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EDITORIAL

Chronic bronchial infection in stable COPD: To treat or not to treat

There is no doubt that the main risk factor for the development of chronic obstructive pulmonary disease (COPD) in developed countries is tobacco smoking,[1] but there are other factors that may aggravate the course of COPD or may even be responsible for the persistence of bronchial inflammation and progression of the disease after quitting smoking. Among these factors, bronchial infection by potentially pathogenic microorganisms (PPMs) has generated great interest and its potential treatment has been included in guidelines of COPD treatment.[2-4]

The repeated isolation of PPMs, mainly *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*, from bronchial secretions in stable COPD (outside a period of exacerbation) has been associated with increased bronchial and systemic inflammation, increased respiratory symptoms, faster decline in lung function, frequent and severe exacerbations, poor quality of life, higher frequency of bronchiectasis, increased frequency of cardiovascular events, and even higher mortality.[5-11] This clinical impact of the presence of PPMs in the airways of patients with stable COPD has generated the concept of chronic bronchial infection (CBI) in contrast to the usual term of bronchial colonization, that should be reserved for the presence of bacteria, usually commensal bacteria, without invading tissues or causing damage.[10,12] However, the precise definition of CBI has been elusive; a group of experts have proposed that the isolation of the same PPM in at least three sputum samples separated by at least one month over one year could define CBI,[12] but this definition still needs to be validated and globally accepted.

Existing evidence suggest that the concept of CBI should be differentiated from the single isolation of a PPM in sputum. There is evidence that CBI by *P. aeruginosa* in COPD patients is associated with a higher mortality[8,13]; however no significantly increased risk of death has been observed associated with a single isolation of this microorganism.[13] This finding could have important therapeutic consequences because we should avoid the progression from a single isolation to established CBI; however definitive evidence of this progression in patients with COPD is still lacking. Nevertheless, the recognised impact of CBI highlights the importance of microbiological monitoring of respiratory samples (usually sputum) even in the stable phase of COPD, in particular in the most challenging patients with frequent exacerbations.[4]

Whatever the definition of CBI is, the repeated isolation of PPMs in sputum of patients with COPD is one of the main characteristics of the so-called "infective phenotype" of COPD, characterised by the production of coloured sputum, poor quality of life and frequent and severe exacerbations.[14] The first consequence of the identification of this phenotype is that these patients must be examined by chest computed tomography to evaluate the presence and extent of bronchiectasis. There is evidence from prospective studies that frequent and severe exacerbations may lead to the development of bronchiectasis in COPD patients,[11] which, in turn, closes the vicious circle because the presence of bronchiectasis is also a risk factor for the presence of CBI, especially by *P. aeruginosa*, more exacerbations and reduced survival.[15,16]

The second consequence is that due to the deleterious effect of CBI, treatment strategies should be applied to prevent lung damage.[2,12,16] Unfortunately, there are no therapeutic trials for CBI specifically in COPD patients (with or without bronchiectasis), and the current strategies are based on the experience of treatment of CBI in bronchiectasis patients.[17,18] Based on this experience, some recommendations have been published regarding the use of antibiotic treatment for CBI in COPD, including macrolides as immunomodulatory agents against neutrophilic inflammation, and systemic or inhaled antibiotics.[6,12] These recommendations take into account four different factors: 1) the frequency of exacerbations, 2) the presence of bronchiectasis, 3) the isolation of *P. aeruginosa*, and 4) whether there is a single isolation of a PPM or a CBI. Recommendations for antibiotic treatment are depicted in colours in Fig. 1; the darker the color the stronger the recommendation for antibiotic treatment.[6] Extreme cases would be COPD patients with frequent exacerbations, bronchiectasis, and CBI by *P. aeruginosa*, who must receive antibiotic treatment, according to the bronchiectasis guidelines,[19,20] with the

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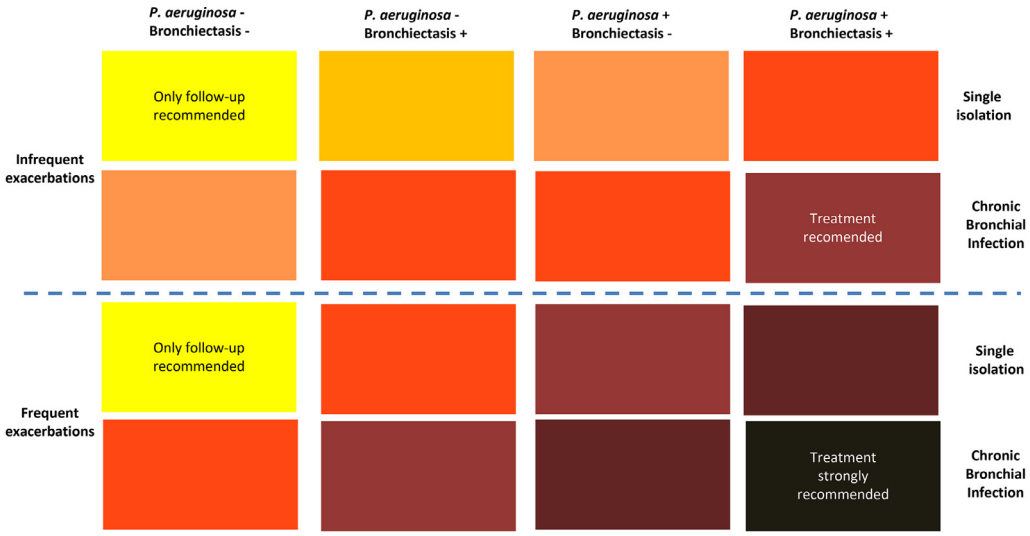

Fig. 1 Strength of the recommendation of antimicrobial treatment of CBI in COPD.
The darker the color, the stronger the recommendation of treatment; from yellow: only follow-up in COPD patients with a single isolation of a PPM, without frequent or severe exacerbations, no bronchiectasis, and no *P. aeruginosa* isolation; to dark gray: strong recommendation of treatment in COPD patients with CBI by *P. aeruginosa* and bronchiectasis with frequent or severe exacerbations.
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objective of eradicating, or at least reducing the bronchial bacterial load, if at all possible. The other end of the spectrum would be represented by a patient with infrequent exacerbations, without bronchiectasis and a single isolation of a PPM non *P. aeruginosa*, who would only require the usual follow-up, but no antibiotic treatment at this stage. Between these extremes, there is a whole range of intensities in the recommendations for antibiotic treatment, which must be individualized, mainly considering the presence of multiple and/or severe exacerbations as a possible consequence of the CBI (Fig. 1).[6]

Interestingly, there is a group of patients with COPD, who despite optimal inhaled bronchodilator and anti-inflammatory treatment, usually in the form of triple therapy (long-acting anticholinergic agent -LAMA-, long-acting beta-2 agonist -LABA- and inhaled corticosteroid -ICS-) still suffer from exacerbations.[21] One reason for this is that triple therapy does not address the infectious component of exacerbations. These patients who still exacerbate despite optimal inhaled therapy must be investigated for the presence of bronchiectasis and CBI and be treated accordingly.[12]

The type of treatment for CBI in COPD is still controversial due to the lack of evidence; however, there is consensus among specialists that long-term macrolides can be a good option in CBI by PPMs other that *P. aeruginosa*, while inhaled antibiotics are preferred in cases of CBI by this pathogen.[12,22] Some large observational studies in patients with COPD and bronchiectasis have observed significantly better outcomes with the use of long-term macrolides compared with ICS in terms of a reduction in moderate or severe exacerbations and even in improved survival.[23] These results are probably related to the fact that the use of ICS may increase the risk of CBI by *P. aeruginosa* and pneumonia in COPD patients, in particular in patients with low blood eosinophil counts.[24] As a consequence of the excessive use of ICS in patients with COPD,[25] some important questions arise: What is the risk of ICS treatment in a COPD patient with CBI independently of the presence of bronchiectasis? Should these patients always be initially treated with macrolides? There are no clear responses, but these questions received the highest scores among 230 questions selected in an international consensus about research priorities in COPD for the next decade.[26]

In conclusion, the scientific community should be aware of the great importance of CBI in stable COPD and the urgent need for therapeutic studies with preventive antibiotics focused on preventing exacerbations, avoiding the development of irreversible bronchial damage or bronchiectasis and, in turn, improving the quality of life and the prognosis of our patients.

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COMMENT

The public health impact of e-cigarette use: Revisiting Geoffrey Rose's prevention strategies

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E-cigarettes are mass-marketed consumer products promoted by the industry as harmless devices and smoking cessation aids. Whether e-cigarettes help smokers to quit or undermine public health remains splitting the public and the health community. Although some countries and healthcare providers (HCPs) recommend e-cigarettes for smoking cessation, no e-cigarette medical device has ever been approved and launched in the market.[1]

Thirty-eight years ago, Rose described two main primary prevention strategies.[2] The high-risk individual approach aims to identify the most susceptible individuals and offer medical treatment to eliminate or reduce disease risk factors. The population-based strategy seeks to control disease determinants in the whole population.[2] Public health policies can achieve a population-wide impact, reducing population-risk and lowering disease incidence. Motivating and supporting smokers to quit in clinical practice is a high-risk strategy. While embracing the moral/ethics of clinical practice, this strategy usually reaches a population minority limiting its public health impact.[2] The high-risk strategy is adequate to target those who seek medical care, mostly dependent smokers with co-morbidities. However, targeting young yet disease-free smokers, mainly primary-care users, obtains further health gains, saving lives and downscaling smoking-associated mortality and disability.

Importantly, implementing comprehensive tobacco control can change social norms, prevent tobacco uptake by youth, promote smoking cessation at a population-level and prevent smoking relapse.[3] The population strategy while controlling population-risk and reducing smoking prevalence

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achieves broad-ranging primary prevention but fails to help heavy/reluctant smokers needing intensive treatment.

Prevention is a continuum: both strategies are useful and potentially synergistic.[2] Implementing broad-reach cessation interventions together with comprehensive tobacco control maximises population impact, reducing health inequalities.[3]

While most smokers contemplate quitting, they are often ambivalent, and need support and treatment.[4] Supporting respiratory patients who smoke to quit is the most cost-effective intervention to improve patients' health and quality of life. Systematically identifying smokers and advising them to quit can increase motivation and foster quit attempts, even among reluctant smokers.[4] Smoking-cessation brief advice given to all smokers does not result in the highest quit rates but has the greatest impact, as many try to quit. This should be standard care. Additionally, smokers assisted with evidence-based counselling and pharmacotherapy can achieve higher quit rates.[4] The unacceptable paradox is that brief advice remains neglected in healthcare. While HCPs lack smoking cessation training, few health systems offer smoking cessation best practice.[3] A recent survey evaluated smoking cessation support among 8000 European smokers.[5] Among smokers reporting a health visit, less than half received any kind of advice or support to quit. Those suffering from respiratory diseases, multiple comorbidities or older than 55 were more likely to receive advice; less than one in five smokers had attempted to quit in the previous year. Support to quit was scarce and inconsistent. Furthermore, clinicians failed to advise younger smokers, undermining early cessation and primary prevention.[5]

Eurobarometer surveys reveal a downward trend of healthcare-assisted quitting towards unassisted quitting or e-cigarette use.[6] Moreover, population-based surveys suggest that e-cigarettes used as consumer products do not promote smoking cessation and may promote relapse in ex-smokers.[1,7-10]

Furthermore, while e-cigarettes in clinical trials may help some smokers to stop smoking, 50 to 80% persist using them by the end of the trial[1], undermining long-term nicotine abstinence.[11]

While smoking-cessation best practice is disregarded by HCPs and health systems; the industry is mass-marketing e-cigarettes as harm reduction tools with governments' complacency; undermining evidence-based assisted smoking cessation and smoke-free policies, and re-normalizing smoking.[1]

We should also consider that e-cigarettes use the inhaled route to administer nicotine, a powerful pathway for addiction and systemic toxicity; dual use is common[1] and potentially more harmful.[12] Therefore, these products do not help smokers to overcome nicotine addiction, postpone quitting in current smokers, hook new consumers through experimentation, and maintain or aggravate health risks.[1,11,12]

According to Rose, large numbers of people at small risk cause more disease burden than the small number who are at high-risk. This epidemiologic scenario is common, limiting the population impact of a high-risk strategy.[2] This explains why encouraging smokers to switch to potentially less harmful products, instead of quitting, and promoting e-cigarette use among youths, who otherwise would not have uptake cigarettes, has the potential to foster population-wide nicotine use and a heavy disease burden. Even if e-cigarette use may lower individual health risk in comparison to combustible cigarettes (an unresolved assumption: e-cigarette aerosol may deliver lower levels of toxicants, but the evidence on long-term hazards is lacking); promoting nicotine use at a population-level may result in a public health tragedy. The higher prevalence of inhaled-nicotine users may increase population risk-factors, raising the incidence and burden of chronic diseases. This is supported by simulation models that quantified the balance of population-health benefits and harms associated with e-cigarettes.[13] While built on the current evidence and the highly optimistic supposition of 95% relative harm reduction of e-cigarette use compared to smoking, the study concludes on a net population-level harm.[13] Lastly, e-cigarette use is increasing globally, especially among youths, threatening the current worldwide downward trend of combustible cigarettes.[1,14,15]

Taken together, Rose's vision of population-health, and the current evidence on e-cigarettes (potential health harms and addiction risk of persistent use, and alarming youth use), support that the English Health Minister decision to launch the "swap to stop" campaign distributing free e-cigarette kits to one million smokers[16]; is neither a proven nor a safe public health strategy to reduce smoking-associated mortality and disease burden.

According to the English Minister, "vaping" would be a "powerful tool" to help people quit smoking and, together with initiatives to prevent youth uptake of smoking, would contribute to reducing smoking by 5% in England by 2030.[16] However, this strategy does neither follow evidence-based medicine good practice nor medical ethics "*primum non nocere*" i.e. "first do not harm". The evidence on the potential health effects of e-cigarette use is expanding. While their long-term health effects are yet uncertain, the precautionary principle demands tacit public health action. E-cigarettes are neither medical devices nor medicines, but consumer products banned in more than 40 countries. They have been claimed by manufacturers as safer products emitting less and lower concentrations/amounts of known carcinogens and other toxicants, leading to reduced exposure and health risks. However, the somewhat lower concentrations of some substances do not necessarily translate into proportionate reductions in health risks.[17] Their aerossol provides, in addition to inhaled nicotine, particulate matter, inhaled carcinogens and many other toxic and irritating substances to the respiratory, cardiovascular and immune systems.[1] These devices also offer specific hazards, such as the inhalation of heavy metals leaking through the heated filament, an acute lung injury syndrome (EVALI), and device explosion.[1] While the health effects of second-hand e-cigarette aerosol (SHA) are less studied, SHA emissions of toxicants and particulate matter seem to be significantly lower than those from second-hand tobacco smoke, with the exception of some metals (Ag, Ni, and ZN).[18] This reduction may, however, not consistently reduce or eliminate health hazards for vulnerable populations such as chronic respiratory or cardiovascular patients, children, pregnant women, or non e-cigarette users exposed to it. Furthermore, lifetime environmental exposure is cumulative and all preventable harmful exposures should be avoided.

Following the World Health Organisation and the European Respiratory Society recommendations, we urge for

strong tobacco control and prevention of nicotine use among youth by effectively regulating novel products or banning their sales. Ethics underpin clinical and public health practice; it is our duty to encourage and support tobacco/nicotine users to become nicotine-free. We must not embrace the "pharmaceuticalization of the tobacco industry"[19] promoting e-cigarettes as safer alternatives to smoking or smoking cessation aids instead of offering evidence-based treatment and pharmacotherapy. We must not neglect our main job: advocate for comprehensive tobacco control; take everyday opportunities to ask our patients about tobacco and nicotine use and support them to quit and breathe clean air for life.

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The authors declare that they have written the manuscript respecting ethical in clinical practice.

Conflicts of interest

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COMMENT

Diagnosis of COVID-19 by sound-based analysis of vocal recordings

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Commentary

The COVID-19 pandemic has had a significant impact on the world, with widespread illness, death, and economic disruption. The pandemic constantly evolves as new virus variants emerge, and governments respond with new measures. The development of a diverse range of diagnostic tests[1] has been triggered to deal with the situation, which can be summarised in three major categories: molecular tests, rapid antigen tests and serology. Molecular tests have been the reference (real-time polymerase chain reaction - RT-PCR), but common to all, these are invasive, although minimally, and costly diagnostic techniques. Although at-home rapid antigen tests are currently available, they are invasive and uncomfortable, vary in accuracy depending on how they are done and must be quickly accessible.[1] These characteristics may raise perceived barriers to COVID-19 testing and limit the detection of the disease. Vaccines have been unevenly distributed and accepted, and cases are still increasing in some areas. It is unclear what the future holds for the pandemic, but it will likely continue to require effort from all involved.

SARS-CoV-2 infection primarily affects the respiratory tract, including the upper and lower airways, and contributes to the disruption of normal vocalisations. Given this, some research groups have attempted to develop more convenient and accessible COVID-19 diagnostic methods by using machine learning to analyse voice recordings and other audio signals, such as coughing, breathing sounds, and breathing rate. Voice and cough analysis are an attractive approach to screening for respiratory disease symptoms[2,3] as sound recordings are simple to acquire and non-invasive. However, due to subtle differences in voice and cough characteristics, artificial intelligence is required to detect specific disease patterns, discard confounding factors that induce similar manifestations, and reduce the effects of environmental noise. Geographic and idiolectal linguistic variations can also affect analyses of these samples.

Most existing algorithms rely on crowdsourced audio sample databases. However, such databases do not ensure the quality of the recordings and contain only a limited number

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of positive cases. Notable examples of respiratory audio-based sample collection include studies that used the Coswara dataset[4] and the COVID-19 Sounds database.[5] The accuracy reached by these studies' algorithms is debatable as the results derive from unreliable data sources, either due to unconfirmed COVID-19 status or an uncontrolled recording environment.

For this reason, some authors have chosen to conduct their own recording protocols to ensure the reliability of their results. With a sample of 70 SARS-CoV-2-positive patients and 70 healthy individuals, Robotti et al.[6] demonstrated that machine learning could accurately discriminate both groups (accuracy, 90.24%). Shimon et al.[7] included 57 patients (25 SARS-CoV-2-positive), achieving an average accuracy of 80%. Pinkas et al.[8] included recordings of 29 SARS-CoV-2-positive and 59 SARS-CoV-2-negative patients and achieved an accuracy of 79%.

Matias et al.[9] used crowdsourced databases combined with quality assessment algorithms of voice recordings to overcome the above mentioned issues and detect SARS-CoV-2 infection with a more reliable and less noisy dataset. Such an approach reached accuracy values ranging from 75% to 84% on Coswara, and from 67% to 81% on a sub-set of COVID-19 sounds dataset.

The available literature suggests that machine learning tools using voice recordings and other audio signals could provide a non-invasive, low-cost way to screen and flag for SARS-CoV-2 infection, the results of which could later be confirmed with a clinically validated test. Such algorithms are powerful in their ability to automatically learn hidden patterns from data and decision rules. Combined with signal processing and expertise in feature engineering, they can form reliable tools to help track infection in a more decentralised way. This is particularly important in diseases where infection isolation is critical.

Nevertheless, future studies should validate the robustness of these algorithms in real-world settings and assess the feasibility of adapting this approach to other areas, such as other respiratory infections, such as seasonal influenza. Additionally, machine learning tools could also be used to monitor other chronic respiratory illnesses including asthma, COPD, obstructive sleep apnoea, and tuberculosis.[8] In the future, this strategy might contribute to more decentralised screening for respiratory diseases, facilitating early diagnosis and monitoring disease progression, potentially improving outcomes for patients with these conditions, and reducing pressure on the healthcare system.

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ORIGINAL ARTICLE

Ventilatory associated barotrauma in COVID-19 patients: A multicenter observational case control study (COVI-MIX-study)

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Abbreviations: C-PAP, continuous positive airway pressure; PSV, pressure support ventilation; COT, conventional oxygen therapy; HFNO, high flow nasal oxygen; C-ARDS, coronavirus acute respiratory distress syndrome; ICU, intensive care unit; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation; NIRS, non invasive respiratory support; P-SILI, patients self-inflicted lung injury; VILI, ventilator induced lung injury; PNX, pneumothorax; PMD, pneumomediastinum; qCSI, Quick COVID-19 Severity Index; ECMO, Extra-Corporeal Membrane Oxygenation; HRCT, high-resolution computed tomography.

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High flow nasal cannula;
Invasive mechanical ventilation

Abstract
Background: The risk of barotrauma associated with different types of ventilatory support is unclear in COVID-19 patients. The primary aim of this study was to evaluate the effect of the different respiratory support strategies on barotrauma occurrence; we also sought to determine the frequency of barotrauma and the clinical characteristics of the patients who experienced this complication.
Methods: This multicentre retrospective case-control study from 1 March 2020 to 28 February 2021 included COVID-19 patients who experienced barotrauma during hospital stay. They were matched with controls in a 1:1 ratio for the same admission period in the same ward of treatment. Univariable and multivariable logistic regression (OR) were performed to explore which factors were associated with barotrauma and in-hospital death.
Results: We included 200 cases and 200 controls. Invasive mechanical ventilation was used in 39.3% of patients in the barotrauma group, and in 20.1% of controls ($p<0.001$). Receiving non-invasive ventilation (C-PAP/PSV) instead of conventional oxygen therapy (COT) increased the risk of barotrauma (OR 5.04, 95% CI 2.30 - 11.08, $p<0.001$), similarly for invasive mechanical ventilation (OR 6.24, 95% CI 2.86-13.60, $p<0.001$). High Flow Nasal Oxygen (HFNO), compared with COT, did not significantly increase the risk of barotrauma. Barotrauma frequency occurred in 1.00% [95% CI 0.88-1.16] of patients; these were older (p=0.022) and more frequently

immunosuppressed (p=0.013). Barotrauma was shown to be an independent risk for death (OR 5.32, 95% CI 2.82-10.03, p<0.001).
Conclusions: C-PAP/PSV compared with COT or HFNO increased the risk of barotrauma; otherwise HFNO did not. Barotrauma was recorded in 1.00% of patients, affecting mainly patients with more severe COVID-19 disease. Barotrauma was independently associated with mortality.
Trial registration: this case-control study was prospectively registered in clinicaltrial.gov as NCT04897152 (on 21 May 2021).

