotherapy trials currently underway, and we are eagerly awaiting the results. Table 1 summarizes the current immunotherapy and targeted adjuvant trials.

We have been seeing an overwhelming number of FDA-approved tyrosine kinase inhibitors (TKIs),

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Table 1. Ongoing Phase III Adjuvant Trials in NSCLC

Therapy	Comparator arm	N	Biomarker	End Point	Trial Number
Durvalumab	Placebo	332	ctDNA	DFS	NCT04385368
Durvalumab	Placebo	1,360	PD- L1 positivity	DFS in patients with PD- L1 ≥25% in tumor cells, >1% and all randomized patients	NCT02273375
Atezolizumab	Observation	1,280	PD-L1 positivity	DFS in all patients (including PD-L1 subgroup)	NCT02486718
Pembrolizumab	Placebo	1,177	PD-L1 positivity	DFS	NCT02504372
Nivolumab	Observation	903	PD-L1 positivity	DFS and OS in all patients; DFS in patients with high PD- L1 (≥50% staining)	NCT02595944
Crizotinib	Observation	168	*ALK* fusion	OS	NCT02201992
Erlotinib	Observation	450	*EGFR* mutation	OS	NCT02193282
Osimertinib	Placebo	688	*EGFR* mutation	DFS	NCT02511106
Alectinib	Platinum Doublet	255	*ALK* fusion	DFS	NCT03456076
Icotinib	Placebo	124	*EGFR* mutation	DFS	NCT02125240
Selpercatinib	Placebo	170	*RET* fusion	EFS	NCT04819100
Almonertinib	Platinum Doublet	606	*EGFR* mutation	DFS	NCT04762459

OS: Overall Survival; DFS: Disease-Free Survival; EFS: Event-Free Survival; ctDNA: Circulating tumor DNA.

immunotherapies, and chemoimmunotherapy combinations in the late stage-setting of NSCLC. Unfortunately, and paradoxically, we haven't observed this progress in the early stages, where we are aiming for cure. With the approval of osimertinib and the possible role of adjuvant atezolizumab, we are finally starting to move the needle in this space. Besides the historic small benefit of adjuvant chemotherapy, reiterated by Harada and colleagues, cisplatin-based chemotherapy is still playing an important role as the backbone for most adjuvant TKI studies and for all the adjuvant immunotherapy trials. Therefore, selection of the least toxic adjuvant chemotherapy regimen will be even more important as we start to incorporate TKIs and checkpoint inhibitors in the adjuvant treatment of these patients. Based on the real-world data presented on adjuvant platinum-vinorelbine, this regimen should be discouraged in today's practice. First, do no harm, right?

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Cystic disease with sparing of lung bases

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A 39-year-old male smoker presented to the outpatient clinic with complaints of dry cough and dyspnea on moderate exertion. Laboratory test results were unremarkable. Chest CT showed multiple bilateral pulmonary cysts, predominantly in the upper lung fields (Figure 1).

Pulmonary cysts are characterized on CT as rounded, low-attenuation areas in the lung parenchyma, with a well-defined interface with the adjacent normal lung. The cyst wall can vary in thickness but is typically thin. The cysts usually contain air but can sometimes contain fluid. A cystic pattern is seen in a number of diseases, the most characteristic of which are lymphangioleiomyomatosis, Langerhans cell histiocytosis (LCH), lymphocytic interstitial pneumonia, and Birt-Hogg-Dubé syndrome (BHDS).

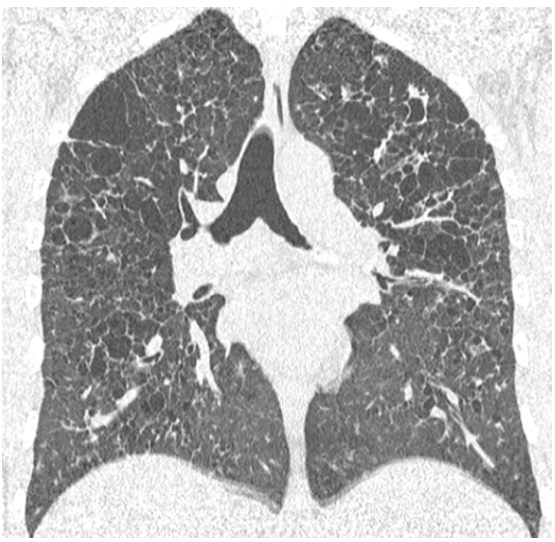

Figure 1. Coronal CT reconstruction showing multiple irregularly shaped cysts, predominating in the upper lung fields. Note the relative sparing of the lung bases.

Some CT criteria can be used in differential diagnosis. In lymphocytic interstitial pneumonia, cysts are less numerous and can be accompanied by ground-glass opacities. Two syndromic conditions can present with pulmonary cysts and renal masses: tuberous sclerosis and BHDS. In BHDS, the cysts are less numerous and larger and predominate in the lower lobes. In tuberous sclerosis, the cysts represent lymphangioleiomyomatosis, are more numerous and diffuse, and also affect the lung bases. In LCH, the cysts can be bizarrely shaped and, most importantly, they predominate in the upper lung fields, with sparing of the lung bases, especially the costophrenic sulci.

LCH is a rare disorder of unknown origin, characterized by an abnormal non-malignant proliferation of monoclonal Langerhans cells (histiocytes).It remains controversial whether LCH is a neoplastic or an inflammatory disorder. Pulmonary LCH is seen almost exclusively in cigarette smokers. Clinically, patients can be asymptomatic or present with cough and dyspnea. In many cases, the disorder is discovered either incidentally on routine examinations or because of complications, such as pneumothorax.[1,2]

In early stages of LCH, CT shows centrilobular nodules, which correspond to granulomas. They tend to cavitate, progressing to cysts. The cysts can be irregularly and bizarrely shaped, which differentiates them from the regular cysts in lymphangioleiomyomatosis. The lesions predominate in the upper lobes and spare the lung bases. In end-stage LCH, there may be only diffuse large irregular cysts without nodules.[1,2]

The finding of irregularly shaped cysts, predominantly in the upper lung fields, with sparing of the costophrenic sulci, and accompanied by small nodules, is highly suggestive of a diagnosis of LCH, generally without the need for lung biopsy, which is reserved for atypical cases. In the case of our patient, the final diagnosis was LCH.

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What is the minimal clinically important difference, and why does it matter?

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PRACTICAL SCENARIO

In a hypothetical randomized controlled clinical trial, researchers compared the effect of bronchodilator A vs. bronchodilator B on FEV_1 in patients with COPD. Although the results showed that A was superior to B in improving FEV_1 and that this difference was statistically significant, did this change in FEV_1 result in fewer symptoms, or did it increase the participants' self-perceived ability to perform activities of daily living?

To answer these and other clinical outcome-related questions, it is crucial to understand the concept of the minimal clinically important difference (MCID).

DEFINING THE MCID

One of the many challenges of translating scientific evidence into clinical practice is the interpretation of data in light of clinical meaningfulness. We commonly find reports of statistical results, such as p-values, confidence intervals, and effect sizes. The MCID conveys results that are meaningful to patients. Depending on what outcome we are measuring, this change may be self-reported or objectively measured.

The MCID refers to the smallest change in an outcome that represents a meaningful change for the patient.[1,2] There are different methods to determine the MCID, but the major points are that the change has to be greater than the measurement error of the instrument that we are using to assess the outcome and it has to be large enough for patients to perceive the clinical change.

MCID IN RESEARCH AND CLINICAL SETTINGS

When designing studies that compare the effects of interventions, researchers should consider including thresholds for the MCID together with statistical significance.[2]

The MCID for a given test can be determined using expert consensus, using patient assessments anchoring the change to a subjective perception of change, or using statistical methods, which generally need validation. Interestingly, the same instrument may have different MCID thresholds according to specific study populations. For example, the six-minute walk test has different MCDI for patients with COPD, patients with heart failure, and apparently healthy adults.

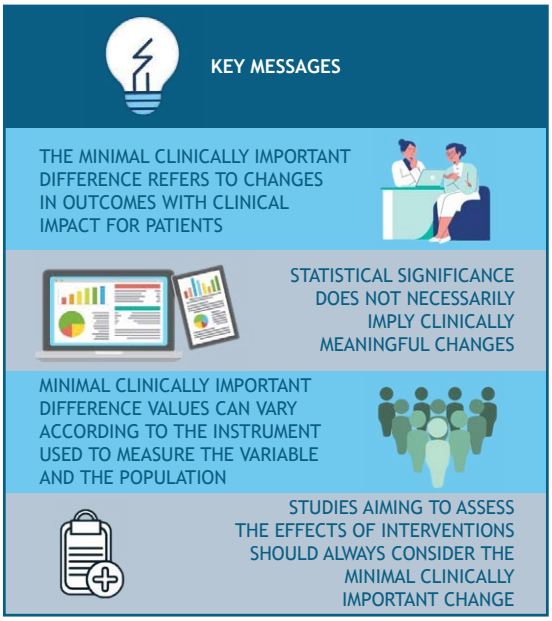

Figure 1. Key messages.

In the hypothetical trial of our practical scenario, the investigators found that the variation in FEV_1 was 241 ± 38 mL in the bronchodilator A group and 91 ± 14 mL in the bronchodilator B group. Considering that the MCID for FEV_1 in patients with COPD is 100 mL, we can conclude that bronchodilator A is statistically superior to bronchodilator B and that the change in FEV_1 is clinically meaningful.

CONCLUSION

Using patient-centered outcomes and aligning clinically relevant effects with statistical significance are important steps in the process of translating scientific clinical knowledge into evidence-based practice. Understanding the concept of the MCID is crucial to analyze and interpret the results of clinical interventions. In both research and clinical settings, we should consider MCIDs when analyzing and interpreting clinical outcome results (Figure 1).

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Out-of-proportion dyspnea and exercise intolerance in mild COPD

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BACKGROUND

Most patients with COPD show only mild airflow limitation on spirometry. Despite FEV_1 normalcy, however, dyspnea on exertion is a frequent complaint. Structural and functional investigations in dyspneic patients with mild COPD showed important abnormalities in gas exchange efficiency, caused by a complex interaction among small airway disease, emphysema, and microvascular dysfunction.[1] Cardiopulmonary exercise testing is invariably useful to indicate whether patients presenting with out-of-proportion dyspnea can or cannot be ascribed to mild COPD.[2]

OVERVIEW

A 47-year-old woman (smoking history of 15 pack-years) was referred to a pulmonary clinic due to chronic dyspnea (modified Medical Research Council scale score = 2) and progressive exercise intolerance. Lung function tests revealed a mild obstructive ventilatory defect, preserved FEV_1, lung hyperinflation (↑functional residual capacity), gas trapping (↑RV), and ↓DL_{CO} (Figure 1A). Excess ventilation, as shown by high minute ventilation ($\dot{V}_E$)/carbon dioxide output ($\dot{V}CO_2$), was observed at rest and throughout the incremental cardiopulmonary exercise test (Figure 1B, first graph). These findings were associated with ↑Borg dyspnea scores as a function of work rate (Figure 1B, second graph). Conversely, dyspnea scores regarding heightened $\dot{V}_E$ were initially within the expected range for women of same age.[3] However, $\dot{V}_E$ at ~ 35 L/min caused an upward inflection in dyspnea scores (Figure 1B, third graph; red arrow) concomitant to critical constraints to V_T expansion (V_T/inspiratory capacity ~ 0.70). She subsequently stopped exercising at low peak O_2 uptake (69% of the predicted value) and work rate (48% of predicted) despite preserved "breathing reserve" (peak

A	Pre BD	Z score	% pred	Post BD	% pred
FVC	3.49	0.79	117	3.43	115
FEV_1	2.24	−0.41	90	2.19	88
FEV_1/FVC	0.64	−2.23	77	0.63	77
TLC	5.69	2.29	128		
RV	2.29	2.00	153		
FRC	3.63	2.21	149		
IC	2.05	0.53	106		
DLco	5.15	−1.96	69		

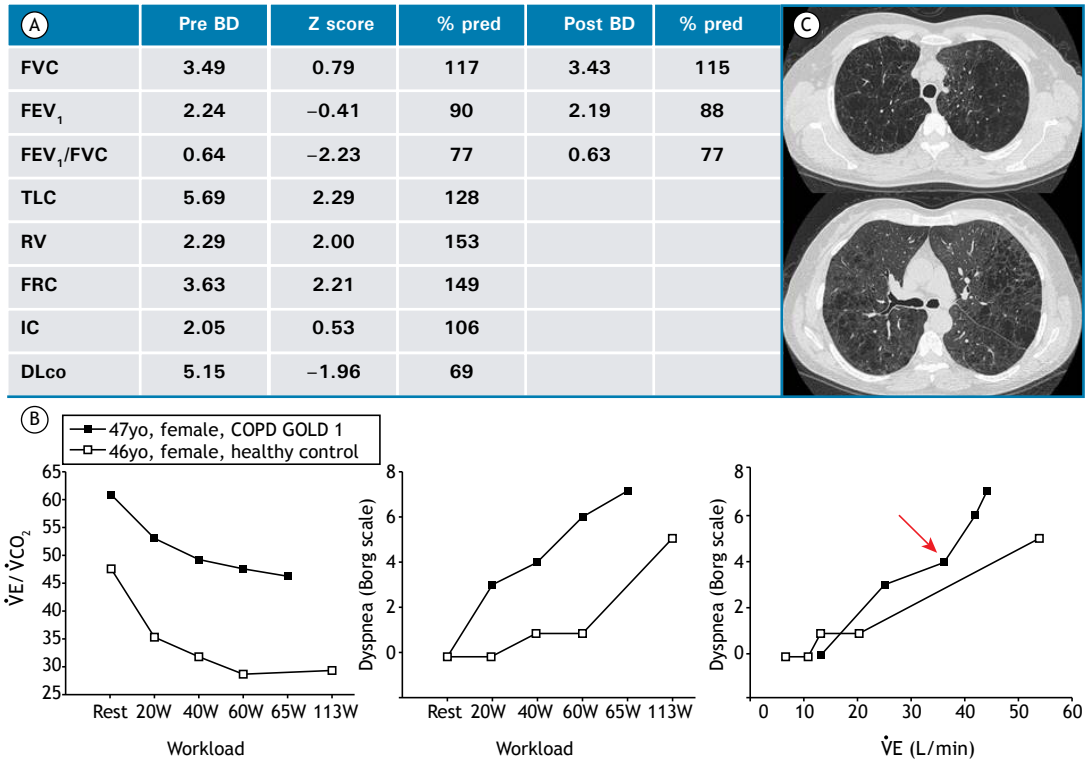

Figure 1. Data of a 47-year-old female smoker with out-of-proportion dyspnea and mild COPD. In A, lung function results with the patient at rest, In B, ventilatory response and dyspnea perception during incremental cardiopulmonary exercise testing. In C, chest CT scans showing extensive emphysema. BD: bronchodilator; FRC: functional residual capacity; IC: inspiratory capacity; yo: years old; GOLD 1: FEV_1 ≥ 80% of predicted; $\dot{V}_E$: minute ventilation; and $\dot{V}CO_2$: carbon dioxide output.

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$\dot{V}_E$/estimated maximum voluntary ventilation ~ 0.6). Echocardiography was unremarkable, but a chest CT unveiled extensive emphysema (Figure 1C).

The efficiency of the lungs as gas exchangers improves on exercise since a lower fraction of V_T is "wasted" in the alveolar dead space (VD). Their efficiency as gas movers is maintained because end-expiratory lung volume decreases, and V_T occurs over the most compliant portion of the pressure-volume relationship of the respiratory system. In patients with mild COPD and dyspnea, enlarged areas of high alveolar ventilation-capillary perfusion relationship leads to a high VD/V_T.[4] Such impairment in gas exchange efficiency is frequently reflected on $\downarrow DL_{CO}$ (Figure 1A).[5] The excess ventilation is associated with a high drive to the respiratory muscles, leading to increased dyspnea at a given exercise intensity (Figure 1B, second graph). Because the ventilatory pump can still respond to such a high drive, dyspnea remains proportional to the heightened $\dot{V}_E$. As $\dot{V}_E$ further increases and the expiratory time becomes progressively shorter, acute (dynamic) gas trapping ensues; thus, V_T eventually occurs too close to TLC. At that point onwards, dyspnea increases faster than does $\dot{V}_E$ because the ventilatory pump can no longer translate the high drive into the mechanical act of breathing (Figure 1B, third graph).[2]

CLINICAL MESSAGE

Although spirometry is useful for the diagnosis and gradation of airflow limitation, it provides an incomplete view of the functional abnormalities that are germane to a key, patient-centered outcome in COPD: physical activity-related dyspnea. $\downarrow DL_{CO}$, and $\uparrow$exertional $\dot{V}_E/\dot{V}CO_2$ signal gas exchange inefficiency in mild COPD, establishing a causal link between mild COPD and exercise intolerance in individual patients.

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ORIGINAL ARTICLE

Isolation of and risk factors for airway infection with *Pseudomonas aeruginosa* in patients with non-cystic fibrosis bronchiectasis

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Study carried out in the Hospital de Messejana Dr. Carlos Alberto Studart. Fortaleza (CE) Brasil.

ABSTRACT

Objective: To identify microorganisms in sputum samples of patients with stable non-cystic fibrosis bronchiectasis and to determine risk factors related to the isolation of *Pseudomonas aeruginosa* (PA) in those patients. **Methods:** Consecutive patients were recruited from a tertiary hospital outpatient clinic in the city of Fortaleza, Brazil. The patients were submitted to spirometry, six-minute walk test, HRCT, and sputum collection. Data on serum fibrinogen levels, disease severity, sputum color, and history of azithromycin treatment were collected. **Results:** The study included 112 patients, and females predominated (68%). The mean age was 51.6 ± 17.4 years. Most patients presented with mild-to-moderate disease (83%). The mean six-minute walk distance was 468.8 ± 87.9 m. Mean FEV_1 and FVC, in % of predicted values, were 60.4 ± 21.8% and 69.9 ± 18.5%, respectively. The mean serum fibrinogen level was 396.1 ± 76.3 mg/dL. PA was isolated in 47 patients, other potentially pathogenic microorganisms (PPMs) were isolated in 31 patients, and non-PPMs were isolated in 34 patients. Purulent sputum was identified in 77 patients (68%). The patients with PA, when compared with those without it, presented with more severe disease, higher serum fibrinogen levels, and lower FVC%. In addition, purulent sputum and long-term azithromycin treatment were more common in those with PA. The multivariate regression analysis showed that the independent factors associated with PA were serum fibrinogen level > 400 mg/dL (OR = 3.0; 95% **CI:** 1.1-7.7) and purulent sputum (OR = 4.3; 95% **CI:** 1.6-11.3). **Conclusions:** In our sample, the prevalence of PA in sputum was 42%. Sputum color and inflammatory markers were able to predict the isolation of PA, emphasizing the importance of routine sputum monitoring.

Keywords: Bronchiectasis; Pseudomonas aeruginosa; Sputum/microbiology.

INTRODUCTION

Bronchiectasis is a growing health problem worldwide. The disease prevalence has increased by more than 40% in Europe and the USA in the past 10 years.[1] Non-cystic fibrosis bronchiectasis is characterized by non-reversible bronchial dilatation, usually accompanied by cough, sputum production, and recurrent respiratory infections.[2]

Chronic bacterial infections are often present in patients with bronchiectasis, contributing to the maintenance of the vicious circle of inflammation and progressive destruction of airways. Systemic inflammation is crucial for disease progression, and that can be associated with more adverse events and worse outcomes. There are various inflammatory markers that can be used for evaluation of disease progression, including interleukins, TNF-α, C-reactive protein (CRP), and fibrinogen.[3] Inflammation is associated with airway bacterial infection and may be responsible for airway destruction and loss of lung function. *Haemophilus influenzae* and *Pseudomonas aeruginosa* have been the most common potentially pathogenic bacteria in bronchiectasis.[3,4]

Murray et al.[5] developed a quick and easy qualitative method to identify sputum color in patients with stable bronchiectasis. The sputum color chart uses photographs of sputum from patients with bronchiectasis, providing accurate representation of three major color grades, and showed good interobserver reliability between the doctor and the patient. Bacterial infection causes a pronounced increase in inflammatory markers that might be reflected by sputum purulence. This characteristic can be explored by clinicians using a sputum color chart.

Effects of *P. aeruginosa* on airway destruction might be indirectly reflected by lung function impairment.[6] Guan et al.[7] reported that a group of 144 patients with bronchiectasis and isolates of or infection with *P. aeruginosa* had poorer spirometry results. A recent study involving 186 patients followed at a bronchiectasis tertiary referral center in Portugal reported that patients with

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chronic bacterial infection had worse lung function when compared with those without that type of infection.[8]

Most studies on this topic have addressed the diversity of isolates of potentially pathogenic microorganisms (PPMs).[9,10] In patients with bronchiectasis, the few available data are mainly based on *P. aeruginosa* infection.[11] There is insufficient knowledge on *P. aeruginosa* infection, its associations, and useful clinical methods to distinguish *P. aeruginosa* from other PPMs.

Because of the importance of identifying bronchiectasis patients who are potentially infected with *P. aeruginosa*, new severity scores have been developed, such as FACED—an acronym for FEV_1, Age, Chronic colonization with *P. aeruginosa*, Extent (of CT findings), and Dyspnea.[12]

Based on the hypothesis that patients infected with *P. aeruginosa* are a distinct group of patients within the group of patients with non-cystic fibrosis bronchiectasis, the objective of the present study was to assess the prevalence of *P. aeruginosa* isolation/infection in outpatients with bronchiectasis. Moreover, we expected that positive results could be associated with factors such as inflammatory markers and sputum color, as well as with clinical, radiological, and lung function parameters.

METHODS

This was a cross-sectional study involving a group of adult patients with non-cystic fibrosis bronchiectasis who were consecutively selected from an outpatient clinic of a tertiary hospital between March of 2018 and October of 2019. Bronchiectasis was diagnosed on the basis of chest HRCT performed within the previous 12 months. Eligible patients had to remain exacerbation free for four weeks. Exacerbation was defined as the presence or worsening of three or more of the following key symptoms for at least 48 h: cough; high sputum volume/consistency; purulent sputum; breathlessness; exercise intolerance; fatigue; malaise; and hemoptysis.[2] The study protocol was approved by local research ethics committee (Protocol no. 1.844.662). All participants gave written informed consent.

We collected data on demographics; history of childhood respiratory infections (pertussis, pneumonia, and measles); history of pulmonary tuberculosis; diagnosed asthma, COPD, connective tissue disorders, and immune deficiencies; smoking status; history of long-term use of azithromycin; and treatment at the time of the last evaluation in a clinically stable phase. The participants were assessed regarding perception of dyspnea (modified Medical Research Council dyspnea score), sputum purulence/color (sputum color chart),[5] severity of bronchiectasis (FACED score),[12] and lung function (spirometry). Clinical assessment was performed by the attending doctor. Serum fibrinogen levels were also measured and compiled.

Samples of spontaneous sputum were obtained from all of the patients in the morning of their clinical visit. Gram-stained smears of the samples showing ≥ 25 leukocytes/field and ≤ 10 epithelial cells/field (magnification, ×100) were considered valid sputum samples and processed for qualitative culture for bacteria (including AFB) and fungi. All microbiological samples were plated on blood agar, chocolate agar, Wilkins-Chalgren agar, Löwenstein-Jensen medium, and Sabouraud agar. In addition, the samples were smeared for Ziehl-Neelsen staining. The cultures were evaluated for growth after 48 h. Negative bacterial cultures were discarded after 5 days, negative fungal cultures were discarded after four weeks, and Löwenstein-Jensen cultures were discarded after six weeks. Bacterial/fungal load ($\times 10^5$ CFU/mL) was calculated when a PPM was isolated. On the basis of culture results, the patients were divided into PA group (*P. aeruginosa*), PPM group (other than *P. aeruginosa*), and non-PPM group. The sputum color chart was shown to the patients so that they could identify one of the three typical color grades: clear (mucoid), pale yellow/pale green (mucopurulent), and dark yellow/dark green (purulent).[5]

HRCT scans were assessed for the number of lobes involved (the lingula was considered a separate lobe) and the most common type of bronchial dilatation (cylindrical, varicose, or cystic).(13)

Spirometry was performed using an electronic spirometer (WinDX; (Creative BioMedics Inc., San Clemente, CA, USA) in accordance with the American Thoracic Society/European Respiratory Society guidelines,[14] and FEV_1 and FVC results were collected and analyzed.

Exercise capacity was evaluated using the six-minute walk test, which measures the distance that a participant can walk on a flat 30-m corridor in six minutes.[15] The patients, under direct supervision of one of the investigators, were asked to walk as fast as possible from one end of the corridor to the other, as many times as possible, within the established time. All patients performed two tests, with a minimum time interval of 30 min, and the best result was recorded.

The FACED score has been used as a tool to assess the severity of bronchiectasis.[12] As previously mentioned, the score incorporates five dichotomous variables, and the scores of each variable are summed up to provide the total score, which can range from 0 to 7 points. The total score classifies bronchiectasis into three levels of severity: mild (0-2 points), moderate (3-4 points), and severe (5-7 points). The FACED score has been validated for use in Brazil.[16]

Sample size

A previous study showed that the prevalences of *P. aeruginosa* and other microorganisms in patients with bronchiectasis were 15% and 40%, respectively.[17] For the purpose of multivariate logistic regression analysis, the dependent variable was dichotomized as PA group or non-PA group (i.e., PPM + non-PPM groups), assuming that the rates of these groups were 15% and 40%,

respectively. Defining $\alpha < 0.05$ and $\beta < 0.20$, at least 57 participants were required for one arm.

Statistical analysis

Categorical variables were described as absolute and relative frequencies, whereas continuous variables were described as mean and standard deviation, when appropriate.

One-way ANOVA was used in order to compare the means of the three groups individually, followed by a post hoc analysis with Bonferroni correction to clarify the differences between the pairs of groups (PA vs. PPM; PA vs. non-PPM; and PPM vs. non-PPM). For comparison of proportions, the chi-square test with post hoc analysis for pairwise comparisons was used with Bonferroni-adjusted p value.[18] As previously mentioned, the dependent variable was dichotomized as PA group or non-PA group. The independent factors selected for the multivariate analysis were those considered to be clinically relevant or potential confounders for the identification of PA isolates: sex (female); FVC (< 80% of the predicted value); sputum color[5] (purulent); serum fibrinogen level (> 400 mg/dL); and FACED total score[12] (≥ 5). Multicollinearity was assessed using the variance inflation factor (VIF); a VIF < 2.5 was regarded as an exclusion of any significant interaction.[19] The results were reported as OR and 95% CI. The significance level was set at $p < 0.05$. All statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

The flow chart of patient recruitment is shown in Figure 1. A total of 122 consecutive patients with non-cystic fibrosis bronchiectasis were initially included in the study. Of those, 10 did not meet the inclusion criteria and were excluded. Therefore, the total sample comprised 112 patients.

Table 1 shows that 77 patients (68%) were female. The mean age was 51.7 ± 17.4 years. According to the FACED score, 83% of the patients presented with mild-to-moderate disease. Mucopurulent/purulent sputum predominated (n = 77; 68%). Of those 77 patients with mucopurulent/purulent sputum, 70 (62% of the total sample) were submitted to long-term azithromycin treatment (500 mg, three times/week).

The etiology of bronchiectasis was determined by means of the review of clinical medical records. An underlying etiology was identified in 65% of the patients. In 35% of the patients no cause was established (classified as idiopathic bronchiectasis). The remaining etiologies were described as post-tuberculosis bronchiectasis, in 30%; post-infection bronchiectasis, in 5%; Kartagener syndrome, in 8%; and other etiologies, in 22%.

The microorganisms identified in the sputum of the patients are detailed in Table 2, whereas Table 3 shows the comparison of the selected variables between the groups (PA, PPM, and non-PPM). Significant differences were found regarding the following variables: serum fibrinogen levels, which were higher in the PA group when compared with the PPM group (425.4 ± 78.3 mg/dL vs. 380.5 ± 72.2 mg/dL; p = 0.04) and the non-PPM group (425.4 ± 78.3 mg/dL vs. 357.4 ± 75.5 mg/dL; p = 0.001); FVC in % of predicted values, which was lower in the PA group when compared with the PPM group (64.3% ± 16.5% vs. 75.9% ± 14.7%; p = 0.02); proportion of patients with purulent sputum, which was higher in the PA group when compared with the PPM (66.0% vs. 32.3%; p = 0.003) and non-PPM groups (66.0% vs. 14.7%; p < 0.001); severe bronchiectasis,

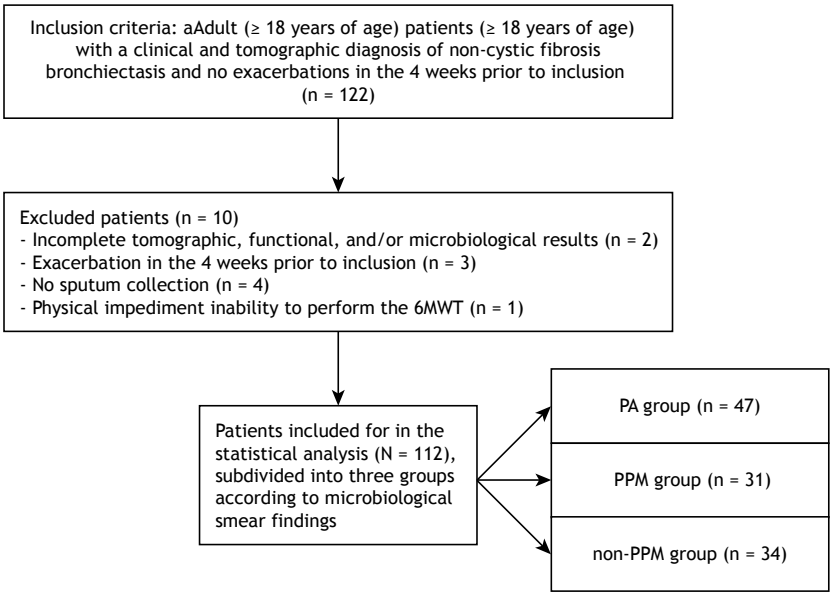

Figure 1. Flow chart of patient recruitment. 6MWT: six-minute walk test; PA: *Pseudomonas aeruginosa*; and PPM: potentially pathogenic microorganisms (other than *P. aeruginosa*).

Table 1. Characteristics of the patients.[a]

Variable	(N = 112)
Sex	
Female	77 (68)
Male	35 (31)
Age, years	51.7 ± 17.4
Smoking status	
Never smokers	81 (73)
Former smokers	31 (27)
BMI, kg/m2	22.5 ± 4.5
FACED score	3 [1-4]
Disease severity (FACED score)	
Mild	60 (53)
Moderate	34 (30)
Severe	18 (16)
Exacerbations in the last year	
0	40 (35)
1-2	54 (48)
> 3	18 (16)
Hospitalizations in the last year	
Yes	19 (17)
No	93 (83)
FEV_1, % of predicted	60.4 ± 21.8
FVC, % of predicted	69.9 ± 18.5
FEV_1/FVC	71.1 ± 15.0
6MWD, m	468.8 ± 87.9
Fibrinogen, mg/dL	396.1 ± 76.3
mMRC score	
0-1	45 (40)
≥ 2	67 (60)
Number of lobes involved	
< 2	8 (7)
≥ 2	104 (93)
Group	
PA	47 (42)
PPM	31 (27)
Non-PPM	34 (30)
Sputum color chart classification	
Mucoid	35 (31)
Mucopurulent	31 (27)
Purulent	46 (41)
Long-term azithromycin treatment	70 (62)

FACED: acronym for FEV_1, Age, chronic Colonization by *Pseudomonas aeruginosa*, Extent (of CT findings), and Dyspnea; 6MWD: six-minute walk distance; mMRC: modified Medical Research Council (scale); PA: *P. aeruginosa*; and PPM: potentially pathogenic microorganisms (other than *Pseudomonas aeruginosa*). [a]Values expressed as n (%), mean ± SD, or median [IQR].

which was higher in the PA group when compared with the non-PPM group (29.8% vs. 2.9%; p = 0.002); and long-term azithromycin treatment, which was more common in the PA group when compared with the non-PPM group (80.9% vs. 41.2%; p < 0.001).

The multivariate logistic regression analysis was performed to determine the factors associated with the *P. aeruginosa* isolates (Table 4). Independent variables were gender, FACED score, serum fibrinogen level, FVC%, and sputum color classification. All of the factors had a VIF < 2.0. The independent factors associated with the isolation of *P. aeruginosa* were fibrinogen > 400 mg/dL (OR = 3.00; 95% CI: 1.10-7.77) and purulent sputum (OR = 4.33; 95% CI: 1.60-11.38).

DISCUSSION

The present cross-sectional study showed that, in our sample of patients with steady-state bronchiectasis, 47 (42%) harbored *P. aeruginosa* in the airways. The rate of *P. aeruginosa* isolates was significantly higher than was that of *H. influenzae*, corroborating the findings in a study by Guan et al.[7] Multivariate logistic regression analysis identified that high levels of serum fibrinogen and purulent sputum were associated with isolation of *P. aeruginosa*. We would like to emphasize that the use of the sputum color chart by Murray et al.[5] provided novel evidence about this rapid and practical way for clinicians to predict the presence of *P. aeruginosa* in the airways and distinguish it from other microbiological statuses. This useful tool indicates the severity of inflammation, airway destruction, and proteolytic enzyme activity/presence of neutrophilic airway disease, such as non-cystic fibrosis bronchiectasis, as well as COPD or asthma.[20-22]

The correlation of sputum color with positive cultures is not very clear, findings of positive and negative relationships having been described.[22-24] A recent meta-analysis[25] analyzing six studies on sputum staining and positive cultures in COPD patients showed that the isolation of bacteria in sputum is less likely to occur when sputum is classified as mucoid. More patients with purulent sputum presented with bacterial colonization than did patients with mucopurulent or mucoid sputum.

We found that the presence of a systemic inflammatory response (as evidenced by elevated circulating fibrinogen levels) was associated with the isolation of *P. aeruginosa*. Fibrinogen levels were higher in the PA group when compared with the PPM and non-PPM groups, which might explain the role of *P. aeruginosa* in systemic inflammation. Previous studies found that airways harboring *P. aeruginosa* showed significantly higher airway inflammation.[7,26-29]

Menéndez et al.[29] conducted a prospective observational study and found progressive increases in the levels of systemic proinflammatory cytokines and CRP in hospitalized patients with bronchiectasis from whom *P. aeruginosa* was isolated during acute and chronic phases of exacerbations. The level of systemic inflammation remained high after the acute phase. Jin et al.[30] found that systemic inflammatory markers, including CRP and fibrinogen, were significantly elevated in COPD patients with bronchiectasis. The use of other inflammatory markers is necessary to detect the severity of inflammation so that better treatment can be provided for patients with bronchiectasis. We

decided to measure serum fibrinogen levels, because serum fibrinogen is a biomarker for which routine measurements are available in clinical practice.

Ergan Arsava & Cöplü,[31] studied 50 patients with stable bronchiectasis and found that fibrinogen and CRP levels were higher in those with airway colonization than in those without it. In a subgroup of patients colonized with *P. aeruginosa,* those levels were even higher than were those in their counterparts.

In our study, the presence of *P. aeruginosa* in the airways of patients was associated with reduced FVC. This could be explained by the effects of *P. aeruginosa* on inflammation and destruction of the airways. Studies have shown that when *P. aeruginosa* or *H. influenzae* dominates the microbiome of patients with bronchiectasis, their lung function is significantly reduced.[10,32]

The frequency of exacerbations and hospitalizations in the previous year in our sample of patients with *P. aeruginosa* was not statistically significant. This could be explained by the long-term use of azithromycin by these patients. A clinical trial conducted by Richardson et al.[32] demonstrated a significant reduction in the number of exacerbations in patients treated with erythromycin when compared with those treated with placebo. A meta-analysis of nine studies (530 patients) demonstrated that macrolide use reduced the number of patients with exacerbations and the

Table 2. Microorganisms isolated from sputum samples of patients with non-cystic fibrosis bronchiectasis (N = 112).

Isolate	n
Pseudomonas aeruginosa	47
Nonmucoid strain	28
Mucoid strain	19
Haemophilus influenzae	12
Klebsiella pneumoniae	9
Moraxella catarrhalis	1
Streptococcus pneumoniae	1
Methicillin-sensitive *Staphylococcus aureus*	1
Other PPM[a]	7
Non-PPM	34

PPM: potentially pathogenic microorganisms. [a]*Achromobacter xylosoxidans* (n = 2); *Aspergillus* sp. (n = 3); *Candida albicans* (n = 1); and *Mycobacterium tuberculosis* (n = 1).

Table 3. Comparisons between the groups formed according to the microbiological status of the patients.

Variable	Group			p
	PA (n = 47)	PPM (n = 31)	Non-PPM (n = 34)	
Age, years*	52.6 ± 19.0	53.8 ± 16.5	48.5 ± 16.0	0.430
Female*	32 (68.0)	19 (61.3)	26 (23.4)	0.400
BMI, kg/m^2†	22.7 ± 5.0	21.9 ± 3.9	22.9 ± 4.5	0.650
Disease severity (FACED)†				
Mild/moderate	33 (70.0)	28 (90.3)	33 (97.1)	0.003
Severe	14 (29.8)‡	3 (9.7)	1 (2.9)	
Number of lobes involved				
< 2	3 (6.4)	3 (9.7)	2 (5.9)	0.810
≥ 2	44 (93.6)	28 (90.3)	32 (94.1)	
Serum fibrinogen, mg/dL*	425.4 ± 78.3‡,§	380.5 ± 72.2	357.4 ± 75.5	0.001
FEV_1, % of predicted*	55.1 ± 18.9	63.7 ± 21.8	62 ± 25.3	0.180
FVC, % of predicted*	64.3 ± 16.5‡	75.9 ± 14.7	69.5 ± 22.7	0.020
6MWD, m*	457.5 ± 98.8	459.1 ± 85.8	493 ± 87.5	0.180
mMRC dyspnea scale score				
0-1	15 (31.9)	15 (48.4)	15 (44.1)	0.290
≥ 2	32 (68.1)	16 (51.6)	19 (55.9)	
Sputum color chart classification†				
Mucoid/mucopurulent	16 (34.0)	21 (67.7)	29 (85.3)	0.001
Purulent	31 (66.0)‡,§	10 (32.0)	5 (14.7)	
Exacerbations in the last year				
0-2	35 (74.5)	29 (93.5)	30 (88.2)	0.050
3-4	12 (25.5)	2 (6.5)	4 (11.8)	
Hospitalizations in the last year				
Yes	10 (21.3)	4 (12.2)	5 (14.7)	0.500
No	37 (78.7)	27 (87.1)	29 (85.3)	
Long-term azithromycin treatment	38 (80.9)‡	18 (58.1)	14 (41.2)	0.001

PA: *Pseudomonas aeruginosa*; PPM: potentially pathogenic microorganisms (other than *P. aeruginosa*); FACED: acronym for FEV_1, Age, chronic Colonization by *P. aeruginosa*, Extent (of CT findings), and Dyspnea; 6MWD: six-minute walk distance; and mMRC: modified Medical Research Council. *ANOVA with Bonferroni correction. †Chi-square test and post hoc analysis for pairwise comparisons. ‡PA vs. non-PPM ($p < 0.05$). §PA vs. PPM ($p < 0.05$).