Introduction

One established complication of mechanical ventilation in critically ill patients is barotrauma.[1]

The recent pandemic of SARS-CoV2 has drawn attention to the fact that acute respiratory syndrome in COVID-19 patients (C-ARDS) has been disproportionally associated with this complication compared to traditional ARDS during the first wave.[2,3]

A wide range in frequency of barotrauma has been reported in the literature in C-ARDS patients worldwide depending on the hospital setting. In a multicenter study involving up to 72,000 patients in the emergency department in Spain, the frequency reported was 0.56%,[4] while in China, the frequency was double and around 1%.[5]

Conversely, in the United States in intensive care units (ICU), barotrauma frequency reached 15% in mechanically ventilated COVID-19 patients.[3]

Considering that C-ARDS patients who underwent invasive mechanical ventilation (IMV) have been treated with a protective ventilation strategy as is customarily used in patients with traditional ARDS,[6,7] the higher percentage of barotrauma in COVID-19 patients could lie outside the ventilatory strategies.

In fact, pneumothorax, pneumomediastinum and subcutaneous emphysema, otherwise known as barotrauma, have also been described in C-ARDS spontaneous breathing patients or those under non-invasive respiratory support (NIRS), which represented the majority of hospitalized patients, and not only during IMV.[8,9]

It is thought that vigorous breathing with uncontrolled effort can increase transpulmonary pressure gradient across lung regions, and global and regional strain, inducing the phenomenon known as patient self-inflicted lung injury (P-SILI).[10] At this stage, adequate ventilatory support becomes fundamental to avoiding lung damage, reducing in the meantime ventilator induced lung injury (VILI).

Therefore, in this multicentre study, we aimed to investigate, as a primary aim, the effect of the different respiratory support strategies on barotrauma occurrence and, as secondary aims, the frequency of barotrauma and the clinical characteristics of the patients who experienced this complication.

Materials and methods

Study design

This retrospective case-control observational study was conducted in 9 intensive care units (ICUs) and 15 medical wards in Italy from 1 March 2020 to 28 February 2021. After approval by the Ethics Committee for the coordinating centre (approval number CEUR-2021-3659, Ethics Committee of Friuli-Venezia-Giulia Region, Italy), all local investigators were responsible for obtaining the required permissions in their centres according to the national regulation. The study was prospectively registered on clinicaltrial.gov (NCT04897152).

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. Data were anonymously collected using a unique alphanumeric code for each participant. The Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed.[11] All data were anonymously collected on the electronic data manager Castor (EDC, 2019, Amsterdam, The Netherlands) in compliance with the European General Data Protection Regulation (GDPR) 2016/679.[12]

Population

We considered eligible all adult (i.e., ≥18 years/old) patients admitted to hospital for SARS-CoV-2 pneumonia. SARS-CoV-2 infection was ascertained through polymerases chain reaction nasal swab. We included in the study all patients who developed barotrauma during hospital stay; barotrauma was defined as the occurrence of pneumothorax (PNX) and/or pneumomediastinum (PMD), irrespective of the presence or absence of subcutaneous emphysema.

Patients were excluded if one of the following criteria was present: 1) iatrogenic cause of barotrauma (i.e., pneumothorax from central vein catheter insertion or pleural effusion drainage); 2) absence of radiological imaging; or 3) do-not-intubate or do-not-resuscitate order (for palliative care).

Controls were selected among COVID-19 patients without barotrauma and matched 1:1 with cases per period and unit of admission. In other words, controls were included considering patients without barotrauma that were admitted in the same week and in the same treatment unit as the ones experiencing barotrauma, respecting all inclusion and exclusion criteria.

All patients received standard care, according to current clinical practice guidelines and evidence-based recommendations/indications at the time of enrolment.

First and additional aims

The first study aim is to describe the effect of the different respiratory support strategies on barotrauma occurrence.

Additional aims describe the frequency of barotrauma and eventual required treatments.

Finally, the characteristics of respiratory failure, blood tests, infections, hospital length of stay and mortality of patients experiencing barotrauma are compared with those of a matched control group to find possible similarities or important clinical differences.

Data collection

For all patients, we recorded (1) demographic and anthropometric data; (2) comorbidities; (3) severity of COVID-19, stratified as asymptomatic infection, mild, moderate, severe and critical illness, through the World Health Organization (WHO) case definition,[13]; (4) the Quick COVID-19 Severity Index (qCSI)[14]; and (5) 4C mortality score.[15] We also recorded the arterial partial pressure to inspired oxygen fraction ratio (P_aO_2/F_IO_2), the alveolar-to-arterial difference of oxygen (A-a DO_2) and the respiratory rate. In addition, whenever available, the following blood tests were recorded: white blood cell (WBC) and lymphocytes counts, C-reactive protein, procalcitonin (PCT), pro-adrenomedullin, interleukin 6 (IL-6), lactate dehydrogenase (LDH) and D-dimer.

We collected the need, the type and the time spent under conventional oxygen therapy (COT), high-flow nasal oxygen (HFNO), continuous positive airway pressure (C-PAP), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV) or Extra-Corporeal Membrane Oxygenation (ECMO), the consecutive modalities together with the need for sedatives, neuromuscular blocking agents and prone position. Notably, COT, HFNO, C-PAP and NIV were defined as non-invasive respiratory support (NIRS).

In every centre, a radiologist reviewed high-resolution computed tomography (HRCT) to compute a severity score, as reported by Salaffi et al.[16] In particular, the radiologist evaluated both lungs on three levels and for every single area assigned a score from 0 to 4 according to the nature of abnormalities and another 4-point score according to the percentage of lung area involvement. The scores, according to the abnormalities and their extent, were then multiplied by each other and added to the scores of all 6 levels (3 levels on each side). The final severity score ranged from 0 to 96: the higher the score the more severe was the disease.

The occurrence of co-infections with the need for antibiotic therapy was also recorded.[17]

Finally, we computed the rate of patients requiring re-intubation after first extubation attempt or tracheostomy, the days from hospital to ICU admission, the hospital length of stay and in-hospital mortality.

Sample size estimation

The primary aim of the study is the effect of the different respiratory support strategies, in particular IMV, on barotrauma. Assuming a proportion of 25% of patients receiving IMV in the control group and of 38% of patients in the case group,[18] we calculated a sample size of 392 patients to detect an odds ratio (OR) of 1.890 for barotrauma with an 80% of power and alpha error of 5% with a two-sided Fisher's Exact test.

Statistical analyses

Categorical variables were presented as absolute values (percentages), and continuous variables were described as either mean and standard deviation or median and ranges, according to variable distribution. Normality was assessed using the Shapiro-Wilk Test. Categorical variables were compared using the chi-squared test or Fisher's exact test, while continuous variables were compared using a student t-test or Mann-Whitney U test, according to the distribution of the data. Univariable and multivariable conditional logistic regressions were performed to explore which factors were associated with barotrauma and in-hospital death, stratifying by referral centres. A multiple imputation approach was used to account for missing data, replacing missing values with 50 sets of simulated values and adjusting the obtained parameter estimates for missing-data uncertainty. All clinically relevant variables or those that were significant at $p<0.05$ in univariable analysis were included in the multivariable analysis, taking into account potential collinearities. Overall survival was described according to the Kaplan-Meier approach. Comparisons among survival distributions were performed using the log-rank test. Two-sided p values of less than 0.05 were determined to be statistically significant. Statistical analyses were performed using Stata/IC 17.0 (StataCorp LP, College Station, USA).

Results

Among 19,809 patients with C-ARDS admitted in the study period, the frequency of barotrauma was 1.00% [95% CI 0.88-1.16]. Forty-six patients were excluded due to exclusion criteria. Finally, 200 cases and 200 matched controls were included for the final statistical analysis (Fig. 1).

Baseline patients' characteristics were balanced between the two groups, except for age, immunosuppressive therapies and chronic liver disease (Table 1). In particular, patients who experienced barotrauma were older (p=0.022), more frequently on domiciliary immunosuppressive therapy (p=0.013) and with less deranged liver function tests (p=0.015).

High flow nasal oxygen strategy was more represented in the group with barotrauma than without (42.4% vs. 32.1% respectively, p=0.035). Similarly, C-PAP/PSV was reported in 86% of patients in the barotrauma group and in 50.3% of patients in the group without barotrauma ($p<0.001$). Invasive mechanical ventilation was used in 39.3% of patients in barotrauma group, a higher frequency compared to the non-barotrauma group, in which only 20.1% of patients received it ($p<0.001$), as reported in Table 2.

However, considering mean days of ventilation in the barotrauma versus no barotrauma group, adjusted for the type and duration of ventilation, we found a protective effect of CPAP/PSV (5.3±4.6 vs 9.2±7.6 p <0.001), while IMV showed a direct effect (10±10.5 vs 5.3±6.0 p 0.017) and no effect from HFNO (8.1±9.2 vs 7.8±7.3 p 0.955). PEEP level was available in 89 control vs 144 cases, and their value in barotrauma vs no barotrauma was similar (9.2± 2.0 vs 9.08±2.2, p=0.621). In addition, patients with barotrauma more frequently received sedatives ($p< 0.001$) and prone positioning ($p< 0.001$) and had higher re-intubation ($p<0.018$) and tracheotomy ($p<0.001$) rates. ECMO was instituted in 10 (5.2%) patients with barotrauma, whereas none required it in controls ($p<0.017$).

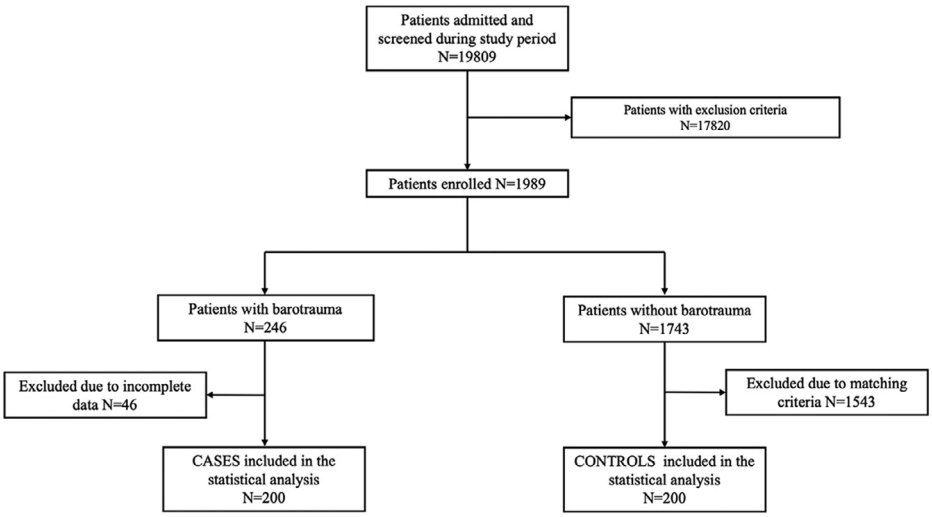

Fig. 1 Study flow chart.

Additional aims

The frequency of barotrauma was 1.00% [95% CI 0.88-1.16]. Isolated PMD occurred in 90 cases (0.45 [95% CI 0.37-0.56]), whereas isolated PNX occurred in 61 patients (0.31 [95% CI 0.24-0.40]) and combined PMD-PNX occurred in 49 patients (0.25%) – [95% CI 0.18%-0.33%]. PNX was more frequent on the right side (55 of 108 cases; 50.9%), followed by on the left-side (29/108; 26.9%) and bilateral in 24 cases (22.2%).

Hemodynamic instability was reported in 55 patients (27.6%). PNX required draining with a chest tube in 73 cases (66.3%), whereas six patients (5.5%) required surgery and one (0.9%) talc pleurodesis. Detailed data are reported in Table 3.

As shown in Supplementary Table 1 (in the ESM), patients with barotrauma were characterized by a more prominent hypoxemia (p=0.004), higher respiratory rate (p=0.001), and higher qCSI and 4C scores at the admission (p<0.001 for both scores) compared to controls.

Patients who experienced barotrauma also showed a higher inflammation profile of serum procalcitonin, pro-adrenomedullin, interleukin-6, LDH and D-dimer than the control group (see Supplementary Table 2 in the ESM).

Table 4 shows univariate and multivariate analyses of risk factors for barotrauma.

In more detail, both invasive and non-invasive ventilation were significantly related to the risk of barotrauma compared to conventional oxygen therapy. In particular, the multivariate analysis showed that receiving C-PAP/PSV versus COT has an OR 5.04 (95% CI 2.30-11.08, p<0.001) for barotrauma, while receiving IMV versus COT has an OR of 6.24 (95% CI 2.86-13.60, p<0.001).

Compared with HFNO, patients with C-PAP/PSV have a 3-times higher risk of barotrauma (OR 3.00, 95% CI 1.09-8.27, p=0.033), while patients receiving IMV had an OR 4.12 for barotrauma (95% CI 1.51-11.27, p=0.006). Patients that underwent only COT, only HFNO, only CPAP/PSV, only IMV versus COT/HFNO, COT/HFNO/CPAP/PSV, COT/HFNO/PSV/IMV intended as an escalation support presented less barotrauma events (p<0.001) as shown in Supplementary Table 3. However, HFNO, compared with COT, did not significantly increase the risk of barotrauma at the uni- and multivariate analysis (OR 1.40, 95 CI 0.49-4.01, p=0.534).

Table 1 Baseline patients' characteristics.

	Overall (n=400)	Barotrauma group (n=200)	Controls (n=200)	*p-value*
Males, n (%)	295 (73.8)	155 (77.5)	140 (70)	0.088
Age, years, median (IQR)	68 (59-75)	69.5 (62-76)	66.5 (57-75)	**0.022**
BMI, median (IQR)	26.7 (24.5-30.4)	26.3 (24.5-30.1)	27.1 (24.4-30.7)	0.466
Cardiovascular disease, n/N (%)	196/399 (49.1)	103 (51.5)	93/199 (46.7)	0.341
COPD, n/N (%)	39/399 (9.8)	15 (7.5)	24/199 (12.1)	0.125
Solid cancer, n(%)	31/399 (7.8)	14 (7)	17/199 (8.5)	0.565
Haematologic disease, n(%)	29 (7.3)	16 (8)	13 (6.5)	0.563
Diabetes, n/N (%)	84 (21)	42 (21)	42 (21)	1.000
CKD, n/N (%)	37/399 (9.3)	21 (10.5)	16/199 (8.0)	0.397
Iatrogenic immunosuppression, n/N (%)	29/399 (7.3)	21 (10.5)	8/199 (4.0)	**0.013**
Liver disease, n(%)	7 (1.8)	0 (0)	7 (3.5)	**0.015**

Legend. IQR: interquartile range; BMI: Body Mass Index; COPD: Chronic obstructive pulmonary disease: CKD: Chronic kidney disease.

Table 2 Ventilation strategies applied during hospital stay.

	Overall (n=400)	**Barotrauma** (n=200)	**No barotrauma** (n=200)	***p-value***
HFNO, n/N (%)	147/394 (37.3)	84/198 (42.4)	63/196 (32.1)	**0.035**
CPAP/PSV °, n/N (%)	257/379 (67.8)	160/186 (86.0)	97/193 (50.3)	**<0.001**
IMV°, n/N (%)	116/390 (29.7)	77/196 (39.3)	39/194 (20.1)	**<0.001**
Sedation, n/N (%)	186/300 (62)	142/196 (72.5)	44/104 (42.3)	**<0.001**
Pronation, n/N (%)	156/298 (52.4)	127/193 (65.8)	29/105 (27.6)	**0.001**
Curarization, n/N (%)	187/295 (63.4)	119/191 (62.3)	68/104 (65.4)	0.600
Necessity of re-OTI, n/N (%)	20/287 (7.0)	18/189 (9.5)	2/98 (2.0)	**0.018**
Tracheostomy, n/N (%)	56/290 (19.3)	53/191 (27.8)	3/99 (3.0)	**<0.001**
ECMO, n/N (%)	10/292 (3.4)	10/192 (5.2)	0/100 (0)	**0.017**

°as intended before barotrauma.
Legend. CPAP/PSV: Continuous positive airway pressure ventilation/Pressure support ventilation, ECMO: extracorporeal membrane oxygenation, HFNO: high flow nasal oxygen; IMV: invasive mechanical ventilation; OTI: orotracheal intubation.

Barotrauma appeared significantly related to the extension of lung involvement (OR 2.31, 95% CI 1.22-4.39, p=0.010) and with thromboembolism at presentation (OR 5.46, IC95% 2.83,10.55, p<0.001).

Fungal infections were significantly associated with barotrauma (OR 5.27, 95% CI 2.10-13.24, p <0.001) as shown in Supplementary Table 4.

Table 3 Characteristics of barotrauma and barotrauma management.

Barotrauma findings (n=200)	
Pneumomediastinum, n (%)	90 (45)
Pneumothorax, n (%)	61 (30.5)
Both, n (%)	49 (24.5)
Days from hospital admission and barotrauma diagnosis (median, IQR)	10 (6-18)
Pneumothorax side (n=108)	
Right sided, n (%)	55/108 (50.9)
Left sided, n (%)	29/108 (26.9)
Bilateral, n (%)	24/108 (22.2)
Barotrauma findings, size (n=122)	
Large (≥ 2 cm), n (%)	83 (68.0)
Small (<2 cm), n (%)	39 (32.0)
Haemodinamics (n=199)	
Stable, n (%)	144 (72.4)
Unstable, n (%)	55 (27.6)
Pneumothorax management (n=110)	
Conservative management, n (%)	120 (60)
Chest tube, n (%)	73 (36.5)
Surgical treatment, n (%)	6 (3)
Pleural talcage, n (%)	1 (0.5)
Days of chest tube maintenance, median (IQR)	9 (4-19)
Barotrauma evolution (n=199)	
Spontaneous reabsorption, n (%)	66 (33.2)
Resolution after chest tube/surgery, n (%)	34 (17.1)
Unresolved, n (%)	82 (41.2)
Recurrency, n (%)	11 (5.5)
Unknown, n (%)	6 (3.0)

Legend. IQR: interquartile range.

Barotrauma was found to be an independent risk factor for death (OR 5.32, 95% CI 2.82-10.03, p<0.001) as shown in Table 5. Patients receiving C-PAP/PSV versus HFNO have an OR 3.06 (95% CI 0.82-11.44, p=0.097) for in-hospital death. On the other hand, patients under CPAP/PSV versus COT have an OR of 22.22 for in hospital death (95% CI 5.42-91.20, p<0.001).

As expected, the barotrauma group showed a longer hospital stay, 27 days versus 12 days, p <0.001. Overall mortality in the barotrauma group compared with patients without was 54.8% versus 17.2%, respectively (p<0.001) (see supplementary Table 4). Of these patients, 64 over 113 (56.6%) received IMV and 77 over 274 who received no NIRS (28.1%) died, p < 0.001.

The log-rank test showed no significant difference in survival of patients in the barotrauma group receiving NIRS versus IMV (p=0.37). When analysing the whole population, the log-rank test showed no significant difference in overall survival as well (p=0.12), as shown in Fig. 2.

Discussion

The main findings of the investigation are, first, that HFNO compared to COT did not increase the risk of barotrauma. Second, C-PAP/PSV or IMV increased the risk of barotrauma compared with HFNO. Third, barotrauma frequency in this study was lower than in previous reports in COVID-19 cohorts, and we confirm that the right-side was the most affected. Fourth, hemodynamic instability in our study was more frequent than in previous findings, and many patients required chest tube drainage. Fifth, patients with barotrauma exhibited lower P_aO_2/F_IO_2 ratio, highest BMI and extended lung disease involvement. Sixth, elevated plasma cytokine concentration was associated with barotrauma. Furthermore, C-PAP/PSV and IMV increased the risk of death compared with COT.

Mirò et al. and Ayazi et al. found that those patients who experienced barotrauma were more tachypnoeic.[4,19]

It could be assumed that high respiratory rates at admission might mirror the increased respiratory effort with the greater risk of developing self-induced positive end-expiratory pressure (auto-PEEP), contributing to barotrauma.[20,21]

Table 4 Factor associated with barotrauma (univariable and multivariable analysis).