Table 4. Multivariate logistic regression analysis of factors associated with isolation of *Pseudomonas aeruginosa* in the sputum of patients with non-cystic fibrosis bronchiectasis.

Factor	OR	95% CI	p
Purulent sputum	4.33	1.60-11.38	0.003
Fibrinogen >400 mg/dL	3.00	1.10-7.77	0.020
Female	0.98	0.34-2.78	0.970
Severe disease	2.42	0.61-9.60	0.200
FVC < 80% of predicted	2.32	0.82-6.50	0.110

number of exacerbations per patient.[33] The small number of hospitalizations was probably related to the small number of exacerbations in our study.

More severe disease, measured by the FACED score, was associated with the isolation of *P. aeruginosa*. This is expected because this tool incorporates colonization by *P. aeruginosa* in its metrics, emphasizing the importance of chronic infection in the severity of bronchiectasis.[12]

The number of lobes involved on CT scans was not found to be associated with the isolation of *P. aeruginosa*. Therefore, we cannot rule out or confirm that the presence of *P. aeruginosa* is a factor related to greater radiological structural damage in these patients.

The limitations of the present study include the following: i) the sample size was small, but we were able to identify variables with biological plausibility; ii) patients were recruited at a referral facility, making it difficult to extrapolate our results to other realities; iii) the follow-up period was short, and no molecular methods were used in order to understand the role that each microorganism plays in disease progression; and iv) the observational, cross-sectional design makes it difficult to establish temporal order and causal direction.

The present study is relevant because we might assume that a useful clinical method such as a sputum color chart[5] is able to predict airway infection with *P. aeruginosa*. Identifying sputum color in association with clinical manifestations of infection might be a useful strategy for clinicians to manage these patients while awaiting formal sputum microbiology results. In addition, the use of serum fibrinogen as a marker is a simple and reliable method to identify infected patients and should therefore be part of routine clinical practice. Larger multicenter longitudinal studies are needed to improve the characterization of other PPMs and their individual clinical impact.

AUTHOR CONTRIBUTIONS

IL and AA: study design; data collection; literature search; and approval of the final version. MRF: study design; data collection; literature search; drafting of the manuscript; approval of the final version. FL: drafting of the manuscript; and approval of the final version. EDBP: study design; drafting of the manuscript; final revision; and approval of the final version.

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ORIGINAL ARTICLE

Brazilian version of the Clinical COPD Questionnaire, administered by interview: reliability and validity measurement properties

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ABSTRACT

Objective: To test the reliability, validity, and interpretability of the Brazilian version of the Clinical COPD Questionnaire (CCQ) in patients with COPD. **Methods:** Fifty patients with COPD completed the CCQ by interview on two occasions. At the first visit, the CCQ was administered twice, by two different raters, approximately 10 min apart; the patients also underwent spirometry and were administered the COPD Assessment Test, the modified Medical Research Council scale, and Saint George's Respiratory Questionnaire (SGRQ). At the second visit (1-2 weeks later), the CCQ was readministered. We tested the hypothesis that the CCQ total score would correlate positively with the total and domain SGRQ scores ($r \geq 0.5$). **Results:** Of the 50 patients, 30 (60%) were male. The mean age was 66 ± 8 years, and the mean FEV_1 was 44.7 ± 17.9% of the predicted value. For all CCQ items, Cronbach's alpha coefficient (95% CI) was 0.93 (0.91-0.96). To analyze the interrater reliability and test-retest reliability of the CCQ, we calculated the two-way mixed effects model/single measure type intraclass correlation coefficient (0.97 [95% **CI:** 0.95-0.98] and 0.92 [95% **CI:** 0.86-0.95], respectively); the agreement standard error of measurement (0.65 for both); the smallest detectable change at the individual level (1.81 and 1.80, respectively) and group level (0.26 and 0.25, respectively); and the limits of agreement (−0.58 to 0.82 and −1.14 to 1.33, respectively). The CCQ total score correlated positively with all SGRQ scores ($r \geq 0.70$ for all). **Conclusions:** The Brazilian version of the CCQ showed an indeterminate measurement error, as well as satisfactory interrater/test-retest reliability and construct validity.

Keywords: Pulmonary disease, chronic obstructive; Health status; Patient reported outcome measures; Validation study.

INTRODUCTION

Assessments of disease impact and clinical stability in patients with COPD should help physicians to make therapeutic decisions.[1] Patient-reported outcome measures (PROMs), such as the Clinical COPD Questionnaire (CCQ) and the COPD Assessment Test (CAT), are useful to assess disease impact cross-sectionally and clinical stability longitudinally.[1] In accordance with GOLD recommendations, the CCQ and the CAT are comprehensive and suitable PROMs for the assessment of symptoms in patients with COPD.[2]

Most COPD patients prefer CCQ to CAT, because the CCQ incorporates more details about daily respiratory problems than does the CAT and, therefore, reflects their health status better. Some patients also point out that the CCQ presents a system of response options which is easier to understand when compared to that of CAT.[3] Furthermore, the International Primary Care Respiratory Group[4] elected the CCQ as the best PROM to evaluate COPD patients in primary care. The CCQ was the only PROM that received top marks in the survey.

The selection of a suitable PROM for health status assessment should be based on the quality of its measurement properties—a PROM should be reliable and valid. There are numerous PROMs that can be used in order to measure health status. However, careful selection is of utmost importance to avoid the risk of imprecise or biased results, which could lead to wrong conclusions.[5] Measurement properties may differ

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between populations and therefore should be tested and considered appropriate for the specific population to be assessed.[6]

The CCQ was developed by van der Molen et al.[7] in 2003 with the purpose of promoting the evaluation of clinical control in patients with COPD. The domains selected as the most important for clinical control were functional state, symptoms, and mental state.[7] A Portuguese version of the CCQ for use in Brazil is available on the CCQ website, but its measurement properties have yet to be investigated. The present study aimed to analyze the internal consistency, reliability, measurement error, and construct validity, as well as the floor and ceiling effects, of the Brazilian version of the CCQ, when administered by interview, in patients with COPD.

METHODS

Patient selection

Patients referred to a public outpatient clinic specializing in COPD were invited to participate in the study. Inclusion criteria were as follows: having a confirmed diagnosis of COPD, being ≥ 40 years of age, being a smoker or a former smoker, having no other comorbidity (such as cardiovascular, neurological, orthopedic, rheumatic, or respiratory diseases other than COPD) that negatively impacted on the activities of daily life, and having a Mini-Mental State Examination[8] score ≥ 25 (literates) or ≥ 19 (illiterates). Exclusion criteria were having changes in clinical stability or disease impact in the month prior to the study or during data collection, assessed by closed questions, and not participating in the evaluations of the study. All patients who agreed to participate signed an informed consent form. This study was approved by the Human Research Ethics Committee of the Federal University of Santa Catarina (CAAE no. 33299214.8.0000.0121).

Study design

The study was conducted in a public outpatient clinic specializing in COPD in two visits in the morning period between 2017 and 2019. The selected PROMs—CAT, CCQ, modified Medical Research Council (mMRC) scale, and Saint George's Respiratory Questionnaire (SGRQ)—were administered by interviews due to the low level of education of part of the sample. The PROMs were administered in a dedicated room where only the patient and the rater were present. The raters only read the instructions and items of the PROM and wrote down the choices of the patients. The raters are physiotherapists with experience in assessing health status in patients with COPD. At the first visit, spirometry was performed, and the CAT, the mMRC scale, and the SGRQ were administered. In addition, CCQ was first administered by rater 1 and then, approximately 10 min later, by rater 2, for interrater reliability analysis. At the second visit, between one and two weeks later, the CCQ was readministered by rater 1 for test-retest reliability analysis.[9]

Assessments

Lung function was assessed following the standards recommended by the American Thoracic Society/European Respiratory Society[10] using a spirometer (KoKo Sx 1000; nSpire Health Inc., Longmont, CO, USA). The reference values for post-bronchodilator spirometric variables were those established by Pereira et al.[11] The severity of airflow limitation was based on FEV_1 and classified as GOLD I, II, III ou IV.[12]

The CAT[13] and the mMRC[14] scale scores, as well as the number of exacerbations within the last 12 months, regardless of hospital admissions, were used in order to classify the impact of COPD on health status and the risk of future events as GOLD A, B, C, or D.[12]

The SGRQ[15] was used in order to assess health-related quality of life. The questionnaire consists of 76 items distributed into three domains (symptoms, activity, and psychosocial impact). The total score ranges from 0 to 100, higher scores meaning poorer quality of life.

The CCQ[7] was used in order to evaluate clinical control. It consists of 10 items distributed into three domains (symptoms, mental state, and functional state). Total and domain scores range from 0 to 6, higher scores representing poorer control.

Statistical analysis

Data normality was analyzed by the Shapiro-Wilk test. The level of statistical significance was set at $p < 0.05$. The internal consistency of the CCQ items was analyzed by the Cronbach's alpha coefficient (α) and the corresponding 95% CI.[16] To compare the scores between raters and between test and retest, the Student's t-test or the Wilcoxon test was used according to data normality. Interrater and test-retest reliability of the CCQ scores were analyzed by the two-way mixed effects model/single measurement type intraclass correlation coefficient ($ICC_{3,1}$) and the corresponding 95% CI.[17] For interrater reliability, test-retest reliability, and measurement error analyses, we calculated the agreement standard error of measurement ($SEM_{agreement}$), the smallest detectable change at the individual level ($SDC_{individual}$) and group level (SDC_{group}), and the limits of agreement (LoA).[9] To visualize the total score and the agreement between the CCQ measurements, Bland-Altman plots[18] were used. To analyze construct validity, the following hypothesis was used: the total CCQ score would positively correlate with the total and domain SGRQ scores, and the correlation coefficient (r) would be ≥ 0.5. The percentage of occurrence of minimum and maximum CCQ scores was used in order to analyze the floor and ceiling effects, respectively, which were classified as absent or present.[9]

RESULTS

Fifty patients with COPD were included in the study. The general characteristics of the sample are described in Table 1.

The median administration time of the CCQ by interview was 2.76 min (2.38-3.38 min). In the internal consistency analysis, the values of α (95% CI) for all of the CCQ items (CCQ total score) and for the symptoms (items 1, 2, 5, and 6), mental state (items 3 and 4), and functional state domains (items 7, 8, 9, and 10) were, respectively, 0.93 (0.91-0.96); 0.77 (0.66-0.85); 0.79 (0.64-0.87); and 0.94 (0.91-0.96).

Table 1. General characteristics of the sample.[a]

Variable	(N = 50)
Male gender	30 (60)
Age, years	66 ± 8
BMI, kg/m^2	24.7 ± 4.7
Smoking history, pack-years	50 [23-73]
Pulmonary function	
FEV_1/FVC	0.53 [0.44-0.61]
FEV_1, L	1.15 [0.80-1.69]
FEV_1, % of predicted	44.7 ± 17.9
FVC, L	2.14 [1.69-2.80]
FVC, % of predicted	66.2 [54.0-75.5]
GOLD, severity	
I	1 (2)
II	17 (34)
III	21 (42)
IV	11 (22)
GOLD, classification	
A	12 (24)
B	19 (38)
C	0 (0)
D	19 (38)
CAT score	18 ± 10
mMRC scale score	1 [1-4]
SGRQ score	
Total	38.3 [18.0-67.8]
Symptoms	44.6 ± 22.9
Activity	51.5 [25.1-85.1]
Psychosocial impact	28.9 [14.4-55.8]

CAT: COPD Assessment Test; mMRC: modified Medical Research Council; and SGRQ: Saint George's Respiratory Questionnaire. [a]Values expressed as n (%), mean ± SD, or median [IQR].

Table 2 shows the CCQ total and domain scores in each administration. Differences between raters were observed for the total, the mental state domain, and the functional state domain scores, as well as for the mental state domain score between test and retest ($p \leq 0.05$ for all). Table 2 also shows the analysis of interrater reliability, test-retest reliability, and measurement error. All $ICC_{3,1}$ were ≥ 0.80, 95% CI ranges being broader between test and retest than between raters. The results of $SEM_{agreement}$, $SDC_{individual}$, and SDC_{group} were similar between raters and between test and retest for the CCQ total score, but they were lower between raters for the symptoms and mental state domains, as well as between test and retest for the functional state domain. Figure 1 also presents the measurement error by the LoA ranges of the CCQ total score, which were broader between test and retest than between raters.

Table 3 and Figure 2 show the correlations between the CCQ scores and SGRQ scores. All correlations were strong ($r > 0.70$), except for the correlation between the CCQ mental state domain and the SGRQ symptoms and activity domains, which were good ($0.50 < r < 0.70$).[19]

Only 4 patients had a minimum score (8%), and 1 had a maximum score (2%), indicating the absence of the floor and ceiling effects.[9]

DISCUSSION

In the present study, the measurement properties of the Brazilian version of the CCQ were tested in a sample of patients with COPD in Brazil. The results suggest that this PROM is reliable and valid when administered by interview. To our knowledge, this was the first study to analyze the measurement properties of the Brazilian version of the CCQ.

The internal consistency analysis of the Brazilian version of the CCQ revealed values between 0.77 and 0.94. In the original development study of the CCQ,[7] these values ranged from 0.78 to 0.91. Among the domains, the highest value was in the functional state domain,[7] which was similar in the present study.

Table 2. Scores, reliability, and measurement error of the Clinical COPD Questionnaire between measurements.[a]

CCQ	Rater 1 (Test)	Rater 2					Rater 1 (Retest)				
	Score	Score	$ICC_{3,1}$ (95% CI)	SEM_a	SDC_i	SDC_g	Score	$ICC_{3,1}$ (95% CI)	SEM_a	SDC_i	SDC_g
Total	1.85 [0.77-3.52]	1.65 [0.60-3.07]	0.97 (0.95-0.98)	0.65	1.81	0.26	1.50 [0.80-3.10]*	0.92 (0.86-0.95)	0.65	1.80	0.25
Symptoms	2.21 ± 1.44	2.25 ± 1.60*	0.92 (0.86-0.95)	0.47	1.30	0.18	2.30 ± 1.42	0.81 (0.69-0.89)	0.77	2.14	0.30
Mental state	1.5 [0.0-4.0]	1.00 [0.00-3.50]*	0.96 (0.92-0.97)	0.70	1.91	0.27	0.75 [0.00-2.50]	0.80 (0.67-0.88)	2.04	5.66	0.80
Functional state	1.75 [0.68-3.5]	1.50 [0.44-3.00]	0.93 (0.85-0.96)	1.46	4.06	0.57	1.37 [0.25-3.06]*	0.90 (0.83-0.94)	0.90	2.49	0.35

CCQ: Clinical COPD Questionnaire; $ICC_{3,1}$: two-way mixed effects model/single measurement type intraclass correlation coefficient; SEM_a: agreement standard error of measurement; SDC_i: smallest detectable change at the individual level; and SDC_g: smallest detectable change at the group level. [a]Values expressed as median. [IQR] or mean ± SD. *$p > 0.05$ vs. rater 1 (test).

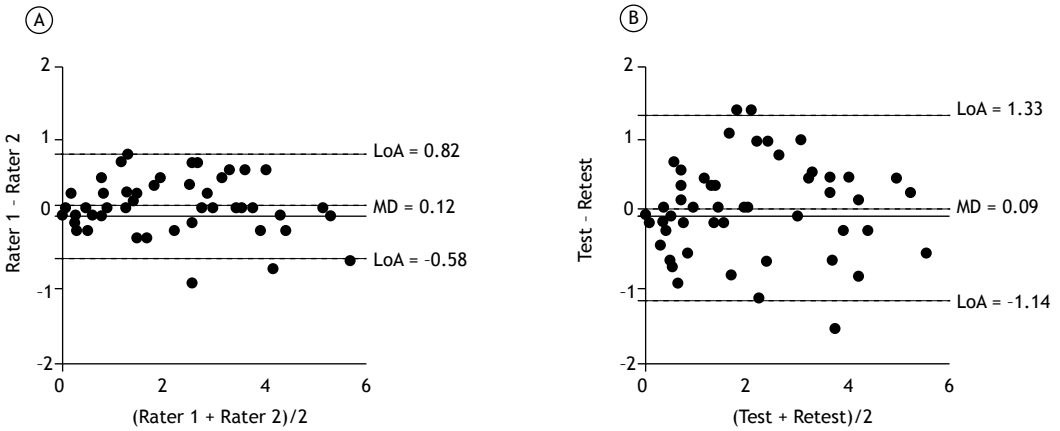

Figure 1. Bland-Altman plots of the total Clinical COPD Questionnaire score, showing interrater reliability (in A) and test-retest reliability (in B). LoA: limit of agreement; and MD: mean difference.

In other validation studies, values above 0.70[20-25] were also found. By definition, internal consistency determines the degree of interrelationship between items.[26] Values below 0.70 indicate a lack of correlation between the PROM items.[27] However, values above 0.95 may indicate that the PROM contains many items that are evaluating the same construct, suggesting redundancy.[28] Therefore, the internal consistency of the Brazilian version of the CCQ and its domains was positive ($0.70 \leq \alpha \leq 0.95$)[9] and sufficient ($\alpha \geq 0.70$).[29]

This study presented the reliability analysis of the Brazilian version of the CCQ between two raters and over a time interval. The minimum ICC was 0.80. In the study that presented the measurement properties of the original CCQ version,[7] the ICC was 0.94 for the total score between test and retest. Our finding is similar to those reported in the validation studies for the Italian[20] (ICC = 0.99) and Persian[30] (ICC = 0.98) versions of the CCQ. Reliability is defined as the proportion of the total variance in the measurements that is due to true differences among patients. Statistical analysis should preferably be done by calculating the ICC, because it considers systematic errors between repeated measures.[26] In the present study, we chose to use the $ICC_{3,1}$, in which each individual is evaluated by each rater, these being the only raters of interest, and reliability is calculated from a single measure.[17] ICCs range from 0 to 1; values close to 1 indicate small error variation when compared with patient variation. This means that such values also depend on the heterogeneity of the population, that is, when the population is more homogeneous, it is easier to find an ICC closer to 0.[6] Considering an ICC of at least 0.70 as a quality criterion, it can be said that the reliability of the Brazilian version of the CCQ between raters and between test and retest was positive[9] and sufficient[29] in our sample.

There were differences in the scores between the administrations of the CCQ. However, comparison tests are not recommended by the Consensus-based Standards for the Selection of Health Measurement Instruments[29] for reliability analysis. This is due to the fact that such tests show only the agreement between administrations for the central values but do not provide information about agreement between administrations for individual values.[31] In the present study, the CCQ scores in the three administrations were higher in the symptoms and the functional state domains, corroborating the results in the original validation of the CCQ.[7]

Measurement error was analyzed by means of $SEM_{agreement}$, $SDC_{individual}$, SDC_{group}, and LoA to determine interrater and test-retest reliability for the Brazilian version of the CCQ. The $SEM_{agreement}$ of the total CCQ score was the same between raters and between test and retest (0.65). Tsiligianni et al.[3], studying a sample of clinically stable COPD patients, reported a lower value of SEM for the CCQ regarding test-retest reliability. However, those authors calculated SEM using a different equation, which does not consider the variance due to systematic differences between raters.[6] This measurement property represents the systematic and random error of a patient's score which is not attributed to real changes in the construct to be measured.[26] In the present study, we calculated SEM, which represents the standard deviation of repeated measures of an individual; and then SDC, which consists of the minimum change that must be overcome to guarantee a real change in the individual.[26] This means that an observed change must be greater than the limit of SDC to be considered true.[6] LoA were demonstrated in Bland-Altman plots to support the interpretation of measurement error size. It is possible to visualize the magnitude of the measurement error when we relate LoA with the score range. By definition, 95% of the differences between repeated measures must be within the LoA range. A value outside that range can indicate a real change.[6] In order to know whether the measurement error is acceptable or not, one must also analyze the minimal important change (MIC). SDC and MIC can be used to decide whether a real and clinically relevant change has occurred with a patient.[28] Other studies about CCQ

Table 3. Correlations of the Clinical COPD Questionnaire (CCQ) domain scores with the Saint George's Respiratory Questionnaire (SGRQ) total and domain scores.

SGRQ	CCQ domain		
	Symptoms	Mental state	Functional state
Total	0.83*	0.78*	0.88*
Symptoms	0.75**	0.64*	0.73*
Activity	0.75*	0.64*	0.82*
Psychosocial impact	0.78*	0.81*	0.85*

*p < 0.01; Spearman's rank correlation. **p < 0.01; Pearson's rank correlation.

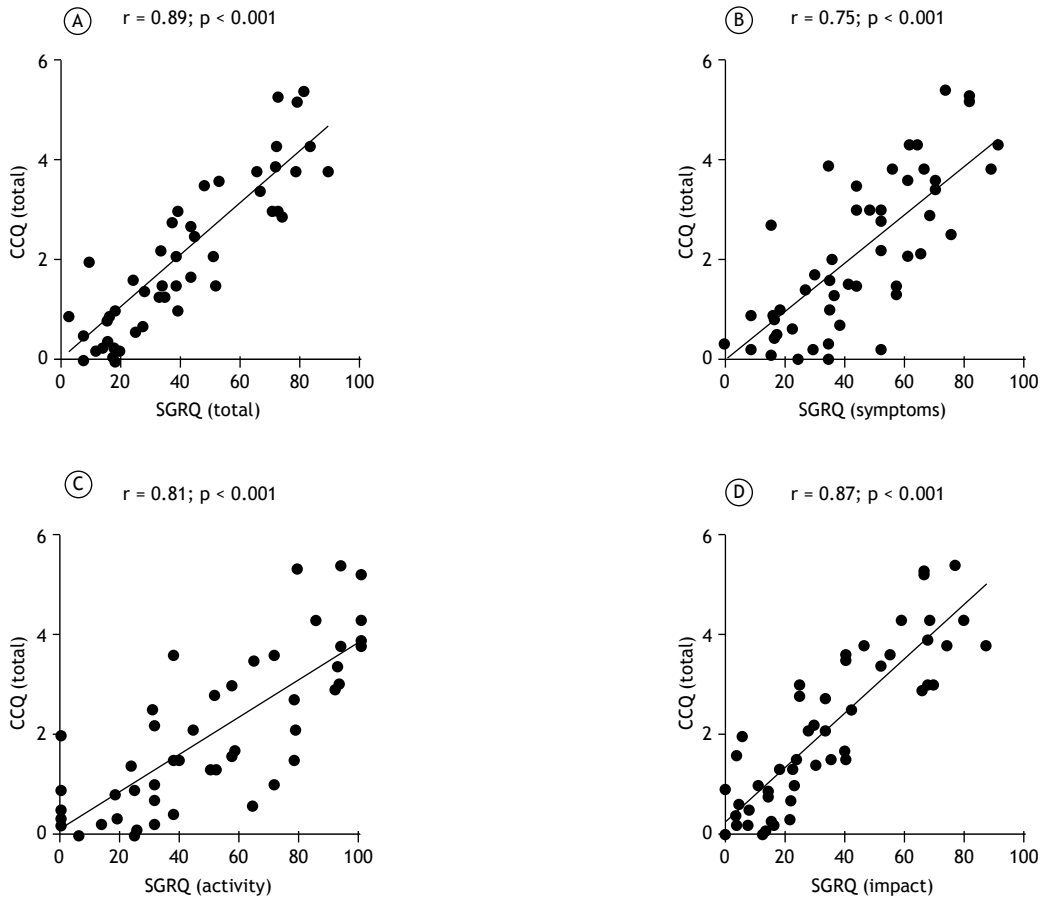

Figure 2. Correlations of the Clinical COPD Questionnaire (CCQ) total score with the Saint George's Respiratory Questionnaire (SGRQ) total score (in A) and domain scores (in B, C and D).

described a MIC value close to 0.4.[32-35] In the present study, however, MIC was not calculated. Therefore, the interrater and test-retest measurement errors of the Brazilian version of the CCQ was classified as undetermined.[9,29]

According to the results, the hypothesis related to the construct analysis was confirmed. There was a positive correlation of r values of at least 0.5 between the total score of the Brazilian version of the CCQ and the SGRQ total and domain scores. For the elaboration of the hypothesis, the minimum r value (0.53) found between the CCQ total score and the SGRQ scores in the validity study of the original CCQ version was considered.[7] Other studies also reported similar r values between the CCQ and the SGRQ.[22,33] Similar results were also found between the CCQ and other PROM scores that assess overall and specific health-related quality of life in patients with COPD[20,21]. The CCQ symptoms and functional state domain scores showed a strong correlation (r > 0.70)[19] with all SGRQ domains. The CCQ mental state domain score strongly correlated only with the total and the impact domain scores of SGRQ, probably because this is the only SGRQ domain that has questions about psychosocial changes.[15] The construct validity estimates the degree to which PROM scores are consistent with assumptions based on the hypothesis that the PROM validly measures the construct that is intended to be measured.[9,28] In the sample studied, the construct validity of the CCQ reached the quality criteria, being rated as positive[9]

and sufficient,[29] because the hypothesis of the construct validity was met.

In the interpretability analysis, the floor and ceiling effects were not observed. In similar studies, the floor and ceiling effects were not detected in the CCQ total score either.[21,22] The presence of a floor or ceiling effect may indicate that extreme items are missing in the lower or upper end of the PROM and can limit its ability to discriminate patients and to measure changes.[9]

Due to the low level of education of part of the sample studied, the CCQ was administered by interview. As expected, the completion of the CCQ by interview in the present study was slightly longer than that of the original self-administered CCQ reported in the original study (approximately 2 min).[7] Agreement between the self-administered CCQ scores and clinician-administered CCQ scores obtained during a medical visit, as well as between self-administered CCQ scores and clinician-administered CCQ scores obtained through semi-structured, in-depth interviews, have been reported.[36] However, this was the first study to analyze measurement properties of the CCQ completed by interview, with no interference from the raters. A meta-analysis[37] reported that, in general, the self-completion and assisted completion of a PROM produce equivalent scores, supporting that the interview format is a valid mode of administration. Moreover, in the present study, assisted completion of the CCQ allowed the unprecedented analysis of interrater reliability and measurement error.

The time interval between the administrations of the CCQ by the raters might have been too short to avoid recall bias and, therefore, might have compromised interrater reliability. However, as far as we know, there is not a recommendation regarding an appropriate time interval for the application of a PROM by raters in the literature. In addition, although the 95% CI range between raters was shorter than it was between test and retest, interrater and test-retest $ICC_{3,1}$ were similar and higher than 0.70.[9,29] Another possible limitation of the study was the cross-sectional design, which prevented the sufficiency of the measurement error from being tested. However, this was the first study that reported the values of $SEM_{agreement}$, $SDC_{individual}$, SDC_{group}, and LoA of the Brazilian version of the CCQ. These values reveal that the changes are real, and not due to measurement error, by showing how much the score needs to change before ensuring that a real change has occurred, providing conditions to interpret longitudinal measurements. In addition, the values of $SEM_{agreement}$, $SDC_{individual}$, SDC_{group}, and LoA are presented in the same measurement unit of the PROM being studied, which facilitates the interpretation of the scores by health professionals in clinical practice.[6]

In conclusion, the Brazilian version of CCQ has sufficient internal consistency and reliability, that is, the PROM items are interrelated, and their scores are stable and capable of reproducing consistent results in repeated measures between different raters and over time. In addition, the Portuguese version of the CCQ for use in Brazil demonstrates sufficient construct validity, and the correlations between the CCQ total scores and the SGRQ scores are consistent. In the present study, $SEM_{agreement}$, $SDC_{individual}$, SDC_{group}, and LoA parameters of the measurement error were shown. However, it is recommended that further studies be conducted to test the sufficiency of measurement error by calculating the MIC. No floor or ceiling effects in the total score of the Brazilian version of the CCQ were found. To our knowledge, this was the first study to evaluate the measurement properties of the CCQ in a sample of patients with COPD in Brazil, which contributes to disseminating this PROM to and promoting its use by health professionals and researchers in order to assess the health status of their patients.

AUTHOR CONTRIBUTIONS

AR, FRF, and RM: conception and planning of the study; interpretation of evidence; drafting and revision of preliminary and final versions; and approval of the final version. APQ: drafting and revision of preliminary and final versions; and approval of the final version. CMR: conception and planning of the study; interpretation of evidence; and approval of the final version. MMB: revision of preliminary and final versions; and approval of the final version. JK and TvdM: drafting and revision of preliminary and final versions; and approval of the final version.

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ORIGINAL ARTICLE

Sleep quality and architecture in COPD: the relationship with lung function abnormalities

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Study carried out at the Clinical Laboratories of Queen's University Affiliated Teaching Hospitals (Kingston General Hospital and Hotel Dieu Hospital), Kingston (ON) Canada.

ABSTRACT

Objective: Impaired respiratory mechanics and gas exchange may contribute to sleep disturbance in patients with COPD. We aimed to assess putative associations of different domains of lung function (airflow limitation, lung volumes, and gas exchange efficiency) with polysomnography (PSG)-derived parameters of sleep quality and architecture in COPD. **Methods:** We retrospectively assessed data from COPD 181 patients ≥ 40 years of age who underwent spirometry, plethysmography, and overnight PSG. Univariate and multivariate linear regression models predicted sleep efficiency (total sleep time/total recording time) and other PSG-derived parameters that reflect sleep quality. **Results:** The severity of COPD was widely distributed in the sample (post-bronchodilator FEV_1 ranging from 25% to 128% of predicted): mild COPD (40.3%), moderate COPD (43.1%), and severe-very severe COPD (16.6%). PSG unveiled a high proportion of obstructive sleep apnea (64.1%) and significant nocturnal desaturation (mean pulse oximetry nadir = 82.2% ± 6.9%). After controlling for age, sex, BMI, apnea-hypopnea index, nocturnal desaturation, comorbidities, and psychotropic drug prescription, FEV_1/FVC was associated with sleep efficiency ($\beta = 25.366$; $R^2 = 14\%$; $p < 0.001$), whereas DL_{CO} predicted sleep onset latency ($\beta = -0.314$; $R^2 = 13\%$; $p < 0.001$) and rapid eye movement sleep time/total sleep time in % ($\beta = 0.085$; $R^2 = 15\%$; $p = 0.001$). **Conclusions:** Pulmonary function variables reflecting severity of airflow and gas exchange impairment, adjusted for some potential confounders, were weakly related to PSG outcomes in COPD patients. The direct contribution of the pathophysiological hallmarks of COPD to objectively measured parameters of sleep quality seems to be less important than it was previously assumed.

Keywords: Pulmonary disease, chronic obstructive; Respiratory function tests; Sleep; Sleep apnea, obstructive; Comorbidity.

INTRODUCTION

COPD can potentiate the complex effects of disturbed sleep on the respiratory system, including changes in central respiratory control, airway resistance, gas exchange, and respiratory muscle contractility.[1] In fact, patients with COPD frequently report impaired sleep,[2-4] which was ranked as the third most troublesome disturbance, after dyspnea and fatigue.[2] They also endorse the morning as the worst time of the day vis-à-vis energy levels and willingness to undertake activities of daily living.[5] Accordingly, low sleep efficiency,[6,7] disturbed sleep architecture,[3] and challenges in initiating and maintaining sleep[3,4,8] have been confirmed by overnight polysomnography (PSG) in this population of patients.

The mechanisms leading to impaired sleep in COPD are still controversial.[9,10] Altered respiratory mechanics and gas exchange abnormalities[11] may render patients more susceptible to nocturnal hypoventilation and hypoxemia. Previous studies demonstrated that airflow obstruction[7] and lung hyperinflation[7,12] were correlated with poorer sleep quality, whereas nocturnal O_2 desaturation may disrupt normal sleep architecture.[13] Reduction in the neural respiratory drive to the respiratory muscles during sleep[14] may also contribute to nocturnal hypoventilation and sleep disturbances. Unfortunately, moreover, sleep quality may also be negatively affected by a plethora of factors that are common in COPD patients, such as senescence, obesity, cardiovascular/metabolic comorbidities,[15] and polypharmacy.[10] These features are even more prevalent in patients with greater lung function impairment.[15] Accordingly, we hypothesized that the effect(s) of resting pulmonary function abnormalities on impaired sleep quality[7,12,13] could be influenced by some of these features, such as obesity, nocturnal (de)oxygenation, comorbidities, psychotropic drug prescription, and/or alcohol consumption), which are frequently observed in elderly individuals with COPD.

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Our objective, therefore, was to assess—after careful adjustment for the abovementioned confounders—putative associations of different domains of lung function (airflow limitation, lung volumes, and gas exchange efficiency) with PSG-derived parameters of sleep quality and architecture in COPD.

METHODS

Study design and population

This was a retrospective cross-sectional study. Using pre-specified criteria, data of all consecutive patients ≥ 40 years of age who were referred to the Clinical Laboratories of Queen's University Affiliated Teaching Hospitals (Kingston General Hospital and Hotel Dieu Hospital, both located in the city of Kingston, Canada) for spirometry with post-bronchodilator assessment, whole-body plethysmography, DL_{CO}, and overnight PSG between 2008 and 2016 were reviewed (Figure 1). These exams were requested at the discretion of the attending physicians to evaluate respiratory (lung function) and sleep-related (PSG) complaints. In the case of sequential pulmonary function measurements, the last assessment was recorded for analysis. The following data were obtained from PSG reports: age, sex, BMI, smoking status (former/current smoker vs. never smoker), main diagnosis, comorbidities, alcohol consumption (on the day of the exam), and medicine prescription.

Participants were included based on informed diagnosis or suspicion of COPD by the attending physician, post-bronchodilator (albuterol, 400 µg) $FEV_1/FVC < 0.70$, and previous or current history of smoking. Exclusion criteria included conditions that could affect sleep quality (neuromuscular disease, previous stroke with neurologic sequelae, or active cancer), chronic respiratory disease (bronchiectasis, interstitial lung disease, TLC < 80% of the predicted values), lack of sleep during PSG (total sleep time (TST)/total recording time [sleep efficiency] < 20%), central apnea index > 5 events/h, and/or use of nocturnal CPAP or oxygen supplementation.

Subjects were unnamed and identified by unique identification numbers. The study (#6020749) was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (FWA #00004184; IRB #00001173). Informed consent was waived by the institutional research committee given the retrospective design of the study and the guarantee of anonymity of all individual data included in the study.

Procedures

Spirometry (including inspiratory capacity [IC]), body plethysmography, and DL_{CO} measurements were performed with automated testing equipment (V6200 Autobox; SensorMedics, Yorba Linda, CA, USA) in the

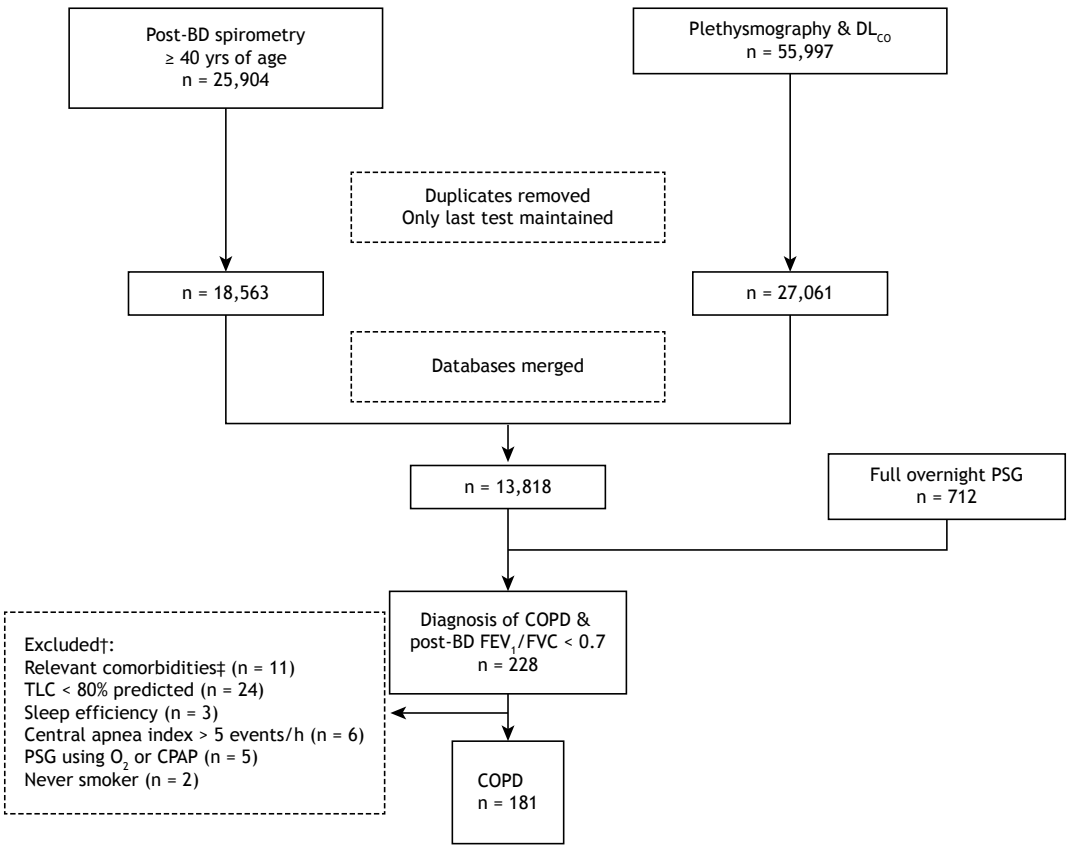

Figure 1. Flow chart of the study selection process. BD: bronchodilator; yrs: years; and PSG: polysomnography. †Participants may present with more than one reason. ‡Neuromuscular disease, cystic fibrosis, or pulmonary fibrosis.

Pulmonary Function Laboratory at Hotel Dieu Hospital in accordance with international standards (American Thoracic Society/European Respiratory Society).