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Male sex	1.51	0.95,2.40	0.080			
Age	1.03	1.01,1.04	**0.005**	2.00	1.13,3.52	**0.017**
BMI	0.99	0.95,1.04	0.698	1.02	1.00,1.04	**0.029**
Cardiovascular disease	1.21	0.81,1.81	0.352			
COPD	0.55	0.27,1.13	0.105			
Solid cancer	0.81	0.39,1.69	0.577			
Haematologic disease	1.25	0.58,2.69	0.563			
Diabetes	1	0.62,1.62	1.000			
CKD	1.35	0.68,2.71	0.391			
Immunosoppression	2.77	1.19,6.41	**0.018**			
qCSI	1.13	1.07,1.18	<**0.001**			
PaO2/FiO2 ratio ad admission	0.99	0.99,0.99	**0.004**			
Respiratory rate ad admission	1.05	1.01,1.10	**0.014**	1.00		0.834
(A-a)DO2	1.00	0.99,1.01	0.667			
Ventilation strategies						
HFNO vs. COT	0.55	-0.44,1.54	0.275	1.40	0.49,4.01	0.534
CPAP/PSV vs. COT	2.06	1.35,2.76	<**0.001**	5.04	2.30,11.08	<**0.001**
CPAP/PSV vs. HFNO	1.51	0.56,2.46	**0.002**	3.00	1.09,8.27	**0.033**
IMV vs. COT	2.33	1.63,3.04	<**0.001**	6.24	2.86,13.60	<**0.001**
IMV vs. HFNO	1.78	0.84,2.73	<**0.001**	4.12	1.51,11.27	**0.006**
IMV vs. CPAP/PSV	0.27	-0.34,0.89	0.382	1.37	0.70,2.70	0.359
IMV/CPAP/PSV vs COT/HNFO	7.81	4.44,13.74	<**0.001**			
IMV vs NIRS	3.52	2.08,5.98	<**0.001**			
Extent (%) of lung involvement						
25-49% *vs.* 0-24%	1.35	0.55,3.32	0.514	0.93	0.33,2.63	0.895
50-74% *vs.* 0-24%	3.91	1.61,9.52	**0.003**	2.07	0.75,5.76	0.161
50-74% *vs.* 25-49%	2.90	1.68,5.02	<**0.001**	2.31	1.22,4.39	**0.010**
≥75% *vs.* 0-24%	4.33	1.63,11.52	**0.003**	1.80	0.57,5.72	0.318
≥75% *vs.* 25-49%	3.21	1.65,6.23	**0.001**	2.01	0.92,4.41	0.081
≥75% *vs.* 50-74%	1.11	0.60,2.04	0.743	0.87	0.43,1.77	0.699
White blood cells (n/μL)	1.00	1.00,1.00	0.836			
Lymphocytes count(n/μL)	1.00	1.00,1.00	0.472			
CRP (mg/L)	1.01	1.01,1.01	**0.014**	1.00	0.99,1.01	0.348
Procalcitonin (ng/mL)	1.12	0.96,1.31	0.156			
Proadrenomedullin (mmol/L)	1.00	0.98,1.01	0.682			
Interleukin 6 (pg/mL)	1.00	1.00,1.00	0.105			
LDH (IU/L)	1.00	1.00,1.00	0.421			
D-dimer test (FeU/mL)	1	1.00,1.00	0.938			
Bacterial co-infections	2.56	1.48,4.43	**0.001**	1.79	0.93,3.46	0.081
Fungal co-infections	5.65	2.73,11.66	<**0.001**	5.27	2.10,13.24	<**0.001**

Legend. BMI: Body Mass Index; COPD: Chronic obstructive pulmonary disease: CKD: Chronic kidney disease, (A-a)DO2: alveolar-arterial gradient; GGO: ground glass; paO2/FiO2 ratio: ratio of arterial oxygen partial pressure (paO2 in mmHg) to the fraction of inspired oxygen (FiO2), CPAP/PSV: Continuous positive airway pressure ventilation/pressure support ventilation, HFNO: high flow nasal oxygen; IMV: invasive mechanical ventilation; NIRS: noninvasive respiratory support; CRP: C reactive protein; PCT: procalcitonin; LDH: lactate dehydrogenase.

HFNO seems to reduce the work of breathing and to improve respiratory mechanics in COVID-19 patients; it provides a homogeneous distribution of tidal volume without any inspiratory assistance; and it promotes alveolar recruitment in not-dependent regions preventing alveolar overdistension.[22−24]

Therefore, HFNO might theoretically mitigate the risk of P-SILI during spontaneous breathing and limit the rate of non-invasive treatment failure.

Although both C-PAP and HFNO have been recommended for mild to moderate acute hypoxemic respiratory failure treatment in patients with COVID-19, the RECOVERY-RS trial revealed that only an initial strategy of C-PAP reduced the risk of tracheal intubation or mortality compared with COT and caution is needed because failed NIV carries increased mortality. Yet, there was no significant difference between an initial strategy of HFNO compared with COT.[25]

In patients with COVID-19 and moderate hypoxia, Crimi et al. showed that HFNO does not significantly reduce the escalation of respiratory support.[26] However, this field is still matter of debate, and we can only speculate about the possible role

Table 5 Indipendent risk factors for in-hospital death.

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p-value	OR	95% CI	p-value
Male sex	0.65	0.39,1.10	0.106			
Age	1.08	1.05,1.10	<**0.001**	1.09	1.06,1.13	<**0.001**
P_aO_2/F_IO_2 ratio at admission	1.00	0.99,1.00	0.400			
Respiratory rate at admission	1.01	0.98,1.05	0.455			
Barotrauma	8.21	4.77,14.14	<**0.001**	5.32	2.82,10.03	<**0.001**
Ventilation strategies						
HFNO vs. COT	3.15	0.68,14.61	0.143	7.27	1.25,42.29	**0.027**
CPAP/PSV vs. COT	24.71	7.80,78.30	<**0.001**	22.22	5.42,91.20	<**0.001**
CPAP/PSV vs. HFNO	7.85	2.24,27.51	**0.001**	3.06	0.82,11.44	0.097
IMV vs. COT	29.05	9.28,90.95	<**0.001**	30.70	7.49,125.78	<**0.001**
IMV vs. HFNO	9.23	2.66,32.04	<**0.001**	4.22	1.17,15.27	**0.028**
IMV vs. CPAP/PSV	1.18	0.63,2.20	0.613	1.38	0.68,2.82	0.374
IMV/CPAP/PSV vs HFNO/COT	18.00	7.69,42.16	<**0.001**			
IMV vs NIRS	3.63	2.09,6.31	<**0.001**			
Bacterial co-infections	1.66	0.93,2.94	0.085			
Fungal co- infections	3.32	1.90,5.81	<**0.001**	1.64	0.86,3.13	0.132

Legend. P_aO_2/F_IO_2 ratio: ratio of arterial oxygen partial pressure (paO2 in mmHg) to the fraction of inspired oxygen (FiO2), CPAP/PSV: Continuous positive airway pressure ventilation/pressure support ventilation, HFNO: high flow nasal oxygen; IMV: invasive mechanical ventilation; NIRS: non-invasive respiratory support.

of HFNO in avoiding barotrauma. In our study, in fact, we found that, compared with COT, HFNO did not increase the risk of barotrauma after uni- and multivariate analysis. Moreover, only a few case reports have been published about pneumomediastinum and pneumothorax in spontaneously breathing patients under HFNO.[27,28] It is therefore difficult to define any pathophysiological correlation.

Concerning C-PAP/PSV and IMV, as expected, both were significantly related to the risk of barotrauma compared to COT.

Comparing our data with the literature, we showed that the frequency of barotrauma is slightly lower than previously reported when considering the entire in-hospital spectrum of COVID-19 disease, as shown in earlier studies from China.[5]

A recent large multicentre study involving 71,904 COVID-19 patients carried out across 61 emergency departments (ED) in Spain reported an overall pneumothorax incidence at presentation of 0.56%.[4] In contrast, McGuiness et al. in 89 mechanically ventilated patients with COVID-19 infection

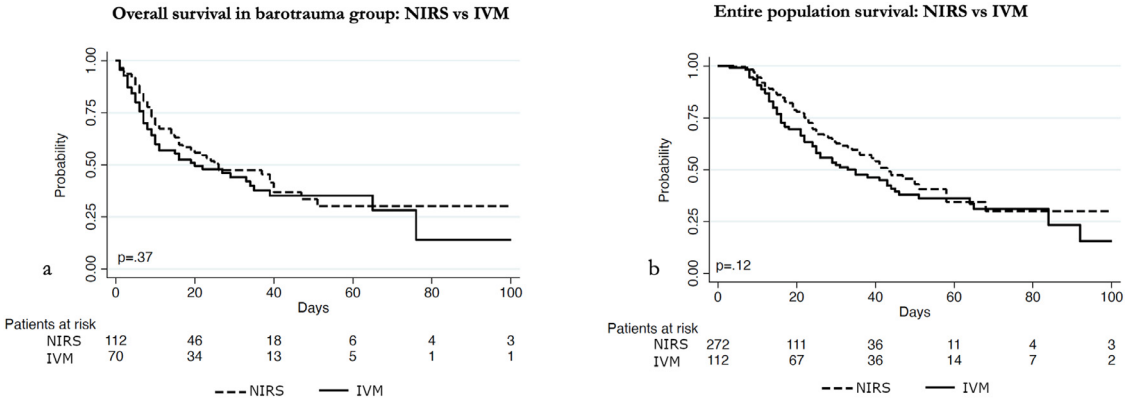

Fig. 2 Survival Kaplan Meier curves.
In Fig. 2 (a) Kaplan-Meier survival curves show overall survival of patients with COVID-19 infection who developed barotrauma when on IMV and on NIRS. Patients in IMV and NIRS were represented by continuous and dotted curves respectively, with no difference in overall survival (p=0.37).
In Fig. 2 (b) Kaplan-Meier survival curves describe overall survival of patients with COVID-19 infection when on IMV, and when in NIRS. Patients in IMV and NIRS were represented by continuous and dotted curves respectively, with no difference in overall survival (p=0.12).
Legend. IMV: invasive mechanical ventilation; NIRS: non-invasive respiratory support

reported an incidence of barotrauma of about 15% in mechanically ventilated COVID-19 patients.[3]

Wang et al. reported a frequency of pneumothorax of 10% in a monocentric cohort study conducted in ICU.[29] A recent meta-analysis of 1,814 invasively ventilated COVID-19 patients found that in one out of six patients (14.7%), there was a barotrauma, and it was associated with increased mortality.[30] Probably the 10% and 15% frequencies of barotrauma reported in these ICU studies were related to the denominator (the number of beds available in ICU), and we suppose that many of these patients were admitted due to barotrauma that had developed before ICU admission, leading to overestimation of its frequency in this setting.

In the modern era, all patients admitted to ICU requiring invasive mechanical ventilation should undergo protective ventilation strategy to reduce ventilator-induced lung injury (VILI).[31−33] The current ventilatory approach, which became universally accepted after the ARDS Network trial, is based on reducing the tidal volume to about 6 mL kg^{-1} of ideal body weight (IBW) while maintaining the airway plateau pressure below 30 cmH_2O.[34] Following these guidelines, barotrauma has become very rare in the last two decades, and IMV did not worsen the risk of barotrauma in our study. In contrast, an uncontrolled application of NIV could be much more dangerous if not used appropriately in terms of time, volume and pressure, and possible be implicated in Patient-Self-Induced-Lung-Injury (P-SILI) despite the beneficial effects of C-PAP on recruiting collapsed lung's zone.[35,36]

The vigorous breathing on spontaneous ventilation, also due to altered respiratory drive after viral central nervous system involvement, increases transpulmonary pressure, global and regional strain (barotrauma), self-inflicted lung injury (P-SILI), and can be responsible for the higher inflammation profile.[37,38]

To this end, it is rational to think that protective ventilation was present during IMV and absent during spontaneous breathing and NIV use outside the ICU area, especially in the first phase of the pandemic when ICU beds were fewer than required. Nevertheless, barotrauma events in COVID-19 patients are not restricted to patients receiving positive-pressure ventilation.

SARS-COV-2 is known to strongly activate the host's immune system, triggering a deadly cytokine storm, which contributes to alveolar damage in CARDS. In this setting, patients with an active cytokine storm seem naturally more susceptible to stress-induced lung injury. To date, only a single center retrospective analysis on ICU patients found that fungal infections were more frequent in patients experiencing barotrauma (68.4% vs. 18.9%).[39] However, there is still lack of evidence to support the hypothesis of a correlation between barotrauma and fungal infections in units other than ICU.

Barotrauma is a potentially life-threatening complication especially in patients on mechanical ventilation and need to be recognized early in relation to the potential impending hemodynamic instability. Patients developing a tension pneumothorax, or a rarer tension pneumomediastinum with hemodynamic instability, require urgent decompression. In the literature, among those patients who developed PM, 46% had simultaneous or new bilateral pneumothorax and most required bilateral chest tube insertion, 38% progressed to intubation and 31% died.[40,41]

Beitler et al. in non-COVID-19 patients with barotrauma reported that these patients required a high vasopressor support to begin prone positioning.[42] We found that barotrauma implies a severe grade of acute lung injury to HRCT scan. Another report in a small cohort highlighted the use of ECMO as respiratory and hemodynamic support.[43]

We found that pro-adrenomedullin and interleukin-6 levels were associated with barotrauma at the univariate analysis. Although the role of P-SILI is not completely clear, the severe and prolonged inflammation caused by the increase in transpulmonary pressure can lead to extensive endothelial disruption, pulmonary vasoconstriction, oedema, atelectasis and alveolar injury, as reflected by increased biomarkers such as those previously mentioned.[44−46]

In relation to length of stay, we found an association between patients with barotrauma and longer hospital stay in agreement with previous studies.

Fungal but not bacterial infection was significantly associated with barotrauma, being probably the clinical expression of a more severe disease with a dysregulated host immunity.

Martinelli et al. failed to demonstrate that pneumothorax would be an independent marker of poor prognosis in COVID-19.[47] Mirò et al. also failed to attribute the in-hospital mortality increase in patients with barotrauma.[4]

In contrast, Kangas-Dick et al.[48] and Gazivoda et al.[49] found that barotrauma was associated with patients' deaths, and our data support these findings.

To the best of our knowledge, COVI-MIX is the largest multicentre case-control study that investigates patients with COVID-19 and barotrauma throughout the entire clinical spectrum of the disease, including patients from ED to ICU.

However, some limitations of our study should be highlighted: first, the retrospective design; second, the fact that missing data regarding ventilation parameters were not available for all our analysis; and third, we argue that during the 2020 and 2021 peaks of the pandemic surge, COT, HFNO, and IMV were used as escalation therapies. However, at that moment, the hospitals, particularly the Italian ones, used every imaginable type of ventilation, transforming the wards into real war trenches, and we cannot exclude that approaches other than escalation were used.

Conclusions

COVID-19 patients experienced barotrauma, especially during C-PAP/PSV and IMV. HFNO in this study was not demonstrated to increase the risk of pneumothorax or pneumomediastinum. The frequency of barotrauma in our cohort of patients was lower than in other studies in the literature. Patients with barotrauma were sicker, and more had important systemic inflammatory responses.

Declarations

The Italian COVI-MIX Study Group is represented by Prof. Luigi Vetrugno.[1,2]

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Ethics approval and consent to participate

Ethics Committee of Friuli-Venezia-Giulia Region, Italy, approved the study with approval number CEUR-2021-3659. Consent to participate was waived.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used and analysed during the current study is available from the corresponding author on reasonable request.

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Authors' contributions

LV, NC, AF contributed to conceptualization, data collection, formal analysis and writing the manuscript. CD contributed to conceptualization, formal analysis and writing the manuscript. AC, FL, FF, GC, DLG, PN, SMM, MB, AC, MC, GF, DF, RL, SM, MS, ES, CT, FB and VP contributed to formal analysis and writing the manuscript.

MI, MDM contributed to conceptualization, formal analysis and writing the manuscript. MI, MDM are responsible for statistical analysis. All authors read and approved the final manuscript.

Declaration of Competing Interest

None.

Acknowledgments

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.11.002.

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ORIGINAL ARTICLE

Inspiratory Effort and Respiratory Mechanics in Patients with Acute Exacerbation of Idiopathic Pulmonary fibrosis: A Preliminary Matched Control Study

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KEYWORDS
Acute exacerbation of idiopathic pulmonary fibrosis;

Abstract
Background: Patients with acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) may experience severe acute respiratory failure, even requiring ventilatory assistance. Physiological data on lung mechanics during these events are lacking.

Abbreviations: IPF, idiopathic pulmonary fibrosis; AE-IPF, acute exacerbation of IPF; ARDS, acute respiratory distress syndrome; ARF, acute respiratory failure; bpm, breaths per minute; MV, invasive mechanical ventilation; ETI, endotracheal intubation; NIV, non-invasive mechanical ventilation; PEEP, positive end-expiratory pressure; PBW, predicted body weight; PSV, pressure support; SILI, self-inflicted lung injury; HACOR, heart rate, acidosis, consciousness, oxygenation, respiratory rate; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; SAPS II, simplified acute physiology score; RICU, Respiratory Intensive Care Unit; ΔPes, esophageal pressure swing; ΔPL, dynamic transpulmonary pressure; RR, respiratory rate; VE, minute ventilation; VILI, ventilator-induced lung injury; Vte, expiratory tidal volume; Vte/ΔPL, expiratory tidal volume/transpulmonary pressure ratio; CRS, respiratory system compliance; DynCRS, dynamic respiratory system compliance; IQR, interquartile range.

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Acute respiratory failure;
ARDS;
Esophageal manometry;
Respiratory mechanics;
Esophageal pressure swing;
Dynamic transpulmonary pressure;
Non-invasive mechanical ventilation;
Inspiratory effort

Methods: Patients with AE-IPF admitted to Respiratory Intensive Care Unit to receive non-invasive ventilation (NIV) were retrospectively analyzed. Esophageal pressure swing (ΔP_{es}) and respiratory mechanics before and after 2 hours of NIV were collected as primary outcome. The correlation between positive end-expiratory pressure (PEEP) levels and changes ~~of~~ in dynamic compliance ($dynC_{RS}$) and PaO_2/FiO_2 ratio was assessed. Further, an exploratory comparison with a historical cohort of ARDS patients matched 1:1 by age, sequential organ failure assessment score, body mass index and PaO_2/FiO_2 level was performed.
Results: At baseline, AE-IPF patients presented a high respiratory drive activation with ΔPes = 27 (21−34) cmH2O, respiratory rate (RR) = 34 (30−39) bpm and minute ventilation (VE) = 21 (20−26) L/min. Two hours after NIV application, ΔPes, RR and VE values showed a significant reduction (16 [14−24] cmH2O, $p<0.0001$, 27 [25−30] bpm, p=0.001, and 18 [17−20] L/min, p=0.003, respectively) while no significant change was found in dynamic transpulmonary pressure, expiratory tidal volume (Vte), dynCRS and dynamic mechanical power. PEEP levels negatively correlated with PaO_2/FiO_2 ratio and $dynC_{RS}$ (r=−0.67, p=0.03 and r=−0.27, p=0.4, respectively). When compared to AE-IPF, ARDS patients presented lower baseline ΔP_{es}, RR, VE and dynamic mechanical power. Differently from AE-IPF, in ARDS both Vte and $dynC_{RS}$ increased significantly following NIV (p=0.01 and p=0.004 respectively) with PEEP levels directly associated with PaO_2/FiO_2 ratio and $dynC_{RS}$ (r=0.24, p=0.5 and r=0.65, p=0.04, respectively).
Conclusions: In this study, patients with AE-IPF showed a high inspiratory effort, whose intensity was reduced by NIV application without a significant improvement in respiratory mechanics. In an exploratory analysis, AE-IPF patients showed a different mechanical behavior under spontaneous unassisted and assisted breathing compared with ARDS patients of similar severity.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a life-threatening lung disease characterized by progressive deterioration of lung function and a median survival time of 3-5 years from diagnosis.[1] Acute exacerbation of IPF (AE-IPF) leads to an acute deterioration of respiratory function, and severe hypoxemia, further worsening the prognosis.[2] During these events, the typical usual interstitial pneumonia pattern (UIP) — the radiological and histological hallmark of IPF— overlaps with diffuse alveolar damage (DAD), sharing similarities with acute respiratory distress syndrome (ARDS) and often requiring respiratory support.[3] Several studies show that. the need for mechanical ventilation (MV) is associated with high mortality[4,5] in IPF patients. This is probably related to the pathophysiological properties of UIP-like fibrotic lung (i.e. collapsed induration) areas, elevated lung elastance, high inhomogeneity) that makes it more susceptible to ventilatory-induced lung injury (VILI).[3,6]

Based on a large number of clinical observations available in literature, and on some physiopathological speculations,[3,7] we have theorized an elastic model with the aim of explaining the mechanical behavior of the fibrotic lung when subjected to positive end-expiratory pressure (PEEP) during invasive MV, namely the "squishy-ball" theory. According to this hypothesis, the application of PEEP on a UIP-like lung pattern can determine the protrusion of the more distensible areas through a dense anelastic fibrotic tissue circle. This causes increased rigidity and worse compliance, thus easing tissue breakdown. Despite lack of extensive evidence, we suggested considering MV only in selected cases of AE-IPF.[3] In this scenario, non-invasive mechanical ventilation (NIV) may therefore represent an alternative option to assist these patients, although no specific recommendations have been made so far.[3,8,9] In ARDS, the efficacy of NIV in reducing the patient's inspiratory effort early after application has been related to a favorable clinical outcome.[10] Indeed, the mitigation of the respiratory drive might result in a lower risk of self-inflicted lung injury (SILI) during spontaneous breathing. SILI is very likely to worsen outcomes in patients undergoing acute respiratory failure (ARF).[11]

To the best of our knowledge there are still no available data on inspiratory effort and lung mechanics in patients with AE-IPF either during unassisted or assisted spontaneous breathing. The aims of this study were to explore inspiratory effort and respiratory mechanics, at baseline and 2 hours after NIV in AE-IPF patients and to compare the data with ARDS patients matched for clinical severity.

Materials and methods

Study setting and design

This retrospective single center cohort study was carried out at the Respiratory Intensive Care Unit (RICU) of the University Hospitals of Modena (Italy) and conducted in accordance with the pre-existing Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 348/18). Informed consent to participation in the study and permission for their clinical data to be analyzed and published were obtained from participants, as appropriate. For study purposes we further conducted a retrospective sub-analysis of data prospectively collected within a pre-registered clinical trial ClinicalTrial.gov (NCT03826797) and in accordance with the pre-existing Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 266/16).

Study population

Patients with IPF developing an AE and consecutively admitted to the Respiratory Intensive Care Unit and to the Intensive Care Unit of the University Hospital of Modena over the period August 1st, 2016 to January 1th, 2022 were retrospectively considered eligible for enrollment.

Inclusion criteria were as follows: age >18 years; previously established diagnosis of IPF with a UIP pattern on a high resolution computed tomography (HRCT) scan; occurrence of acute exacerbation of IPF as defined by an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality on chest HRCT scan and presence of ARF with PaO_2/FiO_2 ratio <300 mmHg;[12] having received a NIV trial while on RICU stay; inspiratory effort assessment and monitoring through esophageal manometry.

Patients were excluded if they presented any of the following: acute cardiogenic pulmonary edema, concomitant hypercapnic respiratory failure ($PaCO_2$ >45 mmHg) of any etiology, neuromuscular disease or chest wall deformities, home long-term oxygen therapy, lack of core data (i.e. clinical characteristics at baseline and physiological measurement) in medical record analysis.

AE-IPF population was then matched 1:1 by age, PaO_2/FiO_2 ratio, body mass index (BMI), sequential organ failure assessment (SOFA) score, to a group of patients with ARDS under spontaneous breathing, extracted from our dataset and treated between 2016 and 2022. All patients underwent a common and standardized intervention (including esophageal pressure monitoring) and data were collected using a standard collection protocol. The values of PaO_2/FiO_2 ratio used for matching these groups were those measured immediately before starting NIV.

General measurements

Medical reports, electronical charts and available clinical and physiological datasets were investigated to collect data on demographics, clinical characteristics, arterial blood gases, PaO_2/FiO_2 ratio, respiratory rate (RR), blood lactate level, clinical severity (as assessed by the SOFA score on RICU admission), esophageal manometry and respiratory mechanics before and after NIV trial.

Physiological measurements

According to our local protocol, esophageal manometry was performed with a multifunctional nasogastric tube with a pressure transducer (NutriVent™, SIDAM, Mirandola, Italy) connected to a dedicated monitoring system (OptiVent™, SIDAM, Mirandola, Italy) recording swings in esophageal (P_{es}) and dynamic transpulmonary (P_L) pressures. The NutriVent was placed before starting NIV as previously reported[10] and according to (or following the) the recommended calibration protocol.[13,14] In order to avoid using absolute values for P_{es} and P_L, we always referred to ΔP_{es} and ΔP_L from the end-expiratory level, respectively, calculated as recommended.[15] For all the measurements, the beginning of the inspiratory phase was identified at the instant of P_{es} initial decay while the end of inspiration was considered to be the value of P_{es} where 25% of the time had elapsed from maximum deflection to baseline (eFigure 1, Supplementary Materials). The respiratory flow was measured through an external heated pneumotachograph (Fleisch No.2, Lausanne, Switzerland) inserted between the patient's oronasal facemask (Bluestar™, KOO Medical Equipment, Shanghai, PRC) and a connector with a side port for measurements. Expiratory tidal volume (Vte) was obtained by numerical integration of the flow signal; Vte was then adjusted to the predicted body weight (PBW) to derive Vte/kg of PBW. Minute ventilation (VE) was calculated as the product of Vte and RR. $Vte/\Delta P_L$ was measured as a surrogate for respiratory system compliance and named "dynamic compliance" ($dynC_{RS}$). Air Leaks from the oronasal facemask were computed using dedicated ventilator-integrated software (GE Healthcare Engstrom Carestation™, GE Healthcare, Finland) based on the equation: leaks (L/min) = (inspiratory Vt − expiratory Vt) x RR. A surrogate of mechanical power (i.e. "dynamic mechanical power") was then calculated as 0.098 * RR * Vte * (ΔP_L + Positive end-expiratory pressure [PEEP]).[15] In every patient of both groups, measurements were recorded under standardized conditions over five consecutive minutes of unassisted spontaneous breathing, and repeated 2-hours after the initiation of NIV. Data were numerically stored and downloaded from a USB stick at each time point.

NIV trial

According to our local protocol, patients treatment was escalated to a trial of NIV if deemed indicated by the attending clinician, blinded to the study purposes and physiological measurements. The criteria to upgrade to NIV included PaO_2/FiO_2 ratio below 100 mmHg and/or RR > 30 bpm and/or persistence of respiratory distress and dyspnea despite HFNC set at 60 L/min. NIV was started and set by a skilled respiratory physician. Patients were connected to a conventional circuit via an appropriately sized oronasal facemask equipped with a dedicated output for probes (Bluestar™, KOO Medical Equipment, Shanghai, PRC) to a high-performance ventilator (GE Healthcare Engstrom Carestation™, GE Healthcare, Finland) set in pressure support mode. A heat and moisture exchanger (HME) (Hygrobac, DAR, Mirandola, Italy) was inserted into the ventilator circuit's Y-piece. The delivered FiO_2 was adjusted to target a SpO_2 of 88−94%. None of the patients received any kind of sedation under NIV treatment. PEEP was initially set at 6 cmH_2O and subsequently fine-tuned to target a peripheral oxygen saturation (SpO_2) >92% with a delivered inspiratory fraction of oxygen (FiO_2) less than 0.7. Pressure support (PS) was increased from 10 cmH_2O, according to tidal volume (Vte/kg of body weight predicted-PBW), to target a Vte/kg <9.5 mL/kg of PBW[16] and a RR <30 breaths/min. The inspiratory trigger and respiratory cycling were set at 3 L/min and at 25% of the inspiratory peak flow, respectively. An oronasal fitted mask was tightened to target a leak flow lower than 20 L/min. According to our local protocol, after 2 hours of NIV patients were re-assessed on a clinical and physiological basis.

Analysis plan

The primary aim of the study was to explore inspiratory effort and respiratory mechanics, at baseline and 2-h following NIV application, in patients with AE-IPF. Data were displayed as median and IQR (interquartile range) for continuous variables and numbers and percentages for

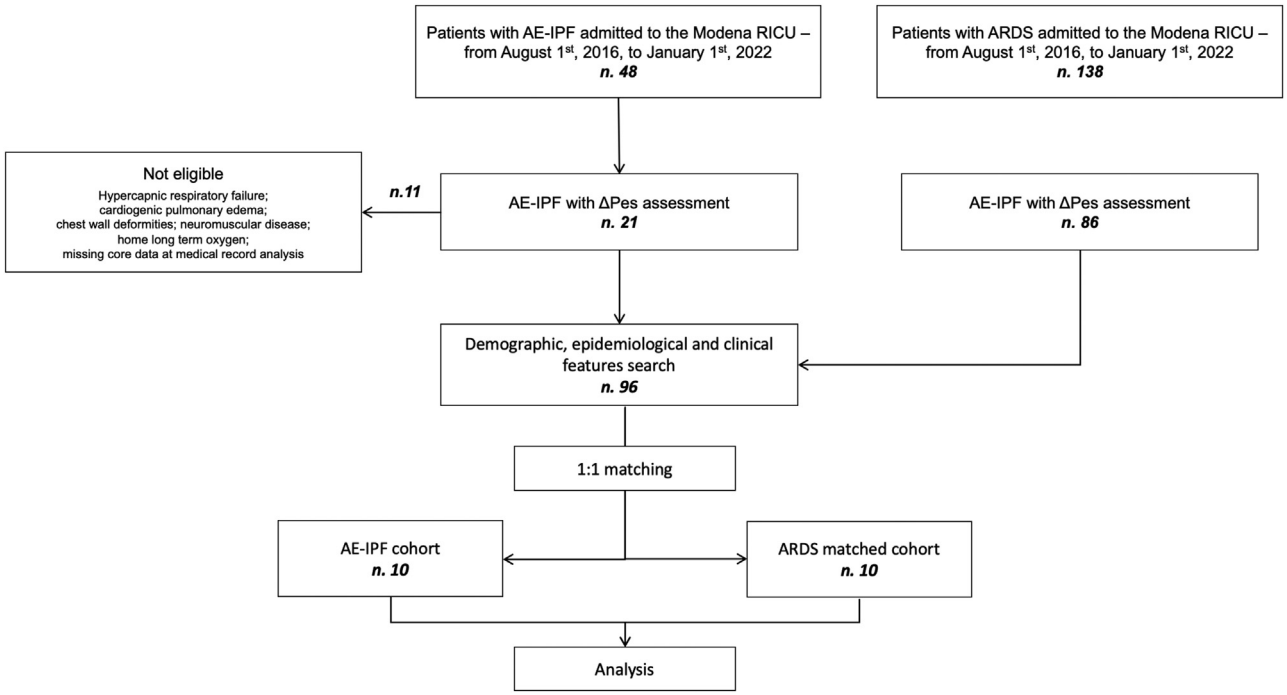

Fig. 1 Study algorithm. AE-IPF = acute exacerbation of idiopathic pulmonary fibrosis; ARDS = acute respiratory distress syndrome; RICU = Respiratory Intensive Care Unit; ΔP_{es} = esophageal pressure.

dichotomous variables. The paired Student's *t*-test assessed the difference between variables before and after NIV application, when distributed normally; otherwise, the Wilcoxon test was used. The relationship between PEEP and relative change in $dynC_{RS}$ and PaO_2/FiO_2 ratio 2 hours after starting NIV was tested with the Pearson correlation coefficient and assessed through linear regression. As an exploratory analysis, we compared the mechanical variables of AE-IPF patients with an ARDS population extracted from our dataset and including patients~~,~~ studied by our group between 2016 and 2022. The ARDS comparison cohort was built using a one-to-one propensity score matching procedure with the nearest-neighbor method without replacement. The logit of the score was taken with a caliper of 0.2 in order to maximize the number of patients without comprising the match. Comparison between continuous variables was performed with Student's *t*-test distributed normally; otherwise, the Wilcoxon test was used. Dichotomous variables were compared using the χ^2 test or Fisher's exact test, where appropriate. ANOVA and Kruskal-Wallis were used to test an interaction for whether the change in physiological variables 2 hours after NIV were different between groups. Statistics was performed using SPSS version 25.0 with PSMATCHING3 R Extension command (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, Ca, USA) unless otherwise indicated.

Results

Clinical features of study population

The flowchart of this study is shown in Fig. 1. Over the study period a total of 48 patients with AE-IPF were eligible for enrollment. Of these, 10 patients were analyzed. All of them were diagnosed with IPF based on the presence of a definite UIP pattern on HRCT scan. Patients were predominately male (7/10) with a median age of 75 years (65—78) (Table 1). The median value of clinical severity scores was 2 (2 — 2), 12.5 (9.8 — 21) and 30.5 (29 — 37.5) for SOFA, APACHE II and SAPS II scores respectively. The median time interval between IPF diagnosis and AE-IPF onset was 25 (15—33) months, while time lapse from hospital admission to NIV upgrade while in AE was 12 (7.5—27) hours. All patients died as inpatients.

Respiratory mechanics during AE-IPF

Respiratory mechanics of IPF before and after 2 hours of NIV are shown in Table 2. During unassisted breathing, IPF patients displayed a median value of ΔP_{es} (ΔP_L) of 27 (21 — 34) cmH_2O and a RR of 34 bpm. $DynC_{rs}$ was 28 mL/cmH_2O while dynamic mechanical power was 71 J/min. After 2 hours of NIV, ΔP_{es} was significantly reduced (16 [14 — 24] cmH_2O, $p<0.0001$). Similarly, NIV application lowered both RR and VE (27 [25 — 30], p 0.001 bpm and 18 [17 — 20] L/min, p.003, respectively) while ΔP_L, Vte, $dynC_{RS}$ and dynamic mechanical power did not change significantly.

In AE-IPF patients, after two-hours of NIV, PEEP levels were significantly inversely correlated with PaO_2/FiO_2 ratio (r=—0.67, p=0.03, Fig. 2, panel A). Similarly, an inverse correlation between PEEP levels and $dynC_{RS}$ variation was observed (r=-0.27, p=0.4, Fig. 2, panel B), although statistical significance was not reached.

AE-IPF as compared with ARDS

AE-IPF and matched ARDS groups were similar for clinical severity scores (APACHE and SAPS II, Table 1) at inclusion.

Table 1 General and clinical characteristics in the study groups on admission.

Parameter	AE-IPF	ARDS	p value
Number of patients	10	10	
Age, years	75 (65–78)	75 (65–78)	0.9
Male, n	7 (70)	7 (70)	0.9
BMI, kg/m^2	23 (21–25)	23 (21–25)	0.9
Charlson index, score	3 (3–5)	4 (3–5)	0.9
Kelly scale, score	1 (1–1)	1 (1–1)	0.9
SOFA, score	2 (2–2)	2 (2–2.5)	0.9
APACHE, score	12.5 (9.8–21)	11 (10–21)	0.9
SAPS II, score	30.5 (29–37.5)	33 (32–38)	0.8
HACOR, score	7 (6–8)	5.5 (5–6)	0.01
†PaO_2/FiO_2, mmHg	108 (80–126)	105 (83–125)	0.9
†pH, value	7.49 (7.47–7.52)	7.48 (7.44–7.5)	0.9
†$PaCO_2$, mmHg	31 (28–32)	33 (29–34)	0.3
Blood lactate, mmol/L	1.2 (1–1.9)	1 (0.9–1.2)	0.1
Serum creatinine, mg/dL	0.9 (0.7–1.4)	0.7 (0.6–1.4)	0.9
*PEEP, cmH_2O	6 (5.5–6.5)	7 (6–8)	0.1
*PSV, cmH_2O	12 (10–12)	12 (10–12.5)	0.7

Data are presented as number (n) and percentage for dichotomous values or median and interquartile ranges (IQR) for continuous values.
* PEEP and PSV values reported were those measured during the first 2 hours of NIV.
† The values of PaO_2/FiO_2 ratio used for matching these groups as well as pH and PCO_2 values were those measured during high-flow nasal oxygen immediately before starting NIV.
AE-IPF = acute exacerbation of IPF; ARDS = acute respiratory distress syndrome; BMI = body mass index; HACOR = heart rate, acidosis, consciousness, oxygenation, respiratory rate; SOFA = sequential organ failure assessment; APACHE II = Acute Physiology and Chronic Health Evaluation II; SAPS II = Simplified Acute Physiology Score; PEEP = positive end-expiratory pressure; PSV = pressure support; IQR = interquartile range

Further, no group differences were found between pressure values set during the NIV trial (Table 1). All ARDS patients presented a pulmonary ARDS occurring from lung infection (4 viral, 4 bacterial and 2 pneumocystosis).

Before starting NIV, ARDS patients showed a lower ΔP_{es} as compared to matched AE-IPF patients (24 [22 – 28] cmH_2O, p=0.004). Similarly, ARDS group showed a lower baseline RR (27 [26 – 30] bpm, p=0.0004), VE (18 [17 – 21] L/min, p=0.04) and dynamic mechanical power (48 [52 – 62] J/min, p=0.01). Conversely, ARDS patients showed comparable values of baseline Vte (9.9 [9.6 – 11] mL/kg of PBW, p=0.1) and baseline $dynC_{RS}$ (28 [25 – 33] mL/cmH_2O, p=0.3).

Compared to AE-IPF, patients with ARDS still presented a lower median value of RR, ΔP_{es}, ΔP_L, and dynamic mechanical power 2-hours after the initiation of NIV (21 [18 – 22] bpm, p<0.0001, 9 [8 – 13] cmH_2O, p=0.001, 21.5 [19.5 – 25] cmH_2O, p=0.003, 44 [40 – 68] J/min, p=0.01). At that time point both Vte and $dynC_{RS}$ were significantly higher in ARDS as compared to AE-IPF (11.6 [11 –14.2] cmH_2O, p=0.001 and 41 [35 –46] mL/cmH_2O, p=0.001 respectively). Two-hours after starting NIV and differently from AE-IPF, ARDS patients showed a direct correlation between PEEP levels and $dynC_{RS}$ (r=0.65, p=0.04, eFigure 2, panel A), while no direct association was found with PaO_2/FiO_2 ratio (r=0.24, p=0.5, eFigure 2, panel B). When testing whether there was a difference between groups concerning the change in physiological variables 2-hour after NIV, ΔP_L displayed an opposite response to NIV, being increased in

Table 2 Physiological variables of the AE-IPF population at baseline and 2 hours apart of NIV.

Parameter	Before NIV	After 2 hours NIV	P-value
RR, bpm	34 (30–39)	27 (25–30)	0.001
ΔP_{es}, cmH_2O	27 (21–34)	16 (14–24)	<0.0001
ΔP_L, cmH_2O	27 (21–34)	27 (25–36)	0.2
VE, L/min	21 (20–26)	18 (17–20)	0.003
Vte, mL/kg of PBW	9.1 (8.7–10.1)	9.3 (8.7–9.9)	0.2
$DynC_{RS}$, mL/cmH_2O	28 (19–31)	26 (18–28)	0.1
Dynamic mechanical power, J/min	71 (49–94)	60 (51–74)	0.1

Data are presented as median value and interquartile range.
AE-IPF = Acute exacerbation of IPF; bpm = breaths per minute; IQR = interquartile range; NIV, non-invasive mechanical ventilation; ΔP_{es}, change in esophageal pressure; ΔP_L, change in dynamic transpulmonary pressure; RR, respiratory rate; VE, minute ventilation; Vte, expiratory tidal volume; $DynC_{RS}$ = dynamic respiratory system compliance; PBW = predicted body weight.
*Mechanical power = 0,098 * (ΔP_L + PEEP) * Vte * RR.*

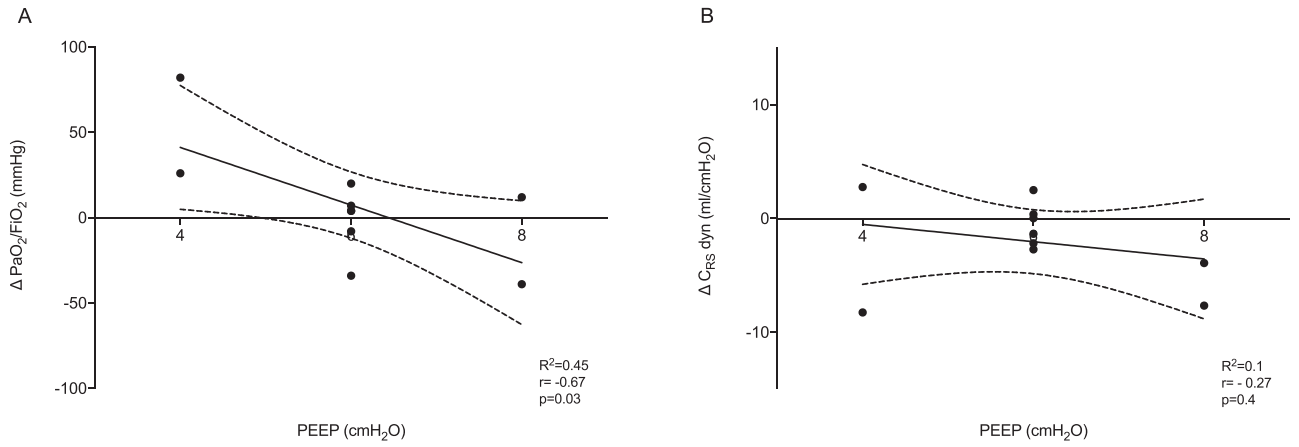

Fig. 2 Correlation between PEEP values and change in both PaO_2/FiO_2 and $dynC_{RS}$ ratio in AE-IPF (panel A and B, respectively). PEEP levels were inversely correlated with both PaO_2/FiO_2 ratio (r=—0.67, p=0.03) and $dynC_{RS}$ (r=—0.27, p=0.4) in AE-IPF, although statistical significance was not achieved for the latter. *AE-IPF = Acute exacerbation of IPF; ARDS = acute respiratory distress syndrome; $dynC_{RS}$ = respiratory system compliance; PEEP = positive end-expiratory pressure*.

AE-IPF and reduced in ARDS (p=0.04, Fig. 3, panel B). Vte, and $dynC_{RS}$ increased following NIV application in the ARDS cohort as compared to AE-IPF, (p=0.01 and p=0.002 respectively, Fig. 3 panel D and E), whereas no significant change in ΔP_{es}, VE and dynamic mechanical power was found (Fig. 3, panel A, C, and F).

Discussion

To the best of our knowledge this is the first study that quantifies the inspiratory effort and explores the respiratory mechanics in patients with AE-IPF under spontaneous unassisted and noninvasive assisted breathing. Overall, when compared to ARDS, patients with AE-IPF: 1) report a peculiar increase in inspiratory effort which reflects a high activation of the respiratory drive during unassisted breathing; 2) reduce effort and respiratory frequency but not transpulmonary pressure under short-term NIV without any improvement in dynamic compliance; 3) show a detrimental effect of increased values of external PEEP to PaO_2/FiO_2 ratio and $dynC_{RS}$. All these issues deserve discussion.

First, keeping spontaneous breathing preserved may have several potential benefits in patients with ARF including the avoidance of sedation and/or use of myorelaxants, the prevention of muscle mass loss, the spare of diaphragmic function, and the risk reduction for delirium onset. This seems even more important in AE-IPF for which the upgrade to invasive MV is often burdened by a high risk of VILI with unfavorable outcomes.[4,5,17] However, a growing body of evidence has strengthened the hypothesis that the presence of intense respiratory effort during ARF plays a critical role in promoting SILI[10,18-20] and unfavorable ventilatory outcomes.[10] In patients with IPF, specifically, the excessive inspiratory effort may be even more detrimental as fibrotic lungs are a patchwork of different tissue elasticities.[7] Thus, during spontaneous breathing, pleural pressure swing distribution is even more inhomogeneous and lung tissue deformation occurs unevenly; some lung areas being subjected to harmful level of stress/strain.[21] In our cohort, the baseline value of inspiratory effort of AE-IPF was 27 cmH_2O, as quantified by the esophageal manometry; the inspiratory effort was even higher than that reported in matched patients with ARDS. Similarly, baseline RR became more elevated in AE-IPF than in ARDS. Although it is difficult to give reasons for the difference observed in the activation of respiratory drive, we can speculate that $dynC_{RS}$ may not be fully representative of the regional lung stretch, the fibrotic lung being subjected to anisotropic behavior during inflation.[7] In line with this, we could hypothesize that the physical stimuli derived from micro-strain could act as a mechanical input in the hyperactivation of respiratory drive of AE-IPF patients.[22] Furthermore, given that the baseline $dynC_{RS}$ was similar between groups, one could speculate that factors other than gas exchange impairment might have boosted the respiratory drive of IPF patients, namely lung inflammation.[23]

Secondly as expected, and similarly to ARDS patients, NIV was effective in reducing both inspiratory effort and RR in AE-IPF. However, the change in respiratory mechanics was different between the two types of patients. Indeed, $dynC_{RS}$ displayed a significant improvement following NIV in ARDS but not in AE-IPF. Moreover, the values of dynamic transpulmonary pressure resulted persistently high in AE-IPF patients 2 hours following NIV application, thus suggesting a less favorable interaction with the ventilatory assistance.