Standard PSG measurements were collected in the Sleep Laboratory at Kingston General Hospital. Continuous recordings using the Sandman Elite SD 32+ digital sleep recording system (Embla; Mallinckrodt/Nellcor Puritan Bennett [Melville] Ltd, Mansfield, MA, USA) included four electroencephalography channels (C4A1, C3A2, O2A1, and O1A2); two electrooculogram channels (ROCA1 and LOCA2); submental electromyography; bilateral anterior tibialis electromyography; electrocardiography; chest and abdominal respiratory belts; nasal pressure via nasal cannula; finger pulse oximeter (SpO_2); and a vibration snore sensor. Sleep was staged, and obstructive apneas and hypopneas were defined using established criteria.[16] Apneas were defined as central if there was a lack of respiratory effort during the period of absent airflow. Daytime sleepiness was assessed using the Epworth Sleepiness Scale. A score equal to or higher than 10 points was considered as excessive daytime sleepiness. Obstructive sleep apnea (OSA) was defined as an apnea/hypopnea index (AHI) ≥ 5 events/h and accompanied by excessive daytime sleepiness or an AHI ≥ 15 events/h regardless of coexistent symptoms.[17] Sleep efficiency values < 85% were defined as abnormally low.[18,19] Pulmonary function tests and PSG were routinely performed only if the subject was clinically stable in the preceding four weeks.

Statistical analysis

Statistical analysis was performed with the IBM SPSS Statistics software package, version 24.0 (IBM Corporation, Armonk, NY, USA). Values are reported as means and standard deviations unless otherwise specified. An estimated sample size of 139 subjects was required to detect associations between continuous dependent variables (PSG-derived sleep parameters) and 15 predictors, considering a significance level of $p < 0.05$, a desired statistical power of 0.8, and an effect size (f^2) of 0.15.[20]

Univariate linear regression analyses were initially performed to evaluate associations of resting lung function variables (FEV_1/FVC, IC/TLC, RV/TLC, and DL_{CO} in % of predicted values) and potential confounders (age, sex, BMI, AHI, parameters of nocturnal desaturation, comorbidities, psychotropic drug prescription, and alcohol intake) with PSG parameters that reflect sleep quality and architecture.[21-24] Thereafter, first-level multivariate analyses (backward stepwise method) were performed, including pulmonary function and PSG variables (AHI and parameters of nocturnal desaturation), as well as anthropometric and demographic variables, that showed $p \leq 0.10$ in univariate models. If pulmonary function parameters remained as independent predictors of sleep performance in the first-level models, these multivariate analyses were further adjusted for presence of comorbidities, psychotropic drug prescription,[25] and alcohol intake on the day of PSG[26] if p was ≤ 0.10 in univariate models (final models). The significance level for retention of a variable in the multivariate model was set at $p \leq 0.05$.

RESULTS

The severity of COPD was widely distributed among the 181 patients included (post-bronchodilator FEV_1 ranging from 25% to 128% of predicted): mild COPD, in 73 patients (40.3%); moderate COPD, in 78 (43.1%); and severe-very severe COPD, in 30 (16.6%). As expected, these participants presented with impaired ventilatory mechanics and gas exchange (DL_{CO}) at rest according to the predicted values (Table 1).

The subjects included in the study also showed reduced mean sleep efficiency when compared with historical controls, 144 (79.5%) of whom presenting reduced values (< 85%). PSG also unveiled a high proportion of OSA (116 subjects; 64.1%) and significant nocturnal desaturation (Table 1). The presence of OSA diagnosed by PSG was only related to lower slow wave sleep, expressed as % of TST ($\beta = -4.212$; $R^2 = 4\%$; $p = 0.015$). As anticipated, a high prevalence of comorbidities and prescription of psychotropic medication was reported (Table 2). Of 157 subjects in the sample, 22 (14.0%) reported alcohol consumption on the day of PSG.

Univariate linear regression analyses revealed that the selected resting lung function measures weakly correlated with PSG-derived parameters that reflect sleep quality and architecture (Table 3). In multivariate analyses, the pulmonary function parameters that remained as independent predictors of sleep efficiency, sleep onset latency, and rapid eye movement (REM) sleep (in % of TST) were FEV_1/FVC, DL_{CO}, and DL_{CO}, respectively. As planned, these models were subsequently adjusted for the presence of comorbidities, psychotropic drug prescription, and alcohol consumption when these variables showed to be related to PSG-derived parameters of sleep quality in univariate analyses (data not shown). The resultant multivariate regression models depicting the final independent predictors are presented in Table 4.

DISCUSSION

The major finding herein observed is that, after controlling for age, sex, AHI, nocturnal desaturation, comorbidities, psychotropic drug prescription, and alcohol consumption, selected parameters of resting lung function were weakly related to sleep quality and architecture in COPD: lower FEV_1/FVC ratio was related to poorer sleep efficiency, whereas lower DL_{CO} was associated with longer sleep onset latency and lower % of REM sleep.

PSG assessment of sleep quality is commonly found in research involving COPD.[3,6-8,12,27] The parameters that in fact correlate with subjective estimates of sleep quality, however, are controversial. We mainly analyzed variables that have been posited to correlate with

Table 1. Baseline characteristics of the patients included.[a]

Variable	(N = 181)
Male sex, n (%)	98 (54.1)
Age, years	63.5 ± 11.2
Weight, kg	92.3 ± 24.7
Height, m	1.66 ± 0.08
BMI, kg/m^2	33.4 ± 8.5
Resting lung function	
FEV_1	
Pre-BD, L (% predicted)	1.73 ± 0.64 (68.8 ± 20.3)
Post-BD, L (% predicted)	1.84 ± 0.65 (73.4 ± 20.2)
FVC	
Pre-BD, L (% predicted)	2.99 ± 0.88 (84.2 ± 18.0)
Post-BD, L (% predicted)	3.16 ± 0.89 (89.2 ± 17.9)
FEV_1/FVC	
Pre-BD	0.57 ± 0.11
Post-BD	0.58 ± 0.11
TLC, L (% predicted)	5.88 ± 1.27 (109.4 ± 16.3)
IC, L (% predicted)	2.38 ± 0.74 (99.2 ± 23.7)
IC/TLC	0.40 ± 0.09
FRC, L (% predicted)	3.51 ± 1.07 (132.4 ± 42.9)
RV, L (% predicted)	2.71 ± 0.97 (132.9 ± 43.3)
RV/TLC	0.46 ± 0.10
DL_{CO}, mL/min/mmHg (% predicted)	17.0 ± 5.9 (74.2 ± 21.7)
Polysomnography	
Epworth Sleepness Scale	7.7 ± 4.6
TST, min[†]	297.1 ± 81.3
Sleep efficiency, %	69.0 ± 17.2
Sleep onset latency, min[†]	27.5 ± 34.0
Wake after sleep onset, min[†]	109.3 ± 68.3
NREM sleep stage 1, % TST[†]	13.5 ± 10.7
NREM sleep stage 2, % TST[†]	61.4 ± 12.4
Slow wave sleep, % TST[†]	11.3 ± 10.4
REM sleep, % TST	13.5 ± 8.3
AHI, events/h	21.9 ± 28.2
Central apnea index, events/h	2.9 ± 6.1
Baseline SpO_2, %	93.6 ± 2.7
Nadir SpO_2, %	82.2 ± 6.9
SpO_2 below 90%, % TST	23.3 ± 32.4
Arousal index, events/h	7.0 ± 6.6

BD: bronchodilator; IC: inspiratory capacity; FRC: functional residual capacity; TST: total sleep time; NREM: non-rapid eye-movement sleep; REM: rapid eye movements sleep; TST: total sleep time; and AHI: apnea-hypopnea index.[a]Values expressed as mean ± SD, except where otherwise indicated. [†]n = 153.

subjective sleep quality as assessed via retrospective self-reported inventories or via ordinal scales included in prospective sleep diaries. Sleep efficiency and TST demonstrated to be significantly correlated with subjective sleep quality in a community-dwelling study including more than one thousand older adults regardless of sex.[21] The amount of slow-wave and/or REM sleep stages[22-24] and sleep onset latency[24] showed to be good predictors of subjective sleep satisfaction in smaller and older studies. Although several weak relationships were observed in univariate regressions, few lung function variables remained in the multivariate models only predicting sleep efficiency, sleep onset latency, and % of REM sleep, and all final multivariate models demonstrated low coefficients of determination (R^2). This means that only a small proportion of the variance in the dependent variables could be predicted from the independent variables.Previous studies have also failed to find significant and/or robust associations between spirometric variables and sleep efficiency in COPD.[6,27] It has long been recognized, however, that due to the complexity of COPD, it is advisable to take into consideration physiological measures other than FEV_1.[28] In fact, indexes of hyperinflation and gas trapping have proven to be more useful than has FEV_1 in predicting cardinal symptoms of the disease,

Table 2. Prevalence of reported comorbidities and prescription of inhaled and psychotropic medication (N = 181).

Variable	n (%)
Comorbidities	
Systemic hypertension	85 (46.9)
GERD	52 (28.7)
Depression	47 (25.9)
Coronary artery disease	25 (13.8)
Cancer	22 (12.1)
Diabetes mellitus	19 (10.5)
Chronic pain	19 (10.5)
Osteoarthritis	13 (7.2)
Heart failure	11 (6.1)
Hypothyroidism	10 (5.5)
Atrial fibrillation	8 (4.4)
Chronic kidney disease	7 (3.9)
Inhaled medication	
SABA	98 (53.9)
ICS	97 (53.4)
LABA	97 (53.4)
LAMA	72 (39.6)
SAMA	24 (13.2)
Psychotropic medication	
Serotonin reuptake inhibitors	38 (20.9)
Benzodiazepines	23 (12.7)
Antipsychotics (olanzapine, clozapine, quetiapine, risperidone)	13 (7.2)
Other hypnotics (trazodone, zolpidem)	12 (6.6)
Opioids	10 (5.5)
Tricyclic antidepressants	8 (4.4)

GERD: gastroesophageal reflux disease; SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; and SAMA: short-acting muscarinic antagonist.

such as dyspnea and exercise intolerance,[29] as well as survival.[30] Accordingly, the IC/TLC ratio[12] and the length of the zone of apposition of the diaphragm[7] were associated with sleep efficiency. In the present study, however, which was adjusted to control for confounders, the significant relationships of gas trapping and lung hyperinflation with sleep efficiency observed in univariate regressions were no longer present in multivariate analyses. It is conceivable, therefore, that impaired respiratory mechanics and increased work of breathing[11] contributed only with a small fraction to the reduction of sleep efficiency. Accordingly, we recently showed that an evening dose of formoterol/aclidinium, when compared with placebo, improved overnight dynamic respiratory mechanics and inspiratory neural drive, but no positive effects on PSG outcomes (including sleep efficiency) were found.[31] A lower FEV_1/FVC ratio is a sign of more severe airflow obstruction, possibly resulting in increased overnight symptoms (dyspnea, cough, and phlegm) and leading to frequent awakenings or difficulty in sleep onset.[3,4,32]

DL_{CO}, in turn, persisted as the single pulmonary function variable independently related to sleep onset latency and % of REM sleep. Low resting DL_{CO} has been reported to be associated with increased symptoms even in smokers without COPD and in patients with mild-moderate disease.[33] Consequently, DL_{CO} might also be related to disturbed sleep because of a higher burden of overnight respiratory symptoms, such as nocturnal cough and dyspnea. In line with this premise, Chang et al.[32] found that the burden of COPD (particularly productive cough), evaluated through the COPD Assessment Test, was an independent factor for poor sleep quality. Recently, Lehmann et al.[34] found that the use of two bronchodilators (indacaterol/glycopyrronium) improved subjective sleep quality, lung function, and daily symptoms. The extent to which each of these mechanisms can improve sleep quality remains to be determined. From a physiological point of view, DL_{CO} is a marker of alveolar-capillary membrane destruction from the early stages of COPD.[35] Low DL_{CO}, therefore, reflects impaired vascular function across multiple anatomical sites, which was associated with poorer perceived sleep quality and % of REM sleep.[36] Interestingly, REM sleep is partially facilitated by nitric oxide,[37] a substance continuously synthesized by endothelial cells to maintain vascular homeostasis. Additional research is needed to explore the relationship between endothelial function/nitric oxide-mediated pathways and REM sleep in COPD.

From a clinical standpoint, detection and management of sleep disturbances seem relevant to reducing the

Table 3. Regression coefficients (R) from univariate linear regression analyses investigating the relationship of demographic, anthropometric, pulmonary function, and selected polysomnography-derived variables (apnea-hypopnea index and SpO_2) with polysomnography parameters of sleep quality.

Variable	TST (min) (N = 153)	Sleep efficiency (%) (N = 181)	Sleep onset latency (min) (n = 153)	Wake after sleep onset (min) (n = 153)	Slow wave sleep (%TST) (n = 153)	REM sleep (%TST) (N = 177)
Age (years)	−0.261*	−0.345*	−0.032	0.415*	−0.216*	−0.161*
Sex (male = 1)	−0.207*	−0.193*	−0.187*	0.237*	−0.259*	0.020
BMI (kg/m²)	−0.031	−0.058	−0.102	0.057	−0.056	−0.133†
Resting lung function						
FEV_1/FVC	0.146†	0.186*	−0.191*	−0.164*	0.122	0.082
IC/TLC	0.102	0.165*	−0.199*	−0.130	−0.042	0.093
RV/TLC	0.042	−0.156*	0.115	0.174*	0.042	−0.123‡
DL_{CO} (% predicted)	0.035	0.104	−0.227	0.059	−0.163*	0.255*
Polysomnography						
AHI, events/h	−0.235*	−0.155*	0.040	0.281	−0.308*	−0.115
Baseline SpO_2, %	−0.024	0.006	0.053	−0.036	−0.131	0.154*
Nadir SpO_2, %	−0.018	−0.029	0.058	−0.018	0.016	0.121
SpO_2< 90%, % TST	−0.060	−0.041	0.044	0.029	0.168*	−0.213*

TST: total sleep time; REM: rapid eye movement; IC: inspiratory capacity; and AHI: apnea-hypopnea index. *p < 0.05. †p = 0.07. ‡p = 0.09.

Table 4. Multivariate linear regression models that retained pulmonary function parameters as independent variables to predict sleep quality and architecture.[a]

	β (95% CI)	SE	R	p
Sleep Efficiency (N = 181)			0.379	< 0.001
Constant	86.704	9.870		< 0.001
Age (years)	−0.530 (−0.720 to −0.298)	0.107		< 0.001
Post-BD FEV_1/FVC	25.366 (3.250-47.4821)	11.207		0.025
Sleep onset latency (n = 147)			0.361	< 0.001
Constant	48.846	9.501		< 0.001
DL_{CO} (% predicted)	−0.314 (−0.554 to −0.074)	0.121		0.011
Heart failure (Yes=1)	43.016 (19.801-66.232)	11.746		< 0.001
% of REM sleep (n = 178)			0.384	< 0.001
Constant	7.263	2.198		0.001
DL_{CO} (% predicted)	0.085 (0.029-0.140)	0.028		0.001
Antipsychotic drug use (Yes = 1)	−6.127 (−10.587 to −1,668)	2.256		0.007
Alcohol intake (Yes = 1)	3.664 (0.242-7.087)	1.173		0.036

BD: bronchodilator; and REM: rapid eye movement.. [a]Age, sex, BMI, apnea-hypopnea index, polysomnography parameters of oxygen desaturation, comorbidities, psychotropic drug prescription, and alcohol intake were assessed in multivariate linear regression models if p ≤ 0.10 in univariate linear regression analyses.

burden of COPD.[9] Albeit to a small extent, selected lung function parameters reflecting the severity of airflow limitation and impairment in gas exchange were indeed related to sleep quality and architecture in COPD. It seems reasonable to consider these functional abnormalities in conjunction with other clinical signs of the disease (nocturnal wheezing, cough, and phlegm), COPD-related psychological distress, and polypharmacy in order to estimate the likelihood of poor sleep quality in individual patients.[9] Surprisingly, despite the high prevalence of diagnosed OSA (64.1%) in this sample of predominantly overweight participants, the presence of OSA, as well as the magnitude of overweight (BMI) and AHI, did not interfere with the observed relationships between lung function and sleep performance.

The main limitations in the present study are related to its cross-sectional design and retrospective nature. The former precludes strong mechanistic inferences. Although clinical information was carefully obtained from the institutional routine on the day of PSG, some additional potential clinical confounders may still have escaped. Anxiety and depression are highly prevalent[38] and associated with sleep disturbance in COPD[39]: lack of assessment of these disorders by objective validated tools may have influenced our results. In addition, the fact that duration of COPD, exercise capacity, history of exacerbations, nocturnal/early-morning respiratory symptoms, adherence to prescribed psychotropic medications/duration of use, duration of alcohol consumption, and smoking on the

day of PSG were not assessed restricted the possibility of further adjustment of the multivariate models. To our knowledge, although our sample represents the largest series to date in which sleep performance was objectively measured by overnight PSG and correlated with basic and advanced pulmonary function test results, we cannot rule out that if these additional potential confounders had been controlled, weaker relationship(s) could have been found.

In conclusion, selected pulmonary function variables reflecting the severity of airflow limitation and gas exchange efficiency, adjusted for some potential confounders, were weakly related to PSG outcomes in COPD patients. The direct contribution of these pathophysiological hallmarks of COPD to objectively measured sleep quality seems to be less important than it is generally thought, highlighting the complex pathogenesis of sleep disorders in this population of patients.

AUTHOR CONTRIBUTIONS

RDM and DCB: study design; data collection and analysis; and drafting of the manuscript. ND, HD, and AFE: data collection and interpretation. MF, DEO, SF, and JAN: study design; data interpretation; and reviewing of the manuscript. All authors approved the final version of the manuscript.

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Effectiveness and toxicity of adjuvant chemotherapy in patients with non-small cell lung cancer

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ABSTRACT

Objective: Adjuvant chemotherapy (AC) improves survival of patients with resected non-small cell lung cancer (NSCLC). However, the cisplatin-vinorelbine regimen has been associated with a significant risk of clinically relevant toxicity. We sought to evaluate the effectiveness, safety, and feasibility of AC for NSCLC patients in a real-world setting. **Methods:** This was a single-center, retrospective cohort study of patients with stage I-III NSCLC undergoing surgery with curative intent between 2009 and 2018. AC was administered at the discretion of physicians. The patients were divided into two groups: AC group and no AC (control) group. Study outcomes included overall survival (OS) and recurrence-free survival (RFS), as well as the safety profile and feasibility of the cisplatin-vinorelbine regimen in a real-world setting. **Results:** The study involved 231 patients, 80 of whom received AC. Of those, 55 patients received the cisplatin-vinorelbine regimen. Survival analyses stratified by tumor stage showed that patients with stage II NSCLC in the AC group had better RFS ($p = 0.036$) and OS ($p = 0.017$) than did those in the no AC group. Among patients with stage III NSCLC in the AC group, RFS was better ($p < 0.001$) and there was a trend toward improved OS ($p = 0.060$) in comparison with controls. Of those who received the cisplatin-vinorelbine regimen, 29% had grade 3-4 febrile neutropenia, and 9% died of toxicity. **Conclusions:** These results support the benefit of AC for NSCLC patients in a real-world setting. However, because the cisplatin-vinorelbine regimen was associated with alarming rates of toxicity, more effective and less toxic alternatives should be investigated.

Keywords: Lung neoplasms; Chemotherapy, adjuvant; Cisplatin/toxicity; Vinorelbine/toxicity.

INTRODUCTION

Lung cancer is one of the most common cancers and the leading cause of cancer-related deaths both in men and women worldwide, with an estimated 1.7 million deaths in 2018.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers.[2] Clinical outcomes and treatment strategies for NSCLC are directly related to stage at diagnosis. Unfortunately, only 25% of the patients with NSCLC have non-metastatic disease at diagnosis, and recurrence rates are often high even when patients are treated with curative intent.[3]

In order to improve patient outcomes, adjuvant cisplatin-based chemotherapy after surgical resection has been extensively studied in the last decades.[4-8] The Adjuvant Navelbine International Trialist Association (ANITA) trial[4] demonstrated that cisplatin and vinorelbine significantly improve five-year survival rates (by 8,6%; p = 0,017) in patients with stage IB-IIIA NSCLC. However, a subgroup analysis indicated that the benefit is mainly seen in patients with stage II or IIIA disease.[4]

The benefit of adjuvant chemotherapy in NSCLC was confirmed in a meta-analysis evaluating more than 4.500 patients in five clinical trials.[5] It showed that platinum-based adjuvant chemotherapy resulted in a 5.4% absolute improvement in overall survival (OS) in patients with stage II or III NSCLC (hazard ratio [HR] = 0.89; 95% CI: 0.82-0.96; p = 0.005).[5] Based on these results, platinum-based adjuvant chemotherapy has become the standard of care for patients with completely resected stage II or IIIA NSCLC, and the most commonly used regimen is a combination of cisplatin and vinorelbine.[4-8]

Although effectiveness of the cisplatin-vinorelbine regimen has been well established, the combination of cisplatin and vinorelbine is associated with clinically relevant toxicity. High rates of grade 3-4 adverse events can compromise treatment adherence, leading to dose reductions and delays, as well as to treatment discontinuation, which is known to be associated with worse outcomes.[4-8] Studies providing real-world data on

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long-term efficacy and safety of adjuvant chemotherapy in NSCLC are scarce and have heterogeneous methods and outcomes. Therefore, the primary objective of the present study was to evaluate the effectiveness and safety of adjuvant chemotherapy for NSCLC patients in a real-world setting.

METHODS

Study design and participants

In this retrospective cohort study, patients undergoing surgical treatment for localized NSCLC were consecutively evaluated and treated between June of 2009 and January of 2018 at the *Instituto do Câncer do Estado de São Paulo* (ICESP), located in the city of São Paulo, Brazil. The ICESP has a dedicated multidisciplinary thoracic oncology team responsible for evaluating and discussing the cases of patients considered candidates for surgery with curative intent.

We included patients with histologically confirmed NSCLC and TNM stage I-III NSCLC[3] undergoing surgery with curative intent. In accordance with the institutional guidelines, all patients were submitted to pre-operative staging with CT or PET/CT to exclude metastases and with mediastinoscopy or EBUS for mediastinal staging, when indicated. Exclusion criteria included metastatic disease, primary tumor not amenable to complete resection, and a concurrent diagnosis of other malignancies. Data on clinical and demographic characteristics, as well as on treatment received, toxicity, and oncologic outcomes were obtained from electronic medical records. The study was approved by the local research ethics committee (ID 1011/16).

Treatment

The thoracic surgery team defined the type of surgery required to achieve a tumor-free resection margins (lobectomy or pneumonectomy and lymph node dissection) by using an open surgery or video-assisted thoracic surgery, in accordance with the International Association for the Study of Lung Cancer recommendations.[2,3]

Adjuvant chemotherapy, radiation therapy, or both were prescribed at the discretion of the physicians involved, in accordance with institutional guidelines or by tumor board consensus. At our institution during the study period, adjuvant chemotherapy was recommended for patients with completely resected stage II-III NSCLC and was considered on a case-by-case basis in patients with stage IB NSCLC. In addition, patients must have an ECOG performance status of 0-1 and adequate hepatic, renal, and hematological function. Standard adjuvant chemotherapy as defined by institutional guidelines is cisplatin (80 mg/m^2 on day 1) and vinorelbine (30 mg/m^2 on days 1, 8, and 15) every three weeks for four cycles. Alternative platinum-based chemotherapy regimens are allowed in specific settings. Although adjuvant radiation therapy is not part of our routine protocol, it was considered on a case-by-case basis in patients with positive margins or N2 lymph node status.

Statistical analysis

Patient characteristics and treatment-related toxicities were summarized by descriptive statistics. Continuous variables were expressed as median and range, whereas categorical variables were presented as absolute numbers and proportions. Differences in continuous variables between the groups were evaluated by Student's t-test. Categorical variables were compared between groups with the use of Fisher's exact test.

The Kaplan-Meier method was used in order to estimate survival function, and curves were compared by the log-rank test. The primary outcome was OS, defined as the time from the date of surgery to the date of death from any cause or the date of the last medical visit. Recurrence-free survival (RFS) was also analyzed and defined as the time from surgery to disease recurrence or death. Patients presenting with no events of interest were censored at the last follow-up date.

Potential prognostic factors were evaluated by univariate and multivariate analysis with Cox proportional hazards regression, which provided the HR and 95% CI. Prognostic factors evaluated in the univariate analysis included age, gender, TNM stage, lymph node status, histology, and use of adjuvant chemotherapy. For the multivariate model, we included the use of adjuvant chemotherapy and factors showing $p \leq 0.10$ in the univariate analysis as long as they were not associated with each other. The chi-square test was used in order to evaluate the association between variables.

Statistical analyses were conducted with the Stata statistical software package, version 15.1 (StataCorp LP, College Station, TX, USA). The level of significance was set at 5% ($p < 0.05$).

RESULTS

Patient characteristics

The study included 231 consecutive patients who met the eligibility criteria. The median follow-up time was 24 months. Of the 231 patients, 80 patients received adjuvant chemotherapy, and 151 were followed after surgical treatment (controls). Of the 80 patients who received adjuvant chemotherapy, 55 patients (68%) received the cisplatin-vinorelbine regimen. Alternative regimens included carboplatin and paclitaxel (n = 17; 21.2%), cisplatin and gemcitabine (n = 5; 6.2%), cisplatin and paclitaxel (n = 1; 1.2%), and carboplatin and vinorelbine (n = 1; 1.2%). Among the patients who received cisplatin and vinorelbine, the median cumulative dose of cisplatin was 286 mg/m^2 (range:

72-320 mg/m^2), and that of vinorelbine was 292 mg/m^2 (range: 60-360 mg/m^2).

Patients in the adjuvant chemotherapy group were younger than those in the control group (median age: 63.0 years vs. 67.6 years; p < 0.001) and more frequently underwent pneumonectomy (15.0% vs. 7.9%; p < 0.005). The proportion of early stage disease was higher in the control group, with stage I NSCLC in 56.3% (p < 0.001) and negative lymph nodes (N0) in 67.5% (p < 0.001). Of the patients who received adjuvant chemotherapy, only 2.5% had stage I NSCLC, and 31.2% had negative lymph nodes (N0). Table 1 summarizes the characteristics of the study participants.

Effectiveness

In the univariate analysis, factors associated with shorter OS were TNM stage (stage II vs. stage I: HR = 2.57; 95% CI: 1.40-4.71; p = 0.002; and stage III vs. stage I: HR = 3.81; 95% CI: 2.06-7.07; p < 0.001) and lymph node status (N2 vs. N0: HR = 1.82; 95% CI: 1.07-3.11; p = 0.027). Adjuvant chemotherapy use and TNM stage were included in the multivariate model. Lymph node status was not included, because it is part of the TNM stage (p < 0.001).

The multivariate analysis confirmed that TNM stage was a negative prognostic factor for OS (stage II vs. stage I: HR = 3.93; 95% CI: 2.06-7.49; p < 0.001; and stage III vs. stage I: HR = 6.31; 95% CI: 3.23-12.35; p < 0.001), whereas adjuvant chemotherapy use was associated with longer OS in comparison with the control group (HR = 0.43; 95% CI: 0.25-0.72; p = 0.001). The results of univariate and multivariate Cox regression analyses are presented in Table 2.

During the study follow-up period, 97 patients (67%) had disease recurrence or died. Given the discrepancy between the study groups regarding tumor stage and the importance of this factor for oncologic outcomes, survival analyses were carried out according to tumor stage. Among stage II NSCLC patients, those who received adjuvant chemotherapy had longer RFS than did those who did not (median RFS: not reached vs. 25.5 months; HR = 0.50; 95% CI: 0.26-0.95; p = 0.036). Adjuvant chemotherapy was also associated with longer OS. The median OS was not reached in the adjuvant chemotherapy group,

Table 1. Characteristics of the patients included in the study (N = 231).[a]

Characteristic	Group		P
	Adjuvant chemotherapy (n = 80)	No adjuvant chemotherapy (n = 151)	
Age, years	63.0 [45.3-79.1]	68.3 [34.0-87.9]	< 0.001*
Sex			0.388†
Male	36 (45.0)	73 (48.3)	
Female	44 (55.0)	78 (51.7)	
Type of surgery			0.005†
Pneumonectomy	12 (15.0)	12 (7.9)	
Lobectomy	61 (76.2)	134 (88.7)	
Other	7 (8.7)	5 (3.3)	
Histology			0.747†
SCC	21 (26.2)	48 (31.8)	
Adenocarcinoma	53 (66.2)	92 (60.9)	
Other	6 (7.5)	10 (6.6)	
Not available	0 (0)	1 (0.7)	
Stage			< 0.001†
I	2 (2.5)	85 (56.3)	
II	44 (54.9)	41 (27.1)	
III	34 (42.5)	24 (15.9)	
Not available	0 (0)	1 (0.7)	
Lymph node status			< 0.001†
N0	25 (31.2)	102 (67.5)	
N1	27 (33.7)	17 (11.3)	
N2	27 (33.7)	14 (9.3)	
Not available	1 (1.2)	18 (11.9)	
ECOG-PS before chemotherapy	22 (27.5)	-	
0	48 (60.0)	-	
1	1 (1.2)		
2	9 (11.2)		
Not available			
Radiation therapy			
Yes	13 (16.2)	5 (3.3)	

SCC: squamous cell carcinoma; and PS: performance status. [a]Values expressed as median [range] or n (%). *Student's t-test. †Fisher's exact test.

Table 2. Factors associated with overall survival after surgery for resection of non-small cell lung cancer (Cox regression).

Factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Adjuvant chemotherapy (yes vs. no)	0.97 (0.60-1.55)	0.909	0.43 (0.25-0.72)	0.001
Age (> 60 years vs. ≤ 60 years)	1.26 (0.76-2.08)	0.367		
Sex (male vs. female)	1.44 (0.90-2.29)	0.123		
TNM stage				
I	Reference		Reference	
II	2.57 (1.40-4.71)	0.002	3.93 (2.06-7.49)	< 0.001
III	3.81 (2.06-7.07)	0.000	6.31 (3.23-12.35)	< 0.001
Lymph node status				
N0	Reference			
N1	0.93 (0.48-1.82)	0.854		
N2	1.82 (1.07-3.11)	0.027		
Histology (SCC vs. adenocarcinoma)	1.38 (0.84-2.27)	0.192		

HR: hazard ratio; and SCC: squamous cell carcinoma.

whereas, in the control group, it was 33.8 months (HR = 0.42; 95% CI: 0.21-0.85; p = 0.017). Five-year OS rates were 62.1% (95% CI: 42.5-76.7%) and 12.3% (95% CI: 0.8-39.4%) in the adjuvant chemotherapy and control groups, respectively. The Kaplan-Meier curves for RFS and OS in stage II NSCLC patients are shown in Figure 1.

Patients with stage III NSCLC who received adjuvant chemotherapy had longer RFS than did those in the control group, the absolute difference in the median RFS between the two groups being approximately 30 months (median RFS: 36.5 months vs. 6.9 months; HR = 0.32; 95% CI: 0.16-0.64; p < 0.001). There was a trend toward longer OS in the adjuvant chemotherapy group in comparison with the control group (median OS: 36.5 months vs. 20.5 months; HR = 0.48; 95% CI: 0.22-1.03; p = 0.060). Five-year OS rates were 37.9% (95% CI: 17.0-58.8%) and 31.8% (95% CI: 10.8-55.4%) in the adjuvant chemotherapy and control groups, respectively. Figure 2 presents the RFS and OS curves for patients with stage III NSCLC.

Patients who received adjuvant chemotherapy with cisplatin and vinorelbine were compared with controls, and RFS and OS were found to be similar between the two (Figures S1 and S2 in the supplementary material).

Safety

Because the cisplatin and vinorelbine regimen is considered an acceptable chemotherapy regimen and because it was used by most of the patients who received adjuvant chemotherapy in the present study, the safety profile of this regimen was evaluated. Moreover, previous randomized studies and clinical experience have suggested a high toxicity rate.[4-8]

Of the patients who received adjuvant chemotherapy with cisplatin and vinorelbine, 49 (89%) experienced grade 3-4 toxicities, hospitalization being required in 27 (49%). Sixteen patients (29%) had grade 3-4 febrile neutropenia. In addition, 5 patients (9%) died of treatment toxicity (grade 5 toxicity; Table 3).

Twenty-five patients discontinued the adjuvant cisplatin and vinorelbine regimen, treatment toxicity being the main reason for treatment discontinuation (in 68%). Table 4 summarizes the safety profile of adjuvant cisplatin and vinorelbine regimen in comparison with the safety results of the pivotal ANITA trial.[4]

DISCUSSION

Our findings reinforce the survival benefit of adjuvant chemotherapy in patients with NSCLC, both in terms of OS and RFS. A meaningful OS benefit was observed in patients with stage II or III NSCLC. The benefit of adjuvant chemotherapy in NSCLC patients has already been demonstrated in various randomized phase III trials.[4,6-8] In addition, a meta-analysis evaluating 5,584 patients of five clinical trials showed a 5.4% absolute OS gain with cisplatin-based chemotherapy. Among different chemotherapy regimens, cisplatin plus vinorelbine was marginally better than other drug combinations. Furthermore, the cisplatin-vinorelbine combination was the most commonly used regimen, being the largest (41%) and most homogenous study subgroup.[5] When this regimen was separately analyzed, a significant survival benefit was found (absolute benefit, 8.9% at five years; HR = 0.80; 95% CI: 0.70-0.91; p < 0.001).[9] However, among 6,430 patients of 16 clinical trials included in another meta-analysis,[10] which evaluated the role of adjuvant cisplatin-based chemotherapy in NSCLC patients, an increased risk of non-lung cancer-related deaths was observed in those receiving chemotherapy (relative risk = 1.3, p = 0.002).

More recently, Kenmotsu et al.[11] evaluated adjuvant cisplatin-pemetrexed vs. cisplatin-vinorelbine in the NSCLC setting, and, although the superiority of the pemetrexed-containing regimen over the vinorelbine-containing regimen was not demonstrated, both regimens had similar RFS and OS, pemetrexed showing better tolerability and less toxicity. Therefore, the benefits and risks associated with cisplatin-based adjuvant chemotherapy should be taken into account. Although predictive biomarkers of OS benefits from adjuvant treatments (chemotherapy and, possibly in the future, immunotherapy and targeted therapies)

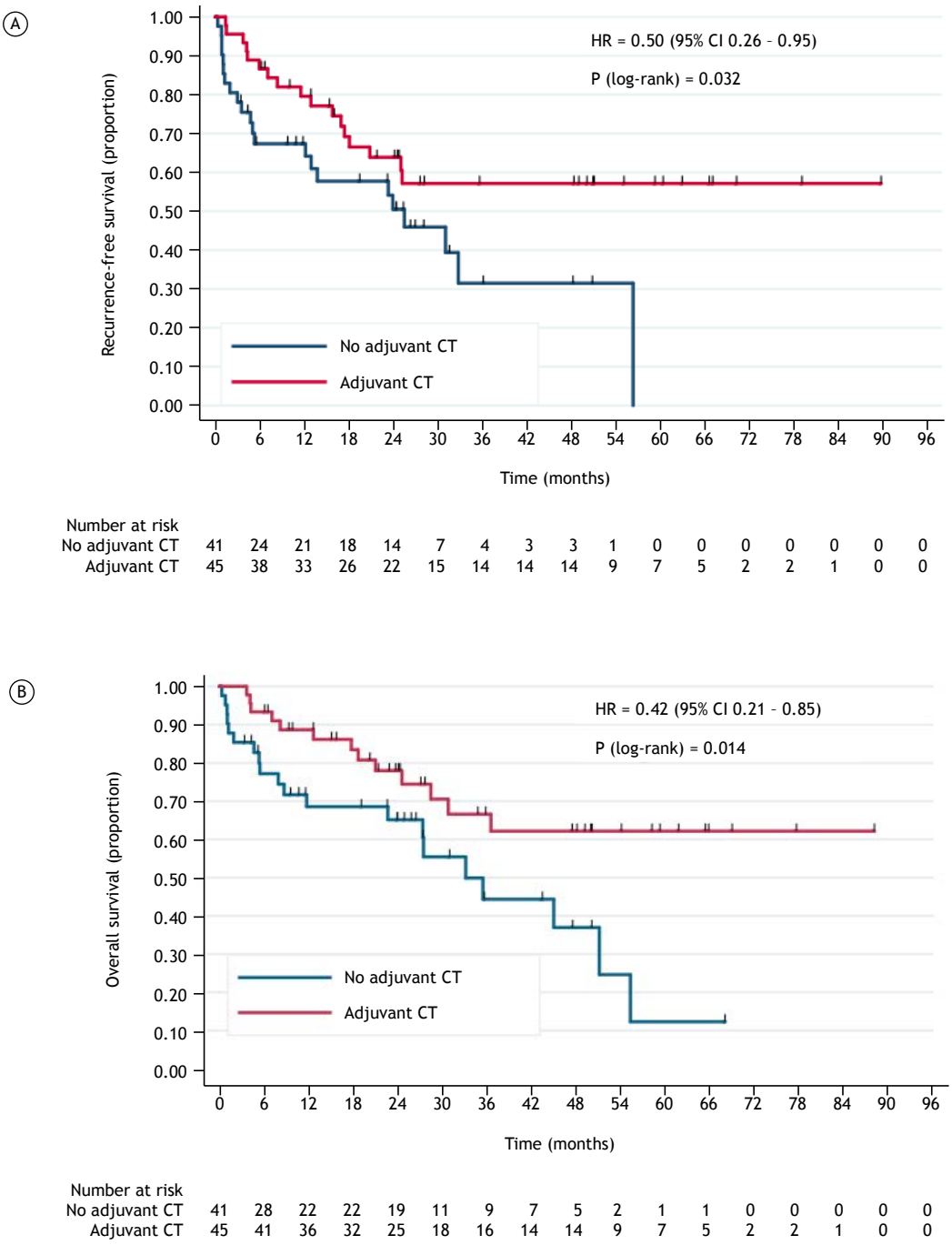

Figure 1. Recurrence-free survival (A) and overall survival (B) curves in patients with stage II non-small cell lung cancer, comparing those who received adjuvant chemotherapy with those who did not (controls). HR: hazard ratio; and CT: chemotherapy.

are of utmost importance for patient selection, they have yet to be identified and validated.

Notably, randomized phase III trials generally enroll a carefully selected population; only a small number of elderly patients are included, with few comorbidities and good performance status, and this does not represent a real-world setting. Therefore, studies addressing real-world evidence are required to evaluate the benefits and risks of the interventions used in clinical trials.[12]. Kolek et al.[13] reported better survival with adjuvant treatment in this setting, with the longest survival in the cisplatin-vinorelbine cohort. Morgensztern et al.[14] presented the results of 19,691 patients with NSCLC and showed a 4.2% treatment-related mortality rate in six months, reinforcing the importance of and need for real-world data.