Third, values of external PEEP applied by NIV were inversely correlated with PaO_2/FiO_2 ratio and $dynC_{RS}$ at 2-hours in AE-IPF, at difference with ARDS patients. These data suggest that the response to PEEP might reflect a different lung recruitability in AE-IPF and ARDS. Nevertheless, it was shown that a negative end-expiratory transpulmonary pressure can be reverted by incrementing PEEP values during controlled MV.[7] These findings may suggest that fibrotic lungs also exhibit end-expiratory de-recruitment in the dependent lung zones during an acute exacerbation. However, PEEP titration to a positive end expiratory transpulmonary pressure seemed to worsen all the static respiratory measurements (namely driving pressure, lung compliance, end-inspiratory transpulmonary pressure). We do believe that the PEEP-induced mechanical derangement in the fibrotic lung may be explained by the "squishy ball effect": high PEEP set to keep alveolar units open during expiration hyper-inflates recruitable lung areas through the anelastic

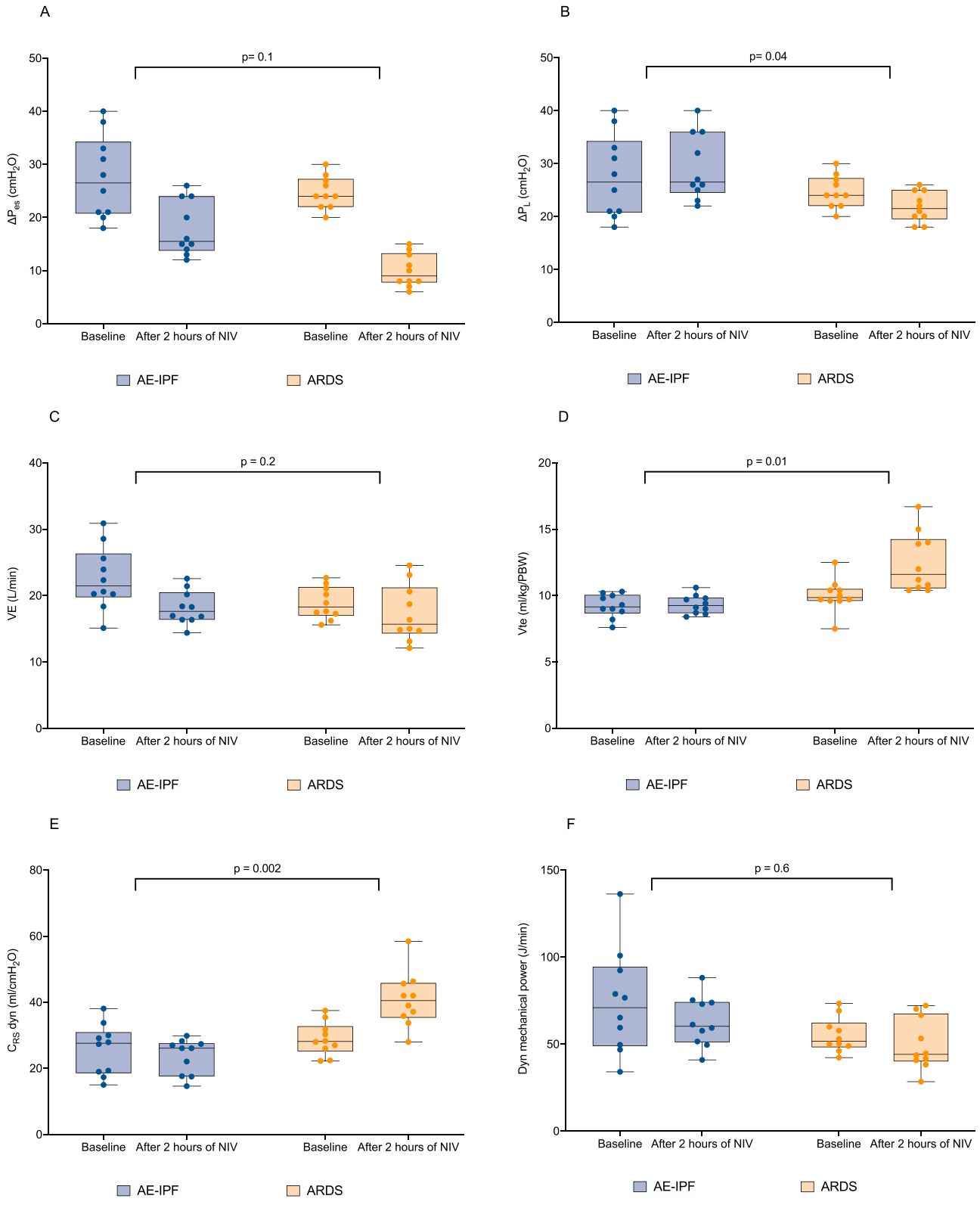

Fig. 3 Measured individual values of ΔP_{es}, ΔP_L, VE, Vte, $dynC_{RS}$ and dynamic mechanical power in the matched study groups both at baseline and 2-hour after initiating NIV. When testing as an interaction for whether the change in physiological variables 2 hours after starting NIV was different between AE-IPF and ARDS, statistical difference was found for ΔP_L (panel B, p=0.04), Vte (panel D, p=0.01) and $dynC_{RS}$ (panel E, p=0.002). *AE-IPF = Acute exacerbation of IPF; ARDS = acute respiratory distress syndrome; NIV = non-invasive mechanical ventilation; ΔP_{es} = esophageal pressure swing; ΔP_L = dynamic transpulmonary pressure; VE = minute ventilation; Vte = expiratory tidal volume; $dynC_{RS}$ = respiratory system compliance.*

surrounding zones, thus enhancing the end-inspiratory transpulmonary pressure effect, and exposing the lung at risk of substantial injury. The dynamic mechanical response exhibited by our patients mirrors the one reported in intubated and mechanically ventilated ones, thus suggesting that the UIP-like fibrotic lung displays a "squishy ball" behavior even with PEEP applied during spontaneous breathing. In this scenario, and given the detrimental effect of PEEP on the hyper-inflation of the recruitable lung zones, a mild sedation intended to lower the RR might be suggested to lower the RR and thus allowing for prolonged expiratory time.

The major strength of the study is the detailed and comprehensive measurement of respiratory effort and mechanics in a cohort of AE-IPF using a standard relatively invasive procedure (esophageal manometry). To our knowledge, these are the first data collected in this regard. Further, the standardized protocol for physiological variables collection applied at our center allows consistent measurements during esophageal manometry. Finally, the presence of a UIP pattern in all patients strengthens the homogeneity of mechanical data.

Our study also has several limits. First, the retrospective design and the reduced sample do only provide a preliminary pathophysiological insight in this condition. However, given that IPF is a rare condition, and that esophageal manometry can be extremely difficult to manage during an acute exacerbation of the disease, we are confident that these data might contribute to a better understanding of the mechanical behavior of fibrotic lung in spontaneous breathing. Second, the lack of a qualitative analysis of radiological images (namely the proportion of hyper-inflated lung tissue[24,25]) during exacerbations may weaken the interpretation of results. Third, a further comparison of AE-IPF patients under HFNC might have contributed to better specify the potential detrimental effect of NIV on the respiratory mechanics in these patients. Fourth, although the cohorts were matched according to clinical, mechanical and oxygenation criteria, the small sample size of the ARDS cohort may not reflect the heterogenous features of this population. Indeed, a more homogenous ARDS population could have improved the quality of the matching. Finally, given the retrospective nature of the study, NIV settings were decided by the attending physician, neither we did assess any specific local nor systemic biomarkers of inflammation (i.e. cytokines) that might have contributed to understand the role of disease severity on the respiratory drive.

Conclusions

In this physiologic, preliminary retrospective study, spontaneously breathing patients with IPF showed an elevated inspiratory effort while on acute exacerbation of the disease. The application of NIV with an external PEEP was effective in reducing their respiratory drive but at the cost of deteriorating mechanics. Additional prospective studies with a larger sample size are required to further define the local mechanical consequences and ~~even~~ the local or systemic biological features in patients with fibrotic lungs during assisted and non-assisted spontaneous breathing. More research is also needed to focus on the different mechanical behavior of AE-IPF compared with ARDS of similar severity.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the pre-existing Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 348/18). Informed consent to participate in the study and to allow their clinical data to be analyzed and published were obtained from participants, as appropriate. For study purposes we further conducted a retrospective sub-analysis of data prospectively collected within a pre-registered clinical trial ClinicalTrial.gov (NCT03826797) and in accordance with the pre-existing Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 266/16).

Consent for publication

Consent for publication was obtained by all patients enrolled, as appropriate.

Availability of data and materials

Data are available at the Respiratory Disease Unit of the University Hospital of Modena, Italy, upon request.

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Author contributions

RT, IC and AC designed the study, enrolled the patients, analyzed the data, and wrote the paper and should be considered as first authors. LT, RF, DA, FG, GB, LM, A Moretti and CC made substantial contributions to the literature review, data collection, and paper writing. CN, EB, SC, VS, SB and MG reviewed the literature, wrote the manuscript and produced the figures. A Marchioni and EC designed the study, wrote, reviewed and edited the manuscript and share senior authorship. All authors have read and approved the final version of the manuscript. RT, IC and AC share first authorship. AM and EC share senior authorship.

Conflicts of interest

Authors have no competing interests with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.08.004.

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ORIGINAL ARTICLE

Impact of systemic inflammatory markers in patients with *ALK*-positive non-small cell lung cancer treated with crizotinib

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KEYWORDS
NSCLC;
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Survival

Abstract
Objectives: To evaluate the prognostic utility of inflammation-based prognostic scores in patients with *ALK*-positive metastatic or non-resectable non-small-cell lung cancer (NSCLC) treated with crizotinib.
Patients and Methods: A total of 82 patients with *ALK*-positive metastatic or non-resectable NSCLC who received ALK TKI crizotinib were included. Pre-treatment modified Glasgow prognostic score (mGPS), prognostic nutritional index (PNI), and systemic immune-inflammation index (SII) were calculated. Multivariable logistic regression and Cox proportional hazards models were used to assess the impact of pretreatment mGPS, PNI, and SII on overall survival (OS), progression-free survival (PFS), and objective response rate (ORR).
Results: The ORR was 77.2%, while 1-year OS and PFS rates were 95.0% and 93.5%, respectively. The univariate analysis revealed significantly higher 1-year PFS (89.4 vs. 64.4%, p=0.043) and OS (92.0 vs. 83.3%, p=0.01) rates in patients with low (<934.7) vs. high (≥934.7) SII scores. Multivariate analysis revealed that PNI ≥0.09 was a significant determinant of poorer 1-year OS rates (hazard ratio [HR]: 2.46, 95% confidence interval [CI] 0.88—4.85, p=0.035). No significant difference was observed in survival rates according to gender, age, smoking status, prior lines of therapy, or mGPS scores, while higher mGPS scores (odds ratio [OR]: 0.1, 95%CI 0.16—1.04; p=0.009) and higher PNI scores (OR: 0.16, 95% CI 0.02—0.55; p=0.035) were associated with poorer ORR.

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Conclusion: Our findings indicate the prognostic significance of PNI and SII in terms of survival outcome and the impact of mGPS and PNI on treatment response in patients with *ALK*-positive NSCLC treated with crizotinib.

Introduction

Lung cancer remains among the most frequent and aggressive malignancies and the leading causes of cancer-related mortality worldwide.[1,2] Non-small lung cancer (NSCLC) accounts for 85% of all lung cancers.[3-5] The management of NSCLC has evolved over years from the traditional platinum-based chemotherapy to personalized therapy with anti-angiogenic agents or tyrosine kinase inhibitors (TKIs) in patients with targetable oncogenic driver alterations.[6-9]

Rearrangement of anaplastic large-cell lymphoma kinase (*ALK*) gene occurs in up to 7% of patients with NSCLC, particularly in younger and never or ex-light smoker patients with adenocarcinoma histology.[9-13] *ALK*-rearranged NSCLC tends to be more aggressive and usually presents at an advanced stage, where brain metastases are very common and pose significant clinical challenges.[14,15]

Crizotinib, a first generation ALK TKI, has been used as the first-line treatment for patients with *ALK*-positive NSCLC because of its superior efficacy over chemotherapy in terms of response rate and survival in stage IIIA-IV patients in PROFILE 1014 phase III randomized trials.[8,16,17] However, crizotinib offers only a median progression-free survival (PFS) of 7.7-11 months.[9,12] Moreover, despite the introduction of more selective second-generation (ceritinib, alectinib, and brigatinib) and third-generation (lorlatinib) ALK TKIs, approximately 30% of patients do not respond to ALK—TKIs even if they harbor *ALK* rearrangement.[18,19] Hence, given the aggressive course of the *ALK*-positive NSCLC along with the high treatment costs, potential severe toxicity, and risk of early progression in case of ineffective treatment, it is worthwhile to establish reliable prognostic markers to predict the efficacy of ALK-TKIs.

Systemic inflammation plays a critical role in proliferation, apoptosis, migration, invasion, and metastasis during carcinogenesis and cancer progression. Activated transcription factors prompt tumor cells to produce chemokines, cytokines, prostaglandins, and growth factors to recruit inflammatory cells including neutrophils, lymphocytes, macrophage, and mast cells.[20] Systemic inflammatory responses play important role in tumor development, enhanced local immunosuppression and thereby in cancer progression and worsened prognosis. Therefore, prognostic value of several inflammation-based scores such as Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), systemic immune-inflammation index (SII) and advanced lung cancer inflammation index (ALI) have become increasingly investigated in NSCLC.[21-28]

The modified GPS (mGPS) is based on a combination of serum albumin level and C-reactive protein (CRP);[29] the PNI is based on a combination of serum albumin level and absolute lymphocyte count,[30] and the SII is based on a combination of NLR and platelet count.[31] While the prognostic significance of GPS, PNI, or SII has been addressed in small cell lung cancer,[29,32] stage III NSCLC,[33] and resectable NSCLC,[27,34] its value in patients with *ALK*-positive NSCLC remains unclear.

This study aimed to retrospectively evaluate the prognostic utility of pre-treatment mGPS, PNI, and SII scores in terms of treatment response and survival outcomes in patients with *ALK*-positive metastatic or non-resectable NSCLC treated with crizotinib.

Patients and methods

Study population

A total of 82 patients with median age of 52.5 (range, 20—77) years (57.3% males) who were diagnosed with metastatic or non-resectable *ALK*-positive NSCLC and received ALK TKI crizotinib between January 2013 and August 2019 were included in this retrospective multicenter study conducted in eight oncology centers across Turkey. Patients who had a concomitant infection including human immunodeficiency virus or hepatitis, systemic steroids, concomitant radiotherapy, or previous or ongoing autoimmune disorder were excluded.

The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee along with the permission for the use of patient data for publication purposes (Date of Approval: 11 May 2022 Reference number/Protocol No: 449).

Study parameters

Data on patient demographics (gender, age), smoking history, Eastern Cooperative Oncology Group Performance Status (ECOG PS), disease characteristics (TNM stage at diagnosis, metastasis sites), laboratory findings within a week prior to the first dose of crizotinib (white blood cells, hemoglobin, neutrophil, platelet, and lymphocyte counts, albumin level and CRP), line of crizotinib therapy as well as follow-up data on treatment response were retrieved from the hospital records. Pre-treatment inflammation-based prognostic scores included mGPS, PNI, and SII.

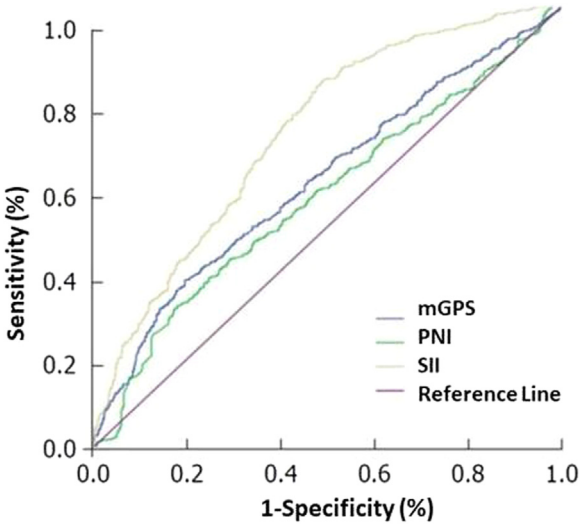

Fig. 1 Receiver operating characteristic (ROC) curve shows the cut-off value of inflammation-based prognostic scores indicative of response to crizotinib. According to ROC analysis, the areas under the curve for mGPS, PNI and SII are 0.859, 0.755 and 0.745, respectively, and the optimal cut-off points are 0.09, 0.09 and 934.7, respectively.

Survival analysis included 1-year overall survival (OS) and PFS rates and were evaluated with respect to clinicopathological variables and inflammation-based prognostic scores. For inflammation-based prognostic scores, receiver operating characteristic (ROC) analysis was performed to determine optimal cut-off values for mGPS, PNI, and SII; and the impact of inflammation-based prognostic scores on survival parameters were analyzed in subgroups of patients (lower vs. higher score) based on the optimum cut-off value defined for each score (Fig. 1).

Multivariable logistic regression and Cox proportional hazards models were used to assess the impact of clinicopathological variables and inflammation-based prognostic factors on OS, PFS and objective response rate (ORR).

ALK rearrangement was determined using fluorescence in situ hybridization and Ventana immunohistochemistry (IHC). Tumor stage was classified according to the 8th edition of AJCC Cancer Staging Manual.[35]

Treatment response assessment

Computed tomography (CT)/magnetic resonance imaging scan examinations were performed every 8 weeks. Treatment response was evaluated based on Response Evaluation Criteria of Solid Tumor (RECIST) ver.1.1[36] and categorized as progressive disease, stable disease (SD), partial remission (PR) and complete remission (CR). ORR was defined as the percentage of the best overall remission (PR + CR) confirmed by the investigator.

Inflammation-based prognostic scores

mGPS was based on combined evaluation of elevated CRP and hypoalbuminemia and scored by 0 (normal CRP and albumin levels), 1 (CRP $>$1.0 mg/dL only), or 2 (CRP was $>$1.0 mg/dL plus albumin $<$3.5 g/dL).[29] PNI was calculated according to the previously described formula: 10 $\times$ serum albumin value (g/ dL) + 0.005 $\times$ peripheral lymphocyte count (/μL).[30] SII was calculated using the formula: platelet count $\times$ neutrophil count / lymphocyte count.[31]

Statistical analysis

Statistical analysis was made using R 3.4.3 and IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY). Descriptive analysis was used for all variables. The survival outcomes measured were PFS and OS. PFS was defined as the period from the date of treatment to first recurrence or last follow-up and OS was defined as the period from the date of treatment to death or last follow-up. The optimal cut-off values of mGPS, PNI and SII for prognostic ability were determined according to ROC curve and the areas under the ROC curve. Patients were divided into high and low mGPS, PNI and SII groups based on cut-off values. PFS and OS rates were calculated and compared using the Kaplan–Meier method and the log–rank test. Univariate and multivariate analyses were performed for prognostic factors with inclusion of variables significant on univariate analysis to a multivariate Cox proportional hazards model. Hazard ratios (HRs) were estimated using the Cox analysis and reported as relative risks with corresponding 95% confidence intervals (CIs). Reverse Kaplan–Meier method was used to compute the median follow–up time. Data were expressed as median (minimum-maximum) and percent (%) where appropriate. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics and treatment response

Median age was 52.5 years (range, 20–77), and 57.3% of patients were males. Overall, 57.3% of patients were non-smokers and 65.9% were in ECOG PS category 1. Tumor characteristics at the time of diagnosis included TNM Stage IV disease in 81.7% of patients along with metastasis to distant lymph nodes in 46.3%. Overall, 26.8% of patients were treated with first-line of crizotinib therapy and 56.1% received second-line therapy (Table 1).

The duration of median follow-up was 19.3 months. The ORR (CR + PR) was achieved in 77.2% of patients, while SD was noted in 7.6% of patients (Table 1).

OS and PFS data

In the overall study population, 1-year OS and PFS rates were 95.0% and 93.5%, respectively, and median OS and PFS times were 66.3 (95% CI 19.9–112.6) months and 27.4 (95% CI 15.2–39.5) months, respectively.

PFS according to clinicopathological variables and inflammation-based prognostic factors

ECOG PS category 1 (85.7%) and category 2 (86.2%) were associated with significantly higher 1-year PFS rates than the ECOG PS category 3 (23.6%, p=0.014), while in

Table 1 Demographic and clinical characteristics and treatment response.

Age, years, median (range)	52.5 (20−77)
Age group, n (%)	
<50 years	29 (35.4)
≥50 years	53 (64.6)
Gender, n (%)	
Female	35 (42.7)
Male	47 (57.3)
ECOG performance status, n (%)	
0	15 (18.3)
1	54 (65.9)
2	12 (14.6)
3	1 (1.2)
Smoking status, n (%)	
Non-smoker	47 (57.3)
Ex-smoker	35 (42.7)
TNM stage at diagnosis, n(%)	
I	3 (3.7)
II	2 (2.4)
III	10 (12.2)
IV	67 (81.7)
Metastasis sites, n (%)	
Liver	8 (9.85)
Lung	37 (45.1)
Brain	28 (34.1)
Adrenal	15 (18.2)
Bone	34 (41.4)
Distant lymph nodes	38 (46.3)
Line of therapy	
1st	22 (26.8)
2nd	46 (56.1)
3rd	10 (12.2)
≥ 4th	4 (4.9)
Treatment response, n (%)	
Absent	17 (20.7)
Present	65 (79.3)
Objective response rate, %	77.2
Stable disease, %	7.6

multivariate analysis, poorer ECOG PS category was a significant determinant of poorer 1-year PFS (HR 3.42, 95% CI 1.34−3.77, p=0.010) (Table 2).