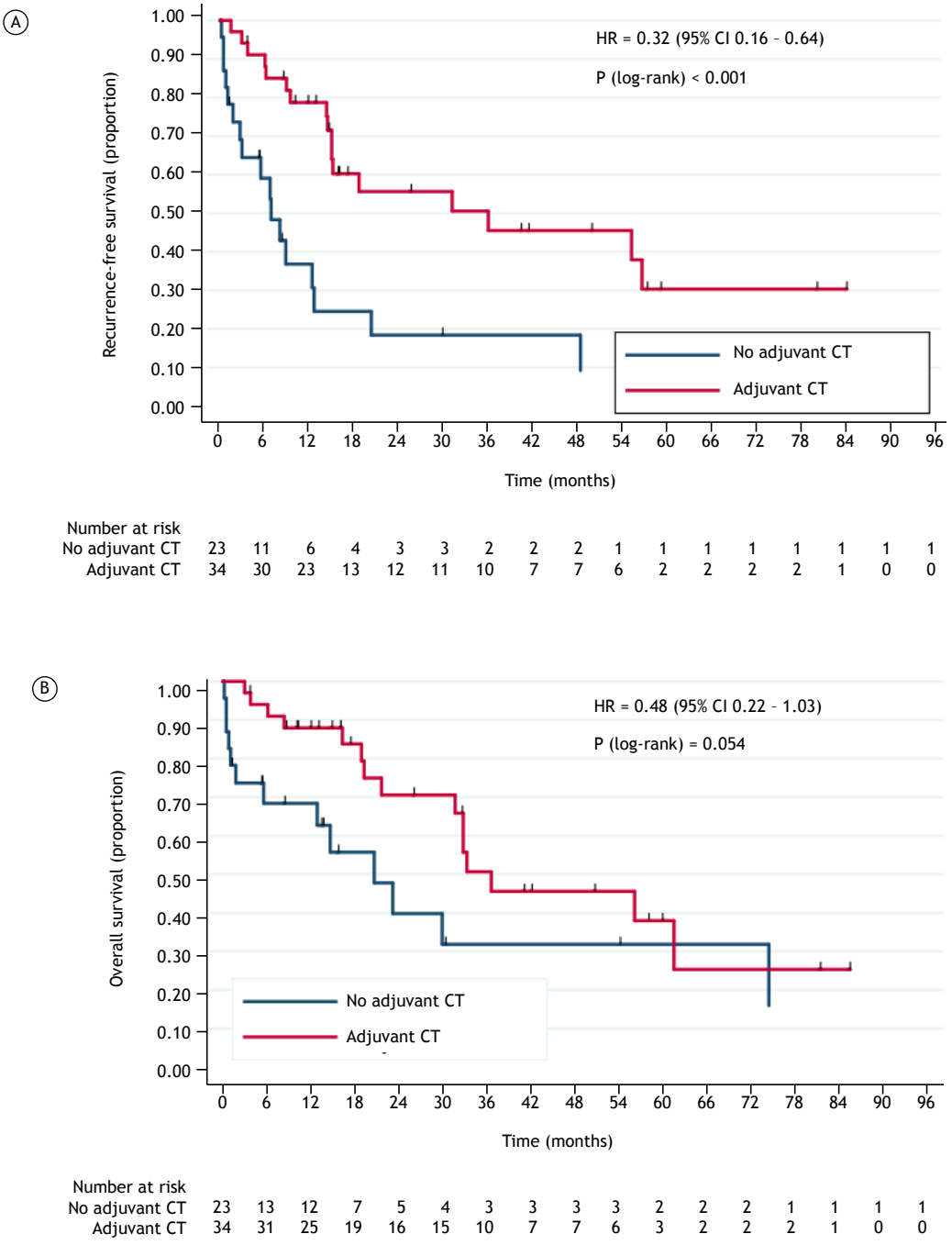

Figure 2. Recurrence-free survival (A) and overall survival (B) curves in patients with stage III non-small cell lung cancer, comparing those who received adjuvant chemotherapy with those who did not (controls). HR: hazard ratio; and CT: chemotherapy.

Another important issue to be discussed is that, although effectiveness was similar, the incidence of toxicity and hospital admissions was consistently higher in the patients treated with the cisplatin-vinorelbine combination. The outcomes in real-world studies should be carefully analyzed. In the ANITA trial,[4] 9% of the patients presented with grade 3-4 febrile neutropenia, and 2% died of treatment-related toxicity, in contrast to a 29% incidence of febrile neutropenia and a 9% mortality rate in our study, which were excessively high for an adjuvant treatment setting. Given that the aim of adjuvant treatment is to improve OS, the difference in the mortality rate between the two studies is noteworthy and potentially exceeds the OS benefit yielded by this treatment. It is of note that 60% of our patients had an ECOG performance

Table 3. Characteristics of the patients who died of adjuvant treatment toxicity.

Patient	Sex	Age, years	ECOG-PS	Staging	Chemotherapy regimen	Toxicity
1	Male	71	1	IIIA	cisplatin + vinorelbine	FN
2	Female	61	0	IIA	cisplatin + vinorelbine	FN + AKI
3	Male	70	1	IIIA	cisplatin + vinorelbine	FN + AKI
4	Male	72	1	IIB	cisplatin + vinorelbine	FN + AKI
5	Male	63	1	IIB	cisplatin + vinorelbine	FN + AKI

PS: performance status; FN: febrile neutropenia; and AKI: acute kidney injury.

Table 4. Safety profile of adjuvant chemotherapy with cisplatin and vinorelbine in patients with non-small cell lung cancer after surgery.

Profile	Present study	ANITA trial[a]
Grade 3-4 toxicity	89%	N/A
Grade 5 toxicity	9%	2%
Grade 3-4 febrile neutropenia	29%	9%
Toxicity as reason for chemotherapy discontinuation	68%	34%
Hospitalization due to toxicity	49%	N/A

[a]Results based on Douillard et al.[4] ANITA: Adjuvant Navelbine International Trialist Association.

status of 1, whereas, in the ANITA trial, 47% had an ECOG performance status of 1,[4] a difference that could explain the higher toxicity observed in our study.

Given the retrospective nature of the present study, selection bias cannot be ruled out. Chemotherapy was prescribed at the discretion of the physicians involved, and the patients who did not receive adjuvant chemotherapy after surgery could have had a worse prognosis a priori. Nevertheless, an indirect comparison reveals that chemotherapy-treated patients show median OS similar to that seen in historical controls.[4-8] Despite the retrospective design and the small sample size, which is prone to treatment bias, our analysis has important strengths. The median cumulative doses of cisplatin and vinorelbine in our study were very similar to those in the ANITA trial.[4] Moreover, our patients were treated at a large cancer center by skilled thoracic oncologists, following standard guidelines and tumor board discussion. These high standards were maintained in patient selection, with 90% of the patients receiving chemotherapy having an ECOG performance status of 0-1. In addition, real-world evidence can validate and extend the results of randomized prospective studies to determine whether they are generalizable. Even regulatory agencies, such as the U.S. Food and Drug Administration, are progressively becoming more interested in data based on real-world evidence.[15]

In conclusion, our study shows that adjuvant chemotherapy improves both OS and RFS in patients with NSCLC in a real-world setting. However, the cisplatin-vinorelbine regimen was not only associated with alarming rates of treatment-related grade 3-4 toxicity but also with a remarkably high risk of treatment-related deaths. Our results endorse the relevance of real-world data to current daily practices and public health policies in patients with NSCLC, especially for treatment with curative intent.

AUTHOR CONTRIBUTIONS

MFVN, RCB, GH, EZM, RC, LLL, TYT, RMT, FSRR, and GCJ: study design and research. MFVN, RCB, GH, EZM, RC, LLL, TYT, RMT, FSRR, and GCJ: data analysis. MFVN, RCB, GH, FSRR, and GCJ: drafting of the manuscript. MFVN, RCB, GH, EZM, RC, LLL, TYT, RMT, FSRR, and GCJ: critical revision of the manuscript for important intellectual content and approval of the final version.

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Peak inspiratory flow in children and adolescents with asthma using dry powder inhalers: a cross-sectional study

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Study carried out in the Serviço de Pneumologia Pediátrica, Instituto de Medicina Integral Prof. Fernando Figueira – IMIP – Recife (PE) Brasil.

ABSTRACT

Objective: To measure peak inspiratory flow (PIF) and assess dynamic lung function in children and adolescents with asthma, as well as to determine the association of PIF with dynamic lung function and clinical variables. **Methods:** This was a cross-sectional study of children and adolescents with asthma using dry powder inhalers (DPIs) regularly. The control group included sex-, age-, weight-, and height-matched individuals without lung disease. Socioeconomic and clinical variables were collected. PIF and dynamic lung function variables were obtained with a specific device. Between-group comparisons were made with the Student's t-test and ANOVA. Multiple linear regression analysis was performed, and Pearson's correlation coefficients were calculated to assess associations between PIF and the other variables. **Results:** A total of 88 individuals (44 asthma patients and 44 controls) participated in the study. PIF and respiratory muscle strength (S-index) values were lower in the asthma patients than in the controls. PIF correlated positively with age, weight, height, and S-index in the asthma group. After controlling for height, we found an increase of 0.05 units in PIF associated with an increase of 1 unit in the S-index in the asthma group. **Conclusions:** PIF appears to be lower in children and adolescents with asthma than in those without asthma, correlating positively with age, height, weight, and respiratory muscle strength.

Keywords: Dry powder inhalers; Asthma; Muscle strength; Child; Adolescent.

INTRODUCTION

The prevalence of asthma is high during childhood and adolescence; the disease results in a high number of emergency department visits and is associated with a significant economic burden related to hospitalizations for uncontrolled asthma.[1-3] Providing asthma education and reducing asthma triggers are essential to reduce the number of emergency department visits and the economic burden of asthma, as is the use of inhaled medications in some cases.[4]

Dry powder inhalers (DPIs) have been increasingly used to deliver inhaled medication, correct inhaler technique and inhalation flow being required for treatment success. In addition, inspiratory flow must be sufficient to overcome the internal resistance of the device and allow the delivery of the correct medication dose, so that the desired therapeutic effect is achieved.[5-7]

Studies have shown that peak inspiratory flow (PIF) varies widely across patients, especially in those with severe airflow obstruction (such as severe asthma patients), and depends on respiratory muscle strength.[8-10] Inspiratory flow decreases during acute exacerbations of asthma and increases during periods of disease remission.[11] There are difficulties in measuring PIF, and only a few centers routinely assess it. The In-Check DIAL (Clement Clarke International Ltd., Harlow, UK) is the only device that simulates the resistance characteristics of different DPIs; however, it is not currently available in all countries. Inhaler devices are often prescribed on the basis of intuition and common sense rather than careful evaluation.[12] Factors influencing drug deposition include inhaler technique, the shape of the inspiratory flow curve, and inspiratory volume.[11,12]

In 2010, the POWERbreathe® K5 (HaB International Ltd., Southam, UK) was launched, with software that allows analysis of lung function variables, including PIF. In addition to measuring PIF, the POWERbreathe® K5 assesses variables such as the S-index (dynamic muscle strength), inhaled air volume, and duration of inhalation, as well as allowing real-time graphical analysis of the inhalation pattern.[13-15] The POWERbreathe® K5 is currently the only device available in Brazil to assess the aforementioned variables.[13]

Given the large number of inhaler devices currently available, the differences among manufacturers regarding PIF rates, and the lack of validated guidelines for prescribing an inhaler device, the objective of the present study was to measure PIF and assess dynamic lung function in children and adolescents with asthma using DPIs, as well as to determine the association of PIF with dynamic lung function and clinical variables.

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METHODS

Study design

This was a cross-sectional analytical study conducted between March of 2018 and September of 2019 at the Pediatric Pulmonology Outpatient Clinic of the *Instituto de Medicina Integral Prof. Fernando Figueira* (IMIP, Professor Fernando Figueira Institute of Integrative Medicine), which is a tertiary referral hospital for pediatric respiratory diseases and which is located in the city of Recife, Brazil. The study was approved by the local research ethics committee (CAAE no. 84171618.3.0000.5201). Eligible individuals were directly invited to participate, and all participants gave written informed consent or assent, as applicable.

Study population

The study population consisted of 88 children/adolescents in the 6- to 18-year age bracket. Participants were divided into two groups: the asthma group (n = 44) and the control group (n = 44). The decision to include a control group was based on the lack of reference values for dynamic lung function in the literature. The eligibility criteria were as follows:

- asthma group—children/adolescents with a clinical diagnosis of asthma[4] followed at the IMIP Pediatric Pulmonology Outpatient Clinic and using DPIs regularly for at least three months. Those who were unable to understand or perform the required maneuvers were excluded, as were those with any chronic lung disease other than asthma.
- control group—children/adolescents without asthma or any other lung disease matched to those in the asthma group for sex, age, weight, and height. All of the individuals included in the control group were selected from among those enrolled in a public school in the city of Recife and were able to understand and perform the required maneuvers.

The sample size was calculated with the use of the free, Web-based, open-source program OpenEpi, version 3.01, differences in mean PIF between asthma patients and controls being taken into account. A sample size of 92 (46 per group) was calculated to be required for a significance level of 95% and a power of 80%.

Procedures

Weight and height were measured on the day of the evaluation and recorded on a data collection form, which included the Asthma Control Test, a five-item questionnaire for assessing asthma control (controlled, partly controlled, or uncontrolled).[16,17] The BMI was calculated with the use of the BVS online calculator for children, the percentiles being determined on the basis of the Centers for Disease Control and Prevention charts.[18] The total daily dose of inhaled corticosteroids (in µg) was classified as low, intermediate, or high on the basis of the GINA guidelines.[19]

The level of physical activity was assessed with an adapted version of the habitual level of physical activity (HLPA) score developed by Santuz et al.[20] The HLPA score used in the present study was as follows: 1, sedentary lifestyle; 2, regular physical activity (≤ 2 h/week); and 3, competitive physical activity or physical activity > 2 h/week.[20] With regard to environmental control, participants/legal guardians were asked about exposure to dust, mold, and pet dander, as well as active/passive exposure to cigarette smoke. Environmental control was considered inadequate if participants/legal guardians reported exposure to any of the aforementioned exposure items.

Participants were asked about the type of inhaler device used and were asked to demonstrate their inhaler technique using placebo devices. Patient inhaler technique was evaluated on the basis of the manufacturer instructions. Patients were instructed to inhale as usual, with or without the assistance of their companions, but without any input from the examiners. Inhaler technique was evaluated by two trained assessors, who evaluated dose preparation, exhalation (exhalation into the device constituting a technique error), inhalation (failure to inhale as rapidly and deeply as possible constituting a technique error), and inspiratory pause (failure to hold breath for 10 seconds constituting a technique error). There are differences across device types regarding dose preparation, which should follow the manufacturer instructions.[21]

PIF was measured with the POWERbreathe® K5, which is an electronic inspiratory loading device. The device includes the Breathe-Link live feedback software, which allows real-time graphical analysis of the breathing pattern.

PIF was measured with participants sitting in a chair with a backrest, wearing a nose clip, and facing a computer screen for visual feedback, which assisted in performing the inhalation maneuver. The assessor put the device mouthpiece in place and instructed participants to keep their lips sealed tightly around the mouthpiece in order to prevent leaks. Participants were then instructed to exhale to RV and then inhale as rapidly and deeply as possible. PIF rates were expressed in liters per second. Because PIF is a dynamic measure, participants performed 8-10 consecutive maneuvers. The highest PIF rate was selected for analysis, provided that the curve was reproducible and acceptable. For a reproducible curve, the three highest PIF rates must differ by no more than 20%. For an acceptable curve, all maneuvers must be performed with no leaks noted (graphical analysis) and the highest PIF rate must be achieved within the first few seconds, without evidence of decrease prior to the highest PIF rate achieved. All participants were able to perform the maneuver correctly, and no test was stopped because of respiratory distress or at the request of the participant.

In addition to PIF measurements, the following lung function variables were obtained: the S-index, which is a dynamic measure of inspiratory muscle strength (in cmH_2O); total V_T (in L); and time to PIF (in s).

Statistical analysis

Statistical analyses were performed with the Stata statistical software package, version 12.1 SE (StataCorp LP, College Station, TX, USA). Between-group comparisons were made with the Student's t-test and ANOVA. Potential confounders were controlled for in a multiple linear regression model, which included all of the variables that differed significantly between the groups in the univariate analysis. Pearson's correlation coefficient was used in order to estimate the strength of association between PIF and the other variables. The level of significance was set at 5%.

RESULTS

A total of 109 individuals were considered eligible for the study. The asthma group comprised 44 children and adolescents who had asthma and who were not experiencing an exacerbation, the mean age, weight, and height of the patients being 14.3 ± 3.5 years, 52.3 ± 13.0 kg, and 156.4 ± 12.2 cm, respectively. The control group comprised 44 children and adolescents who did not have asthma and who were matched to the asthma patients for sex, age, weight, and height, the mean age, weight, and height of the controls being 14.0 ± 3.46 years, 55.85 ± 12.92 kg, and 1.60 ± 0.11 cm, respectively. Therefore, a total of 88 individuals participated in the study (Figure 1). There were no differences between the groups regarding baseline characteristics. Table 1 shows the general characteristics of the patients with asthma.

Table 2 shows a comparison of mean lung function values between the asthma and control groups. There were significant differences between the groups regarding PIF and S-index values.

Table 3 shows the mean PIF rates in the asthma group, by clinical characteristics. A higher level of physical activity translated to a higher PIF rate in the asthma group. In addition, PIF correlated positively with age ($r = 0.56$, $p \leq 0.001$), weight ($r = 0.32$; $p = 0.032$), height ($r = 0.56$, $p \leq 0.001$), and the S-index ($r = 0.96$; $p \leq 0.001$) in the asthma group.

Table 4 shows that height and the S-index correlated positively with PIF, a higher height and a higher S-index translating to a higher PIF rate. The adjusted multiple regression model showed an adjusted r^2 of 93.4% ($F\ [2.40] = 325.64$; $p < 0.001$). After controlling

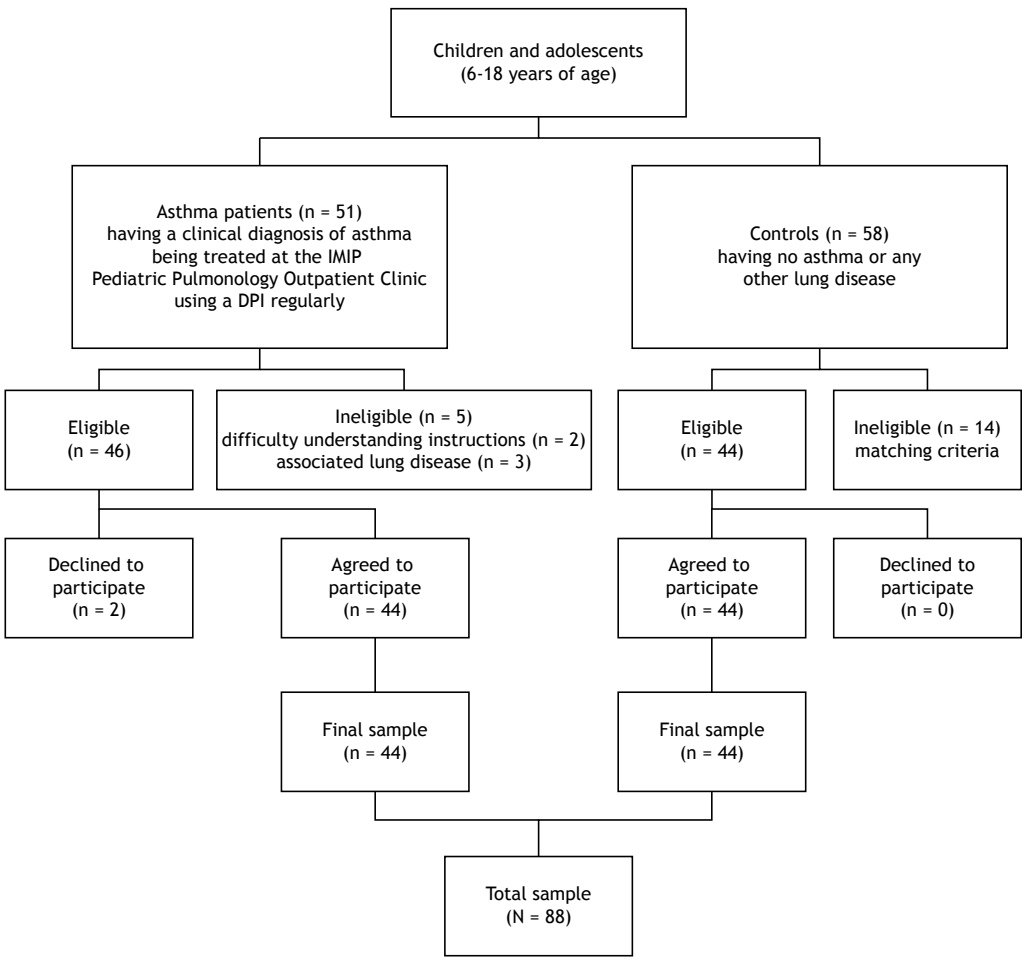

Figure 1. Flow chart of the patient selection process. IMIP: *Instituto de Medicina Integral Prof. Fernando Figueira* (Professor Fernando Figueira Institute of Integrative Medicine); and DPI: dry powder inhaler.

for height, we found an increase of 0.05 units in PIF (in L/s) associated with an increase of 1 unit in the S-index; likewise, after controlling for the S-index, we found an increase of 0.012 units in PIF (in L/s) associated with an increase of 1 cm in height in the asthma group (Table 4).

DISCUSSION

The present study is the first to analyze PIF and dynamic lung function variables in children and adolescents with asthma using an electronic inspiratory loading device, demonstrating that PIF is lower in asthma patients than in controls.

It is known that factors related to patient experience with the inhalation maneuver are related to changes attributable to a learning effect.[21,22] Nevertheless, PIF values were significantly lower in the children and adolescents with asthma, who had to perform the inhalation maneuver on a daily basis, than in the healthy controls, who had never had to perform such a maneuver. This can be explained by the pathophysiology of asthma, which is associated with airway obstruction (particularly small airway obstruction), airway remodeling, or a combination of the two. There is an increase in the negative intrathoracic pressure needed to overcome inhaler device resistance, resulting in narrowing of the airway lumen and decreased inspiratory flow.[23-25] A lower PIF rate in asthma patients might also be related to flattening of the diaphragm from hyperinflation secondary to airway obstruction.[26]

In the present study, children and adolescents with asthma achieved a mean PIF of 4.34 L/s, which is equivalent to 260.4 L/min and higher than the reported rate for children and adolescents with asthma (a mean PIF of ~ 91.1 L/min).[11] This difference can be attributed to the different internal resistances used during the tests. In the aforementioned study,[11] PIF was measured by simulating the internal resistance of the Accuhaler (GlaxoSmithKline, Bretford, UK), which is a medium-resistance inhaler device, whereas, in our study, PIF was measured against a standardized resistance of 3 cmH_2O, which is the minimum resistance imposed by the POWERbreathe® K5, being required in order to actuate the loading valve. In addition, as is well established in the literature, a higher internal resistance translates to a lower PIF rate.[27] The mean PIF rate achieved in the present study (260.4 L/s) is similar to that reported by Kamps et al. (i.e., 186.8 L/s),[8] who measured PIF without simulating the internal resistance of inhaler devices. Our finding of a higher PIF rate might be due to the fact that the mean height was higher in our study population. Kamps et al.[8] found a positive correlation between height and PIF, as we did in our study.

In our study, each participant performed 10 maneuvers for PIF measurement, the highest PIF rate being selected for analysis. This is in contrast with other studies, in which participants perform 1-3 maneuvers. Our decision to have participants perform up to 10 maneuvers was based on a study by Silva et al.[15] and was made in order not to underestimate PIF, given that most of the participants in the study[15] achieved the highest PIF rate in the eighth maneuver, because of the learning effect.

Studies have shown that PIF is reduced during acute exacerbations of asthma; however, we found

Table 1. Biological and clinical characteristics of the patients with asthma (n = 44), as well as level of environmental control and type of inhaler device.

Socioeconomic variable	n	%
Male sex	24	54.5
BMI		
Underweight	4	9.1
Normal weight	24	54.5
Overweight	9	20.4
Obese	7	16
Environmental control		
Adequate	10	22.73
Inadequate	34	77.27
Level of physical activity (HLPA score)		
Sedentary lifestyle	13	30.2
Regular physical activity (≤ 2 h/	16	37.2
week)	15	32.6
Physical activity > 2 h/week		
Type of inhaler device		
Aerolizer	19	43.18
Aerocaps	17	38.64
Turbohaler	2	4.54
CDM Haler	3	6.82
Diskus	3	6.82
Daily inhaled corticosteroid dose		
Low	22	50
Intermediate	14	31.8
High	8	18.2
Inhaler technique		
Correct	25	56.8
Incorrect	19	43.2
Asthma control (ACT)		
Controlled asthma	27	61.36
Partly controlled asthma	11	25
Uncontrolled asthma	6	13.64

HLPA: habitual level of physical activity; and ACT: Asthma Control Test.

Table 2. Comparison of mean lung function values between the asthma and control groups.[a]

Variable	Group		p*
	Asthma (n = 44)	Control (n = 44)	
PIF, L/s	4.34 ± 0.87	4.86 ± 1.33	0.03
Volume, L	1.72 ± 0.65	1.78 ± 0.78	0.70
S-index	78.27 ± 15.21	87.10 ± 23.32	0.04
Time to PIF, s	0.20 ± 0.09	0.18 ± 0.11	0.85

PIF: peak inspiratory flow. [a]Values expressed as mean ± SD. *Student's t-test.

Table 3. Mean peak inspiratory flow rates in the asthma group, by clinical characteristics.[a]

	Variable				p*
PIF, L/s	BMI				
	Underweight	Normal weight	Overweight	Obese	
	4 (4.4 ± 1.2)	24 (4.6 ± 0.8)	9 (4.2 ± 1.0)	7 (3.8 ± 0.6)	0.165
	Level of physical activity (HLPA score)				
	Sedentary lifestyle	Regular physical activity (≤ 2 h/week)	Physical activity > 2 h/week		
	14 (4.2 ± 0.6)	16 (4.0 ± 0.7)	14 (4.8 ± 1.1)		0.045
	Asthma control (ACT)				
	Controlled asthma	Partly controlled asthma	Uncontrolled asthma		
	27 (4.5 ± 0.9)	11 (4.3 ± 0.7)	6 (3.6 ± 0.6)		0.060
	Sex				
	Female	Male			
	24 (4.28 ± 0.61)	20 (4.42 ± 1.12)			0.60
	Daily inhaled corticosteroid dose				
	Low	Intermediate	High		
	22 (4.46 ± 0.87)	14 (4.46 ± 0.85)	8 (4.44 ± 0.89)		0.74
	Inhaler technique				
	Correct	Incorrect			
	25 (4.30 ± 0.93)	19 (4.40 ± 0.81)			0.70

PIF: peak inspiratory flow; HLPA: habitual level of physical activity; and ACT: Asthma Control Test. [a]Values expressed as n of participants and (mean ± SD) PIF. *ANOVA.

Table 4. Descriptive statistics, correlation coefficients, and multiple regression coefficients for the peak inspiratory flow rates and explanatory variables (height and S-index) in the asthma group.[a]

Variable	n	Mean	SD	r*	Regression coefficient (95% CI)	p**
PIF, L/s	44	4.3	0.9	-	-	-
Height, cm	44	156.4	12.2	0.56	0.012 (0.006-0.019)	< 0.001
S-index	44	51.9	15.2	0.96	0.05 (0.05-0.06)	< 0.001

PIF: peak inspiratory flow. [a]The initial explanatory variables were those showing a $p < 0.20$ in Tables 2 and 3 (age, height, weight, S-index, BMI, level of physical activity, and level of asthma control). Multiple regression constant = −0.19. *Pearson's correlation coefficient. **Student's t-test.

no correlation between PIF and the level of asthma control, with most of the asthma patients in our study being classified as having controlled asthma.[8,28]

We found a difference between the asthma and control groups regarding the relationship between PIF and the level of physical activity. This can be explained by the fact that respiratory muscle strength is decreased in children with asthma, and decreased respiratory muscle strength can lead to a decrease in PIF not only by obstructing airflow but also by reducing the number of diaphragm muscle fibers. Aerobic activity is known to improve asthma, whereas a sedentary lifestyle can worsen it; this is consistent with our finding that a higher level of physical activity translates to a higher PIF rate.[29]

In the present study, age correlated positively with PIF in children and adolescents; this might be due to a better understanding and execution of the inhaler technique, resulting in higher PIF values, or to the process of muscle growth and development.[8,30] In adults, age correlates negatively with PIF, the aging process leading to loss of muscle strength and mass and resulting in lower PIF values.[31-33]

In the present study, V_T and time to PIF were similar between the asthma and control groups. In a study by Seheult et al.,[31] mean V_T was slightly lower than in the present study (1.1 L vs. 1.72 L). In a study of children trained in using DPIs, time to PIF was found to change as resistance changed.[34] Mean time to PIF was found to be 0.16 s when high-resistance devices were used and 0.19 s when low-resistance devices were used.[34] These findings are consistent with those of the present study, in which time to PIF was approximately 0.20 s.

S-index values were significantly different between the asthma patients and controls in the present study. The diaphragm is the major inspiratory muscle, and the fact that it is at a biomechanical disadvantage in patients with asthma might be a factor contributing to lower S-index values in this population. In addition, the S-index correlated positively with PIF, a finding that is consistent with those of Kamps et al.,[8] who found a positive correlation between PIF and MIP in children with asthma using DPIs. Like the S-index, MIP is a measure of inspiratory muscle strength. Therefore, the S-index is a dynamic lung function measure that can indicate reduced PIF.

Although Kamps et al.[8] showed a correlation between PIF and a static measure of respiratory muscle strength, no studies have shown a correlation between

PIF and a dynamic measure of lung function (the S-index). Given that this is the first study to show a correlation between PIF and S-index values in children and adolescents with and without asthma, there are currently no reference values for this population. We found mean S-index values of 87.10 cmH_2O and 78.27 cmH_2O for controls and asthma patients, respectively. Although the mean S-index was higher in a study by Silva et al. (i.e., 102 cmH_2O),[15] the study population consisted of healthy adults.

One of the limitations of the present study is that the device used in order to measure PIF does not simulate the internal resistance of the inhaler devices used in clinical practice. Another limitation is that symptoms of upper airway involvement were not evaluated, and they could have an impact on pulmonary function.

In summary, PIF measurement proved to be a practical method that provides important additional information on which to base prescription decisions regarding the use of DPIs. Despite the positive outcomes of inhalation therapy, it should be prescribed on a case-by-case basis after careful patient evaluation. PIF appears to be lower in children and adolescents with asthma using DPIs than in controls without lung disease. Age, weight, height, and respiratory muscle strength appear to correlate positively with PIF.

DPIs should be prescribed on a case-by-case basis after careful patient evaluation, with anthropometric characteristics and lung function variables being taken into account. Patients should be instructed on how to perform the inhalation maneuver correctly and should be encouraged to participate in supervised physical activity or in a pulmonary rehabilitation program.

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AUTHOR CONTRIBUTIONS

CPS: first author; study design and planning; drafting and revision of the manuscript. JSAC, MCAB, and PGMB: research; study design and planning. LBA: study design and planning; final approval of the manuscript.

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Ventilator-associated pneumonia in patients on prolonged mechanical ventilation: description, risk factors for mortality, and performance of the SOFA score

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ABSTRACT

Objective: Ventilator-associated pneumonia (VAP) is a serious complication of mechanical ventilation (MV). However, data on VAP in patients on prolonged MV (PMV) are scarce. We aimed to describe the characteristics of VAP patients on PMV and to identify factors associated with mortality. **Methods:** This was a retrospective cohort study including VAP patients on PMV. We recorded baseline characteristics, as well as 30-day and 90-day mortality rates. Variables associated with mortality were determined by Kaplan-Meier survival analysis and Cox regression model. **Results:** We identified 80 episodes of VAP in 62 subjects on PMV. The medians for age, Charlson Comorbidity Index, SOFA score, and days on MV were, respectively, 69.5 years, 5, 4, and 56 days. Episodes of VAP occurred between days 21 and 50 of MV in 28 patients (45.2%) and, by day 90 of MV, in 48 patients (77.4%). The 30-day and 90-day mortality rates were 30.0% and 63.7%, respectively. There were associations of 30-day mortality with the SOFA score (hazard ratio [HR] = 1.30; 95% CI: 1.12-1.52; $p < 0.001$) and use of vasoactive agents (HR = 4.0; 95% CI: 1.2-12.9; $p = 0.02$), whereas 90-day mortality was associated with age (HR = 1.03; 95% CI: 1.00-1.05; $p = 0.003$), SOFA score (HR = 1.20; 95% CI: 1.07-1.34; $p = 0.001$), use of vasoactive agents (HR = 4.07; 95% CI: 1.93-8.55; $p < 0.001$), and COPD (HR = 3.35; 95% CI: 1.71-6.60; $p < 0.001$). **Conclusions:** Mortality rates in VAP patients on PMV are considerably high. The onset of VAP can occur various days after MV initiation. The SOFA score is useful for predicting fatal outcomes. The factors associated with mortality could help guide therapeutic decisions and determine prognosis.

Keywords: Pneumonia, ventilator-associated; Critical care; Ventilators, mechanical.

INTRODUCTION

In recent years, progress in medical care has led to a decrease in in-hospital mortality of critically ill patients.[1,2] The increase in survival in the acute stage of a critical illness has caused a progressive increase in the population of subjects with chronic critical illness (CCI). The prevalence of CCI is 7.6% of the number of admissions to ICUs in the United States[3] and can be as high as 33% in patients presenting with acute respiratory failure.[4] Although the definition of CCI is heterogeneous, the need for prolonged mechanical ventilation (PMV) is the most important feature to define it.[5,6] One of the latest and most widely used definitions of CCI describes it as the length of ICU stay of 8 or more days, associated with at least one of the following conditions: mechanical ventilation (MV) for 96 h or more, tracheostomy, sepsis, severe wounds, and multiple organ failure.[7] The definition of PMV also varies among authors, although the most widely used one is the need for MV for 21 days or more, at least for 6 h/day.[8,9] Using this definition, the incidence of PMV in patients on MV admitted to an ICU ranges from 6.3% to 9.9%.[10,11]

Infections in patients on PMV are one of the most common complications. In a multicenter study that included 1,419 patients on PMV, the top six complications recorded over a 1-year period were infections, the most frequent of which were urinary tract infection and ventilator-associated pneumonia (VAP), in 34.5% and 31.0% of the patients, respectively.[12] The high risk of infections is due to multiple factors: prolonged use of invasive elements (tracheostomy tube, catheters, etc.), prolonged exposure to environments contaminated with virulent and resistant microorganisms, and immunological alterations due to comorbidities and the recent critical illness of the patient.[13]

VAP is one of the most common hospital-acquired infections. Roughly, 10% of patients requiring MV develop VAP, with a mortality rate of 20-50%.[14,15] It is known that the clinical presentation and management of VAP differ in patients on PMV.[16] The risk of VAP in patients on PMV is lower than that in those who are in the acute stage of MV, but it increases by 1-3% the duration of MV per day, suggesting that between 50% and 66% of tracheostomized patients will develop VAP.[17] The impact

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of respiratory infections on patients on PMV is relevant and has been linked to increased mortality.[18] However, data on VAP in patients on PMV are scarce. Not only do most of the studies about VAP include patients on acute MV, but differences in the definitions of PMV and CCI have revealed that the knowledge on the subject is sparse and almost incomparable.

The SOFA score is a widely used tool for predicting mortality in septic ICU patients.[19] However, its utility in subjects with CCI has yet to be well established.

The objective of the present study was to describe the characteristics of VAP patients on PMV, to determine factors that are associated with 30-day and 90-day mortality, and to evaluate the performance of the SOFA score as a predictor of mortality in this population.

METHODS

Study design

We conducted a retrospective cohort study involving patients on PMV and diagnosed with VAP who were admitted to the Chronic Critical Patients Unit (CCPU) at the *Sanatorio Güemes*, located in the city of Buenos Aires, Argentina, between June of 2015 and October of 2019. Our institution is a 680-bed university-affiliated acute-care general hospital. The CCPU is a 24-bed unit developed for the treatment and rehabilitation of patients with CCI. Patients admitted to the CCPU are mainly referred from ICUs and stroke units. The overall mortality rate in the CCPU is 44.8%, and 179 patients are admitted per year on average. VAP prevention bundles include elevation of head of bed to 30-45 degrees, daily spontaneous breathing trials, oral decontamination, and endotracheal tube cuff pressure monitoring. We used the hospital-acquired infection surveillance registry to identify consecutive patients with a diagnosis of VAP who were admitted to the CCPU. Using electronic medical records, subjects with VAP who were on PMV were selected. The following baseline variables were collected: reason for admission to the institution, demographic data, comorbidities, and age-adjusted Charlson comorbidity index. Variables collected at diagnosis of VAP were number of days on MV, SOFA score, need for vasoactive agents, and PaO_2/FiO_2. Data for the 90-day follow-up period after the diagnosis of VAP were also collected, including microbiological isolate results, adequacy of empirical antibiotic treatment, 30-day mortality, and 90-day mortality. We used these variables to search for factors associated with 30-day and 90-day mortality. Given the retrospective nature of the study, no written informed consent was required. The study was approved by the institutional research department. All data were kept confidential, and the study was carried out in accordance with the Declaration of Helsinki.