Presence vs. absence of treatment response to crizotinib was associated with significantly higher rates of 1-year PFS (91.7 vs. 39.9%, p=0.001), while in multivariate analysis, the presence of crizotinib treatment response was a significant determinant of higher 1-year PFS (HR 0.25, 95% CI 0.10−0.78, p=0.017) (Table 2).

No significant difference was noted in 1-year PFS rates according to gender, age, smoking status, or the line of therapy (Table 2).

While the 1-year PFS rate was significantly higher (89.4 vs. 64.4%, p=0.043) among patients with low (<934.7) vs. high (≥934.7) SII scores, this finding was not confirmed in the multivariate analysis. No significant difference was noted in 1-year PFS rates according to mGPS and PNI scores (Table 2).

OS according to clinicopathological variables and inflammation-based prognostic factors

ECOG PS category 1 (94.0%) and category 2 (88.6%) were associated with significantly higher 1-year OS rates than the ECOG PS category 3 (31.2%, p=0.001), while in multivariate analysis, poorer ECOG PS category was a significant determinant of poorer 1-year PFS (HR 6.32, 95%CI 3.40−9.75, p<0.001) (Table 3).

Presence vs. absence of treatment response to crizotinib was associated with significantly higher rates of 1-year OS (95.1 vs. 50.6%, p<0.001), while in multivariate analysis, the presence of crizotinib treatment response was a significant determinant of higher 1-year OS (HR 0.30, 95% CI 0.07−1.12, p=0.027) (Table 3).

No significant difference was noted in 1-year OS rates according to gender, age, smoking status or the line of therapy (Table 3).

While the 1-year OS rate was significantly higher (92.0 vs. 83.3%, p=0.01) among patients with low (<934.7) vs. high (≥934.7) SII scores, this finding was not confirmed in the multivariate analysis. Multivariate analysis revealed the PNI values ≥0.09 to be a significant determinant of poorer 1-year OS (HR 2.46, 95% CI 0.88−4.85, p=0.035). No significant difference was noted in 1-year PFS rates according to mGPS scores (Table 3).

Logistic regression analysis for the factors predicting response to crizotinib

Logistic regression analysis for the factors predicting the treatment response revealed that higher mGPS scores (OR: 0.1, 95% CI 0.16−1.04; p=0.009) and higher PNI scores (OR: 0.16, 95% CI 0.02−0.55; p=0.035) were associated with poorer ORR (Table 4).

ECOG PS, the line of crizotinib therapy and SII scores had no significant impact on treatment response (Table 4).

Discussion

Our findings in a retrospective cohort of crizotinib-treated *ALK*-positive metastatic non-resectable NSCLC patients revealed 1-year OS and PFS rates of 95.0% and 93.5%, respectively, along with an ORR of 77.2% after a median 19.3 months of follow-up. Poorer ECOG PS category and absence of crizotinib treatment response were significant determinants of poorer 1-year PFS and OS rates, while higher pre-treatment PNI values (≥0.09) served as a significant predictor of poorer 1-year OS rate and albeit not confirmed in the multivariate analysis, higher pre-treatment SII scores (≥934.7) were associated with poorer 1-year PFS and OS rates in the univariate analysis. Increase in pre-treatment mGPS and PNI scores were also associated with inferior ORR.

Given the predominance of stage III-IV disease and prior lines of crizotinib in our study population comprising patients with *ALK*-positive metastatic non-resectable NSCLC, our data on survival outcome and ORR appear consistent with data from a previous study on crizotinib-treated patients with *ALK*-positive advanced NSCLC (n=47), which revealed ORR of 61.7%, disease control rate (DCR) of 93.6%, and PFS of 19 months overall.[37] Notably, the authors also

Table 2 Progression-free survival in relation to clinicopathological and prognostic factors.

		1-year progression-free survival			
		Rate (%)	Univariate analysis	Multivariate analysis	
Variables			p value	p value	HR (95% CI LB–UB)
Age	<50 years	76.2	0.85		
	≥50 years	87.7			
Gender	Female	81.1	0.78	–	–
	Male	90.7			
ECOG PS	1	85.7	**0.014**	**0.010**	3.42 (1.34–3.77)
	2	86.2			
	3	23.6			
Smoking status	Non-smoker	85.9	0.77	–	–
	Ex-smoker	83.9			
Line of therapy	1st	72.5	0.25	–	–
	2nd	88.2			
	3rd	NA			
	≥ 4th	NA			
Treatment response	Absent	39.9	**0.001**	**0.017**	0.25 (0.10–0.78)
	Present	91.7			
mGPS	<0.09	78.6	0.53	0.47	0.76 (036–1.60)
	≥0.09	79.6			
PNI	< 0.09	86.7	0.90	0.47	1.32 (0.61–2.87)
	≥0.09	80.7			
SII	<934.7	89.4	**0.043**	0.30	0.57 (0.19–1.67)
	≥934.7	64.4			

HR: Hazards ratio, CI: confidence interval, NA: not applicable, ECOG PS: Eastern Cooperative Oncology Group Performance Status: mGPS: modified Glasgow prognostic score, PNI: Prognostic nutritional index, SII: Systemic immune-inflammation index.

Table 3 Overall survival in relation to clinicopathological and prognostic factors.

		1-year overall survival			
		Rate (%)	Univariate analysis	Multivariate analysis	
Variables			p-value	p-value	HR (95% CI LB–UB)
Age group	<50 years	88.9	0.40	–	–
	≥50 years	89.9			
Gender	Female	88.9	0.68	–	–
	Male	90.7			
ECOG PS	1	94.0	<**0.001**	<**0.001**	6.32 (3.40–9.75)
	2	88.6			
	3	31.2			
Smoking status	Non-smoker	88.9	0.20	–	–
	Ex-smoker	85.1			
Line of therapy	1st	78.9	0.36	–	–
	2nd	90.8			
	3rd	NA			
	≥4th	NA			
Treatment response	Absent	50.6	<**0.001**	**0.027**	0.30 (0.07–1.12)
	Present	95.1			
mGPS	<0.09	86.7	0.18	–	–
	≥0.09	80.7			
PNI	< 0.09	90.2	0.43	**0.035**	2.46 (0.88–4.85)
	≥0.09	73.7			
SII	<934.7	92.0	**0.01**	0.43	0.61 (0.18–2.07)
	≥934.7	83.3			

HR: Hazards ratio, CI: confidence interval, NA: not applicable, ECOG PS: Eastern Cooperative Oncology Group Performance Status; mGPS: modified Glasgow prognostic score, PNI: Prognostic nutritional index, SII: Systemic immune-inflammation index.

Table 4 Logistic regression analysis of the predictive factors for the response to crizotinib.

	OR	95% CI	p-value
Variables			
ECOG PS	0.54	0.16−4.93	0.59
Line of crizotinib therapy	1.53	0.56−4.12	0.39
mGPS	0.10	0.16−1.04	**0.009**
PNI	0.16	0.02−0.55	**0.035**
SII	0.45	0.19−4.65	0.99

OR: Odds ratio, CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, mGPS: modified Glasgow prognostic score, PNI: Prognostic nutritional index, SII: Systemic immune-inflammation index.

indicated a better ORR (63.9% vs. 45.5%), DCR (94.5% vs. 91%), and PFS (19 vs. 11 months) in patients with more than three metastatic sites than those with less sites and better ORR in younger vs. older (>60 years) patients (40 vs. 71.9%) and in the first vs. second/final application of crizotinib (78.2 vs. 45.8%).[37]

Our findings indicate the potential role of inflammation-based prognostic scores in predicting either the survival outcome (for PNI and SII) or the crizotinib treatment response (for mGPS and PNI) in patients with *ALK*-positive metastatic NSCLC. This is important given these inflammation-based prognostic scores are considered to be readily available, simple and inexpensive tools, implicating their potential to be routinely considered before treatment for patients with NSCLC.[34]

Albeit not confirmed in the multivariate analysis, association of pre-treatment elevated SII scores with poorer PFS and OS in the univariate analysis in the current study seems to be consistent with the notion that systemic immune and inflammatory cells, such as neutrophils, monocytes, platelets and lymphocytes, are associated with prognostic value in several malignancies.[34,38-40] Notably, association of low SII with less aggressive disease phenotype (with female gender, never smoking status, adenocarcinoma histology, lower pathological TNM stage and low CRP) has also been noted in patients with NSCLC.[34]

Undoubtedly, given the suggested role of non-steroidal anti-inflammatory drugs in the prevention and treatment of cancer,[41] patients with NSCLC who have a high SII are likely to benefit from targeted anti-inflammatory agents with aspirin and non-steroidal anti-inflammatory drugs.[34]

In the current study, SII was associated with poorer OS and PFS only in the univariate analysis, whereas SII was determined to significantly predict poorer OS in patients with non-resectable *ALK*-positive NSCLC. However, in a past study on 341 patients who underwent complete resection for NSCLC, SII was noted among the independent factors in predicting overall postoperative cancer-specific survival.[34] In another study including 332 patients with newly diagnosed stage III NSCLC, SII ≥660 and PNI ≤52.95 were reported to be significantly associated with worse OS in the univariate analysis, while SII (HR, 2.105; 95% CI 1.481−2.741) and ECOG PS (HR, 1.744; 95% CI 1.158−2.626) were independently correlated with OS in the multivariate analysis.[33] Authors indicated SII to be an independent prognostic indicator of poor outcomes in patients with stage III NSCLC and to be superior to other inflammation-based factors in terms of prognostic ability.[33]

In a previous study on patients with NSCLC who underwent potentially curative resection, authors reported the association of GPS, PNI and SII with overall cancer-specific survival in the univariate analysis, whereas in multivariate analysis GPS was the only inflammation-based prognostic score independently associated with overall cancer-specific survival.[27]

CRP is a non-specific inflammatory acute-phase protein, and an elevated serum CRP level has been reported to be associated with unfavorable prognosis in patients with NSCLC.[34,42] However, in our study, while mGPS was the only inflammation-based score associated with CPR, no significant impact of mGPS was noted on either PFS or OS rates. Furthermore, subgroup analysis of patients with high SII vs. high mGPS revealed longer OS and PFS times in the latter group.

Nutritional status of patients, as commonly reflected by serum albumin levels, is also considered to predict survival in patients with NSCLC.[34,43] Among the inflammation-based scores used in this study, mGPS and PNI were defined to be based on albumin and other factors. Thus, given the association of elevated pre-treatment scores for PNI with significantly poorer OS rate in the multivariate analysis as well as predictive role of both mGPS and PNI in the treatment response, our findings seem to indicate a stronger prognostic power of albumin over that of CRP and the possibility that prognostic power of CRP might be off-set in multivariate analysis.

Nonetheless, it should be noted that in a previous study on patients with NSCLC who underwent potentially curative resection, based on superiority of GPS over albumin-based index scores such as ALI and PNI in multivariate analysis, the higher prognostic power of CRP has been emphasized along with the likelihood of the prognostic power of albumin to be off-set in multivariate analysis.[34]

However, the biological mechanism underlying the association between CRP, albumin, and increased risk of cancer development is unclear. In this context, it is first hypothesized that CRP increase and albumin decrease are probably regulated by proinflammatory cytokines, especially interleukin (IL)-6 and IL-1. These cytokines are also crucial for neoangiogenesis and disease progression, and thus are significantly associated with the increasing risk of lung cancer development.[44,45] This interaction between CRP, albumin, and cancer biology may explain the different results between inflammatory scores using CRP and albumin values and other scores using blood cells.

Accordingly, our findings emphasize the likelihood of diversity in the prognostic ability of inflammation-based prognostic factors in patients with NSCLC depending on the presence of targetable oncogenic driver alterations such as rearrangement of *ALK* gene and the related aggressive clinicopathological course. In this regard, among patients with *ALK*-positive metastatic or non-resectable NSCLC, PNI rather than SII and GPS seems to be a stronger prognostic indicator of survival outcome, while both GPS and PNI have a significant impact on response to crizotinib treatment.

Certain limitations to this study should be considered. First, owing to the retrospective design establishing the temporality between cause and effect is not possible. Second, given that *ALK*-positive patients represent a rare subpopulation among patients with NSCLC, the relatively small sample size limits the generalizability of our findings.

Third, lack of longitudinal analysis of the examined inflammation-based markers according to crizotinib cycles and/or disease progression. Forth, no available trAEs-related data and the lack of correlational analyses between inflammatory-based scores and the occurrence of trAEs.

Nevertheless, despite these limitations, given the restricted amount of data available on this subject area, our findings represent a valuable contribution to the literature regarding the potential prognostic markers in crizotinib-treated *ALK*-positive NSCLC patients.

Conclusion

Our findings in a retrospective cohort of crizotinib-treated *ALK*-positive NSCLC patients indicated the association of elevated pre-treatment SII scores with poorer OS and PFS in univariate analysis. In multivariate analysis, elevated PNI scores were associated with poorer OS, while elevated mGPS and PNI scores were associated with lower treatment response rates. To the best of our knowledge, this is the first report to demonstrate the prognostic significance of PNI and SII in terms of survival outcome and the impact of GPS and PNI on treatment response in crizotinib-treated *ALK*-positive metastatic or non-resectable NSCLC patients. Accordingly, our findings emphasize potential utility of pre-treatment inflammation-based prognostic scores, in particular albumin-based scores, in predicting survival outcome and treatment response in patients with *ALK*-positive NSCLC.

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CRediT author statement

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Conflicts of interest

The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Test-retest reliability, construct validity and determinants of 6-minute walk test performance in adult patients with asthma

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Abstract
Introduction and objectives: Current knowledge regarding the measurement properties of the 6-minute walk test (6MWT) in patients with asthma is limited. Therefore, the aim of this study was to assess the test-retest reliability, measurement error and construct validity of the 6MWT and identify determinants of 6-minute walk distance (6MWD) in patients with asthma.
Patients and methods: 201 asthma patients referred for pre-pulmonary rehabilitation assessment, were retrospectively analyzed (age 61±12 years, 42% male, FEV_1 78±27% predicted). Patients performed two 6MWTs on subsequent days using a 30 m straight walking course. Other measurements included resting dyspnea, maximal exercise capacity, body composition, pulmonary function, pulmonary and quadriceps muscle strength and symptoms of anxiety and depression. Measurement error (absolute reliability) was tested using standard error of measurement (SEM), minimal detectable change at 95% confidence interval (MDC95%) and Bland and Altman 95% limits of agreement, whereas test-retest reliability (relative reliability) and construct

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validity were assessed using the intra-class correlation coefficient ($ICC_{2,1}$) and correlations, respectively.
Results: The 6MWD showed excellent test-retest reliability ($ICC_{2,1}$: 0.91). The mean change in 6MWD after the second 6MWT was 18m (95%CI 11−24m), with 73% of the patients walking further in the second test. The SEM and MDC95% for the 6MWT were 35 m and 98 m, respectively. The best 6MWD correlated strongly with peak oxygen uptake during CPET and resting dyspnea (r = 0.61−0.64) and had no-to-moderate correlations with body composition, pulmonary function, respiratory and quadriceps muscle strength and symptoms of anxiety and depression (r = 0.02-0.45). Multiple linear regression was able to identify maximal workload, BMI, rollator use, maximal expiratory pressure, FEV_1 and DL_{CO} as independent determinants of the best 6MWD (R^2 = 0.58).
Conclusions: The 6MWT was considered to be reliable and valid in patients with asthma, which strengthens its clinical utility. However, the majority of patients demonstrated a considerable learning effect in the second 6MWT, providing a strong rationale for performing two 6MWTs.

Introduction

Asthma is a chronic respiratory disease with variable expiratory airflow limitation, usually characterized by chronic airway inflammation, that affects many individuals worldwide and inflicts a great burden on society.[1] Due to its complex and heterogeneous nature, asthma typically presents with a variety of respiratory and non-respiratory symptoms[2,3] and is associated with significant comorbidity and an increased mortality risk.[4,5] Currently, asthma management is primarily focused on respiratory symptoms (i.e. pharmacotherapy),[6] potentially overlooking the impact of extra-pulmonary manifestations, including exercise limitation and decreased physical activity, which are commonly reported irrespective of impairments in pulmonary function.[7−9] Considering the fact that impaired physical functioning is a common feature in patients with chronic respiratory disease,[10,11] it is essential for healthcare professionals and clinical scientists to use valid and reliable measures when assessing functional exercise capacity. Tests with good measurement properties are needed to ensure patient progress is well-monitored and above all, accurate. Moreover, daily practice requires tests that are quick and easy to perform in order to guard time management and to retest patients and monitor changes efficiently.

The 6-minute walk test (6MWT) is an easy-to-administer, generally well tolerated and safe field walking test, commonly used as a clinical indicator of functional exercise capacity and a predictor of morbidity and mortality across a wide range of cardiopulmonary diseases.[12,13] The reliability and construct validity of the 6MWT have been demonstrated in several patient populations, such as chronic obstructive pulmonary disease (COPD),[14] chronic heart failure [15] and idiopathic pulmonary fibrosis.[16] Despite the fact that the 6MWT can provide insights in functional limitation in chronic respiratory disease, current knowledge regarding its measurement properties (e.g. reliability, construct validity) in patients with asthma is limited. A considerable learning effect of the 6MWT has been previously established in patients with COPD,[13,14] with the majority of individuals showing an increase in 6-minute walk distance (6MWD) when a second test is performed without any intervention or alteration in clinical characteristics. Information regarding this learning effect in patients with asthma is highly limited.[17] It seems reasonable to hypothesize that the test-retest reliability of the 6MWT will be good in patients with asthma, since a systematic review by Singh et al. examining field walking tests in chronic respiratory disease stated that intra-class correlation coefficients (ICC's) ranged from 0.82 to 0.99.[13] However, the limits of agreement reported in the included studies were large, indicating that there is a certain amount of measurement error and the results from the first test may not be able to predict the outcome of the second test. Therefore, the current study aimed (1) to investigate the measurement error and test-retest reliability of the 6MWT, quantifying a potential learning effect between tests; (2) to evaluate the construct validity of the 6MWT; and (3) to identify the clinical determinants of the best 6MWD in a large cohort of patients with asthma.

Methods

In a retrospective observational study, 217 adult patients with asthma referred for a pre-pulmonary rehabilitation assessment at Ciro (Horn, the Netherlands) between September 2015 and January 2019, were screened for eligibility. Patients were included in the current analysis if they met the following criteria: respiratory physician-based diagnosis of asthma, based on an initial identification of both a characteristic pattern of symptoms and variable expiratory airflow limitation according to national and international guidelines,[1] clinical stability at the time of the assessment (absence of current asthma attack); and two 6MWTs performed on subsequent days. The medical ethics committee of Maastricht University stated that the Medical Research Involving Human Subjects Act (WMO) did not apply for this study and that an official approval of this study by the committee was not required (METC azM/UM 2019-1081).

6MWT

Two 6MWTs were performed according to the official European Respiratory Society (ERS)/American Thoracic Society

(ATS) guidelines[12,18] on subsequent days using a 30 m straight walking course using cones as turnaround points. Use of walking aids (cane, rollator, etc.) was allowed during the 6MWTs and patients were instructed to take all usual medications. Patients were instructed to walk as far as possible and the distance walked (6MWD) was registered after each test. All tests were supervised by a trained and qualified technician who walked behind the patient, providing them with standardized phrases for encouragement every minute and informing them about the remaining time of the test. Patients were permitted to stop (if required) during the test, but were instructed to resume walking once they were able to. Heart rate (beats/min) and oxygen saturation (SpO_2) as measured by pulse oximetry were assessed before, during and at the end of the 6MWTs and perceived dyspnea and leg fatigue (modified Borg scale; range 0-10) were assessed at the start (at rest) and at the end (at peak exertion) of the test. Oxygen supplementation was used if required, and oxygen desaturation during the 6MWT was defined as a drop of $\geq$4% in SpO_2 and an end-SpO_2 of $<$88%. The predicted 6MWD reference values of Troosters et al. were used.[19]

Other measurements

Demographics, anthropometrics, medication use (including maintenance oral corticosteroids (OCS)), smoking status, asthma attack/hospitalization frequency and the use of oxygen and/or walking aids (rollator or cane) were assessed, as part of standard care. To characterize patients with eosinophilic asthma, blood eosinophils were measured as part of the complete blood count plus differential, using cut-off values of both $\geq$150 cells/μL and $\geq$300 cells/μL.[20] The modified Medical Research Council (mMRC) scale was used to evaluate the level of functional limitation due to dyspnea in activities of daily living. The mMRC is a five-point scale, ranging from 0 (dyspnea only with strenuous exercise) to 4 (too dyspneic to leave the house or breathless when getting dressed), in which a higher grade indicates higher functional disability due to dyspnea.[21]

Pulmonary function (Masterlab®, Jaeger, Würzburg, Germany) was measured according to ATS/ERS guidelines using spirometry, with forced expiratory volume in the first second (FEV_1) and FEV_1/forced vital capacity (FVC) ratio as primary outcomes,[22] and whole-body plethysmography, providing residual volume (RV), total lung capacity (TLC) and the RV/TLC ratio.[23] Furthermore, respiratory muscle strength, using maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) measurements, was determined.[24]

Whole-body dual energy X-ray absorptiometry (DEXA) provided information about body composition, by means of lower-limb lean muscle mass (LL-LMM) and calculating fat-free mass (FFM) based on the sum of both lean and mineral bone mass.[25] Subsequently, body mass index (BMI) an FFM index (FFMI) was calculated as body weight (kg) and FFM (kg) divided by height squared (m^2), respectively. Mood status was assessed with the 14-item Hospital Anxiety and Depression Scale (HADS), in which higher scores are equivalent to more symptoms of anxiety or depression.[26] Maximal exercise capacity was evaluated with a symptom limited incremental (+10 W/min) cardiopulmonary exercise test (CPET) performed on a cycle ergometer (Carefusion, Houten, The Netherlands; Oxycon β, Jaeger, Würzburg, Germany), of which maximal power output (W_{max}) and peak oxygen consumption (VO_2peak in mL/min/kg) were the main outcomes.[27,28] Isokinetic quadriceps muscle strength, defined as the highest peak torque in Nm ($PT_{quadriceps}$), was determined using a computerized dynamometer (Biodex System 4 Pro, Biodex Medical Systems, New York, USA).[29,30]

Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics 25.0 (SPSS Inc., Chicago, USA) and GraphPad Prism 9.0 (GraphPad Software Inc., California, USA). Descriptive statistics are used to present the data, as appropriate. The data was screened for extreme outliers, after which none were identified. Continuous variables were tested for normality using the Shapiro-Wilk test. The measurement properties of the 6MWT have been assessed according to the taxonomy developed by the COSMIN initiative.[31] Accordingly, measurement error (as a measure of absolute reliability) was analyzed using standard error of measurement (SEM; $SD*(\sqrt{1-ICC})$), the minimal detectable change at 95% confidence interval (MDC95%; $1.96*SEM*\sqrt{2}$) and Bland and Altman 95% limits of agreement.[31] The two-way random ICC with single measures (ICC2,1)[32] was calculated to assess the test-retest reliability (as a measure of relative reliability) of the 6MWT.[31] Furthermore, the reproducibility of the 6MWT was studied after stratification for sex, age and smoking status. Logistic regression models adjusted for age, sex and BMI were used to identify predictive factors of a change in 6MWD of at least 27 m, which is the minimal clinically important difference (MCID) in patients with asthma,[33] between the two 6MWTs.