Study population and definitions

Patients ≥ 18 years of age who were on PMV and had been in the CCPU for at least 48 h prior to the onset of VAP were included in the study, regardless of having had previous episodes of VAP. Subjects who developed VAP in other units or within 48 h after admission to the CCPU were excluded. In patients with more than one episode of VAP, a new episode was defined as the development of new clinical, radiological, and bacteriological findings after completion of the antibiotic treatment of the previous episode. In accordance with the National Association for Medical Direction of Respiratory Care, we defined PMV as MV for ≥ 21 days for at least 6 h/day.[9] We used the definition of the National Hospital Infection Surveillance Program of Argentina (*Programa de Vigilancia de Infecciones Hospitalarias de Argentina*), which defines VAP on the basis of clinical and radiological criteria[20]: presence of at least one of the major criteria (temperature > 38°C, and white blood cell count > 12,000 cells/mm^3 or < 4,000 cell/mm^3) and at least one of the three minor criteria (purulent sputum, decreased PaO_2/FiO_2, and new or persistent infiltrates on at least two chest X-rays). Microbiological diagnosis of VAP was confirmed by blood cultures (detection of growth of microorganisms, with no other obvious cause); by quantitative cultures of BAL fluid samples (≥ 10^4 CFU/mL); or by quantitative cultures of endotracheal aspirate samples (≥ 10^5 CFU/mL).[20]

Organ function was assessed using the SOFA score,[21] calculated within the first 24 h after the diagnosis of VAP. Comorbidities were assessed by age-adjusted Charlson comorbidity index.[22] We defined VAP-related use of vasoactive drugs as the prescription of noradrenaline or dopamine at any time from the day of the diagnosis of VAP to the end of antibiotic treatment. The PaO_2/FiO_2 ratio recorded was the one obtained at the time closest to the onset of VAP. Microbiological cultures were ordered by attending physicians in accordance with institutional protocols and incubated in standard media. We performed quantitative cultures of the isolates in respiratory samples. Bacterial identification was carried out using conventional biochemical tests and an automated microbiology system (BD Phoenix; Becton Dickinson, Sparks, MD, USA). Antimicrobial susceptibility was determined by disk diffusion, and colistin susceptibility was determined by the automated system (BD Phoenix), in accordance with the Clinical and Laboratory Standards Institute recommendations.[23]

Statistical analysis

Statistical analyses were performed with R Studio, version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as means and standard deviations or medians and interquartile ranges, according to their distribution. Qualitative variables are shown as absolute and relative frequencies. We carried out univariate and multivariate analyses to identify factors associated with mortality. Qualitative variables were compared using the chi-square test or the Fisher's exact test, whereas continuous variables with parametric and nonparametric distribution were compared using

the Student's t-test and the Mann-Whitney U test, respectively. Cox regression models were used in order to find predictors of 30-day and 90-day mortality. All of the variables showing $p < 0.25$ in the univariate analysis were included in the multivariate model. Nested models were selected using Akaike information criterion. Kaplan-Meier curves and log-rank tests were performed for variables associated with 90-day mortality. Hazard ratios and 95% CIs were used in order to identify variables associated with 30-day and 90-day mortality. All tests were two-sided, and statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics

During the study period, 80 episodes of VAP were identified in 62 patients on PMV, 13 of whom had more than 1 episode of VAP (2 episodes in 9 patients, 3 episodes in 3 patients, and 4 episodes in 1 patient). The characteristics of the patients and clinical presentation of VAP are shown in Table 1. There was a slight predominance in males, and 40 episodes (50%) occurred in patients aged > 70 years. The major reasons for hospital admission were community-acquired pneumonia, in 20 patients (25.0%); stroke, in 19 (23.7%); infections other than VAP, in 7 (8.7%); traumatic brain injury, in 7 (8.7%); and congestive heart failure, in 5 (6.2%).

Regarding MV, all of the patients were submitted to tracheostomy, and the median number of days on MV from the onset of VAP was 56 (range, 21-564 days). Pathogens were identified in 65 of the 80 episodes (81.2%), *Pseudomonas aeruginosa* accounting for almost half of the microbiological isolates, whereas no *Staphylococcus aureus* was isolated. There was only 1 episode in which two different isolates were identified (*P. aeruginosa* and *Providencia stuartii*). Antibiotic resistance patterns are shown in Table 2. The most commonly used empirical antibiotic treatment regimens used were meropenem+colistin; meropenem+colistin+vancomycin; and piperacillin/tazobactam+colistin, in 23 (29%), 22 (27%), and 13 (16%) of the overall number of VAP episodes, respectively. Beta-lactam antibiotics were prescribed as definite therapy in 65 (81%) of the episodes (combined with other antibiotics in 28), as were colistin as monotherapy in 11 and aerosolized colistin+parenteral antibiotics in 7 (all cases of *P. aeruginosa* infection).

All but 1 patient completed 30-day follow-up in the unit. That patient was referred to a long-term acute care hospital (LTACH) once the antibiotic treatment was completed. The 30-day and 90-day mortality rates after the diagnosis of VAP were 30.0% and 63.7%, respectively.

Time of onset of VAP

Figure 1 shows the frequency of VAP episodes in relation to duration of MV in days. Between days 21 and 50 of MV, 36 of the 80 episodes of VAP (45.0%) occurred. By day 90, there had already been 62 episodes of VAP (77.5%).

Factors associated with 30-day and 90-day mortality rates

The Cox regression model showed that the SOFA score and use of vasoactive agents were associated with 30-day mortality, whereas age, SOFA score, use of vasoactive agents, and COPD were associated with 90-day mortality (Table 3). In a post-hoc analysis, we explored the interaction between $PaO_2/FiO_2 < 200$ and SOFA score and between $PaO_2/FiO_2 < 200$ and use of vasoactive agents by adding an interaction term to the model. None of the interactions were significant ($p = 0.15$ and $p = 0.09$, respectively). Figure 2 shows Kaplan-Meier curves for the variables associated with 90-day mortality. Among the patients who received vasoactive agents, 22 (68%) had a SOFA score > 5, and 10 (32%) had a SOFA score ≤ 5 ($p < 0.001$).

DISCUSSION

We performed a retrospective analysis of VAP patients on PMV. We found that age, SOFA score, use of vasoactive agents, and COPD were associated with increased mortality. To our knowledge, this is the study with one of the largest cohorts of VAP patients on PMV and the first one to address predictors of mortality. The lack of information on this topic could be partly due to the variety of terms that have been coined to study this population and the different ways in which such terms have been defined over time. We decided to use PMV to include subjects with VAP, because, in a retrospective study, it is easier to identify patients by the length of MV, in accordance with the definition of the National Association for Medical Direction of Respiratory Care.[9] However, using the definition of the Chronically Critically Ill Population Payment Recommendations,[7] all of our patients could be considered patients with CCI.

In our cohort, we found an elderly population with a significant burden of comorbidities, mainly due to neurological impairment. This is in line with a study on VAP in an LTACH.[24] In that study, 19 patients had 23 episodes of VAP, 69% of whom required MV due to a neurological cause. Neurological impairment probably explains the difficulty in weaning from MV and the need for PMV.

Regarding microbiological isolates, all of the episodes of VAP in our study were caused by gram-negative bacilli, almost half of them being *P. aeruginosa*, corroborating one study involving subjects with VAP in an LTACH,[24] reports of the U.S. National Healthcare System Network,[25] and a study on VAP in tracheostomized patients.[26] *P. aeruginosa* is one of the leading causes of VAP worldwide.[27,28] Prior *P. aeruginosa* colonization of the airway is a crucial factor for developing VAP.[29] It is possible that patients on PMV and submitted to tracheostomy have higher rates of colonization,

Table 1. Patient characteristics.[a]

Characteristic	All patients (N = 80)	Group					
		30-day survivor (n = 56)	30-day nonsurvivor (n = 24)	p	90-day survivor (n = 29)	90-day nonsurvivor (n = 51)	p
Male	52 (65)	37 (66)	15 (62)	0.95	20 (69)	32 (61)	0.75
Age	69.5 [58-80]	65.0 [56.5-80.0]	71.5 [65.0-80.5]	0.11	61 [38-80]	71 [63-80]	0.01
Cause of admission							
Medical	60 (75)	41 (73)	19 (79)	0.4	25 (86)	35 (68)	0.11
Surgical	11 (14)	7 (13)	4 (17)		1 (3)	10 (20)	
Trauma	9 (11)	8 (14)	1 (4)		3 (10)	6 (12)	
Charlson comorbidity index	5 [2-6]	4.0 [2.0-6.0]	5.5 [4.5-6.0]	0.041	4 [2-5]	5 [3-6]	0.054
Comorbidities							
Critical illness polyneuropathy	73 (91)	52 (93)	21 (87)	0.42	28 (97)	45 (88)	0.41
Neurological injury	52 (65)	38 (68)	14 (58)	0.57	24 (83)	28 (55)	0.02
Focal neurological deficit	30 (37)	23 (41)	7 (29)	0.45	16 (55)	14 (27)	0.02
Persistent vegetative state	11 (14)	6 (11)	5 (21)	0.39	5 (17)	6 (12)	0.51
Altered sensorium	10 (12)	6 (11)	4 (17)	0.71	2 (7)	8 (16)	0.31
COPD	24 (30)	13 (23)	11 (46)	0.079	2 (7)	22 (43)	< 0.001
Congestive heart failure	14 (17)	8 (14)	6 (25)	0.4	4 (14)	10 (20)	0.72
Diabetes mellitus	13 (16)	7 (12)	6 (25)	0.29	3 (10)	10 (20)	0.36
Malignant disease	10 (12)	9 (16)	1 (4)	0.27	5 (17)	5 (10)	0.48
Chronic renal failure	8 (10)	5 (9)	3 (12)	0.93	3 (10)	5 (10)	1
Obesity	7 (9)	2 (4)	5 (21)	0.024	1 (3)	6 (12)	0.25
Immunosuppression	4 (5)	3 (5)	1 (4)	1	0 (0)	4 (8)	0.29
Days on MV from the onset of VAP	56.0 [40.0-88.0]	54.0 [40.5-88.5]	58.5 [42.5-94.0]	0.49	64 [45-93]	49 [35-81]	0.23
Days of hospital stay from the onset of VAP	62.5 [43-97]	62.5 [43.0-96.0]	66.5 [46.5-102.0]	0.4	63 [43-103]	62 [43-94]	0.59
SOFA score	4 [3-7]	4 [3-5]	8 [4-10]	< 0.001	4 [3-5]	4 [3-8]	0.21
Patients with a SOFA score > 5	27 (34)	11 (20)	16 (67)	< 0.001	7 (24)	20 (39)	0.26
Vasoactive agents during the episode	32 (40)	15 (27)	17 (71)	< 0.001	8 (28)	24 (47)	0.14
PaO_2/FiO_2	242 [187-323]	270 [200-340]	200 [157-246]	0.004	310 [194-354]	223 [187-270]	0.01
Patients with PaO_2/FiO_2 < 200[b]	20 (31)	10 (23)	10 (48)	0.08	5 (24)	15 (34)	0.58
GCS score	9 [7-10]	9.0 [7.5-10.0]	9.0 [6.0-10.5]	0.55	9 [8-10]	9 [6-11]	0.93
Patients with GCS score ≤ 5	12 (15)	6 (10)	6 (25)	0.19	2 (7)	10 (20)	0.19
Sedative therapy	18 (22)	7 (12)	11 (46)	0.002	3 (10)	15 (29)	0.09
Microbiological isolates							
P. aeruginosa	38 (47)	29 (52)	9 (37)	0.35	13 (45)	25 (49)	0.89
Enterobacteriaceae	20 (25)	14 (25)	6 (25)	1	9 (31)	11 (22)	0.50
ABC	6 (7)	2 (4)	4 (17)	0.062	1 (3)	5 (10)	0.41
Other	1 (1)	0 (0)	1 (4)	1	0 (0)	1 (2)	1
Negative culture	15 (18)	11 (20)	4 (17)	7 (24)	8 (16)	7 (14)	0.53
Inadequate empirical antibiotic therapy[c]	6 (9)	5 (11)	1 (5)	0.7	2 (9)	4 (9)	1

MV: mechanical ventilation; VAP: ventilator-associated pneumonia; GCS: Glasgow Coma Scale; and ABC: *Acinetobacter calcoaceticus-baumannii* complex. [a]Values expressed in n (%) or median [IQR]. [b]n = 62. [c]Evaluated in subjects with identified isolates (n = 65).

Table 2. Antibiotic resistance patterns of the pathogens isolated.[a]

Pathogen	SAM	3GCs	FEP	CIP	TMP/SMX	TZP	IPM	MEM	AMK	CST	TGC
P. aeruginosa	100	46	46	59	100	51	57	59	35	0	100
Enterobacteriaceae	86	38	33	76	71	33	24	24	5	76	72
ABC	100	100	100	100	100	100	100	100	33	0	17

SAM: ampicillin/sulbactam; 3GCs: third generation cephalosporins; FEP: cefepime; CIP: ciprofloxacin; TMP/SMX: trimethoprim/sulfamethoxazole; TZP: piperacillin/tazobactam; IPM: imipenem; MEM: meropenem; AMK: amikacin; CST: colistin; TGC: tigecycline; and ABC: *Acinetobacter calcoaceticus-baumannii* complex. [a]Values expressed in %.

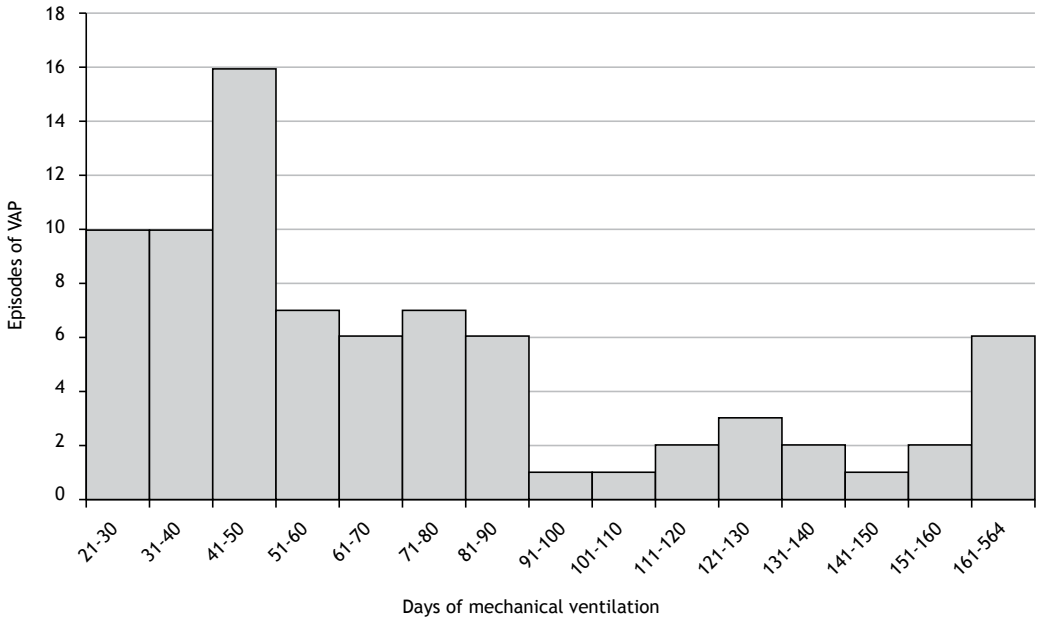

Figure 1. Number of episodes of ventilator-associated pneumonia (VAP) per days of mechanical ventilation. The last episode of VAP occurred on day 564 of mechanical ventilation.

Table 3. Cox regression model for variables associated with 30-day and 90-day mortality.

Variable	30-day mortality, HR (95% CI)	p	90-day mortality, HR (95% CI)	p
Age	1.02 (0.99-1.05)	0.13	1.03 (1.001-1.05)	0.003
SOFA score	1.3 (1.12-1.52)	< 0.001	1.2 (1.07-1.34)	0.001
Vasoactive agents	4.01 (1.24-12.95)	0.02	4.07 (1.93-8.55)	< 0.001
ABC	2.62 (0.8-8.57)	0.11	1.81 (0.55-5.31)	0.27
PaO_2/FiO_2 < 200	1.73 (0.64-4.7)	0.28	1.2 (0.62-2.32)	0.59
COPD	2.59 (0.93-7.18)	0.06	3.35 (1.71-6.6)	< 0.001

HR: hazard ratio; and ABC: *Acinetobacter calcoaceticus-baumannii* complex.

partially explaining such observations. No *S. aureus* was isolated from our patients, which might corroborate the findings of a study that reported a lower proportion of VAP caused by *S. aureus* in late-onset VAP than in early-onset VAP.[30]

The median number of days on MV prior to the onset of VAP was 56, which is considerably lower than that reported by Walkey et al.[24]—median = 166 days (IQR, 66-450). Unlike an LTACH, our unit receives patients immediately after the acute stage of a critical illness, which explains the shorter time from MV to the onset of VAP. The 30-day mortality rate was 30%. The mortality of patients with VAP ranges from 20% to 50%, with an attributable mortality of 13%.[31] However, those data come from cases of VAP during acute MV. Few studies have addressed VAP in patients on PMV. In a small study about VAP in tracheostomized patients, 3 of 12 died,[26] but larger scale studies are needed to establish the mortality rate in this population. Furthermore, the mortality of patients with CCI is considerably high: in-hospital mortality rates range from 17% to 31%, whereas 6-month and 12-month mortality rates are 49% and 68%, respectively.[3,32,33] Infections have been identified as one of the factors associated with mortality in patients with CCI.[33] However, the mortality attributable to VAP in this population has yet to be determined.

We found factors associated with 30-day and 90-day mortality in our population. There are some scores to predict mortality in patients with CCI, such as the

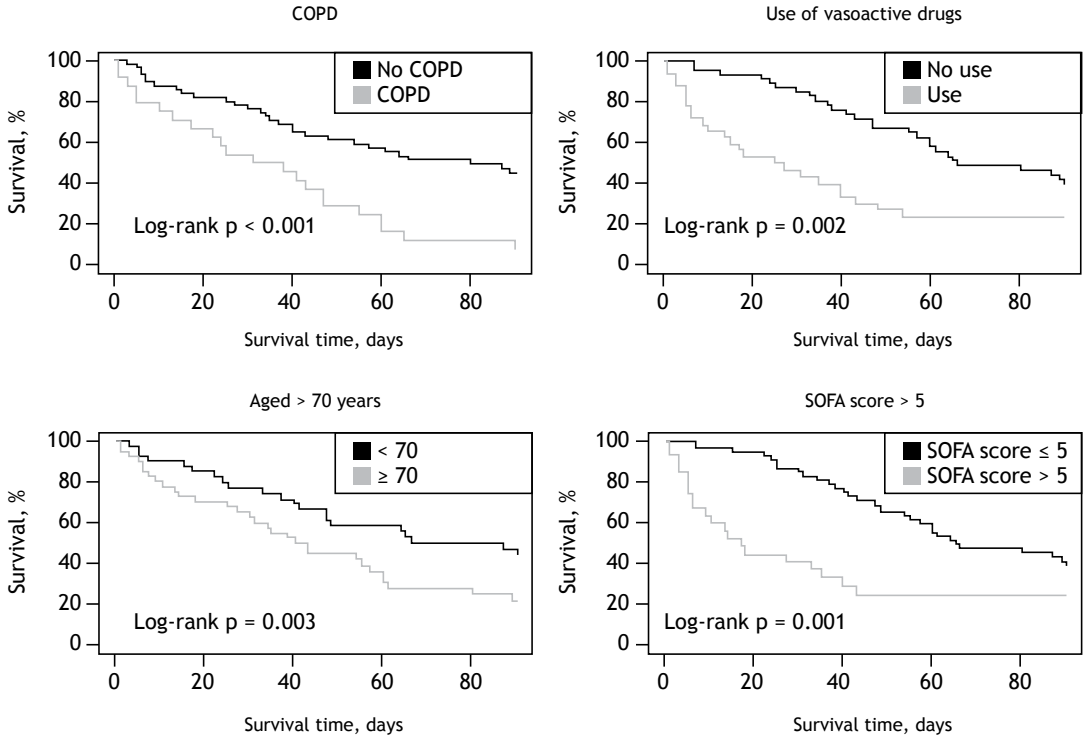

Figure 2. Kaplan-Meier curves for variables associated with 90-day mortality in patients with ventilator-associated pneumonia patients on prolonged mechanical ventilation. Age and SOFA score were dichotomized for the analysis.

designated ProVent score,[34] but they are not specific for VAP. Similar to the predictions based on the ProVent score, we found that age and the use of vasoactive agents were associated with fatal outcomes. Although the SOFA score includes the use of vasoactive agents as a factor, their use on any day of the VAP episode until the end of the antibiotic treatment were taken into consideration, and the SOFA score was calculated using the results obtained for the variables at the time closest to the diagnosis of VAP. We observed that almost two-thirds of the patients who received vasoactive agents had higher SOFA scores, so collinearity cannot be entirely ruled out. However, the effect of vasoactive agents on mortality was greater than that predicted on the basis of the SOFA score, and some patients who received vasoactive drugs had lower SOFA scores. Therefore, the exact influence of each variable has yet to be determined.

The SOFA score is a useful tool for predicting mortality in critically ill patients. Although this tool is used in different ways (differences between SOFA scores obtained on different days, highest score, mean score, etc.), the initial SOFA score has been proven to have value in predicting ICU mortality.[19] In patients with VAP, the SOFA score has also been validated as a prognostic factor,[35,36] although those studies were carried out in acute care ICUs. Tseng et al.[35] included 163 patients with VAP; however, only 42 (26%) of those were tracheostomized, and a subgroup analysis was not performed, which makes it difficult to extrapolate their results to the CCI population.

The relationship between COPD and VAP has been studied to some extent; both conditions interact in a number of levels: COPD patients on MV are at an increased risk of VAP. COPD is an independent factor associated with increased mortality, longer length of MV, longer length of ICU stay, and higher rates of infection with *P. aeruginosa* in patients with VAP.[37-40] Our results are in line with the results in those studies with patients on acute MV.[37-40] However, we found no association between COPD and 30-day mortality, even though there was a trend toward that ($p = 0.06$). This could be due to the small number of patients in our study, but it might also reflect a greater effect of COPD on 90-day mortality. It is probable that the longer the patient is followed from the onset of VAP, the greater will be the effect of chronic conditions on mortality. Similar considerations could be drawn regarding age. In patients with CCI and a high burden of comorbidities, chronic conditions and age weigh more consistently on long-term outcomes, matching overall mortality. Perhaps a shorter endpoint, such as 30-day mortality, is more suitable for this population in order to define the attributable mortality of nosocomial infections. Comparative, prospective studies are needed to shed light on this issue.

The present study has several limitations. First, it is a study carried out in a single center. The settings of care provision for patients on PMV may differ among other centers and have heterogeneous populations. In fact, our results might not be generalizable to patients at LTACHs, because several of those patients may not

have complications or characteristics similar to those of patients with CCI. Second, the retrospective nature of the study may carry biases inherent to this type of design. Some variables and confounders may not have been taken into account given the difficulty of including them in a retrospective study. Although we tried to control for confounders using Cox regression analysis, we cannot fully rule out that other variables not included in the analysis, such as the time of antibiotic therapy initiation or the presence of coinfections, might have affected our results. Third, the definition used for VAP might have led to the inclusion of some patients with ventilator-associated tracheobronchitis, which is a limitation inherent to the definition. Fourth, the sample size was somewhat small, so external validity might have been compromised and the results might not be fully generalizable for some of the findings. This highlights the need for multicenter studies that address the particular aspects of VAP patients on PMV.

In conclusion, we found a high burden of comorbidities in our sample, mostly related to neurological conditions, as well as considerably high 30-day and 90-day mortality rates. We identified factors associated with fatal outcomes, which could help identify patients who might benefit from adequate, early empirical antibiotic treatment, as well as determine prognoses. These findings should be validated by studies with larger samples of patients.

AUTHOR CONTRIBUTIONS

SN: study design; data collection; literature search; data analysis; drafting of the manuscript; and approval of the final version. GR: study design; data collection; literature search; drafting of the manuscript; and approval of the final version. MSZ and ME: study design; drafting of the manuscript; and approval of the final version. MTV: study design; drafting of the manuscript; final revision; and approval of the final version.

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Importance of chest HRCT in the diagnostic evaluation of fibrosing interstitial lung diseases

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ABSTRACT

Many conditions result in chronic interstitial lung disease (ILD), being classified as fibrosing ILDs, including idiopathic pulmonary fibrosis, connective tissue diseases, sarcoidosis, and fibrotic hypersensitivity pneumonitis. HRCT plays an important role in the clinical evaluation of fibrosing ILDs. Current treatment perspectives are encouraging and reinforce the need for HRCT scans of adequate technical quality for early detection of fibrosing ILD. Despite efforts in this regard, the significance and management of imaging findings of early interstitial lung abnormalities have yet to be clarified. After identification of CT findings consistent with fibrosing ILD, radiologists must be able to identify characteristic morphological patterns and, in some cases, features of specific clinical entities. In cases in which HRCT features are not sufficiently specific for a definitive diagnosis, HRCT can aid in selecting the best site for surgical lung biopsy. CT follow-up is useful for identifying progressive fibrosing ILDs and detecting complications unrelated to the underlying disease, including infections, acute exacerbations, and neoplasms. Automated quantification tools have clinical applicability and are likely to be available for use in imaging analysis in the near future. In addition, incorporation of CT evaluation into scoring systems based on clinical and functional parameters for staging fibrosing disease is likely to become valuable in determining prognosis. Knowledge of the clinical applications of CT evaluation is essential for specialists managing patients with fibrosing ILD and can have a positive impact on the clinical course of the disease.

Keywords: Tomography, X-ray computed; Diagnostic imaging; Pulmonary fibrosis.

INTRODUCTION

Fibrosis is the final consequence of cell injury, matrix injury, or both by a variety of mechanisms, including trauma, thermal injury, chemical injury, hypoxia, and immune-mediated injury.[1] In the lung parenchyma, repeated alveolar injury leads to fibrosing interstitial lung diseases (ILDs), including idiopathic pulmonary fibrosis (IPF), connective tissue disease (CTD)-associated fibrosing ILD (CTD-fILD), and fibrotic hypersensitivity pneumonitis (HP), as well as less common diseases such as idiopathic nonspecific interstitial pneumonia (NSIP), Langerhans cell histiocytosis, tobacco-related diseases, sarcoidosis, Erdheim-Chester disease, Hermansky-Pudlak syndrome, asbestosis, silicosis, drug reactions, and IgG4-related sclerosing disease.[1,2] Some patients develop a progressive phenotype characterized by self-sustaining fibrosis, decline in lung function, worsening quality of life, and, ultimately, early mortality, being designated progressive fibrosing ILD.[2]

The differential diagnosis of fibrosing ILDs is difficult because clinical, radiological, and pathological characteristics often overlap, a multidisciplinary approach therefore being required.[3-5] In this context, it is essential to establish a definitive diagnosis because nonpharmacological and pharmacological treatment approaches (including corticosteroids, immunosuppressants, and, more recently, antifibrotic agents) are disease-specific.[6-8]

The role of imaging in the diagnosis of fibrosing ILDs has evolved in recent decades, and HRCT currently plays an essential role in the diagnostic evaluation of fibrosing ILDs, being useful in the initial evaluation of fibrosing ILDs, in making a decision regarding the use of invasive diagnostic procedures, and in patient follow-up. The objective of the present study was to review the role of HRCT in the diagnostic evaluation of fibrosing ILDs.

DIAGNOSIS OF FIBROSING DISEASE

Technical parameters of CT examinations

CT scans of adequate technical quality are essential for accurate interpretation of ILD findings, low-quality CT images leading to misses and misinterpretations.[9] For volumetric image acquisition, the following parameters should be used: a) submillimetric collimation; b) thin-slice reconstructions (≤ 1.5 mm) with the use of a high-resolution filter; c) shortest rotation time and

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highest pitch, in order to reduce image acquisition time and movement artifacts; and d) use of tools for optimizing/reducing radiation dose.[10,11]

The first acquisition is obtained at maximal inspiration, volumetric CT acquisition being preferred because it allows multiplanar image reconstruction in the post-processing stage, clarifying disease distribution, facilitating differentiation between honeycombing and traction bronchiolectasis, and optimizing comparison with follow-up images.[10-12] The technical staff should be trained in providing patients with simple, clear respiratory instructions for chest CT examinations, the voice of the technician being preferred to the automatic instructions from the machine because submaximal inspiratory maneuvers can lead to misinterpretation of ground-glass attenuation and reticulation.[9,10] The second acquisition is obtained at end-expiration and is useful for identifying mosaic attenuation, which is an important finding in the diagnosis of fibrotic HP.[10] A third acquisition can be obtained with the patient in the prone position; it can be sequential or volumetric and can be limited to the lower lobes.[11] Prone CT imaging is useful in patients with clinical suspicion of fibrosing disease and only minor lung involvement, with normal or minimally abnormal chest X-rays, and particularly for distinguishing between position-induced changes and initial interstitial changes (Figure 1).[10]

CT findings

Common HRCT findings of fibrosing disease include reticular opacities, ground-glass opacities, traction bronchiolectasis, and honeycombing, the proportion and distribution of which vary.[10,11] Traction bronchiolectasis is an important finding for the diagnosis of fibrosing ILD and often overlaps with reticular or ground-glass opacities in patients with fibrosing lung disease. It is difficult to distinguish between traction bronchiolectasis and honeycombing in some cases, with significant interobserver variation (Figure 2).[13] The term honeycombing refers to clustered cystic airspaces of typically 3-10 mm in diameter with thick, well-defined walls.[14,15] Although honeycombing typically presents as multiple layers of cysts, a single layer of two or three cysts is enough for a diagnosis of honeycombing.[10] Ground-glass attenuation superimposed on reticular opacities or traction bronchiectasis can be seen in patients with fibrosing ILD.[10] However, the presence of "pure" ground-glass attenuation (i.e., without reticular opacities) might be related to inflammatory activity, and the presence of new bilateral ground-glass opacities in a patient with fibrosing ILD should raise the possibility of an acute exacerbation.[16] A crazy-paving pattern, micronodules, consolidations, and cysts are encountered in specific entities.

Interstitial lung abnormalities and difficulties in early diagnosis

The widespread use of HRCT as a diagnostic tool has increased the detection of interstitial lung abnormalities (ILAs), which are incidental findings potentially consistent with ILD in individuals who are not clinically suspected of having ILD and who may or may not have clinical symptoms and functional limitations.[17,18] ILAs represent early stages of fibrosing ILD in some cases and are of particular interest because antifibrotic therapy has been shown to slow the progression of IPF even in individuals with less extensive disease.[19]

ILAs are nondependent HRCT abnormalities affecting more than 5% of any lung zone (upper, middle, and lower lung zones being demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein). CT findings in patients with ILAs include ground-glass opacities, reticular opacities, architectural distortion, traction bronchiectasis, honeycombing, and nonemphysematous cysts.[18] Morphological findings unrelated to ILAs include dependent lung atelectasis, focal paraspinal fibrosis in close contact with thoracic spine osteophytes, smoking-related centrilobular opacities in the absence of other findings, mild focal or unilateral opacities, interstitial edema (associated with congestive heart failure), and findings

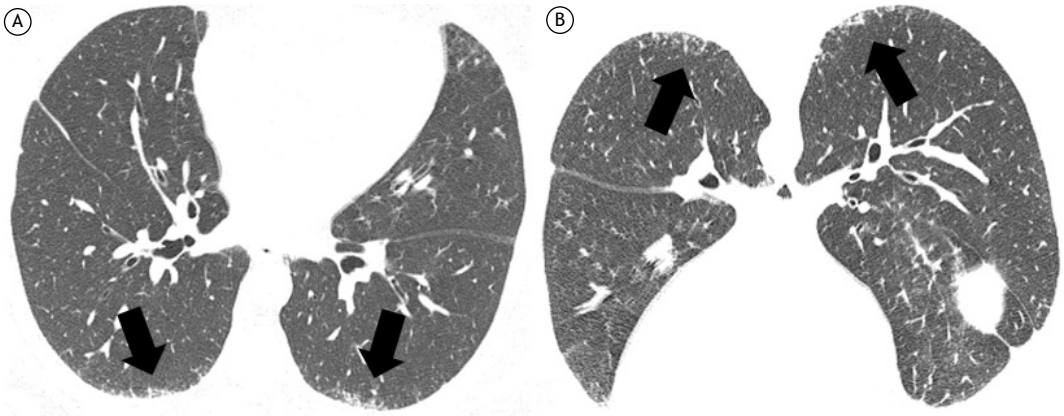

Figure 1. Axial HRCT scans with lung window settings. Note diffuse peripheral lower lobe reticular opacities (arrows in A) that are also seen on prone CT images (arrows in B), characterizing incipient interstitial lung disease.

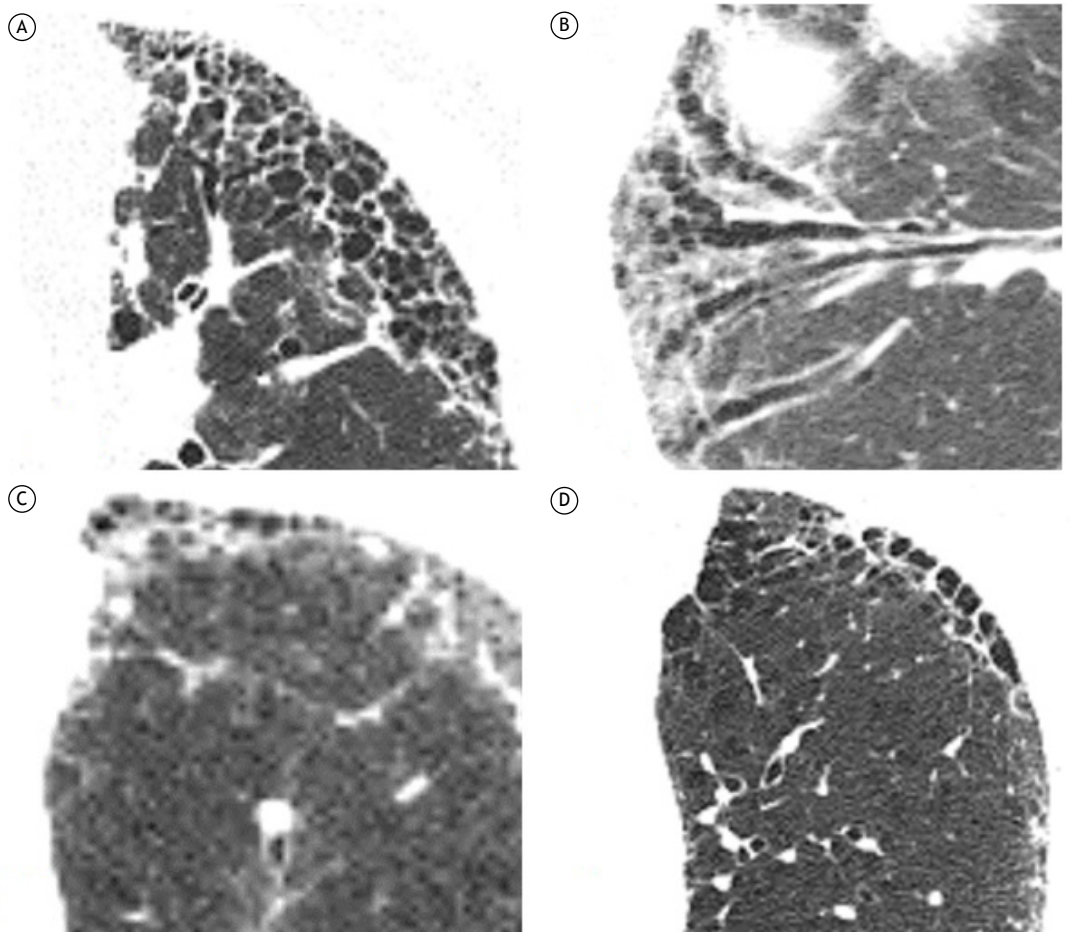

Figure 2. Axial HRCT scans with lung window settings, showing fibrosing interstitial lung disease in different patients. In A, typical honeycombing, presenting as multiple layers of cysts. In B, traction bronchiectasis in an oblique coronal plane. Note the usefulness of multiplanar reconstruction in differentiating between traction bronchiectasis and honeycombing. In C, early honeycombing, presenting as a single layer of cysts. In D, note the difficulty in differentiating between honeycombing and paraseptal emphysema.

of aspiration (patchy ground-glass opacities and a tree-in-bud pattern).[18] ILAs are classified as follows: a) nonsubpleural; b) subpleural nonfibrotic (without architectural distortion, traction bronchiectasis, or honeycombing); and c) subpleural fibrotic (with architectural distortion and traction bronchiectasis, honeycombing, or both).[18]

In patients with ILAs, risk factors for progression to ILD include clinical risk factors (smoking, other inhalational exposures, medications, radiation therapy, previous thoracic surgery, and changes in pulmonary function tests) and specific radiological features. In a study by Putman et al.,[20] the presence of subpleural reticular opacities in the lower lobes and traction bronchiectasis significantly increased the likelihood of ILA progression, and all of the cases in which honeycombing was present progressed to ILD over the course of 5 years. Specific recommendations regarding management and follow-up have been published elsewhere.[18]

DIFFERENTIAL DIAGNOSIS BASED ON CT FINDINGS: MORPHOLOGICAL PATTERNS AND SPECIFIC CLINICAL ENTITIES

After identification of CT findings consistent with fibrosing ILD, HRCT has an important role in narrowing diagnostic possibilities by identifying characteristic morphological patterns or, in some cases, indicating specific clinical entities (such as HP, sarcoidosis, and asbestosis). HRCT findings should be interpreted in the context of an integrated multidisciplinary approach, allowing a definitive diagnosis based on clinical and radiological findings in some cases and reinforcing the need for invasive diagnostic procedures in less typical cases.[3,4] After morphological evaluation by HRCT or surgical biopsy, potential causative factors such as environmental exposures, CTDs, and use of medications should be evaluated clinically.[4] In some cases, a final diagnosis will not be achieved for a number of reasons, including inadequate clinical, radiological, or pathological data and major discordance between clinical, radiological, and pathological findings; such

cases should be classified under the category of "unclassifiable" idiopathic interstitial pneumonia.[4]

Major morphological patterns of fibrosing ILD

Usual interstitial pneumonia

One of the key roles that HRCT plays in the diagnostic evaluation of fibrosing ILDs is determining the likelihood of a usual interstitial pneumonia (UIP) pattern.[3,4,10,11] A histopathological pattern of UIP is associated with multiple diagnoses, including drug-induced lung diseases, occupational diseases, CTDs, HP, and IPF.[3,21]

An official American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and *Asociación Latinoamericana de Tórax* (ALAT, Latin American Thoracic Association) clinical practice guideline recommends that, in patients with clinical suspicion of IPF, HRCT features of the UIP pattern be categorized as follows (Figure 3):

a) UIP pattern—the typical UIP HRCT pattern, with reticular opacities, traction bronchiolectasis, and honeycombing with peripheral distribution and basal predominance. There is high concordance between an HRCT pattern of UIP and a histopathological pattern of UIP.[10,11]

b) probable UIP pattern—an HRCT pattern with reticular opacities and traction bronchiolectasis with peripheral distribution and an apicobasal gradient, without honeycombing. Studies have shown a high correlation between an HRCT pattern of probable UIP and a histopathological pattern of UIP.[10,11]

c) indeterminate-for-UIP pattern—HRCT patterns that do not meet the criteria for a UIP or probable UIP pattern and that are not sufficiently characteristic to suggest a specific diagnosis. An HRCT pattern indeterminate for UIP includes mild ground-glass opacities that are not clearly more extensive than and are dissociated from reticular opacities, as well as ill-defined areas of mosaic attenuation or diffuse axial/zonal distribution.[22,23] Patients with evident but mild fibrosing disease, presumably related to early fibrosing changes, should also be included in this category, prone CT imaging being recommended to differentiate between dependent opacities and initial interstitial changes.

d) HRCT pattern suggestive of an alternative diagnosis—HRCT findings suggestive of diagnoses other than UIP/IPF, including atypical findings (including consolidation, extensive ground-glass attenuation in the absence of an exacerbation, well-defined mosaic attenuation, nodules, and cysts), atypical distribution (including upper-/mid-lung predominance, peribronchovascular involvement, and subpleural sparing), and other findings (including pleural plaques, pleural effusion, esophageal dilation, and extensive lymph node enlargement).

In specific contexts, a diagnosis of IPF can be made on the basis of clinical-radiological correlations; in other contexts, it can be made by correlating HRCT and biopsy findings.[10,11]

NSIP

The NSIP pattern is associated with several diseases, including CTD-fILD, HP, drug-induced lung disease, infections, immunodeficiencies, and idiopathic ILD.[3] HRCT features suggestive of NSIP include ground-glass attenuation, reticular opacities, and traction bronchiolectasis in a predominantly basal and peripheral or diffuse distribution (Figure 4). Honeycombing is an uncommon finding, seen only in advanced cases.[3,24,25] Findings of NSIP and UIP overlap in some patients, subpleural sparing being suggestive of an NSIP pattern on HRCT.[24,25]

Other morphological patterns of fibrosing ILD

There are several other morphological patterns of fibrosing ILD. Pleuroparenchymal fibroelastosis is a recently described rare fibrosing disease that can be idiopathic or associated with a variety of conditions, including complications of bone marrow or lung transplantation, autoimmune diseases, CTDs, infections (with *Aspergillus* spp. or nontuberculous mycobacteria), use of cancer treatment drugs, and occupational exposures. Typical HRCT findings include pleural thickening and subpleural consolidations with traction bronchiectasis, architectural distortion, and volume loss, typically in the upper lobes (Figure 4). Pneumothorax and recurrent infections are common in patients with pleuroparenchymal fibroelastosis, with disease progression occurring in most cases (60%).[4,26]

Despite being classified as an acute/subacute interstitial pneumonia and the fact that the majority of patients recover completely with oral corticosteroids, organizing pneumonia can progress to residual or progressive interstitial fibrosis.[4] It is likely that some patients with fibrotic NSIP fall into this subgroup of patients. A mixed pattern of NSIP and organizing pneumonia can be seen in patients with antisynthetase syndrome-associated myositis.[4,27,28] Fibrotic patterns can also be observed in patients surviving episodes of (idiopathic or secondary) late-stage diffuse alveolar damage; architectural distortion, traction bronchiectasis, and cysts can occur in such patients, predominantly in nondependent lung regions.[3,4]

Morphological patterns such as lymphocytic interstitial pneumonia, desquamative interstitial pneumonia, and smoking-related changes (airspace enlargement with fibrosis) can also be related to fibrotic HRCT features.[3,4]

Specific clinical entities

Fibrotic HP

Fibrotic HP is a fibrosing ILD resulting from chronic exposure to specific antigens, the definitive diagnosis of which depends on a multidisciplinary approach. HRCT plays a central role in various algorithms for

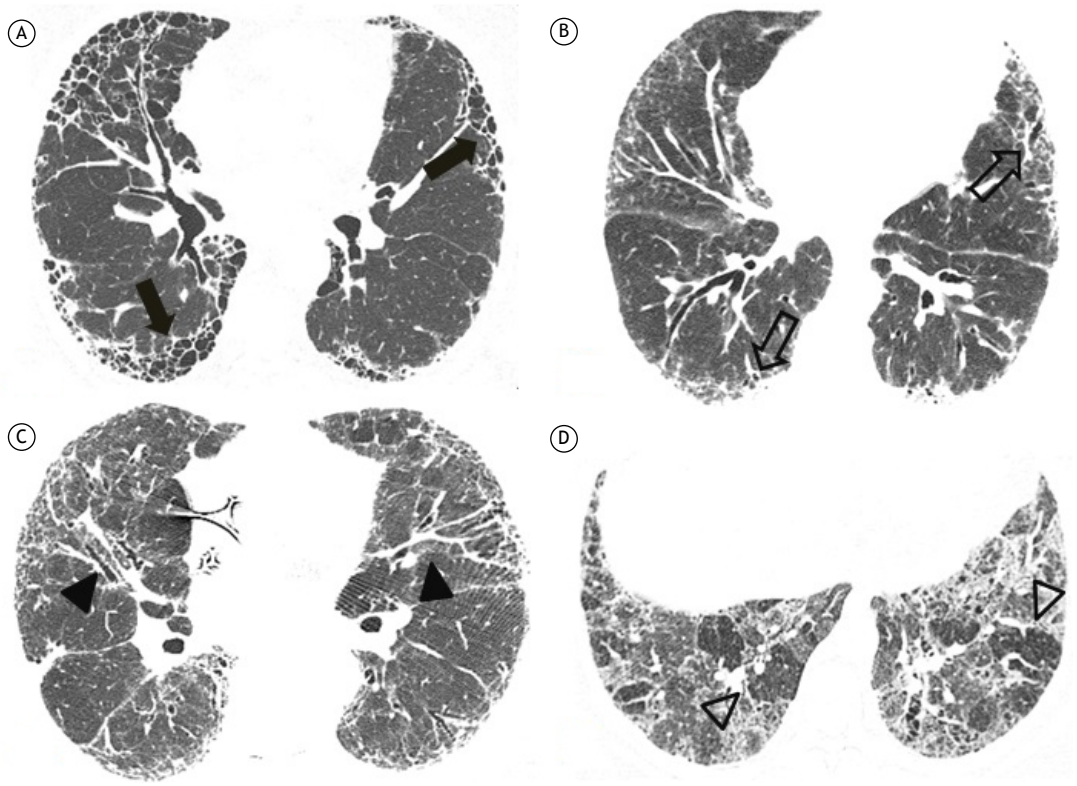

Figure 3. Axial HRCT scans with lung window settings, showing fibrosing interstitial lung disease in patients suspected of having idiopathic pulmonary fibrosis and presenting with different HRCT features of the usual interstitial pneumonia (UIP) pattern. In A, UIP pattern, with extensive honeycombing (arrows), peripheral distribution, and basal predominance. In B, probable UIP pattern, with peripheral reticular opacities and traction bronchiolectasis (open arrows), without honeycombing. In C, indeterminate-for-UIP pattern, with diffuse axial distribution and central involvement (arrowheads), as well as areas of ground-glass opacity, together with reticular opacities. In D, a pattern suggestive of an alternative diagnosis, with extensive areas of ground-glass opacity and a mosaic pattern of lung attenuation (open arrowheads).

the diagnosis of fibrotic HP,[29-32] as well as in an official ATS/JRS/ALAT clinical practice guideline[33] for the diagnosis of fibrotic HP in adults. An HRCT pattern of fibrosing ILD and evidence of small airway disease are suggestive of a diagnosis of fibrotic HP.[33] Fibrosis is most severe in the mid or mid and lower lung zones or equally distributed in the three lung zones with relative basal sparing; on axial images, there is often no central or peripheral predominance of lung fibrosis.[33] Honeycombing can be present in a subpleural or peribronchovascular distribution and, less frequently, with a basal predominance.[24] HRCT features of small airway disease include centrilobular opacities, mosaic attenuation, air trapping, and the "three-density pattern" (formerly known as the "headcheese sign," a combination of three attenuations on inspiratory CT images, i.e., areas of normal lung parenchyma, areas of ground-glass attenuation, and areas of hyperlucency, indicating an association between infiltrative lung disease and airway obstruction).[33,34] Mosaic attenuation has a high diagnostic value, particularly in pulmonary parenchymal segments without overt fibrosis.[10,24,29-32] One recent study showed that the three-density pattern is specific for fibrotic HP, highlighting that areas of decreased attenuation can be seen in cases of IPF as well.[35] Other morphological patterns can be seen, including typical UIP and NSIP.[36] According to current guidelines, HRCT features in patients suspected of having fibrotic HP should be categorized as follows (Figure 5):

a) typical HP pattern—diffuse interstitial fibrosis with middle lung predominance or basal sparing, as well as abnormalities indicative of small airway disease.

b) compatible-with-HP pattern—variant patterns of interstitial fibrosis (UIP pattern and extensive ground-glass opacities with incipient fibrosis), peribronchovascular distribution with subpleural areas axially and upper lung predominance craniocaudally, as well as abnormalities indicative of small airway disease.

c) indeterminate-for-HP pattern—lone patterns (i.e., not accompanied by other findings suggestive of HP), including UIP pattern, probable UIP pattern, indeterminate pattern for UIP, fibrotic NSIP pattern, organizing pneumonia-like pattern, and truly indeterminate HRCT patterns.

Ancillary diagnostic tests such as bronchoalveolar lavage and surgical biopsy can be performed when

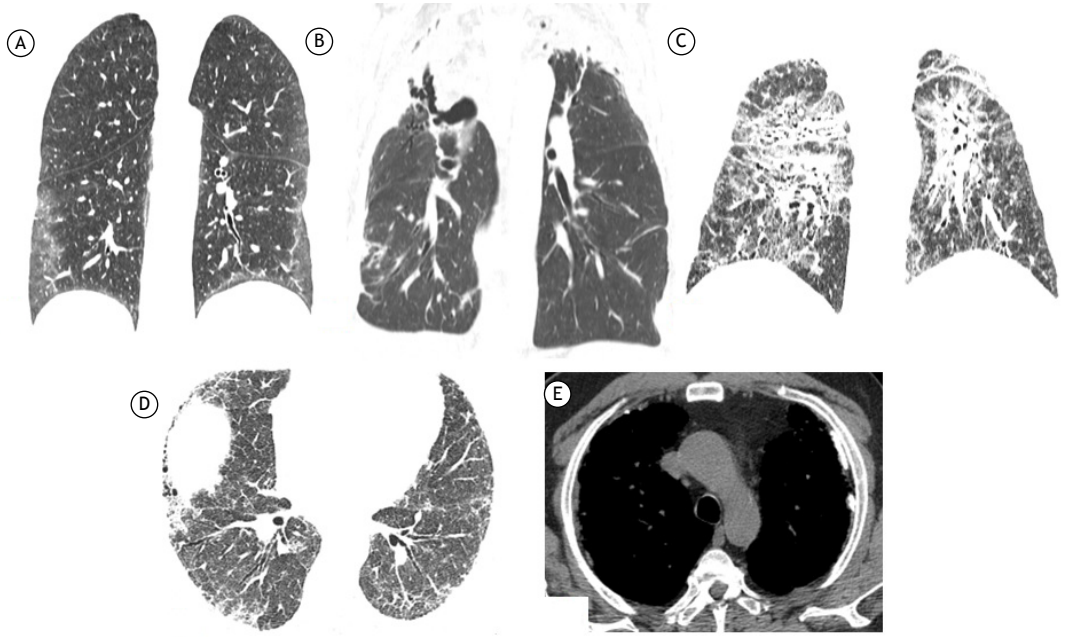

Figure 4. Axial HRCT scans of the chest showing features related to different fibrosing diseases. In A, features suggestive of nonspecific interstitial pneumonia, with a predominance of ground-glass opacities. In B, features of pleuroparenchymal fibroelastosis confirmed by histopathology showing predominantly apical fibrosing disease with upper lobe volume loss and upward hilar retraction. In C, scan of a patient with sarcoidosis, showing fibrosing disease with an upper-lobe predominance. In D and E, scans of a patient with fibrosing lung disease caused by exposure to asbestos. Note the presence of pleural plaques (arrows in E).

a reliable diagnosis cannot be made on the basis of clinical and radiological analysis.[30,33]

CTD-fILD

ILDs are associated with multiple CTDs, with varying prevalence across diseases. The estimated prevalence of HRCT findings consistent with ILD is 70-90% in systemic sclerosis, 15-70% in inflammatory myopathies (being more common in patients with antisynthetase antibodies), 4-68% in rheumatoid arthritis, 20-85% in mixed CTD, 10-30% in Sjögren's syndrome, and up to 30% in systemic lupus erythematosus.[37] Although the patterns of fibrosis in CTD-fILD and other fibrosing ILDs are similar, Chung et al.[38] identified specific CT signs that are more common in the former than in the latter: the "anterior upper lobe" sign—concentration of fibrosis within the anterior aspect of the upper lobes (with relative sparing of the other aspects of the upper lobes) and concomitant lower lobe involvement; the "exuberant honeycombing" sign—extensive honeycomb-like cyst formation within the lungs constituting greater than 70% of the fibrotic portions of lung; and the "straight-edge" sign—isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane without substantial extension along the lateral margins of the lungs on coronal images (Figure 6). The authors[38] compared patients with UIP associated with IPF and patients with UIP associated with CTD-fILD (rheumatoid arthritis or systemic sclerosis in most cases). The positive predictive values of the anterior upper lobe, exuberant honeycombing, and straight-edge signs were 1.99 ($p = 0.028$), 3.69 ($p < 0.001$), and 4.22 ($p < 0.001$), respectively, and the signs were most common in patients with systemic sclerosis. Similarly, Walkoff et al.[39] evaluated the specificity of the "four corners" sign—pulmonary inflammation and/or fibrosis focally or disproportionately involving the bilateral anterolateral upper lobes and posterosuperior lower lobes—in a sample of patients with IPF and systemic sclerosis, and found a significant association between a confidently present four corners sign and a diagnosis of systemic sclerosis.

Sarcoidosis

Approximately 20% of patients with sarcoidosis will develop fibrosing ILD over the course of the disease, with fibrocystic changes, including honeycombing. Typical fibrotic HRCT features include upper lobe and peribronchovascular fibrosis, as well as posterior retraction of the hila, together with mediastinal lymph node enlargement (Figure 4).[11,40]

Asbestosis

Asbestos-related fibrosing ILD usually occurs 20 years or more after exposure. The changes of asbestosis are more pronounced in the lower lobes and subpleurally, and honeycombing can occur, albeit only in advance cases; imaging findings of asbestosis can be indistinguishable from those of various clinical entities, including IPF.[41,42] Akira et al.[42] studied HRCT

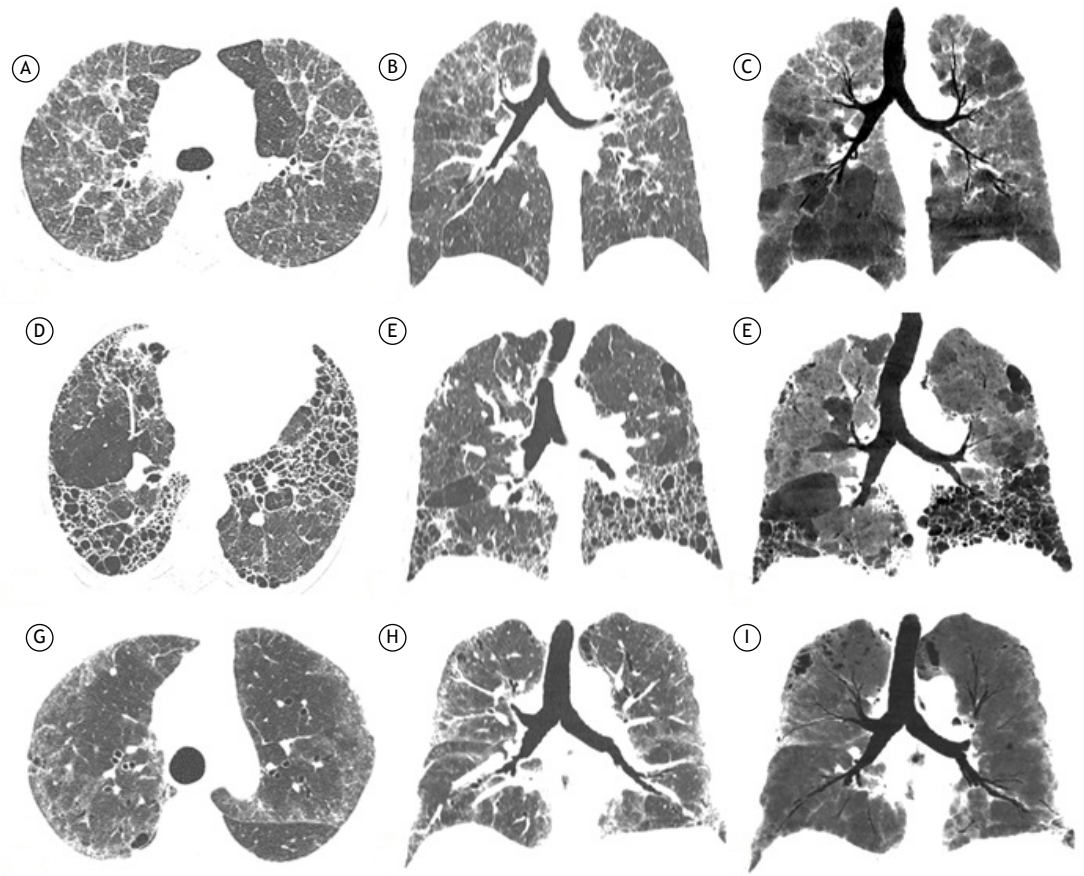

Figure 5. Axial HRCT scans with lung window settings (in A, D, and G), coronal reconstructions (in B, E, and H), and coronal minimum intensity projection reformatted images (in C, F, and I) for three patients with fibrotic hypersensitivity pneumonitis (HP). In A, B, and C, a typical HP pattern, with diffuse interstitial fibrosis axially and relatively spared lower lung zones, as well as marked mosaic attenuation in a predominantly caudal distribution, indicating small airway disease (in C). In D, E, and F, a compatible-with-HP pattern, with predominantly peripheral, basal interstitial fibrosis and extensive honeycombing (characteristic of usual interstitial pneumonia), as well as scattered areas of mosaic attenuation, constituting evidence of small airway disease (in F). In G, H, and I, an indeterminate-for-HP pattern, with areas of ground-glass opacity, reticular opacities, and traction bronchiectasis in a diffuse axial/craniocaudal distribution, as well as no evidence of small airway disease.

scans of patients with asbestosis or IPF and concluded that subpleural dot-like or branching opacities, subpleural curvilinear lines, mosaic attenuation, and parenchymal bands are significantly more common in the former than in the latter. Although the parenchymal abnormalities found in patients with asbestosis can also be found in patients with other diseases, pleural plaques are characteristic of exposure to asbestos, being found in up to 80% of patients with asbestosis on radiographic studies (Figure 4).[41] The diagnosis of asbestosis is based on a thorough clinical and occupational history.

ROLE OF HRCT IN SELECTING THE BEST SITE FOR SURGICAL LUNG BIOPSY

The decision to perform a surgical lung biopsy must be made by a multidisciplinary team with experience in ILDs. In the diagnosis of IPF in particular, current guidelines recommend that surgical lung biopsy be performed in newly diagnosed ILD patients who have an HRCT pattern indeterminate for UIP or suggestive of an alternative diagnosis, conditional recommendations being made for performing surgical lung biopsy in those with a pattern of probable UIP.[10,11,43]

When surgical lung biopsy is indicated, multiple biopsies should be obtained from two to three lobes, because the histological patterns on specimens obtained from different segments can be discordant.[10,11] HRCT is useful for prebiopsy evaluation and selection of the best sampling sites. In order to avoid the possibility that a biopsy specimen was taken from an area not representative of the predominant disease process, biopsy specimens should be obtained from areas that reflect the full spectrum of disease patterns as guided by HRCT evaluation or intraoperative inspection of the lung surface. Areas of honeycombing should be avoided because they show end-stage disease and are likely to be of little use when establishing a diagnosis. Areas that show intermediate or relatively preserved lung parenchyma, or areas of ground-glass

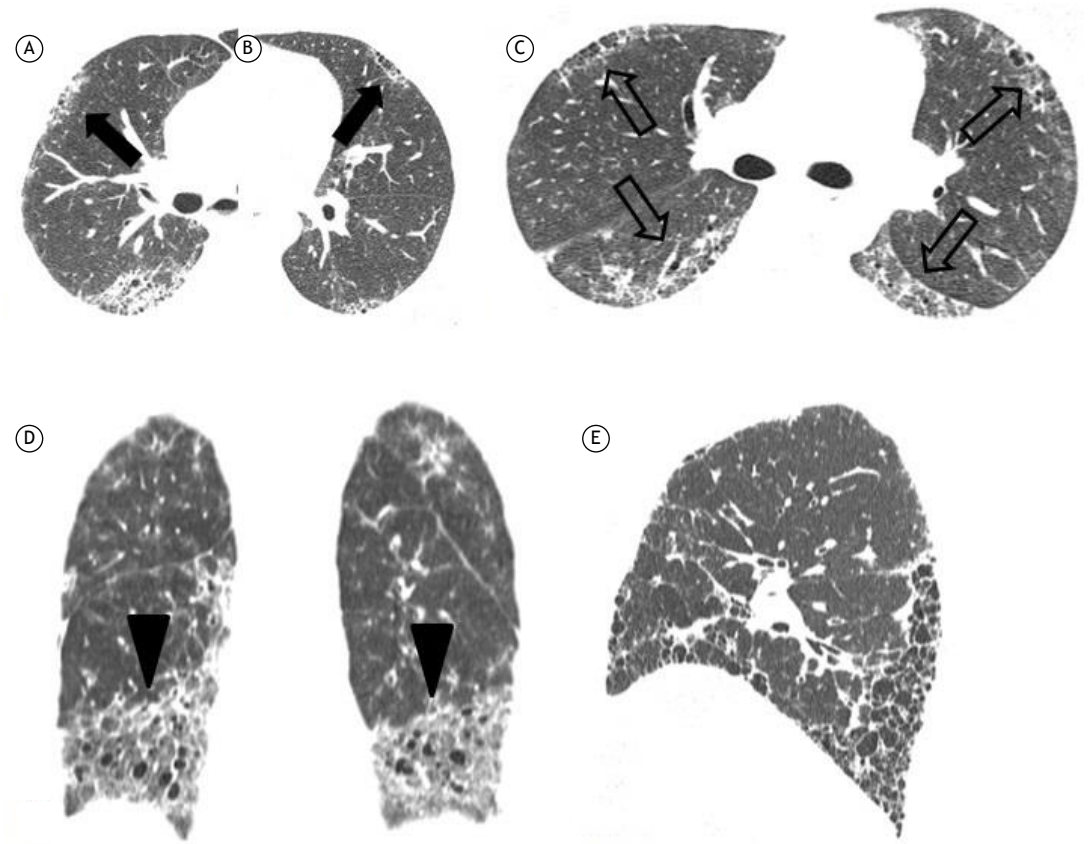

Figure 6. Specific CT signs of fibrosis in connective tissue disease-associated fibrosing interstitial lung disease. In A and B, the "anterior upper lobe" sign (arrows) in a patient with rheumatoid arthritis. In C, the "four corners" sign (open arrows)—fibrosis focally involving the bilateral anterolateral upper lobes and posterosuperior lower lobes—in a patient with systemic sclerosis. In D, the "straight-edge" sign (arrowheads)—isolation of fibrosis to the lung bases with sharp demarcation in the craniocaudal plane. In E, the "exuberant honeycombing" sign—extensive honeycombing constituting most of the fibrotic portions of lung.

opacity should ideally be selected for biopsy because the lung specimen must have fibrotic lung adjacent to normal lung for the pathologist to identify the UIP pattern.[10,44,45] Flaherty et al.[45] specifically addressed the role of histopathological sampling in differentiating between UIP and NSIP, demonstrating histological variability in surgical lung biopsy specimens from multiple lobes and reinforcing the need for having multiple lobes biopsied. Given that the prognosis is worse for UIP than for NSIP, sampling should be optimized so as not to miss areas most likely to demonstrate the histological pattern of UIP.[45]

DISEASE SEVERITY ASSESSMENT, QUANTIFICATION, AND FOLLOW-UP

Disease severity assessment

Given that several fibrosing ILDs have an unpredictable natural history, staging systems can be useful in estimating prognosis and guiding management decisions (e.g., timing of pharmacological treatment and lung transplantation). The most widely used model for assessing chronic fibrosing diseases is a scoring system based on clinical and functional parameters (gender, age, FVC, and DLCO); the GAP model (**G**ender, **A**ge, and lung **P**hysiology) is most commonly used in patients with IPF and has been shown to be accurate in predicting survival.[46,47] Adaptations of this model have recently been tested to include HRCT. Ley et al.[48] replaced DLCO with a visual semiquantitative HRCT score and reported that the resulting model had a performance that was comparable to that of the original GAP model. Chahal et al.[49] evaluated the impact of adding a visual semiquantitative fibrotic score above or below 25% to the GAP model and found that the resulting model shows improved correlation with survival, especially in patients with mild disease. Other multidimensional indices including functional variables and CT evaluation have been proposed to stage systemic sclerosis-related fibrosing ILD, sarcoidosis, and other ILDs.[50,51]

Quantification

Qualitative (visual) and semiquantitative imaging techniques can be used in order to assess ILDs in general and correlate with outcomes in a number of ILDs; however, they are highly dependent on visual

analysis and are of limited use in detecting subtle changes in disease progression. Quantitative imaging, including histogram analysis and textural-based analysis coupled to machine learning, is a new and promising approach, allowing quantification of patterns such as ground-glass opacification, reticulation, and honeycombing.[52] In addition to quantification, automated analysis is useful for interpreting CT patterns, as demonstrated in a study by Walsh et al.,[52] in which a deep learning algorithm had a performance comparable to that of thoracic radiologists in determining the likelihood of UIP in accordance with criteria specified in the 2011 ATS/ERS/JRS/ALAT guidelines.[53] A combination of automated and visual analysis is likely to be the optimal approach to disease staging and outcome prediction in fibrosing ILDs.

Follow-up

Serial CT can reveal changes in the extent of reticulation, traction bronchiectasis, and honeycombing, allowing identification of progressive fibrosing ILDs, which are associated with a worse prognosis.[52] However, the optimum time interval for CT follow-up has yet to be established, and currently there are no formal recommendations to sequencial HRCT follow-up in clinically stable patients.[51] Given that patients with various fibrosing ILDs have a slow disease progression, the longitudinal behavior of fibrosing ILDs can be more easily detected by comparing follow-up CT scans with initial CT scans rather than by comparing follow-up CT scans only (Figure 7). HRCT evaluation of disease progression is one of the recently proposed criteria for the definition of progressive fibrosing ILD.[54] Patients are required to meet at least one of the following criteria for progression of fibrosing ILD within 24 months: a reduction in FVC of at least 10% of the predicted value; a reduction in FVC of 5-10% of the predicted value and worsening of respiratory symptoms or an increased extent of fibrosis on HRCT; or worsening of respiratory symptoms and an increased extent of fibrosis on HRCT. It is important to define progressive fibrosing ILD because recent evidence shows a reduction in the rate of decline in FVC in non-IPF progressive fibrosing ILD patients undergoing treatment with nintedanib.[54]

In addition to determining disease behavior, CT follow-up plays an important role in detecting complications such as pulmonary hypertension, pulmonary embolism, neoplasms, and coronary artery disease, all of which can have an impact on survival (Figure 8).[51]

ACUTE EXACERBATION OF FIBROSING ILD

Acute exacerbation of fibrosing ILD is defined in accordance with current criteria for IPF: an acute, clinically significant respiratory deterioration, typically less than 1 month in duration, categorized as pulmonary or extrapulmonary (pulmonary embolism, pneumothorax, pleural effusion, or any combination of the three). HRCT plays a major role in the diagnosis of acute exacerbations. In patients with episodes of inflammatory exacerbation, noninvasive criteria include HRCT findings of bilateral ground-glass opacities, consolidations, or a combination of the two superimposed on a background pattern consistent with fibrosing ILD but that are not explained by hydrostatic edema, regardless of whether the condition is idiopathic or caused by any other factor, including infection (Figure 8). CT angiography plays an important role in detecting episodes of acute exacerbation caused by pulmonary thromboembolism.[16,55]

FINAL CONSIDERATIONS

The management of patients with fibrosing ILD is complex. In a multidisciplinary approach, CT evaluation is important at various stages of patient management, including early diagnosis, narrowing of the diagnostic possibilities (definition of morphological patterns and, eventually, pointing toward specific clinical entities), disease severity assessment, prognosis, and follow-up, as well as in identifying complications such as infections, neoplasms, and acute exacerbations. Many issues have yet to be resolved, including interobserver variation in the interpretation of scans, the optimum time interval for CT follow-up, and the significance of subclinical ILAs. New approaches involving automated techniques and machine learning can be useful at various stages, and their significance should be investigated in future studies.

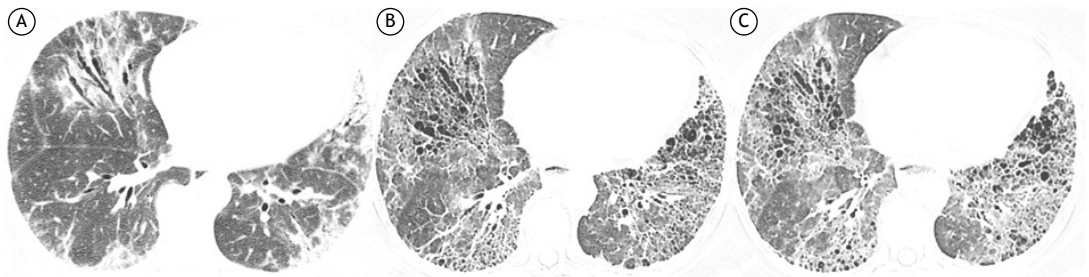

Figure 7. Axial HRCT scans. Initial CT scan (in A) and follow-up CT scans at six years (in B) and six and a half years (in C) in a patient with systemic sclerosis-related fibrosing interstitial lung disease. Although the follow-up scans apparently show no changes in disease progression, a comparison between the initial and follow-up scans reveals a progressive disease phenotype, underscoring the importance of comparing follow-up CT findings with initial CT findings.

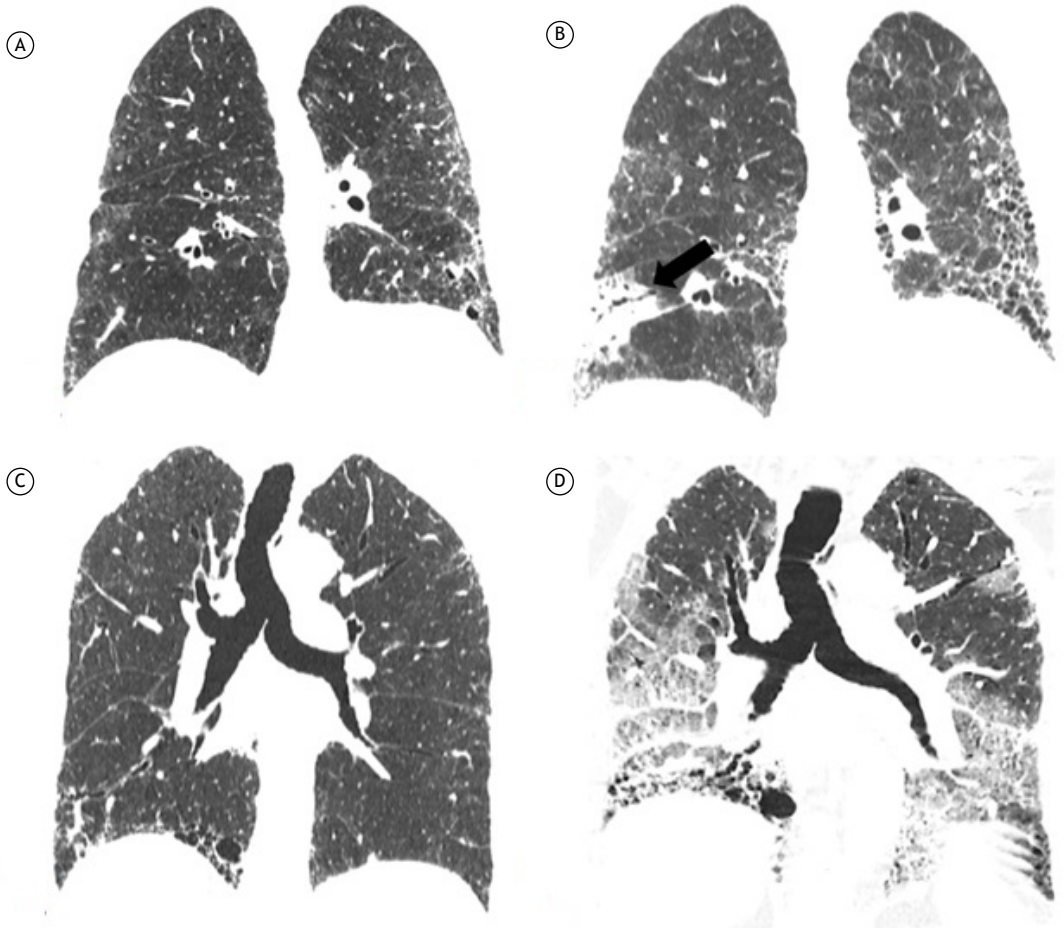

Figure 8. Coronal reconstructions of HRCT scans showing complications of fibrosing interstitial lung disease in two patients. In A and B, scans of a patient with progressive idiopathic pulmonary fibrosis. Initial CT scan (in A) and follow-up CT scan at seven years and 10 months (in B), showing disease progression and an irregular subpleural expansile neoplastic lesion in the right lower lobe, diagnosed as adenocarcinoma (arrow in B). In C and D, scans of a patient with progressive idiopathic pulmonary fibrosis. Initial CT scan (in C) and follow-up CT scan at 15 months (in D), showing disease progression and new bilateral ground-glass opacities, characterizing acute exacerbation of idiopathic pulmonary fibrosis.

AUTHOR CONTRIBUTIONS

PPTST, MFR, and EM conceived and planned the study; interpreted the data; drafted, reviewed, and revised the manuscript; and approved the final version. MACM, DLE, and GSPM drafted, reviewed, and revised the manuscript; and approved the final version.

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REVIEW ARTICLE

Update on and future perspectives for the diagnosis of alpha-1 antitrypsin deficiency in Brazil

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ABSTRACT

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder caused by a mutation in the *SERPINA1* gene, which encodes the protease inhibitor alpha-1 antitrypsin (AAT). Severe AATD predisposes individuals to COPD and liver disease. Early diagnosis is essential for implementing preventive measures and limiting the disease burden. Although national and international guidelines for the diagnosis and management of AATD have been available for 20 years, more than 85% of cases go undiagnosed and therefore untreated. In Brazil, reasons for the underdiagnosis of AATD include a lack of awareness of the condition among physicians, a racially diverse population, serum AAT levels being assessed in a limited number of individuals, and lack of convenient diagnostic tools. The diagnosis of AATD is based on laboratory test results. The standard diagnostic approach involves the assessment of serum AAT levels, followed by phenotyping, genotyping, gene sequencing, or combinations of those, to detect the specific mutation. Over the past 10 years, new techniques have been developed, offering a rapid, minimally invasive, reliable alternative to traditional testing methods. One such test available in Brazil is the A1AT Genotyping Test, which simultaneously analyzes the 14 most prevalent AATD mutations, using DNA extracted from a buccal swab or dried blood spot. Such advances may contribute to overcoming the problem of underdiagnosis in Brazil and elsewhere, as well as being likely to increase the rate detection of AATD and therefore mitigate the harmful effects of delayed diagnosis.

Keywords: alpha 1-antitrypsin deficiency/diagnosis; alpha 1-antitrypsin deficiency/genetics; Genotyping techniques.

INTRODUCTION

Alpha-1 antitrypsin deficiency (AATD) is a rare genetic disorder, albeit the most common hereditary disorder in adults.[1,2] The mutation originates in the *SERPINA1* gene, which encodes alpha-1 antitrypsin (AAT), the most abundant protease inhibitor in human serum.[1] AATD is characterized by a reduction in serum AAT concentrations and is associated with an increased risk of lung disease (e.g., COPD, bronchiectasis), liver disease (e.g., chronic hepatitis, cirrhosis), and other less common conditions.[3-5]

AAT is a member of the serine protease inhibitor superfamily.[6,7] Synthesized mainly by hepatocytes (≥ 80%), AAT is also found in the lung, kidney, and intestine.[8] The main function of AAT is to inhibit neutrophil elastase to protect the lung from excessive proteolytic degradation of elastin and other connective tissue components, as well as from external factors, such as smoking.[6,7] AAT also inhibits numerous other proteolytic enzymes, providing more than 90% of the antiprotease capacity in serum.[6,7] Evidence in recent years has indicated that AAT also has broad-spectrum anti-inflammatory, immunomodulatory, and antimicrobial properties.[6,7]

Early diagnosis of AATD is a priority because it enables implementation of preventive measures, such as avoidance of smoking and of exposure to environmental pollutants, and identifies candidates for therapeutic intervention.[9] Early diagnosis can modify the natural history of AATD and dramatically improve patient outcomes.[10] In clinical practice, however, AATD is largely underdiagnosed due to low clinical suspicion, as well as lack of knowledge about the disease and of appropriate diagnostic tests.[11-13] An estimated 85% of individuals with AATD go undiagnosed,[11] and a significant proportion of individuals are diagnosed at advanced age after years of symptoms and multiple physician visits.[12]

The Latin American Project for the Investigation of Obstructive Lung Disease[14] found spirometric evidence

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of persistent airflow obstruction in 15.8% of the sampled population in Brazil (963 adults > 40 years of age in the city of São Paulo), of whom 12.5% had never been exposed to tobacco smoke, suggesting that other risk factors (e.g., AATD) may have been involved and undiagnosed. Reasons for underdiagnosis of AATD in Brazil include a lack of awareness of the condition among physicians, particularly because a laboratory diagnosis is the only method of identifying AATD in individuals with COPD[15]; a racially diverse population, which may cause individuals of European ancestry, who have a higher frequency of alleles involved in early lung changes, to be overlooked[16]; and, until recently, the lack of rapid and convenient diagnostic methods.[9]

This review study provides an update on the diagnosis of AATD, including tools available in Brazil, and features a diagnostic algorithm that may assist in confirming suspected cases of AATD.