Construct validity was verified according to the COSMIN guidelines by testing convergent, discriminant and known-groups validity.[31] Convergent validity concerns the degree to which a measure is related to other measures of similar constructs, while discriminant validity considers the degree to which a measure can be differentiated from measures of conceptually distinct constructs.[34] To investigate convergent and discriminant validity, Pearson or Spearman correlation coefficients were calculated. It was hypothesized that the best 6MWD would show moderate to strong (positive) correlations ($r = 0.40-0.79$)[35] with measures of maximal exercise capacity, as measured with CPET (i.e., W_{max} and VO_2peak; absolute values), which would support convergent validity. Regarding discriminant validity, we expected only weak to moderate associations ($r = 0.20-0.59$)[35] with absolute values of pulmonary function, body composition, $PT_{quadriceps}$ and symptoms of anxiety and depression (HADS-A and HADS-D). The ability of the 6MWT to discriminate between clinically diverse groups (known-groups validity) was assessed with analyses of variance (one-way ANOVA) with Tukey-HSD *post hoc* in patients grouped by mMRC score. It was hypothesized that patients with higher mMRC scores would have a lower mean 6MWD. Finally, a stepwise multiple linear regression model was built to identify independent determinants of the best 6MWD. Only explanatory variables with a significant correlation coefficient ($p < 0.05$) were used in the model (in absolute values). In case of singularity or multicollinearity (i.e., $r \geq 0.70$) between two independent variables, only the variable with the strongest

Table 1 Patient characteristics.

	Total group		*Females*		*Males*	
Characteristic	*N*	*Value*	*N*	*Value*	*N*	*Value*
Age, years	201	61 ± 12	117	59.3 ± 12.3	84	63.1 ± 10.7*
Weight, kg	201	87.4 ± 22.0	117	83.8 ± 20.8	84	92.4 ± 22.7*
BMI, kg/m^2	201	31.0 ± 7.1	117	31.7 ± 7.3	84	30.1 ± 6.6
BMI <18.5/18.5−24.99/25−29.99/ ≥30 kg/m^2, n (%)	201	2 (1)/41 (20)/ 52 (26)/106 (53)	117	0 (0)/24 (21)/ 28 (24)/65 (56)	84	2 (2)/17 (20)/ 24 (29)/41 (49)
LL-LMM, kg	201	16.6 ± 4.2	117	14.8 ± 3.2	84	19.0 ± 4.2*
FFM, kg	201	51.4 ± 11.1	117	45.7 ± 7.8	84	59.2 ± 10.2*
FFMI, kg/m^2	201	18.1 ± 2.8	117	17.3 ± 2.5	84	19.3 ± 2.8*
Smoking status (current/former/non-smoker), n (%)	195	17 (9)/ 92 (47)/ 86 (44)	113	8 (7)/47 (42)/ 58 (51)	82	9 (11)/ 45 (55)/ 28 (34)
Blood eosinophil count, cells/μL	189	278 ± 244	108	252 ± 213	81	314 ± 277
Blood eosinophil count ≥ 150 cells/ μL, n (%)	189	129 (68.3)	108	67 (57.3)	81	62 (73.8)*
Blood eosinophil count ≥ 300 cells/ μL, n (%)	189	60 (31.7)	108	31 (26.5)	81	29 (34.5)
mMRC ≥2, n (%)	201	159 (79.1)	117	97 (82.9)	84	62 (73.8)
Rollator, n (%)	201	37 (18.4)	117	30 (25.6)	84	7 (8.3)*
Cane, n (%)	201	4 (2.0)	117	1 (0.9)	84	3 (3.6)
FEV_1, L	201	2.08 ± 0.87	117	1.91 ± 0.73	84	2.33 ± 0.99*
FEV_1, % pred[49]	201	78 ± 27	117	81 ± 26	84	74 ± 29
FEV_1/FVC ratio, %	201	60 ± 16	117	63 ± 15	84	56 ± 17*
RV, L	197	2.30 (1.89-2.94)	115	2.13 (1.75-2.63)	82	2.83 (2.16-3.23)*
RV, % pred[50]	197	111 (89-133)	115	111 (92-139)	82	115 (88-131)
RV/TLC ratio, %	197	41 ± 10	115	42 ± 11	82	40 ± 8
TLC, L	197	5.98 ± 1.38	115	5.20 ± 0.90	82	7.06 ± 1.18*
TLC, % pred[50]	197	104 ± 17	115	105 ± 17	82	103 ± 17
MIP, kPa	200	7.85 ± 2.57	116	6.92 ± 2.30	84	9.15 ± 2.36*
MIP, % pred[51]	200	92 ± 27	116	95 ± 30	84	86 ± 22*
MEP, kPa	169	11.40 ± 3.92	107	10.32 ± 3.73	62	13.26 ± 3.54*
MEP, % pred[51]	169	72 ± 25	107	76 ± 28	62	67 ± 18*
HADS-A, points	191	7 (4-10)	113	8 (5-10)	78	6 (4-10)
HADS-D, points	191	7 (4-10)	113	7 (4-10)	78	7 (3-9)
W_{max} CPET, watts	184	90 (68-115)	105	87 (66-101)	79	99 (69-129)*
VO_2peak CPET, ml/min/kg	172	16.4 ± 5.2	100	15.3 ± 4.5	72	17.8 ± 5.7*
VO_2peak CPET, % pred[28]	168	79 (62-104)	96	92 (74-117)	72	64 (50-79)*
$PT_{quadriceps}$, Nm	146	101 ± 38	84	81 ± 25	62	127 ± 37*
$PT_{quadriceps}$, % pred[30]	146	71 ± 19	84	69 ± 19	62	73 ± 19

Summary variables are presented as n (%) for discrete variables, mean ± standard deviation for quantitative variables or median (Interquartile range) for skewed variables. * $p<0.05$ females vs. males. *Abbreviations*. BMI: body mass index; LL: lower-limbs; LMM: lean muscle mass; FFM: fat-free mass; FFMI: fat-free mass index; mMRC: modified Medical Research Council; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; RV: residual volume; TLC: total lung capacity; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; HADS-A: Hospital Anxiety and Depression Scale, Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale, Depression subscale; W_{max}: maximal achieved workload; CPET: cardiopulmonary exercise test; VO_2peak: peak oxygen consumption; $PT_{quadriceps}$: isokinetic peak torque of the quadriceps muscle.

association with the best 6MWD was kept in the model. *A priori*, the level of significance was set at $p < 0.05$.

Results

Characteristics

Two patients were not able to perform a 6MWT and 14 patients only performed one 6MWT (due to medical or administrative reasons) and were excluded accordingly. Demographic and clinical characteristics of 201 included patients with asthma (42% male; mean age 61±12 years) are summarized in Table 1. The vast majority of patients (80%) showed abnormal BMI values, with more than half of the sample being obese (BMI ≥30 kg/m^2). The proportion of patients on maintenance OCS was 19% (Supplemental Data, Table 1). Based on a blood eosinophil count ≥300 cells/μL, 32% of the patients could be characterized as having eosinophilic asthma. Mean FEV_1 was 78±27 % predicted and 79% of the patients had a mMRC dyspnea severity score of 2 or higher. Eighteen percent of the patients used a rollator and

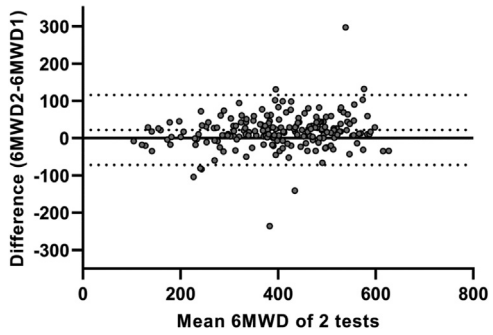

Figure 1 Bland and Altman plot illustrating the difference in six-minute walking distance (6MWD; in meters) between two 6-minute walk tests (6MWTs) conducted on a 30 m straight point-to-point course, plotted against the mean value of these two tests in patients with asthma. The central continuous line represents the zero line; the central dotted line corresponds to the average difference (bias) between the two 6MWTs (18 m); and the lower and upper dotted lines correspond to the lower (−75 m) and upper (110 m) limits of agreement, respectively.

2% used a cane as walking aid. Rollator use was significantly higher in females than in males ($p < 0.05$; Table 1). Forty-four percent of the patients never smoked, whereas 9% was a current smoker.

Test-retest reliability and measurement error of the 6MWT

On average, patients walked 392 m (95% CI 376−408 m) in the first 6MWT and 410 m (95% CI 393−427 m) in the second 6MWT. The mean change in 6MWD was 18 m (95% CI 11−24 m) or 5% ($p < 0.001$). Seventy-three percent of the patients improved their 6MWD in the second test, with 39% having an increase of at least 27 m (MCID of the 6MWT in patients with asthma).[33] 11% of the patients decreased their 6MWD with ≥27 m. After stratification for sex, age and smoking status, no differences in terms of reproducibility of the 6MWT between these subgroups were shown (Supplemental Data, Table 2).

Test-retest reliability between the two 6MWTs was excellent, with an ICC value of 0.91 (95%CI 0.86−0.94; $p < 0.001$). The SEM and MDC95% for the 6MWT were 35 m and 98 m, respectively. Bland and Altman plots confirmed that the majority of patients increased their 6MWD during the second 6MWT (average difference: 18m; Fig. 1). The limits of agreement between first and second 6MWTs ranged from -75 to 110 m. Logistic regression models showed that none of the specific patient characteristics were associated with a lower or higher likelihood of having a meaningful increase in 6MWD (≥27 m[33]) in the second 6MWT (Supplemental Data, Table 3).

On average, the change in oxygen saturation (ΔSpO_2) during the first and second 6MWT was -1.9% and -2.0% (Supplemental Data, Table 4). Of the 201 patients, 20 patients (10.0%) showed a desaturation in 6MWT1 and 25 patients (12.4%) in 6MWT2. The reliability of ΔSpO_2 when two 6MWTs were performed was only modest (ICC 0.68; $p < 0.001$). When comparing the change in heart rate and Borg symptom scores, relative reliability was modest with ICC's ranging from 0.44−0.57 ($p < 0.001$, Supplemental Data, Table 4).

Table 2 Correlations between best 6-minute walk distance and other outcome measures in patients with asthma.

Outcome measure	*n*	*Pearson r*	*p-value*
Age, years	201	-0.15	0.037
Weight, kg	201	-0.25	<0.001
BMI, kg/m^2	201	-0.38	<0.001
LL-LMM, kg	201	-0.03	0.664
FFM, kg	201	-0.02	0.832
FFMI, kg/m^2	201	-0.18	0.013
mMRC score, points	201	-0.64	<0.001
FEV_1, L	201	0.19	0.006
FEV_1/FVC ratio, %	201	-0.08	0.242
RV, L	197	0.08[&]	0.297
TLC, L	197	0.26	<0.001
RV/TLC ratio, %	197	-0.21	0.004
MIP, cmH_2O	200	0.45	<0.001
MEP, cmH_2O	169	0.37	<0.001
HADS-A, points	191	-0.15	0.040
HADS-D, points	191	-0.22	0.002
W_{max} CPET, watts	184	0.50[&]	<0.001
VO_2peak CPET, ml/min/kg	172	0.61	<0.001
$PT_{quadriceps}$, Nm	146	0.31	<0.001

See Table 1 for definition of abbreviations. [&] Spearman's ρ correlation coefficient

Construct validity of 6MWD

The mean 6MWD on the best test was 418 m (95% CI 402-435 m) or 68% of the predicted values (95% CI 65-70% predicted). In Table 2, correlation coefficients between the best 6MWD and other outcomes are presented. A strong correlation was found with VO_2peak (r = 0.61) and mMRC score (r = -0.64), whereas W_{max} presented a moderate correlation (r = 0.50). Regarding pulmonary function, FEV_1, RV and FEV_1/FVC ratio showed very weak correlations (r = 0.08-0.19), and TLC and RV/TLC ratio weak correlations (r = 0.26 and -0.21) with best 6MWD. Very weak-to-moderate correlations were found with age, measures of body composition (BMI, FFM, and LL-LMM), MIP/MEP, $PT_{quadriceps}$, HADS-A and HADS-D (i.e., r = 0.02−0.45; Table 2). Mean 6MWD decreased as functional impairment attributable to dyspnea (mMRC scores) increased, supporting known-groups validity (Fig. 2). ANOVA showed a significant overall difference ($p < 0.001$) in best 6MWD among mMRC groups, with non-significant Tukey-HSD *post hoc* mean differences between mMRC score 0 and 1-2 and between mMRC score 3 and 4 (Fig. 2).

Determinants of the best 6MWD

All the variables with a significant correlation coefficient ($p < 0.05$) were considered in a stepwise multiple linear regression model (Table 3). Weight had to be excluded due to *singularity* with BMI and VO_2peak had to be excluded due to *multicollinearity* with W_{max} (i.e., $r > 0.70$). As there was a significant difference in best 6MWD between male (463±105 m) versus female patients (386±119 m), sex was included as an independent variable in the model. In addition, the use of a rollator during the 6MWT was added to the regression model, since

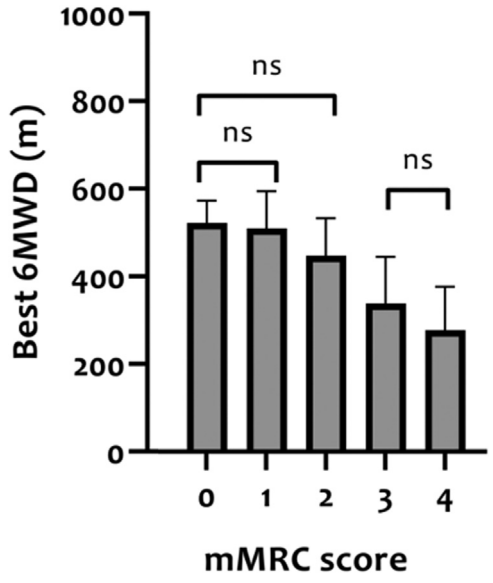

Figure 2 Distance covered in the 6MWT (best 6MWD) stratified according to modified Medical Research Council (mMRC) resting dyspnea severity scores in patients with asthma. The ability of the 6MWT to discriminate between clinically diverse groups (known-groups validity) was assessed with analyses of variance (one-way ANOVA) with Tukey-HSD post hoc. ns = non-significant difference between groups.

additional analyses showed that several patient characteristics and 6MWT performance were statistically different between patients who required a rollator and patients who did not (Supplemental Data, Table 5). Subsequently, the following variables were included in the model assessing the best 6MWD: age, sex, rollator use, BMI, FFMI, mMRC, FEV_1, RV/TLC ratio, TLC, MIP, MEP, $PT_{quadriceps}$, HADS-A and HADS-D scores, and W_{max}. Out of these, W_{max}, rollator use, MEP, BMI and FEV_1 were shown to be independent determinants of the best 6MWD, explaining 58.4% of the variability (Table 3).

Discussion

The 6MWT showed good test-retest reliability in patients with asthma when two tests were performed on subsequent days. Nevertheless, in the majority of patients the distance walked in the second test improved, indicating a consistent learning effect. As a matter of fact, about four in every ten patients increased their 6MWD in the second test with at least 27 m, which is considered the MCID of the 6MWT in patients with asthma.[33] This was supported by Bland and Altman analyses, presenting limits of agreement largely exceeding this 27 m cutoff. Our results also show that there is a large interval (MDC95% of 98 m) within which a patient's true score will lie with repeated testing, 95% of the time, which suggests important within-participant variability on repeated testing in this population. Interestingly, none of the possible determinants were able to predict a clinically important increase in the second 6MWT in this patient population. Consequently, it is recommended to test all patients with asthma twice.

Numerous studies have reported a learning effect when repeated 6MWTs are performed in patients with COPD, with a pooled mean improvement of 26.3 m.[13] To date, there is only one study available supporting a learning effect in asthma when two 6MWTs are performed on the same day.[17] The learning effect of 19 m (95% CI 11–27 m) or 4%, with 80% of the patients walking further in the second test, is in line with the 18 m (or 5%) reported in our study, in which 73% of the patients improved their 6MWD in the second test. This is consistent with the general assumption that the learning effect is most probably present in different chronic respiratory diseases and even in healthy subjects.[13,36–38] The few studies reporting exercise intolerance in patients with asthma using the 6MWT, all state that 6MWTs were performed in accordance with international guidelines, without specifying the use of a second test, hampering the interpretation of these results.[3,7,38,39] The learning effect established in the current study indicates that the vast majority of patients could have an underestimation regarding their baseline functional exercise capacity if only one 6MWT was performed. This is supported by the magnitude of the measurement error of the 6MWT in this study, which suggests that there is important within-patient variability on repeated testing. Thus, the well-known learning effect on the second 6MWT[13] is demonstrated for the first time in a large sample of asthmatics and our data provide a strong rationale for performing two 6MWTs in clinical settings as well as in clinical studies. To date, it remains unclear whether the learning effect extends beyond a second 6MWT.

Table 3 Stepwise multiple linear regression analysis with the best 6MWD as the dependent variable.

	(R^2 = 0.584)					
	Unstandardized coefficients		Standardized coefficients		95%CI for B	
	B	Standard error	Beta	p-value	Lower Bound	Upper Bound
(Constant)	455.031	37.132	N/A	N/A	381.352	528.710
W_{max} CPET	1.469	.236	.609	<0.001	1.001	1.937
Rollator use	-87.277	24.634	-.255	0.001	-136.157	-38.397
MEP	6.344	1.715	.251	<0.001	2.941	9.746
BMI	-4.941	1.124	-.303	<0.001	-7.170	-2.711
FEV_1	-34.906	11.555	-.289	0.003	-57.834	-11.979

See Table 1 for definition of abbreviations. Variables entered in model: age, sex, rollator use, BMI, FFMI, mMRC, FEV1, TLC, MIP, MEP, PTquadriceps, HADS-A and HADS-D scores, and Wmax.

Current knowledge regarding the potential use of a third 6MWT is based on small studies in patients with COPD, showing inconsistent results.[40,41]

Strong associations with oxygen uptake during CPET and dyspnea during daily life demonstrate a good convergent validity of the 6MWT in patients with asthma, supporting the general conceptualization of the 6MWT to be a test of functional exercise performance.[12] In addition, 6MWD and measures of constructs that theoretically should not be highly related to it (e.g. body composition, pulmonary function, symptoms of anxiety and depression) were, in fact, not found to be highly correlated, strengthening the discriminant validity of the 6MWT in this patient population. For example, FEV_1 was very weakly associated with the distance covered in the 6MWT, which is in line with prior studies,[7,10] and only increases the added value of a field exercise test, such as the 6MWT. Indeed, based on the lung function attributes a healthcare professional cannot adequately estimate the exercise performance of the individual patient.[13] So, a field exercise test needs to be conducted to better understand the exercise capacity of an individual patient with asthma.

A considerable number of independent determinants of 6MWD in patients with asthma were identified, explaining about half of its variance, suggesting that there are other contributors to 6MWD that are not yet completely understood. For instance, dynamic hyperinflation, which has been proven to play a major role in exercise limitation in COPD,[42] has also been reported in patients with asthma, with studies showing a direct association with worse overall health, lower wellbeing and impaired activities of daily life.[43] Interestingly, severe asthmatic patients seem to develop dynamic hyperinflation during a 6MWT to the same extent as individuals with COPD, without leading to changes in dyspnea perception.[44]

Methodological strengths and limitations

The current in-depth analyses of the measurement properties of the 6MWT in patients with asthma are novel and of clinical importance, potentially enhancing the standard operating procedures for the 6MWT in this patient population. Methodological factors that could potentially affect test performance were kept constant when conducting the tests. 6MWTs were conducted by trained and certified personnel using standardized phrases of instruction and encouragement throughout the tests. Additionally, both 6MWTs were performed with the same provision of supplemental oxygen and walking aids used in the first test were also used in the second test.