GENETICS

The *SERPINA1* gene is located on the long arm of chromosome 14 (14q31-32) and is transmitted by simple autosomal codominant Mendelian inheritance through two alleles, one from each parent.[6,7] Approximately 125 variants of the *SERPINA1* gene have been identified which, for clinical purposes, are classified as normal, deficient, null, and dysfunctional.[7]

The normal allele is Pi*M. The most common deficiency alleles are Pi*S and Pi*Z, which encode abnormal proteins that undergo polymerization in the liver. The normal genotype Pi*MM is present in approximately 80-95% of the population and expresses 100% of serum AAT. The five deficient genotypes (Pi*MS, Pi*SS, Pi*MZ, Pi*SZ, and Pi*ZZ) are present in the remaining 5-20% of the population and express 80%, 60%, 55%, 40%, and 15% of serum AAT, respectively.[4] In addition, there are about 25 rare deficiency alleles that express low amounts of AAT, and 25 null alleles that express undetectable amounts (< 1%) of AAT.[7] Recent studies have indicated that certain epigenetic mechanisms may account, at least in part, for differences in the clinical expression of lung disease in patients with the deficient PI*ZZ and PI*SZ genotypes.[17,18]

EPIDEMIOLOGY

AATD affects mainly Whites of European heritage. The estimated prevalence of the most common severe genotype (Pi*ZZ) is 1:2,000-5,000 individuals in Europe, and 1:5,000-7,000 individuals of European descent residing in countries such as Canada, the United States, Australia, and New Zealand.[19] Epidemiological studies estimate Pi*Z genotype frequencies by using cohort and prevalence studies to develop inverse distance weighted interpolation maps that provide information about genotype distribution worldwide. According to this method, there are an estimated 6,000 individuals with the Pi*ZZ genotype in Brazil.[7,20] Another perspective is to determine the proportion of patients with COPD who are affected by AATD. A recent epidemiological study reported that the prevalence of Pi*ZZ/prevalence of COPD ratio in Europe was 0.12% (0.08-0.24%), differences being wide among the countries.[21] Numbers may be even higher in other countries; in Argentina, for example, the prevalence of AATD (Pi*ZZ or Pi*SZ) among COPD patients > 40 years of age was found to be 0.83%.[22]

Due to the absence of specific studies, little is known about the epidemiology of "rare" and "null" AATD alleles,[7] which may be more prevalent than previously assumed. A retrospective review of 3,511 AATD genetic studies performed in the laboratory of the Spanish Registry of Patients with Alpha-1 Antitrypsin Deficiency, from 1998 to 2010, detected 1.6% of cases with rare AAT alleles, most commonly Pi*I and Pi*Mmalton.[23]

Brazil has a racially diverse population that includes immigrants from European countries. Although epidemiological data on the prevalence of AATD in the general population in Brazil are lacking,[24] a cross-sectional study involving 926 COPD patients from five different regions of Brazil found an overall prevalence of 2.8% for AATD and 0.8% for the Pi*ZZ genotype.[16] These figures align with estimates that severe AATD is responsible for 0.1% to 1% of COPD cases[21,22] and reinforce the need for vigilance and increased screening for AATD in the population with COPD in Brazil.[16]

CLINICAL MANIFESTATIONS

AATD predisposes patients to various diseases; low serum AAT levels, other genetic characteristics, and environmental influences contribute to disease development and progression.[25] The major clinical manifestations of severe AATD are lung disease (emphysema) and liver disease (chronic hepatitis, cirrhosis, and hepatoma). Lung disease occurs when serum AAT levels are insufficient to overcome the relatively excessive action of neutrophil elastase—the so-called 'protease-antiprotease imbalance'—which results in degradation of elastin and other extracellular matrix components of the lower respiratory tract.[4] Liver disease occurs as a complication of intrahepatocytic accumulation of unsecreted, polymerized AAT.[4] Less common conditions associated with AATD include neutrophilic panniculitis and systemic vasculitis (typically granulomatosis with polyangiitis).[4,25-27]

In patients with AATD-associated lung disease, the most common physiological impairment is chronic airflow obstruction, demonstrated by a post-bronchodilator FEV_1/FVC ratio < 0.7, reduced FEV_1, and decreased DLCO. Air trapping is common, and a degree of hypoxemia may be present, even in mild or moderate cases. Emphysema in AATD is predominantly located in the lower lobes, although it may be found in the upper lobes in some individuals.

[28] Patients with the most severe forms of AATD have airflow obstruction and reduced DLCO; the decline in DLCO is greater than is that in FEV_1 in severe disease, and, therefore, DLCO might be a more appropriate test for patient follow-up.[29] Given the heterogeneity of the clinical and functional expression of AATD, initial assessment of the lung disease associated with AATD must include complete evaluation of the respiratory physiology, exercise capacity, symptom intensity, and disease impact, as well as performance of HRCT of the chest. Blood gas analysis may be part of a more comprehensive evaluation in certain cases in which oxygen saturation is low.[28]

Liver disease associated with the Pi*ZZ phenotype has two forms of presentation, one in early childhood (e.g., neonatal cholestasis) and one in adulthood, when some individuals (not necessarily those with previous liver disease during childhood) develop chronic liver disease that progresses to fibrosis.[4] An analysis of the 2019 Swedish registry data found a prevalence of any liver disease of 10% among 1,595 Pi*ZZ individuals.[30] Male gender, age over 50 years, and repeatedly elevated liver function test results were consistently associated with an increased risk of liver disease in adulthood.[30,31] Previously, a retrospective study[32] based on 17 autopsied individuals diagnosed with AATD in the city of Malmö, Sweden, between 1963 and 1982, found a prevalence of cirrhosis of 41% and a prevalence of primary liver cancer of 29%. The significantly higher risk in males suggested a possible additive effect of exogenous factors (e.g., alcohol consumption and exposure to occupational toxins).

CLINICAL SUSPICION

The risk of developing lung and liver disease varies according to the AATD genotype (homozygous or heterozygous combinations of deficient and null alleles). Individuals with serum AAT levels < 50 mg/dL (< 11 μM) are at a higher risk of pulmonary disease, the majority (> 90%) being Pi*ZZ homozygotes or having rare or null genotypes.[25] For reasons yet to be clear, 30-50% of the individuals with the PI*ZZ genotype do not develop lung disease during their lifetime or have only minor symptoms. This variable disease expressivity, not accounted for by risk factors such as smoking, suggests the presence of as yet unidentified genetic disease modifiers.[17,18] The risk of liver disease is higher in individuals who are homozygous or heterozygous for alleles associated with intrahepatocyte polymerization (e.g., Z, Mmalton, and Siiyama).[27,31]

The time to the onset of respiratory symptoms in AATD varies considerably, but, in general, symptoms tend not to appear before adulthood. The decline in pulmonary function depends on factors such as exposure to tobacco smoke or environmental pollutants, occupational exposure to toxins, coexisting asthma, lower respiratory tract infections, and predisposing family factors.[25,33] Although respiratory symptoms may appear in smokers about 35 years of age and nonsmokers about 45 years of age, in the real-world setting, the average age at the diagnosis of AATD is usually above 50-55 years, irrespective of smoking history.[34] Primary symptoms are dyspnea on exertion, wheezing, and increased cough and phlegm.[25,33]

A lack of awareness of AATD is the major barrier to diagnosis. Because clinical manifestations of AATD-related lung disease are indistinguishable from those of COPD, a laboratory diagnosis is required.[35] The WHO and scientific societies, such as the American Thoracic Society, the European Respiratory Society, and the Spanish Society of Pulmonology and Thoracic Surgery, as well as the Spanish Guidelines for COPD and the GOLD, recommend that all COPD patients be tested for AATD at least once in their lifetime regardless of their smoking history or age.[4,10,36-38] Other candidates for AATD testing are patients with bronchiectasis, severe bronchial asthma showing progressive bronchial obstruction or evidence of pulmonary emphysema, unexplained liver disease at any age, systemic vasculitis, or neutrophilic panniculitis (Chart 1).[2,25] Predispositional testing should be undertaken in first degree relatives (siblings, children, and parents) and partners (for family genome purposes) of individuals with AATD.[4,10,36-38]

The underdiagnosis of AATD in Brazil highlights the need for testing COPD patients in accordance with recommendations of international guidelines.[9] Three studies undertaken in Brazil found that systematic screening for AATD in COPD patients increased the chances of identifying patients with mutations in the *SERPINA1* gene.[16,39,40]

LABORATORY DIAGNOSIS

Standard diagnostic methods

The standard approach to diagnosing AATD centers around determining AAT concentration in blood, usually by nephelometry, and then identifying specific alleles by studying the phenotype and/or genotype.[2,5,41]

The reference value for serum AAT level determined by nephelometry in healthy adults is 116-232 mg/dL (21-41 μmol/L).[42] However, because AAT is an acute phase reactant, along with C-reactive protein (CRP) and amyloid A, its plasma levels increase in response to inflammatory or infectious stimuli.[6,7,25] Moreover, because COPD is associated with systemic inflammation, AAT levels can be elevated in COPD patients when compared with age-matched controls, thus increasing the challenges of identifying possible heterozygotes among the COPD population.[43,44] Although the presence of inflammation does not generally influence a diagnosis of AATD in Pi*ZZ homozygotes, in order not to miss carriers or other patients with a deficiency, it may be useful to take a more general approach by measuring CRP and AAT levels at the same time. A normal level of CRP confirms that AAT levels are true and not falsely elevated. If the

Chart 1. Candidates for determination of alpha-1 antitrypsin levels.[a]

Individuals with COPD
Adults with bronchiectasis in whom the most common causes have been ruled out
Adults with bronchial asthma who develop progressive bronchial obstruction or show evidence of pulmonary emphysema
Blood relatives of patients with diagnosed AATD
Individuals with many family members presenting with dyspnea and chronic cough
Individuals with liver disease of unknown cause
Individuals in whom protein profile analysis shows absence of alpha-1 glycoprotein peak
Individuals with panniculitis or vasculitis of unknown cause

Adapted from Miravitlles et al.[2] and the Portuguese consensus document for the management of alpha-1-antitrypsin deficiency.[25] AATD: alpha-1 antitrypsin deficiency. [a]Routine determination of serum AAT levels is not recommended.

level of CRP is increased, AAT levels may be falsely elevated, which requires a repeat measurement of AAT levels under conditions of clinical stability.[45] A simple and practical recommendation is to measure AAT concentrations when the patient is free from inflammation or infection.

Protein phenotyping uses isoelectric focusing (IEF) electrophoresis to identify the most common AAT variants (S, Z, M, and others) present in the sample. Although IEF is the biochemical gold standard for detecting AATD variants, it requires significant expertise in interpretation and has limitations.[46] Most notably, neither does the method identify all pathological mutations present in the sample, nor does it identify null variants that produce no protein. In cases when a phenotype study does not permit a diagnosis (e.g., null, rare, and very rare variants), genotyping must be performed.

Genotyping uses PCR probes to identify the most common AATD alleles, mainly S and Z, but also others depending on available primers. Gene sequencing may be necessary in cases when a null or deficient variant other than S and Z is suspected.[2,5] Rapid genotyping methods can be used to search for the most common alleles Pi*S and Pi*Z, although misdiagnosis is possible because the methods do not include rare and null alleles.[2] Molecular analysis with direct sequencing of the *SERPINA1* gene can be used in order to identify rare alleles and null variants and to characterize new variants.[2] The technique involves complete analysis of DNA sequences of AAT-coding exons on the *SERPINA1* gene. Occasionally, it may also be necessary to study the intronic and regulatory sequences of the gene.[2,47,48]

In Brazil, some groups have proposed that AATD screening be included in the heel prick test performed routinely in newborns for conditions such as cystic fibrosis and sickle cell anemia, although opponents of the proposal argue that routine AAT measurements in newborns identifying a genetic deficiency could place a psychological burden on the affected children.

New diagnostic methods

New diagnostic methods have been developed and offer a simpler and more portable alternative to plasma/serum samples to conduct AATD testing. For example, dried blood spot specimens provide enough sample to measure AAT levels and to perform IEF electrophoresis phenotyping, providing a sufficient quantity and quality of DNA to detect Pi*S and Pi*Z alleles in a single real-time PCR and direct sequencing.[49] In Spain, a nationwide AATD case detection program conducted with COPD patients using dried blood spot specimens concluded that the screening method was feasible, simple, quick, and cost-efficient for use in this at-risk population.[50,51]

In Brazil, the dried blood spot method for measuring AAT concentrations was developed in 2011. In 2013, an immunonephelometric assay was validated to be used in serum samples and dried blood spots from COPD patients.[52] The cutoff point of 2.02 mg/dL (97% CI: 1.45-2.64 mg/dL) for dried blood spots had a sensitivity of 100%, a specificity of 95.7%, a positive predictive value of 27.2%, and a negative predictive value of 100% for establishing a diagnosis of AATD. Using the maximum value in the confidence interval as a cutoff point reduced the possibility of false-negative results. Although there was only a moderate correlation (r = 0.45) between AAT levels in serum samples and dried blood spots, it was concluded that dried blood spots were a useful alternative to serum samples to screen patients for AATD in Brazil, because the method provides rapid and minimally invasive screening at a low cost.[52]

New genotyping methods, such as the A1AT Genotyping Test (Progenika Biopharma S.A., Derio, Spain), include the analysis of rare and null alleles. This point-of-care test enables simultaneous detection and identification of the 14 most common allelic variants and their associated alleles in exons II, III, and V of the *SERPINA1* gene (Chart 2).[53] The test involves PCR amplification of genomic DNA extracted from blood (whole or dried blood spot) or saliva samples, followed by hybridization with allele-specific probes using Luminex xMAP (Luminex Corp., Austin, TX, USA) technology for high-throughput nucleic acid detection.[53] Two kits are available for sample collection for the A1AT Genotyping Test, a buccal swab kit (ORAcollect DNA; DNA Genotek, Ottawa, ON, Canada) and a dried blood spot kit (AlphaKit+;

Progenika Biopharma). The buccal swab kit is more commonly used in Brazil. The test is minimally invasive, does not require drying time, and can be transported by regular mail because DNA integrity is maintained at room temperature. The buccal swab sample remains stable for two months.[54]

The A1AT Genotyping Test offers worldwide coverage by including some of the more common rare (Mmalton, Mprocida, I, F) and ultra-rare allelic variants among the 14 allelic variants selected.[55] The absence of any of the 14 mutations in the test is reported as an "undetected variant" and suggests that the genotype may be Pi*MM (normal genotype).[56] In cases where serum AAT levels are below 50 mg/dL and none of the 14 mutations are detected, the gene is automatically sequenced by the manufacturer (Progenika Biopharma) to detect rare variants that might not have been included in the test.

By rapidly and simultaneously detecting multiple allelic variants, the A1AT Genotyping Test reduces the diagnostic time frame and the number of samples that need to be sequenced. In Italy, investigators reported a correlation of 100% between the A1AT Genotyping Test and their own diagnostic algorithm, as well as a reduction of 66% in the diagnostic time frame for samples not requiring sequencing (which takes approximately 3 days).[55] A group from Germany reported that the use of the A1AT Genotyping Test resulted in reductions of 79% and 63.4%, respectively, in nephelometric measurements and in the number of samples requiring gene sequencing, when compared with the traditional workflow (conventional PCR), although the number of IEF electrophoresis assays was unchanged. By increasing the number of detected mutations from 2 (S and Z) to 14, Luminex-based method resulted in a median time to the diagnosis of rare genotypes of 14 days, compared with 83 days for traditional methods.[57] Recently, investigators in Spain[56] reported the initial results of an ongoing observational study evaluating a new national circuit for diagnosing AATD based on Luminex multiplex technology using online registration. The analysis included 5,803 samples from buccal swabs (85.9%) and dried blood spots (14.1%) sent by postal mail to a central laboratory. The prevalence of common allele combinations (MS: 19.0%; MZ: 14.4%; SS: 2.9%; SZ: 3.7%; and ZZ: 1.4%) aligned with previously reported estimates for Spain, and the system was effective in achieving a timely diagnosis of AATD.[56]

Diagnostic algorithm

An issue faced by all physicians treating a rare disease is the applicability of guidelines to direct management decisions that are specific to their circumstances. A recent review[58] of 15 available international AATD practice guidelines published between 1989 and 2017 identified substantial variation in management recommendations. The moderate level of agreement on "when to test" (10 statements; 41%) and "how to test" (2 statements; 56%) is thought to reflect regional variations in disease prevalence, clinical manifestations, and health care funding models.[58]

At the Ibero-Latin American forum in 2019, a new algorithm for the diagnosis of AATD was proposed (Figure 1). The algorithm was a joint development by the Spanish Registry of Patients with Alpha-1 Antitrypsin Deficiency and the Latin American Thoracic Association, and applies to regions (including Brazil) where the A1AT Genotyping Test is available. According to the algorithm, patients with COPD, first-degree relatives, and partners of patients with diagnosed AATD, as well as other high risk patients (Chart 1) should be tested for AATD. The algorithm features two pathways: a conventional testing pathway which involves screening for serum AAT levels as the first step, and an alternative pathway which involves

Chart 2. Allelic variants detected with the A1AT Genotyping Test (Progenika Biopharma, Derio, Spain).

Variant	Associated allele	Predicted AAT activity
c.187C>T	Pi*I	Reduced (slight)
c.194T>C	Pi*M procida	Reduced (severe)
c.226_228delTTC	Pi*M malton, Pi*M palermo, Pi*M nichinan	Reduced (severe)
c.230C>T	Pi*S iiyama	Reduced (severe)
c.552delC	Pi*Q0 granite falls	None (protein absent)
c.646+1G>T	Pi*Q0 west	None (protein absent)
c.721A>T	Pi*Q0 bellingham	None (protein absent)
c.739C>T	PI*F	Reduced (slight)
c.839A>T	Pi*P lowell, Pi*P duarte, Pi*Q0 cardiff, Pi*Y barcelona	Reduced (slight)
c.863A>T	Pi*S	Reduced (slight)
c.1096G>A	Pi*Z	Reduced (severe)
c.1130dupT	Pi*Q0 mattawa, Pi*Q0 ourem	None (protein absent)
c.1158dupC	Pi*Q0 clayton, Pi*Q0 saarbruecken	None (protein absent)
c.1178C>T	Pi*M heerlen	Reduced (severe)

Adapted from the U.S. Food and Drug Administration.[53] AAT: alpha-1 antitrypsin; and Pi: proteinase inhibitor.

the genetic diagnosis of the 14 allelic variants that are most commonly associated with AATD as the first step. According to the conventional pathway, serum AAT levels of < 116 mg/dL (assessed by nephelometry) are indicative of "possible AATD" and should be followed by confirmatory testing. Confirmatory tests include phenotyping and/or genotyping to identify the most common variants to establish which *SERPINA1* gene alleles are present. The alternative pathway recommends using the A1AT Genotyping Test (Progenika Biopharma) as the first step to simultaneously identify and genotype the 14 most common deficiency variants of the *SERPINA1* gene. Following a genetic diagnosis, AATD is confirmed based on serum AAT levels. In either pathway, gene sequencing (the most sensitive confirmatory test) may be required if results are discordant between the serum screening test and the genetic/phenotypic test. In a cross-sectional study in Brazil, in a sample of 926 patients who underwent quantification of AAT levels, only 3 required gene sequencing due to discordant results.[16]

The vast majority of patients with AATD will benefit from genetic counseling, prevention of lung damage,

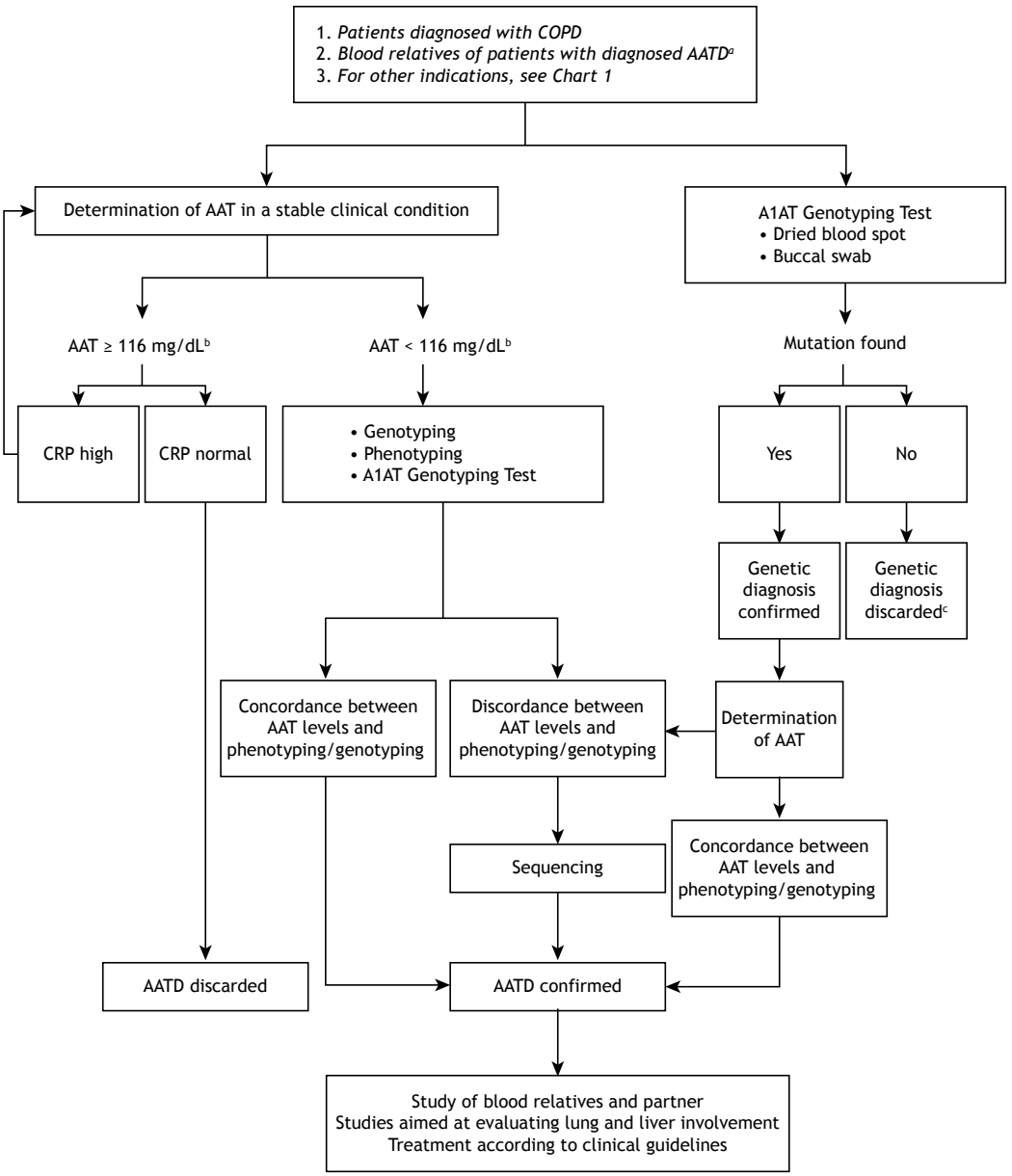

Figure 1. Alpha-1 antitrypsin deficiency diagnostic algorithm. AATD: alpha-1 antitrypsin deficiency; AAT: alpha-1 antitrypsin; and CRP: C-reactive protein. [a]In case of a patient diagnosed with AATD, investigate the partner to assess the risk of the disease in the offspring. [b]Determination in blood by nephelometry. For other techniques, apply a conversion factor. [c]If there is high clinical suspicion of AATD, determine AAT levels in a stable clinical condition.

and therapeutic intervention. Pharmacological and nonpharmacological measures for patients with AATD-associated COPD are similar to those for COPD patients without AATD.[10,37,59] Patients with severe AATD-associated COPD (serum AAT concentrations ≤ 50 mg/dL), never or former smokers, or patients with FEV_1 < 80% of the predicted value who present with impairment of lung function or progression of emphysema despite standard COPD treatment may be candidates for augmentation therapy with purified AAT,[10,37] although specific recommendations may vary by country.[58]

PATIENT ASSESSMENT: COMPLEMENTARY TESTS

After diagnosing AATD, the patient should be examined for the presence and extent of lung and liver involvement, as well as for less commonly associated conditions, such as vasculitis and panniculitis. Clinical history, physical examination, and family history must be taken into account when interpreting the results. Complementary tests to be performed in patients with COPD due to AATD are summarized in Chart 3.

Respiratory function tests

Spirometry is the basic respiratory function test to diagnose COPD. In patients with COPD due to AATD, post-bronchodilator spirometry usually shows a typical obstructive pattern, with a FEV_1/FVC ratio < 0.7, a decrease in FEV_1, and a normal or decreased FVC. In smokers with AATD, the decrease in FEV_1 accelerates in proportion to the smoking history (pack-years). The flow-volume curve shows a reduction in pulmonary flow with a typical concave morphology.[38]

Study of lung volumes in emphysematous patients shows an increase in RV and hyperinflation, translating into an increase in TLC and in the RV/TLC ratio.[38] DLCO is diminished and correlates with a loss of lung parenchyma observed by CT and with the degree of anatomical emphysema.[60,61]

A loss of lung function in patients with AATD may lead to respiratory failure. Investigation of pulmonary emphysema requires post-bronchodilator spirometry and the determination off static lung volumes and DLCO, as well as arterial blood gas analysis if SpO_2 is < 92%. A cardiopulmonary exercise test may also be required. Tolerance to effort may be limited due to airway obstruction, reduced ventilatory capacity, and dynamic hyperinflation.[62] Desaturation in a walking test or in an exercise capacity test most closely correlates with reduced quality of life in patients with AATD.[63]

Current recommendations for managing AATD include an initial clinical evaluation, full pulmonary function testing, arterial blood gas analysis in cases of low SpO_2, and, in follow-up evaluations, annual spirometry.[2,10,25,64,65]

Imaging tests

Plain chest X-rays are usually normal in the early stages of AATD but show characteristic findings of emphysema in up to 85% of cases as the disease progresses. Findings include hyperinflation with diaphragm flattening, increased retrosternal space, small heart, normal or prominent hilar arteries, and decreased caliber of peripheral vessels.[66]

As demonstrated in clinical trials to date, CT scanning expressed in terms of lung density is a useful tool to characterize lung structure and assess the impact of therapeutic interventions in AATD-associated COPD.[67] Quantitative CT provides a reader-independent estimate of the extent and severity of emphysema which correlates with various disease measures and clinical outcomes.

HRCT of the chest is more sensitive than chest X-rays in detecting early emphysematous changes and bronchiectasis. Up to 90% of the patients with severe AATD who smoke will develop emphysema in comparison with 65% of nonsmoking AATD patients.[68] Emphysema is characteristically panacinar, bilateral, and basal (Figure 2), although up to one third of the patients will have upper lobe distribution, more often found in smokers.[69] This pattern is more common in Pi*SZ heterozygotes.[70] CT has been proposed as the best method to evaluate the progression of emphysema, although its application currently remains limited to clinical studies.[71]

Liver tests

Liver function in patients with AATD can be evaluated by determining the levels of alanine transaminase, aspartate transaminase, gamma-glutamyl transferase, bilirubin, and albumin, as well as by performing coagulation tests.[30,31] Other tests, such as ultrasound, transient elastography, and magnetic resonance angiography of the liver, can also be performed when necessary and are highly sensitive for detecting liver involvement.

FINAL CONSIDERATIONS

In Brazil, as elsewhere, the presence of AATD cannot be overlooked. Early diagnosis can have a positive impact on convincing individuals with AATD to avoid smoking and minimize their exposure to environmental pollutants, potentially altering the natural history of the disease and limiting its progression. AAT augmentation therapy may be indicated in certain cases.

AATD case detection should be carried out in all patients with COPD regardless of age, sex, smoking history, or onset of respiratory symptoms. Systematic evaluation of COPD patients in Brazil has shown to be sufficiently effective and is recommended as a screening method.

New diagnostic tools, such as the A1AT Genotyping Test that uses a buccal swab or dried blood spots, can contribute to overcoming the underdiagnosis of AATD

Chart 3. Complementary tests for patients with alpha-1 antitrypsin deficiency-associated COPD.

Test	Type	Clinical utility
Laboratory	Basic biochemistry including liver function tests and serum immunoglobulins[a]	
Respiratory	Forced spirometry	Assessment of obstructive pattern (FEV_1/FVC ratio < 0.7) and its severity (FEV_1)
	Bronchodilation test	Evaluation of reversibility of bronchial obstruction
	Lung volumes and DLCO	Evaluation of the degree of pulmonary hyperinflation and gas exchange capacity at the pulmonary level
Imaging	Chest X-ray	Basic test in all patients with respiratory symptoms
	HRCT of the chest	Confirmation of extension, location, and type of emphysema, as well as presence of bronchiectasis
	Liver ultrasound Elastography Magnetic resonance imaging	Sensitive and useful for detection of liver involvement

[a]Serum immunoglobulins: necessary to detect severe immunoglobulin A deficiency, which contraindicates treatment with intravenous alpha-1 antitrypsin.

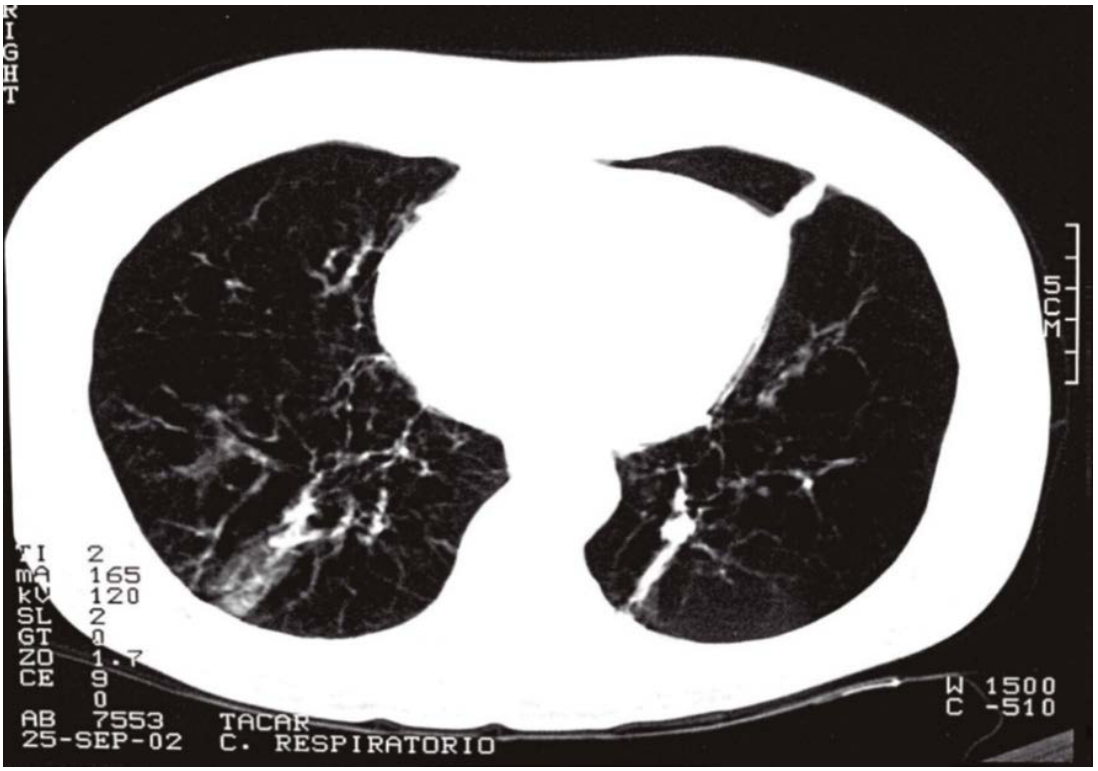

Figure 2. HRCT of the chest of a patient with pulmonary emphysema due to severe alpha-1 antitrypsin deficiency (homozygous Pi*ZZ) showing characteristic panacinar and bilateral emphysema, predominating in the pulmonary bases. Image courtesy of F Casas-Maldonado.

in Brazil, because they offer a minimally invasive, reliable, and rapid alternative to traditional methods. Complementary strategies to improve diagnosis include continuing medical education, easy access to laboratory tests, and public awareness campaigns about AATD and its clinical manifestations. Further studies about the prevalence of and screening tools for AATD would also be useful to support the implementation of efficient and cost-effective programs for the detection and management of patients with AATD in Brazil.

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AUTHOR CONTRIBUTIONS

JRJ, FCM, and MM: conception and planning of the review; interpretation of findings; drafting and revision

of preliminary and final versions; and approval of the final version. FLAF, MVCOC, and MTD: drafting and revision of preliminary and final versions; and approval of the final version.

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ELMO 1.0: a helmet interface for CPAP and high-flow oxygen delivery

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TO THE EDITOR:

A few months after the description of the first case of COVID-19 in China, the disease became a pandemic. More than 50 million people have been infected with SARS-CoV-2, and more than 1 million deaths have been confirmed worldwide.[1] The number of COVID-19 cases in Brazil has been high, Brazil ranking third among the countries with the highest death toll[2]; with no immediate resolution in sight, there is a possibility of a second wave of infection, which several countries are currently facing.[3]

Infection with SARS-CoV-2 causes COVID-19, the clinical spectrum of which ranges from no symptoms to flu-like symptoms such as fever, fatigue, dry cough, and dyspnea.[4] Although most cases progress favorably, 15-20% of patients develop severe forms of COVID-19 (including ARDS), requiring ventilatory support. In a case series of hospitalized patients with COVID-19 in the USA, 14% required admission to the ICU, and those who required mechanical ventilation had high mortality rates (88.1%).[5]

The management of COVID-19–related respiratory failure is quite challenging. First, although noninvasive ventilation can prevent endotracheal intubation and its complications, the high flow rates increase the risk of aerosolization and the spread of the virus, therefore increasing the rate of infection in health professionals.[6] Second, the number of ICU beds available in the beginning of the pandemic was lower than the total number of infected patients requiring noninvasive ventilation.[7] Third, ventilator manufacturers worldwide were unable to meet the surge in demand. The spectrum of COVID-19 presentation includes moderate to severe ARDS, which has the highest rates of morbidity and mortality and is the most challenging with regard to managing ventilatory support.

In this context, a helmet interface—a transparent hood that covers the entire head of the patient, with a soft collar neck seal—allows safe and comfortable delivery of positive airway pressure to patients with moderate to severe acute respiratory failure, potentially reducing intubation rates.[7,8] Under the coordination of the *Escola de Saúde Pública do Ceará Paulo Marcelo Martins Rodrigues*, located in the city of Fortaleza, Brazil, a public-private partnership was established among research funding agencies, universities, and sectors of the industry in the state of Ceará, forming a multidisciplinary task force to develop the first helmet interface manufactured in Brazil. The device was developed in record time (three months) and was designated ELMO 1.0 (*elmo* being a Portuguese word for helmet), being patented in Brazil (BR 20 2020 014212 2; ANVISA no. 82072609001).

The ELMO 1.0 was based on similar devices in the literature[9,10] and consists of a transparent nontoxic autoclavable PVC hood (height, 270 mm; diameter, 290 mm) and a silicone rubber collar neck seal attached to a polypropylene ring. The hood has a posterosuperior inhalation port (inlet) and a contralateral anteroinferior exhalation port (outlet). The silicone rubber collar neck seal can be adjusted to fit different neck circumferences. The ELMO 1.0 is a noninvasive ventilation device that prevents air leaks and droplet dispersion, as well as delivering CPAP as high as 10-15 cmH_2O, being particularly interesting for use in COVID-19 patients requiring oxygen therapy (Figure 1).

Nine prototypes were developed. For quality and patient risk assessment, usability tests were performed with six health professionals (two physicians, two physiotherapists, and two nurses) with experience in mechanical ventilation and four healthy volunteers (one woman and three men; mean age, 38.5 years; range, 24.0-51.5 years).

All usability tests were performed in a technological innovation laboratory designed specifically for the present study. In the laboratory, the health professionals watched an instructional video on how to assemble the system and performed tasks aimed at identifying potential problems when using the ELMO 1.0. They were asked to do the following: 1) check the patient neck circumference; 2) recognize, assemble, and check the ELMO 1.0; 3) place the ELMO 1.0 interface on the patient; 4) initiate delivery of CPAP and oxygen therapy; 5) check the pressure inside the ELMO 1.0 interface by using an analog cuff manometer and a CPAP setting of 10 cmH_2O; 6) give water to a patient receiving helmet noninvasive ventilation with the ELMO 1.0; 7) change the position of the patient; and 8) remove the ELMO 1.0 interface. The problems identified by the health professionals were classified as follows: a) minor problems—problems requiring no immediate changes; b) intermediate problems—problems requiring changes, albeit not immediately; and c) major problems—problems requiring immediate changes.

A total of 22 problems were reported, with suggestions regarding connections for inhaled and exhaled gas flow, access to the patient, and instructions in the manual, as well as other suggestions that were incorporated into the final prototype, which is presented here. The time

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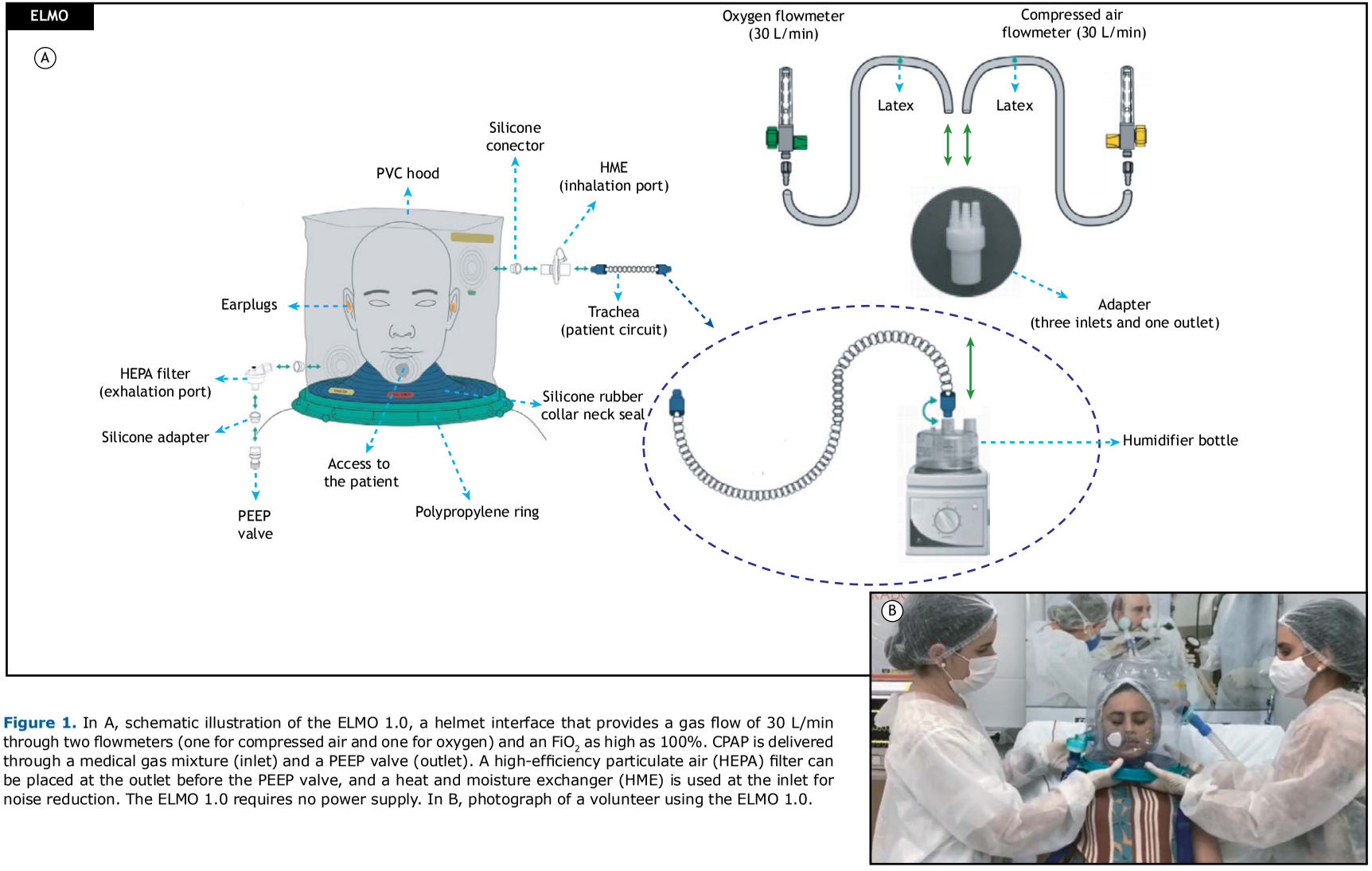

Figure 1. In A, schematic illustration of the ELMO 1.0, a helmet interface that provides a gas flow of 30 L/min through two flowmeters (one for compressed air and one for oxygen) and an FiO_2 as high as 100%. CPAP is delivered through a medical gas mixture (inlet) and a PEEP valve (outlet). A high-efficiency particulate air (HEPA) filter can be placed at the outlet before the PEEP valve, and a heat and moisture exchanger (HME) is used at the inlet for noise reduction. The ELMO 1.0 requires no power supply. In B, photograph of a volunteer using the ELMO 1.0.

to perform each task was measured, assembling and checking the ELMO 1.0 being the task that took the longest to complete (7.0 ± 2.0 min).

After the usability tests were completed, a visual analog scale was used in order to assess interface comfort, ranging from zero (uncomfortable) to 10 (comfortable). The median score was 8.5 (range, 7.0-9.0). Volunteers used the ELMO 1.0 for a mean time of 47.5 min (range, 41.2-57.5 min), during which minimal adverse effects were observed, including hyperemia in the posterior cervical region (in 1 participant), without the need for discontinuation or additional measures.

After approval of the final prototype, we tested the ELMO 1.0 noise level and pressure (CPAP), the former ranging from 45 dB to 65 dB and the latter ranging from 12 cmH_2O to 13 cmH_2O. Carbon dioxide rebreathing was assessed by sidestream capnography with a standard nasal cannula and a gas mixture at different flow rates (30 L/min, 40 L/min, 50 L/min, and 60 L/min) for inspired carbon dioxide tension ($PiCO_2$) measurement. Flow rates greater than 40 L/min resulted in a $PiCO_2$ of 0-1 mmHg, whereas a flow rate of 30 L/min resulted in a $PiCO_2$ of 2-5 mmHg. A higher flow rate translated to a lower likelihood of carbon dioxide rebreathing, a finding that is consistent with the literature.[10]

In a short period of time, we have developed a new helmet interface for comfortable CPAP delivery through a gas mixture (oxygen and compressed air), with minimal adverse effects, effective positive airway pressure, an effective seal, and a reduced risk of carbon dioxide rebreathing. The ELMO 1.0 is a device that can be used in clinical tests to provide ventilatory support for patients with acute hypoxemic respiratory failure secondary to COVID-19 or other causes.

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AUTHOR CONTRIBUTIONS

MAH, GCG, JAL, BST, and DGAM: conception and planning of the study; data collection and tabulation; statistical analysis and creation of tables and figures; drafting and revision of the manuscript; formatting of the manuscript in accordance with the JBP instructions for authors; and approval of the final version.

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Hyperoxemia and excessive oxygen use in COVID-19-related ARDS: preliminary results of a prospective cohort study

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TO THE EDITOR:

Patients with severe COVID-19 pneumonia commonly fulfill the ARDS Berlin definition[1,2] and must be ventilated using protective parameters to avoid ventilator-induced lung injury.[3,4] A target SaO_2 of 92-96% is recommended,[5] because an SaO_2 < 92% or > 96% might be harmful.[6,7]

Experimental studies have demonstrated that exposure to high FiO_2 can induce pulmonary inflammation due to excessive production of reactive oxygen species.[8] Moreover, hyperoxemia (i.e., increased PaO_2) has deleterious systemic effects, such as reduced cardiac output and vasoconstriction in cerebral and coronary circulation.[9] Despite such risks, hyperoxemia and excessive oxygen use are common in patients with ARDS.[10]

During the COVID-19 pandemic, excessive oxygen use causes an additional problem: oxygen shortage. The great number of patients requiring ventilatory support simultaneously may compromise oxygen stocks. In this scenario, avoiding hyperoxemia and excessive oxygen use become an important strategy to spare oxygen. We hypothesized that hyperoxemia and excessive oxygen use might be common events in intubated COVID-19 patients. Therefore, our objective was to determine the frequency of such events during the first two days of mechanical ventilation (MV) in patients with COVID-19.

This is a preliminary analysis from a prospective cohort study that has been conducted in two dedicated COVID-19 ICUs (at the University Hospital of the Federal University of Juiz de Fora and at Hospital Regional Doutor João Penido, both located in the city of Juiz de Fora, Brazil) since 2020, March 1st. The objective of the main study is to describe MV parameter settings in COVID-19 patients. The study was approved by the research ethics committees of the two institutions, and written informed consent was obtained from the next of kin or guardian of the patient.

Consecutive patients ≥ 18 years of age, infected with SARS-CoV-2 (confirmed by RT-PCR), and receiving invasive MV for at least 48 h were eligible for participating in the study. We excluded patients transferred from another hospital who had been on invasive MV, patients for whom life-sustaining treatments were withheld, and patients with hypoxemia (PaO_2 < 55 mmHg regardless of the FiO_2) on day 1 of MV. Ventilatory parameters were set by the attending physician.

Clinical and laboratorial parameters were obtained on the day of admission to the ICU. On day 1 and day 2 of MV (at 8 a.m.), MV parameter settings and arterial blood gas measurements, were recorded. We defined hyperoxemia as a PaO_2 > 100 mmHg and excessive oxygen use as an FiO_2 > 60% in patients with hyperoxemia. Sustained hyperoxemia was defined as the presence of hyperoxemia on days 1 and 2 of MV.

Results are reported as medians and interquartile ranges or absolute and relative frequencies. Differences between patients with normoxemia and those with hyperoxemia were tested using the Wilcoxon test or the chi-square test, as appropriate.

During the study period, 239 patients with confirmed COVID-19 were admitted to one of the ICUs. Of those, 122 were excluded: 82 patients did not receive invasive MV, 24 received invasive MV for less than 48 h, 14 had life-sustaining treatments withheld, and 2 were hypoxemic on day 1. Therefore, 117 patients were included in the study. The median age of the patients was 66 (58-75) years, and 61 (52.1%) were male. On admission, the median Simplified Acute Physiology Score 3 was 48 (41-57), and the median Charlson comorbidity index was 3 (2-5). On day 1 of MV, the medians of the following parameters were: PaO_2/FiO_2 = 191 (142-248) mmHg; plateau pressure = 24 (22-28) cmH_2O; driving pressure = 14 (11-16) cmH_2O; PEEP = 10 (10-12) cmH_2O; and respiratory system compliance = 29.3 (24.7-35.6) mL/cmH_2O. During the period on MV, 72 patients (62%) were placed in the prone position, and 40 patients (34%) needed hemodialysis. All-cause hospital mortality was 63.0%, and ICU mortality was 59.3%.

Hyperoxemia was present in 80 (68.4%) and 74 (63.2%) of the patients on days 1 and 2 of MV, respectively, regardless of FiO_2 ranges. Of the 80 patients with hyperoxemia on day 1, 53 (66.3%) sustained a PaO_2 > 100 mmHg on day 2. Cumulative relative frequency distributions of PaO_2 were similar on days 1 and 2 (Figure 1).

FiO_2 levels decreased on day 2, when compared with those on day 1, in patients with hyperoxemia (Figure 1). There was a reduction in excessive oxygen use on day 2 (28 patients [23.9%]) when compared with that on day 1 (43 patients [36.8%]; p = 0.03; Figure 1). However, there was an increase in the number of patients with hyperoxemia among those with an FiO_2 < 0.6 (46 patients on day 2 vs. 37 on day 1; Figure 1). Together, these findings suggest that intensivists neglected to decrease FiO_2 when gas exchange improved.

The proportion of patients with hyperoxemia in our cohort was higher than that found in a similar study

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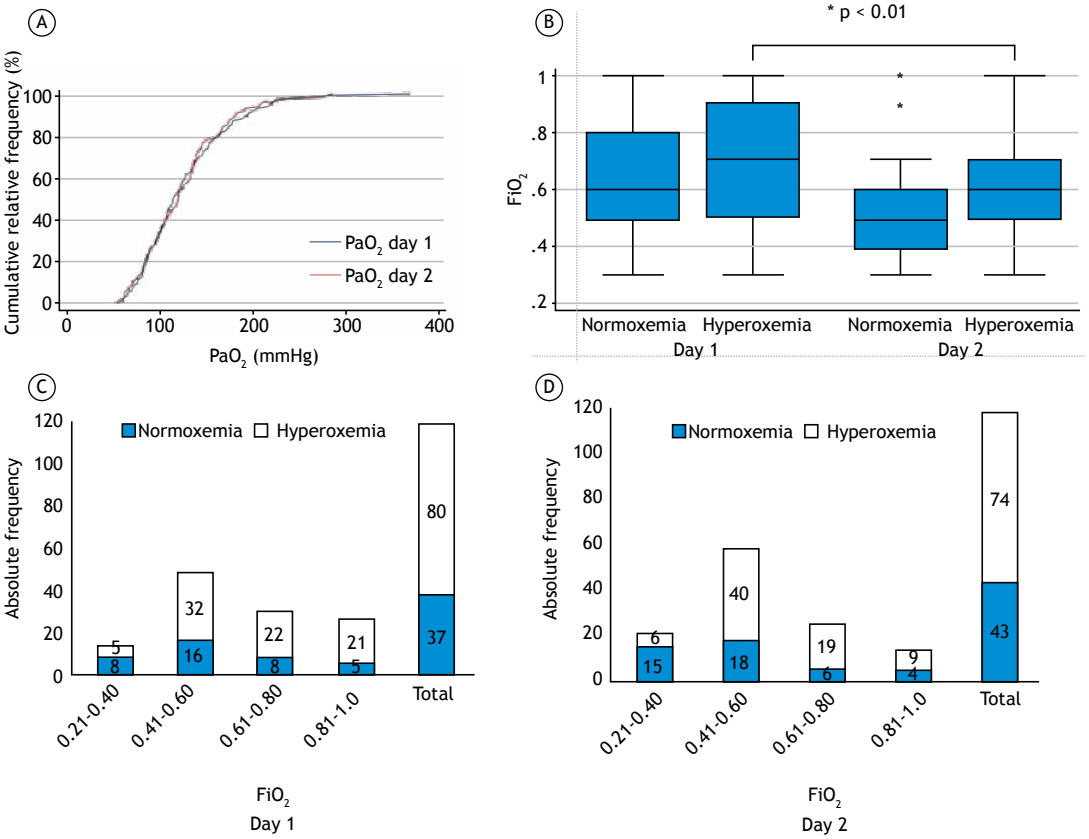

Figure 1. In A, a graph showing that cumulative relative frequency distributions of PaO_2 were similar on day 1 (blue line) and day 2 (red line) of mechanical ventilation (MV). In B, box plot showing FiO_2 levels on days 1 and 2 of MV and classified by the presence of normoxemia or hyperoxemia. There was a significant decrease in FiO_2 on day 2, when compared with that on day 1, among patients with hyperoxemia ($p < 0.01$). In C and D, histograms showing absolute frequencies of normoxemia or hyperoxemia in different ranges of FiO_2 on days 1 (in C) and 2 (in D) of MV.

including patients with ARDS due to other causes.[10] In that study,[10] 30% of the patients presented with hyperoxemia on day 1 of MV; among those, FiO_2 was high in 66%. The great number of patients admitted to ICUs during the COVID-19 pandemic, resulting in work overload of health care professionals, might explain that difference. Moreover, the necessity of using personal protective equipment may reduce the frequency at which COVID-19 patients are seen by physicians, nurses, and respiratory physical therapists, as well as the frequency at which mechanical ventilator settings are adjusted.

During the COVID-19 pandemic, some hospitals have run out of oxygen in Brazil. Our results show the importance of optimizing PaO_2 and FiO_2 levels during the ventilatory support of COVID-19 patients. That can be a useful strategy to minimize the shortage of oxygen.

The present study has limitations. Our analyses were based on arterial blood gas analysis and FiO_2 that were determined at a specific time each day; therefore, they might not reflect the spectrum of values that occurred throughout that day. In addition, we evaluated hyperoxemia and high FiO_2 only in the first two days of MV, and we cannot rule out the possibility that settings after day 2 of MV might have interfered on final outcomes.

In conclusion, hyperoxemia and excessive oxygen use are events that might be common during the first days of MV in COVID-19 patients. Avoiding the occurrence of these events should be used as a strategy to reduce oxygen shortage.

AUTHOR CONTRIBUTIONS

EPG: study conception and design; data acquisition, analysis, and interpretation; drafting and revision of preliminary versions; and approval of the final version. MMR: data analysis and interpretation; drafting and revision of preliminary versions; and approval of the final version. GBC: data acquisition, analysis, and interpretation; revision of preliminary versions, providing intellectual content of critical importance; and approval of the final version. EVC: study conception and design; data acquisition; revision of preliminary versions, providing intellectual content of critical importance; and approval of the final version. BVP: study conception and design; data analysis and interpretation; drafting and revision of preliminary versions; and approval of the final version.

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Evaluation of pulmonary function in post-COVID-19 patients - when and how should we do it?

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TO THE EDITOR:

In December of 2019, initial reports regarding a novel respiratory virus, later designated SARS-CoV-2, emerged from Wuhan, China. This highly transmissible virus spread rapidly. On March 11, 2020, the WHO declared COVID-19 to be a global pandemic, marking the beginning of a new world era. Given the possible clinical consequences of this infection—such as the development of SARS and the high infection and mortality rates—countless investigations and studies were conducted. In 2020, a great deal of knowledge was generated at light speed about the virus itself and its transmission, as well as on the applicability of various drugs/procedures as potential therapeutic approaches. Now, after one year from the beginning of the pandemic and more than 100 million cases of SARS-CoV-2 infection, the majority of whom surviving, we are posed with a new challenge: how and when ought we to follow up these patients?

Looking back, the outbreak of SARS, a novel coronavirus infection that started in southern China and was identified in March of 2003, became a global public health crisis. In the years that followed, various studies regarding the follow-up of survivors were published. The assessment included spirometry and determination of lung volumes and DL_{CO} at 3, 6, 12, 18, and 24 months after the disease onset.[1-3] Significantly impaired DL_{CO} was the most commonly reported lung abnormality, present in 15-50% of the survivors. Low exercise capacity was also reported, measured by the six-minute walk test (6MWT) [1-3] and cardiopulmonary exercise testing (CPET),[4] the latter suggesting extrapulmonary causes for the functional outcomes in those patients. Respiratory muscle strength was measured in two studies,[2,3] using MIP and MEP. It is also important to point out that health status was evaluated using the Medical Outcomes Study 36-item Short-Form Health Survey, whose scores showed a positive correlation with pulmonary function abnormalities.[1-3]

Most recently, a systematic review and meta-analysis[5] on respiratory function in post-COVID-19 patients reported altered DL_{CO} in approximately 40% of the patients. However, the results must be analyzed with caution, because respiratory comorbidities and different timing of evaluations should be considered. It is still unclear whether interstitial abnormalities or pulmonary vascular abnormalities contributed to the decrease in DL_{CO} in those patients.[6] Initial results from the national prospective observational Swiss COVID-19 lung study,[7] after a 4-month follow-up of COVID-19 survivors, identified that low DL_{CO} was the single most important factor associated with previous severe/critical disease, which translated to reduced six-minute walk distance and oxygen desaturation during exercise.

An important aspect to consider is the ideal timing to perform pulmonary function tests. The British Thoracic Society guidelines, regarding patients with COVID-19 pneumonia, recommended that pulmonary function tests be performed at 3 months after discharge if chest X-ray changes have not satisfactorily resolved or if the patient has ongoing respiratory symptoms.[8] Similar recommendations have been made by the Spanish Society of Pulmonology and Thoracic Surgery.[9] That society suggests that simple spirometry and determination of DL_{CO} should be used as a first approach; if interstitial lung disease is suspected, body plethysmography should be included, whereas if symptoms persist, exercise tests, such as 6MWT or CPET, should be carried out. Measuring respiratory muscle strength (MIP, MEP, and sniff nasal inspiratory pressure) may also be considered in such patients.[9]

In the United States, the Yale School of Medicine at New Haven has developed a program to provide a comprehensive evaluation of post-COVID-19 complications, characterize and mitigate pulmonary sequelae, and address persistent symptoms experienced by survivors.[10] There is also an ongoing multicenter prospective observational cohort study in Brazil[11] involving post-COVID-19 patients during a one-year follow-up by means of extensive pulmonary function assessment (spirometry, lung volumes, DL_{CO}, 6MWT, and CPET), CT of the chest, and administration of quality of life questionnaires.

In summary, there are currently a great number of post-COVID-19 patients who ought to be followed up so that respiratory and nonrespiratory complications can be identified. It is of utmost importance that clinical follow-up protocols be established and adapted to the reality of every country for recommending which, when, and how often ancillary tests should be performed. On the basis of the information available so far, survivors of COVID-19 pneumonia should be evaluated at 3 months after discharge. That evaluation should include investigation of respiratory symptoms, X-ray of the chest, spirometry, and determination of DL_{CO}. In the presence of altered or persistent symptoms, whole body plethysmography, exercise testing, and evaluation of muscle strength should be carried out. In addition, patients with a previous

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diagnosis of respiratory disease who get infected with SARS-CoV-2, even without developing pneumonia, should be reevaluated 3 months after the infection being detected, or earlier if there is worsening of symptoms.

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Differential diagnosis between lung injury associated with electronic cigarette use and COVID-19 pneumonia

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TO THE EDITOR:

A 48-year-old woman underwent abdominal MRI for the investigation of a pancreatic cyst. Incidentally, alterations at the lung bases were revealed in the scans (Figure 1A). When specifically asked about symptoms, the patient reported persistent cough and headache for three weeks. She was referred to the ER for further evaluation and to be tested for SARS-CoV-2, showing negative results (RT-PCR and serology). Two days later, she presented with fatigue and fever (38°C) and was hospitalized. A CT of the chest revealed areas of consolidation associated with discrete ground-glass opacities in the lower lobes (Figure 1B), which were interpreted as suspected COVID-19 pneumonia with mild parenchymal extent in the radiological reports. A new round of tests for COVID-19 was performed, showing negative results once again. She was discharged afebrile on antibiotic therapy and was instructed to report for follow-up at the pulmonology outpatient clinic of the institution. Two weeks later, during the clinical evaluation at the outpatient clinic, the patient presented with persistent cough, worsened fatigue, and chills (but no fever). Repeat CT of the chest revealed a small increase in the number of consolidations in the lower lobes (Figure 1C).

Her previous medical history was unremarkable, except for the pancreatic cyst and a diagnosis of depressive disorder (treated with bupropion). She had no history of environmental exposure and was a former smoker (five pack-years; she quit at the age of 27). She reported having used electronic cigarettes in various occasions during the first semester of 2020 (more than 10 times). Her last consumption (together with the use of cannabis) had been one week after the onset of symptoms.

On physical examination, she was breathing normally, showing paroxysmal coughing without expectoration. SpO_2 was 96% on room air. Lung auscultation revealed crackles at the lung bases. The remainder of the physical examination was unremarkable. RT-PCR and serology for SARS-CoV-2 were negative again, as were the results for other viral serological tests. Rheumatologic tests were normal. Bronchoscopy showed normal results, followed by BALF collection and transbronchial biopsy at the left posterior lung base. BALF cytology revealed the presence of 20% of eosinophils, whereas examination of the biopsy specimen revealed signs of pneumonia and a great number of eosinophils. Tests for infection in BALF and in the biopsy specimen resulted negative.

Treatment with prednisolone was started (60 mg/day). A follow-up CT performed 30 days later demonstrated complete resolution of the consolidations, and only linear atelectasis remained at the lung bases (Figure 1D). In parallel, the patient, who had already quit the use of e-cigarettes, showed clinical improvement after corticosteroid therapy.

In March of 2020, the WHO declared COVID-19 a pandemic, a reflection of a ruthless disease with a high rate of transmission in an epidemiological context that virtually makes it imperative to discard this diagnosis at the minimum signs of respiratory and systemic symptoms. One of the major diagnostic methods that have been largely employed in this scenario is chest CT. According to the Radiological Society of North America consensus statement[(1)] on how to report chest CT findings related to COVID-19, four categories were proposed: typical, indeterminate, atypical, and negative for pneumonia. The objectives of that standardized classification system are to provide guidance and confidence to radiologists and help them communicate clearly with other healthcare providers. In that classification system, typical features are those that are reported in the literature to be frequently and more specifically seen in COVID-19 pneumonia during the current pandemic.[(1)] Although CT findings represent an important tool for COVID-19 screening, they can often be limited, even when findings deemed typical are demonstrated. Therefore, various different etiologies are able to induce clinical and radiological findings that are very similar to those in COVID-19 and need to be taken into account as differential diagnoses, including both infectious and noninfectious causes.

E-cigarette, or vaping, product use-associated lung injury (EVALI) is one of such diagnoses. The number of e-cigarettes has been significantly increasing since their introduction in Europe in 2006; about 41 million users were estimated in 2018.[(2)] EVALI seems to be a syndrome characterized by respiratory insufficiency and intense inflammatory response. Patients show fever, leukocytosis, and increased CRP levels, as well as negative viral and bacterial tests. Patients commonly demonstrate an inflammatory phenotype with high concentrations of at least two markers (CRP, ESR, leukocytosis, and procalcitonin).[(3)]

Different products work as vaporizers, including the modern e-cigarettes. All of these devices work through the heating of a liquid inside cartridges, producing

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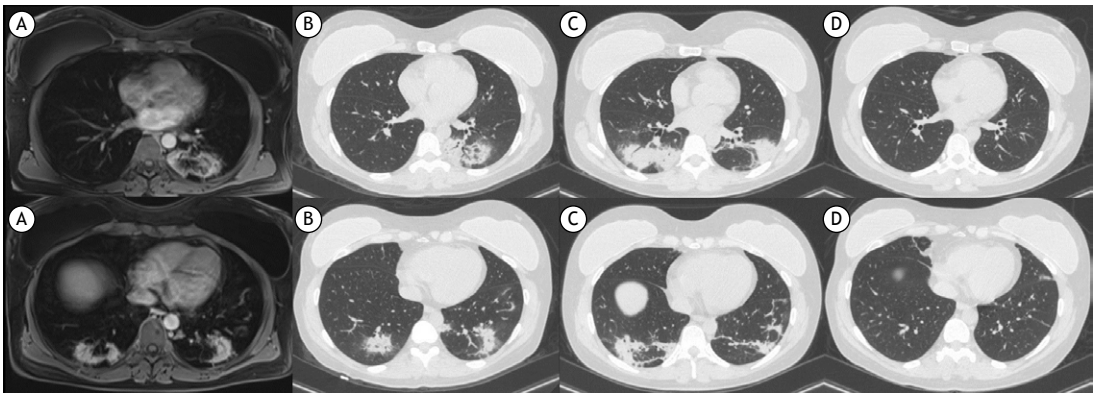

Figure 1. Axial MRI or CT scans of the lower lung fields. In A, axial T1-weighted post-contrast MRI sequence revealing bilateral lung parenchymal alterations enhanced by the paramagnetic contrast agent. In B, chest CT scans performed two days after MRI revealing consolidations and ground-glass opacities, assuming a semi-annular form in the left lower lobe. In C, repeat CT scans performed two weeks later revealing an increase in the extent and redistribution of consolidations in the lower lung fields, a feature commonly found in organizing pneumonia and in eosinophilic pneumonia. In D, follow-up CT scans performed 30 days after the initiation of corticosteroid therapy showing complete resolution of the alterations, except for linear atelectasis.

aerosolized vapor inhaled to the lungs. The liquid in e-cigarettes can contain various components, such as vitamin E acetate (generally used as a diluent for tetrahydrocannabinol oil), being one of the ingredients to be implicated as a major causal agent of EVALI, because it has been found in BALF samples of a wide number of patients.[4] However, there are many other components that are potentially pernicious when they are inhaled. Thus, it is still necessary to have a better understanding about the pathophysiology of EVALI, including studies on the chemistry and toxicology of those components, as well as on the mechanisms of molecular and cellular changes involved.[5]

The imaging presentations of EVALI are quite varied, characterized by ground-glass opacities (the dominating finding in the majority of patients), consolidations, interlobular septal thickening, and mosaic attenuation. Different radiological patterns have been described and correlated with different histopathological presentations, such as acute alveolar damage, eosinophilic pneumonia (EP), organizing pneumonia (OP), alveolar hemorrhage, hypersensitivity pneumonitis, lipoid pneumonia, and other mixed or nonclassifiable patterns.[6] Although imaging findings are varied, a common point between the different patterns seems to exist: the bilaterality of parenchymal changes. These changes may be diffuse or predominate in one of the lung (upper or lower) fields.

In our patient, the initial chest CT demonstrated consolidations and ground-glass opacities in the lower lobes, some assuming annular or semi-annular forms, resembling the reversed halo sign, which is usually seen in the classic OP pattern.[7] The imaging findings in patients with COVID-19 pneumonia, as well as in those with other viral pneumonias, can partially be attributed to secondary OP.[8] The investigation was continued with transbronchial biopsy and BALF analysis, which revealed a high number of eosinophils and EP, respectively. EP has overlapping imaging findings with OP, and they can be distinguished by the indirect demonstration of peripheral eosinophilia or by direct demonstration of eosinophilic infiltrates.[9] EP can have different triggering factors, including the use of e-cigarettes and viral infections. Recently, a case of EP associated with COVID-19 has been reported,[10] and there was clinical and radiological improvement after treatment with prednisolone, which is similar to what occurred with our patient.

In conclusion, in the face of negative laboratory testing for SARS-CoV-2 and other infectious agents, negative rheumatological tests, the fact that our patient reported e-cigarette use, and the rapid clinical response after she discontinued that use and completed corticosteroid therapy, we reached the diagnosis of EVALI-related EP.

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Adherence to long-term home oxygen therapy in patients with chronic respiratory disease in two cities in the state of Minas Gerais, Brazil

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TO THE EDITOR:

Hypoxemia is a common clinical feature in patients with chronic respiratory disease. Long-term oxygen therapy (LTOT) is the recommended treatment for hypoxemia and can effectively improve survival in chronic hypoxemic patients. The criteria for prescribing LTOT are well established by national and international guidelines,[1,2] included a duration of at least 15 h/day in the presence of hypoxemia at rest (i.e., $PaO_2 \leq 55$ mmHg; $SaO_2 \leq 88\%$; or PaO_2 = 56-59 mmHg and $SaO_2 \leq 89\%$ at rest in the presence of pulmonary hypertension, *cor pulmonale*, or polycythemia [hematocrit > 55%]).[1] Most LTOT prescriptions are provided at hospital discharge after remission of lung disease/an exacerbation. Medical societies recommend that patients eligible for LTOT be assessed 90 days after hospital discharge after remission of lung disease/an exacerbation, because more than one third of such patients will no longer need LTOT then.[1-6] Although the benefits of LTOT in the prevention and treatment of pulmonary hypertension and in the reduction of mortality are well documented, studies have reported that adherence to LTOT is poor, ranging from 45% to 70%.[5,7]

Public health care facilities based in municipalities that offer LTOT and have structured protocols (such as the city of São Paulo, Brazil) have demonstrated efficiency in LTOT dispensation.[2] Brazilian municipalities without such protocols might use different procedures 90 days after the initial LTOT dispensation.

Adherence to LTOT in the Brazilian public health care system in the state of Minas Gerais, Brazil, has yet to be studied. Therefore, we sought to investigate adherence to prescribed LTOT in patients treated in the public health care system in the cities of Juiz de Fora and Governador Valadares, both located in the state of Minas Gerais.

This was a prospective cross-sectional study conducted between March of 2019 and March of 2020 and including individuals ≥ 18 years of age receiving LTOT for at least three months. The study was approved by the Research Ethics Committee of the Federal University of Juiz de Fora (Protocol no. 3.084.871), and all participants gave written informed consent. Individuals hospitalized at the time of the study assessment, those whom we were unable to contact for the interview, those with a history of hospitalization/symptom exacerbation in the previous 90 days, those presenting with a disease requiring oxygen supplementation other than the primary respiratory disease, and those presenting with cognitive impairment that prevented them to complete the questionnaires were excluded.

Home visits were conducted for anamnesis and physical examination. Clinical variables related to smoking history, hospitalization, arterial blood gases, and dyspnea were obtained from medical records. Information about arterial blood gases was obtained from the public health care facilities, and samples were collected two days prior to the home visit. Variables related to LTOT use were assessed using medical records and a structured interview. Data were collected regarding daily duration of LTOT (h/day) and oxygen flow rates (L/min) at rest, during exercise, and during sleep. For those using an oxygen concentrator, the duration of LTOT in hours of oxygen consumption was collected at the health care facility by recording the hour-meter readings. Adherence to LTOT was considered adequate if the oxygen equipment was used for a daily period greater than or equal to that prescribed by the physician.[5,6]

Data analysis was performed using the IBM SPSS Statistics software package, version 25.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics are presented as absolute and relative frequencies, mean and standard deviation, or median and minimum-maximum values. Comparisons of prescribed LTOT and oxygen flow rates with actual LTOT use duration of and oxygen flow rates were made with the paired t-test or the Wilcoxon test. The chi-square test was used to identify the differences between the proportions of patients who were adherent to the prescribed LTOT (< 15 h/day or 15-24 h/day). The level of significance was set at $p < 0.05$.

Data from 74 LTOT users diagnosed with chronic respiratory diseases were analyzed. Most individuals were female (n = 47; 63.5%). The mean age was 73 ± 8 years. COPD was the most prevalent diagnosis (n = 61; 82.4%), followed by interstitial lung disease (n = 9; 12.2%), and asthma (n = 4; 5.4%). The median oxygen flow rate was 2 (1-5) L/min, and the median duration of LTOT use was 2.56 ± 3.00 years. Regarding the LTOT device, 82.4% of the patients used an oxygen concentrator and 17.6% used an oxygen cylinder. Nasal cannula was the most common interface (97.3%), followed by tracheostomy (2.7%).

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Table 1. Comparison between prescribed and actual use of long-term home oxygen therapy (N = 74).[a]

Variable	Prescribed use	Actual use	p
LTOT duration, h	15 (8-24)	8 (6-8)	0.008
LTOT flow rate, L/min			
At rest	1 (1-2)	2 (2-4)	0.325
During exercise	2.33 ± 0.57	1.83 ± 0.28	0.317
During sleep	2.0 ± 1.0	1.5 ± 0.5	0.180

LTOT: long-term home oxygen therapy. [a]Values expressed as median (minimum-maximum) or mean ± SD.

No significant differences were found between prescribed and actual oxygen flow rates at rest, during exercise, or during sleep (Table 1). Adherence to LTOT prescription was higher (91.6%) among patients on LTOT = 15-24 h/day than among those on LTOT < 15 h/day (42.1%; p < 0.001). When we classified the patients with COPD regarding severity of the disease and compared the subgroups according to LTOT prescription adherence rate, we found that 58.3% of those classified as GOLD stages 1 and 2 were adherent to LTOT, as were 68.4% of those classified as GOLD stages 3 and 4, that is, the greater the disease severity, the higher the LTOT adherence.

The fact that adherence to LTOT was low in patients with a 15-h/day prescription can be explained by the fact that they had less severe disease, fewer symptoms, and fewer functional limitations. These results corroborate the findings of one study that showed that patients with more severe COPD are more adherent to LTOT than are those with less severe COPD.[6] Our findings have relevant clinical implications, because low adherence to LTOT can compromise the dose-response effect and the clinical benefits of LTOT might not be achieved.

Adherence to LTOT is complex and multifactorial.[7] Studies have shown that although the perception of oxygen therapy might be positive,[8] patients often report it as negative because of social stigma, as well as psychological and behavioral effects,[8-10] such as embarrassment while using the oxygen equipment in public, misunderstanding of oxygen flow prescription, lack of perception of the benefits from treatment, poor functional status, smoking, and fear of oxygen addiction.[8-10] These concerns, along with the clinical cardiorespiratory benefits and increased quality of life that are achieved when LTOT is used appropriately, should be addressed and discussed with patients, families, and caregivers. The lack of standardized oxygen hour meters to record the daily duration of LTOT is a limitation of the present study. Future studies should investigate adherence to LTOT using standardized meters to measure oxygen consumption. Public health care systems should also take that into consideration for LTOT dispensation. The strength of our study lies in the fact that it is based on self-reported data on oxygen consumption in a local population from the state of Minas Gerais.

Some strong points are the fact that this was a prospective study and the fact that patients with a history of symptom exacerbation/hospitalization in the previous 90 days were excluded from the sample because hypoxemia in such cases is still labile. In addition, the present study has high internal validity because of the cultural and socioeconomic context in which it was conducted (i.e., patients with chronic respiratory disease in the state of Minas Gerais, Brazil), which can be different from that of studies conducted elsewhere, particularly in other countries.

In conclusion, adherence to LTOT in patients treated in the Brazilian public health care system is suboptimal, particularly among those who are prescribed LTOT < 15 h/day. There is a need to improve adherence to LTOT in patients with chronic hypoxemia. This can be achieved by using structured protocols and periodic monitoring by a multidisciplinary team.

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Pulmonary talcosis related to cocaine inhalation

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A 49-year-old man sought medical attention with a history of shortness of breath, dry cough, and progressive weight loss. He had a 20-year history of cocaine inhalation and denied intravenous drug abuse or tobacco smoking. A chest CT performed 2 years previously showed multiple centrilobular nodules, distributed predominantly in the upper lobes (Figure 1A). A chest CT performed on admission showed an increased number of these nodules, with areas of confluence and formation of conglomerated masses in the upper lobes, as well as a right-sided spontaneous pneumothorax (Figures 1B and 1C). The conglomerated masses had diffuse high density (Figure 1D). Transbronchial biopsy showed multinucleated giant-cell granulomas with birefringent foreign material consistent with talc (Figure 1E). The final diagnosis was pulmonary talcosis.

Two major types of pulmonary talcosis, one associated with drug inhalation and one associated with intravenous administration of drugs, have been described. Talc results in the development of granulomas in both inhalational and intravenous forms of the disease. Earlier CT manifestations consist of a diffuse micronodular pattern. As the disease progresses, the nodules can become confluent, resulting in fibrosis and heterogeneous conglomerate masses. Such masses may contain areas of high attenuation. On CT, the main difference between the inhalational form and the intravenous form is the development of emphysema in the latter. Barotrauma, as a complication of crack cocaine inhalation, can manifest as pneumothorax, pneumomediastinum, pneumopericardium, or subcutaneous emphysema.[1,2]

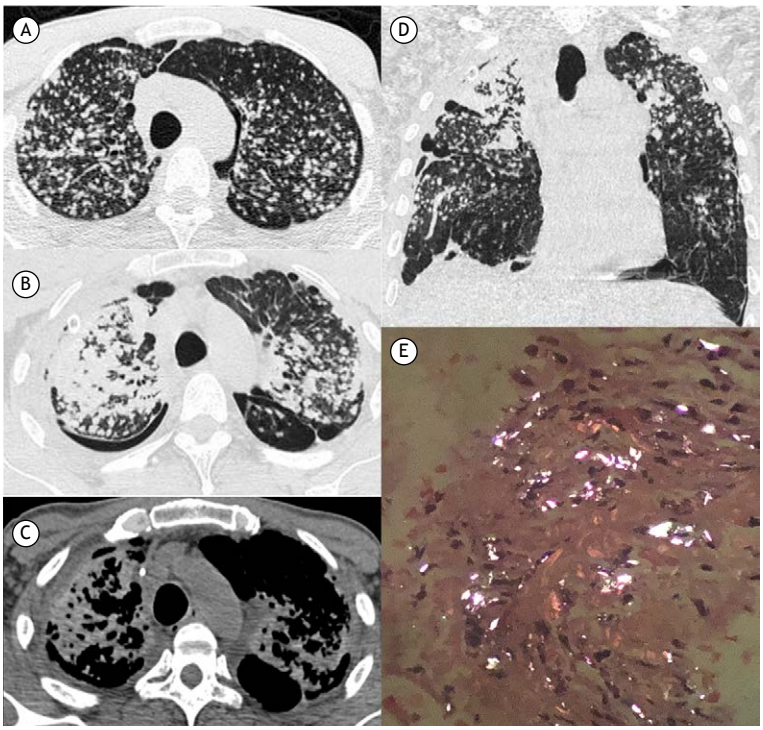

Figure 1. In A, an axial CT image acquired two years previously shows numerous small bilateral centrilobular nodules. Axial CT images acquired on admission with lung (in B) and mediastinal (in C) window settings, as well as a coronal reformatted image (in D), show an increase in the number of centrilobular nodules, with areas of confluence and diffuse high-density conglomerated masses in the upper lobes. Note also the presence of a right-sided spontaneous pneumothorax. In E, a transbronchial lung biopsy demonstrated multinucleated giant-cell granulomas with birefringent foreign material consistent with talc (H&E; magnification, ×100).

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