We acknowledge the fact that the asthma patients included in the current study were referred for pulmonary rehabilitation, resulting in a selected group of patients. Regardless of the fact that our sample showed a broad age range (20-84 years) and a fairly even distribution of males and females, only a minority of patients was aged below 40 years. Of course, this limits the interpretation of the 6MWT measurement properties in patients with asthma to a more narrow age range population. It is worth noting that narrow age-ranges could be identified in most studies conducted in healthy adults to provide reference values for the 6MWT. This also holds true for the reference values[19] used in the current study, which are currently the best option available when assessing a Dutch population. Future research is needed in a large sample from the general population, representing all age groups and well balanced in terms of sex, to formulate new reference values for use in daily clinical practice.

Unfortunately, information regarding comorbidities and functional balance, which have been shown to be variables that can influence the improvement of the second 6MWT in patients with COPD,[14,45] have not been systematically assessed during the baseline pulmonary rehabilitation assessment. Furthermore, the evaluation of known-groups validity in our study is limited, since asthma severity according to GINA guidelines[1] was not determined. Generally, asthma disease severity is assessed retrospectively by a physician after the patient has been on controller treatment for several months.[6,46] However, upon first referral to a pulmonary rehabilitation program, patients may often present a suboptimal disease control due to ineffective or inappropriate treatment or asthma that remains uncontrolled despite sufficient treatment,[1] making an adequate examination of disease severity difficult. As a result, the present study aimed to classify patients based on the type of drug (OCS) that they were prescribed, without inferring severity, other than the fact that a referral to a tertiary center was made. Lastly, we cannot completely rule out the fact that some patients present with clinical features of both asthma and COPD. Asthma patients entering pulmonary rehabilitation are complex in terms of symptoms, frequency of asthma attacks, oral corticosteroid dependency, current smoking, high prevalence of obesity and other comorbidities,[47] which might (at least in part) result in clinical features overlapping with patients with COPD.[48]

Conclusion

The current study demonstrated excellent test-retest reliability and construct validity of the 6MWT in a large cohort of asthmatics of which the majority was older than 40 years, supporting the use of the 6MWT as a primary end-point in future clinical trials. Nevertheless, our data suggest a considerable learning effect when two tests are conducted. In about 40% of the patients, this learning effect is large enough to be clinically important ($\geq$27 m) when the 6MWT is used to assess functional exercise performance and evaluate patient progress. The exact predictive factors of this improvement in walking distance could not be determined. Therefore, it is highly recommended to perform at least two 6MWTs in each patient, after which the best 6MWD should be reported.

Conflicts of interest

FMEF reports grants and personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from GlaxoSmithKline, grants and personal fees from Novartis, personal fees from TEVA, outside the submitted work. BvdB reports personal fees from AstraZeneca and Boehringer Ingelheim, outside the submitted work. MAS reports grants from Netherlands Lung Foundation,

grants from AstraZeneca, grants from Boehringer Ingelheim, and a grant from Stichting Astma Bestrijding, all outside the submitted work. RM, SMJJ, AWV, AAFS, HWHvH, PHK, CB, AJvH have nothing to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2022.10.011.

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ORIGINAL ARTICLE

Gender equity of authorship in pulmonary medicine over the past decade

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KEYWORDS
Pulmonary medicine;
Gender distribution;
Female first and last authorship

Abstract
Background: Gender disparity in authorship broadly persists in medical literature, little is known about female authorship within pulmonary medicine.
Methods: A bibliometric analysis of publications from 2012 to 2021 in 12 journals with the highest impact in pulmonary medicine was conducted. Only original research and review articles were included. Names of the first and last authors were extracted and their genders were identified using the Gender-API web. Female authorship was described by overall distribution and distribution by country/region/continent and journal. We compared the article citations by gender combinations, evaluated the trend in female authorship, and forecasted when parity for first and last authorship would be reached. We also conducted a systematic review of female authorship in clinical medicine.
Results: 14,875 articles were included, and the overall percentage of female first authors was higher than last authors (37.0% vs 22.2%, $p<0.001$). Asia had the lowest percentage of female first (27.6%) and last (15.2%) authors. The percentages of female first and last authors increased slightly over time, except for a rapid increase in the COVID-19 pandemic periods. Parity was predicted in 2046 for the first authors and 2059 for the last authors. Articles with male authors were cited more than articles with female authors. However, male-male collaborations significantly decreased, whereas female-female collaborations significantly increased.
Conclusions: Despite the slow improvement in female authorship over the past decade, there is still a substantial gender disparity in female first and last authorship in high-impact medical

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journals in pulmonary medicine.

Introduction

In modern-day society, gender disparities broadly persist in many professions. Despite the increasing numbers of women in the medical field, they are under-represented in leadership positions,[1,2] editorial boards,[3-5] and conference speakers.[6,7] As authorship plays a crucial role in faculty promotion, grant application, and academic position,[8-10] understanding gender distribution of prominent author positions helps clarify the roles women hold in an academic environment.

In recent years, gender equity in academic medicine has attracted interest from different medical disciplines.[11-17] Except for nursing,[18] obstetrics and gynecology,[19] and dermatology,[20] most clinical specialties have reported that women have lower representation than men in published articles,[12-17] especially in the last author position.[12,14-17] In articles published between 2008 and 2018 in 40 critical care medicine journals, fewer than one-third of first authors and one-fifth of last authors were women.[14]

Gender disparities in authorship vary between geographic areas and journals. The reported proportions of first and last women authors in countries vary by medical specialties. For example, the percentage of women first authors in radiology was reported to rank high in Asian countries like China and South Korea,[21] in contrast to their representation in surgical medicine,[22] neurosurgical science,[23] and critical care medicine.[14,24,25] Female authorship in high-impact journals is low, especially in the last author position.[26,27] Also, articles with male authors are cited more often than articles with female authors.[28,29] so we sought to explore if there are similar trends in pulmonary medicine journals.

This study aimed to investigate the gender distribution of authorship among high-impact medical journals in pulmonary medicine over the past decade. Additionally, to compare authorship distribution in pulmonary medicine to other medical specialties, we reviewed the publications with the topic of gender distribution in the academic literature on clinical medicine. Because the first authorship typically belongs to the person responsible for most of the work, and the last author is often considered the senior author who supervises the project, we used those positions for this paper.

Material and methods

Data source

We included the top eight journals that were ranked by journal citation reports (JCRs, 2020) in the category of the respiratory system (https://jcr2.clarivate.com), according to the Web of Science database core collection. These journals included Lancet Respiratory Medicine, American Journal of Respiratory and Critical Care Medicine (AJRCCM), European Respiratory Journal (ERJ), Journal of Thoracic Oncology, Journal of Heart and Lung Transplantation, Chest, Thorax, and European Respiratory Review. In addition, we included four general medical journals with the highest impact factors (British Medical Journal [BMJ], Journal of the American Medical Association [JAMA], Lancet, and New England Journal of Medicine [NEJM]). For the four general medical journals, only articles with study content related to pulmonary medicine were included, with article titles and abstracts screened independently by two researchers. Any disagreement regarding if it was pulmonary medicine related article was resolved by discussion with a third researcher.

Articles published in the 12 journals between January 1st, 2012, and December 31st, 2021 were searched on Web of Science core collection. Only original research studies and reviews were included. Articles with a single author were excluded.

Article information extraction

The article information was obtained from Web of Science database and extracted by Python programming software, including publication date, journal, article type, title, abstract, citation, and author information. Detailed information about data extraction is available in the Supplement (page 2). Gender was identified for authors listed in the first and last positions. For the authors who had multiple affiliations, the affiliation listed first was used.

Author's gender identification

The extracted authors' names were entered in Gender-API (https://gender-api.com/), which has been used to identify gender based on name with a reported accuracy of over 98%.[30,31] Gender-API reports gender (male, female, or null) and the predicted accuracy of the determination. If the author's gender was not identified (null) or the predicted accuracy was $<$ 60%, a manual search on Google and/or social media was conducted using the author's name and affiliations listed in the publication. The author's photo and/or biographies by pronouns were used to identify gender. When either or both the first and last authors' genders could not be identified, the articles were excluded.

Evaluation on the publications of female authorship in clinical medicine

We also reviewed the publications on female authorship in clinical medicine. Two investigators independently searched the PubMed database for articles with a focus on female authorship in clinical medicine published in English from January 1st, 2012 to December 31st, 2021. The literature search strategy and eligibility criteria for including studies are available in the Supplement page 3.

To explore the association between the percentages of female faculty/physicians and female authorship in different disciplines of clinical medicine, we extracted the percentages of female physicians and female faculty reported by AAMC.[32] The percentages of female first and last authorship from articles published from January 1st, 2018, to December 31st, 2019, in relevant disciplines were calculated as an average.

Statistical analysis

The distribution of female first and last authors was reported as percentages by overall, article type, countries/regions/continents, and journals. The differences were analyzed using chi-square test. To evaluate female first and last authorship changes over time, linear regression was performed to forecast the year in which parity would be reached between women and men for first and last authorship. Similarly, linear regression was used to analyze the changes over time in female first and last authors by country/region, journal, and gender pairs from 2012 to 2021. To understand the pattern of the pairs of first and last authors, we paired the first and last authors by gender to create four categories, including: (1) female-female, (2) female-male, (3) male-female, and (4) male-male.

The Kolmogorov-Smirnov test was used to test the normality of distribution for article citations, and Mann-Whitney test was used to compare the article citations with different pairs of genders. Multi-factor logistic regression was performed to assess the influential factors with the first and last author's gender. Factors in this model included year (reference: 2012), article type (reference: original research), region of the author (reference: North America), and journal (reference: European Respiratory Review). References were chosen as they were closest to the average overall distribution data.

The first and last authors with the highest number of articles in pulmonary medicine during the study period were included in the top 100 most prolific authors.

Statistical analysis was conducted using SPSS (version 22.0; IBM Corp, Armonk, New York), and visualization of statistics was performed using GraphPad Prism version 8 (GraphPad Software, La Jolla, CA). A two-sided $P< 0.05$ was considered significant.

Results

14,875 articles were included in our study, including 13,297 original research studies and 1,578 reviews (Fig. 1A). Of those included articles, 14,411 had the gender of the first author identified by gender-API, with a probability of 99% (98-100). Likewise, the gender of last authors was identified by gender-API in 14,328 articles, with a probability of 99% (99-100). In the remaining articles, a manual search was performed to determine the gender.

For the evaluation, 1,331 articles were screened and 117 articles were included (Fig. 1B).

Manuscript characteristics and authorship position by gender

Of the 14,875 articles included, 37.0% were first-authored by a woman, which was higher than the percentage

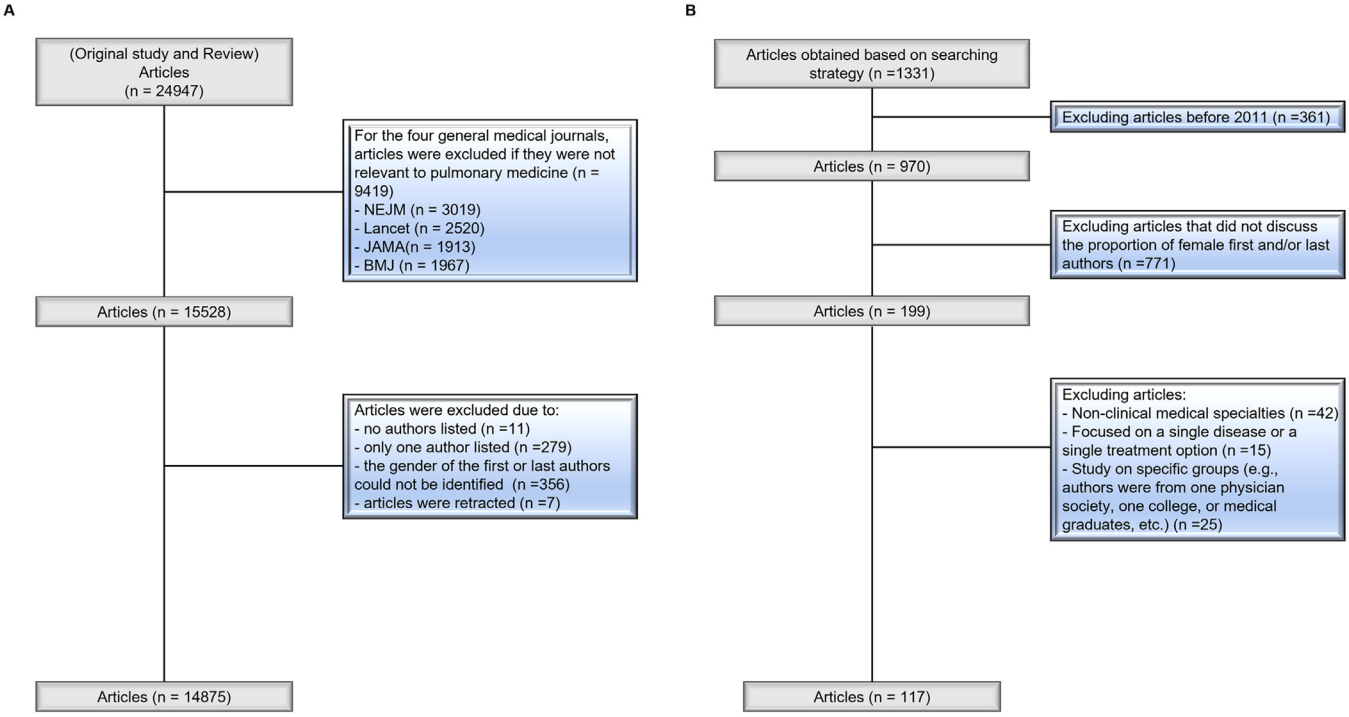

Fig. 1 Flow diagram for selecting articles for **(A)** selection of respiratory system articles published between 2012 and 2021 and **(B)** evaluation on clinical medicine. Abbreviations: BMJ, British medical journal; JAMA, Journal of the American Medical Association; NEJM, New England Journal of Medicine.

Table 1 Manuscript characteristics and authorship position by gender.

	Percentage of female first authors (95% CI)	Percentage of female last authors (95% CI)
Overall	37.0 (36.2–37.8)	22.2 (21.5–22.9)
Article type		
Original research	37.1 (36.3–37.9)	22.2 (21.5–22.9)
Review	35.9 (33.5–38.3)	22.1 (20.1–24.1)
Region		
North America	35.4 (34.3–36.5)	22.9 (21.9–23.9)
Europe	39.8 (38.6–41.0)	22.5 (21.4–23.6)
Asia	27.6 (25.2–30.0)	15.2 (13.2–17.2)
Oceania	46.2 (42.2–50.2)	25.5 (22.0–29.0)
South America	45.5 (37.4–53.6)	20.0 (13.1–26.9)
Africa	34.2 (25.6–42.8)	21.6 (13.9–29.3)
Journal		
European Respiratory Review	37.8 (33.7–41.9)	22.4 (18.9–25.9)
Thorax	44.9 (42.3–47.5)	26.6 (24.2–29.0)
Chest	36.5 (34.8–38.2)	21.2 (19.8–22.6)
Journal of Heart and Lung Transplantation	30.9 (28.5–33.3)	18.1 (16.1–20.1)
Journal of Thoracic Oncology	36.2 (34.1–38.3)	20.9 (19.1–22.7)
ERJ	42.4 (40.4–44.4)	24.6 (22.9–26.3)
AJRCCM	36.5 (34.5–38.5)	21.3 (19.6–23.0)
Lancet Respiratory Medicine	28.0 (24.5–31.5)	20.7 (17.5–23.9)
BMJ	37.0 (33.7–40.3)	26.0 (23.0–29.0)
JAMA	30.1 (24.2–36.0)	18.8 (13.7–23.9)
Lancet	31.7 (26.3–37.1)	23.6 (18.7–28.5)
NEJM	27.3 (22.4–32.2)	27.6 (22.7–32.5)

Abbreviations: CI, confidence interval; ERJ, European Respiratory Journal; AJRCCM, American Journal of Respiratory and Critical Care Medicine; BMJ, British medical journal; JAMA, Journal of the American Medical Association; NEJM, New England Journal of Medicine.

of female last authors (37.0% vs 22.2%, *P< 0.001*) (Table 1). For original research and review articles, female first authors were similar (37.1% vs 35.9% respectively), which was also noted for last authors (22.2% vs 22.1% respectively).

Trends in overall articles gender distribution over time

The percentage of female first authors increased significantly from 2012 to 2021, with an average annual increase of 0.44% (95%CI, 0.13-0.75%, *P= 0.011*) (Fig. 2A), with parity predicted in 2046 (Fig. 2B). Likewise, the percentage of women in the last author position also increased significantly, with an average annual increase of 0.66% (95%CI 0.40–0.91%, *P< 0.001*). At this rate, parity would be reached in 2059.

During the COVID-19 pandemic 2020 and 2021), of 3372 articles published in the 12 journals, 39.0% were first-authored by a female and 25.5% had a female last author (Fig. 2A). While in the two years before COVID-19 (2018 and 2019), of 2581 articles, 36.3% and 23.8% had women first and last authors respectively. More females were first (*P= 0.032*) and last (*P= 0.016*) authors in the COVID-19 pandemic than in non-pandemic periods.

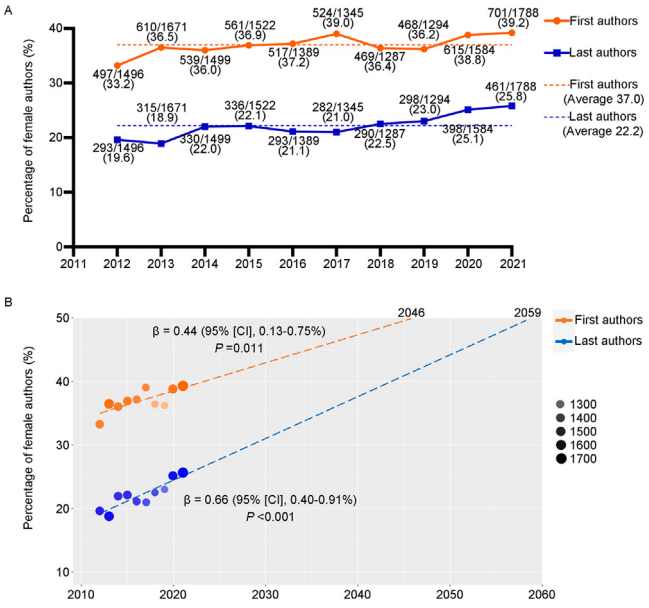

Fig. 2 Trends in overall articles gender distribution over time. **(A)** Trends in female first and last authorship of respiratory system articles published between 2012 and 2021. **(B)** Linear forecast for first and last authors. Abbreviations: CI, confidence interval.

Geographic distribution of female authors

Over 85% of the first and last authors had North American (44.9% and 46.1% respectively) and European affiliations (40.3% and 40.1%, respectively) (eFigure 1A in the Supplement). Regarding authorship on different continents, Oceania had the highest female first (46.2%) and last (25.5%) authors, whereas Asia had the lowest female first (27.6%) and last (15.2%) authors. Over the past decade, female first authors increased significantly in North America (*P= 0.002*) and Asia (*P= 0.028*); and female last authors increased significantly in North America (*P= 0.026*), Europe (*P= 0.004*), and Oceania (*P= 0.045*) (eFigure 2).

When all countries were analyzed together, the United States had the most first and last female author positions (38.1% and 39.5%) in terms of the number of publications, respectively (eFigure 3A). The Netherlands had the highest proportion of female first (52.5%) and last (27.6%) authors by country; and Japan had the lowest proportions (10.1% and 2.6% respectively) (eFigure 3B). Female first authors increased significantly over time in the United States (β=0.66, 95% CI 0.31-1.02%, *P= 0.003*), whereas female last authors increased significantly over time in several countries, including the United States, the Netherlands, Australia, Switzerland, and Denmark (eFigure 4).

Author gender distribution in different journals

In terms of journals, Thorax had the highest female first authors (44.9%), and NEJM had the lowest female first authors (27.3%). In contrast, NEJM had the highest female last authors (27.6%) and Journal of Heart and Lung Transplantation had the lowest female last authors (18.1%) (eFigure 5). Other than NEJM, all journals had a higher percentage of female first authors than female last authors.

Over time, female first authors increased significantly in the European Respiratory Review, Chest, and BMJ; and decreased significantly in Lancet Respiratory Medicine (β=-1.78, 95%CI -3.18 to -0.38%, *P= 0.019*). Female last authors increased significantly over time only in the Journal of Thoracic Oncology (β=1.12, 95%CI 0.71-1.54%, *P= 0.001*) (eFigure 6).

First and last author gender pairs

Of the included articles, 50.9% had males in the first and last author positions (male-male), followed by female-male (26.9%), male-female (12.2%), and female-female (10.0%). Over the past decade, female-female author pairs increased (*P= 0.001*), and between male-male author pairs decreased (*P< 0.001*) (eFigure 7).

High productivity authors

Among the 100 most prolific first and last authors in pulmonary medicine research during the study period, only 10 and 14 were women, respectively (eFigure 8).

Gender disparity in citations

Articles with women as first and last authors were cited less than those with men as first (25 [9-54] vs 29 [11-64] citations, *P< 0.001*) and last authors (24 [9-56] vs 28 [10-61] citations, *P< 0.001*) (eTable 1). In year-by-year data, this pattern was consistent each year from 2018 to 2021 for the articles with female first authors and in 2020 for articles with female last authors. Articles with females as both first and last authors were cited the fewest times (22 [7-49]) (eTable 2), whereas articles with males as first and last authors were cited most (29 [11-65]). Comparisons across the four pairs of first/last author genders were statistically significant (*P< 0.001*).

Multivariable analyses

When using the percentages of female authorship in 2012 as a reference, the odds of female first and last authorship increased overtime (Table 2). Moreover, compared to the female authorship in North America, the odds of being the first author were higher in Europe, Oceania, and South America, but lower for the last author in Europe. In Asia, the odds were lower for the first and last authorship. Furthermore, compared to female authorship in the European Respiratory Review, which had a percentage of female authors equal to the average of the 12 included journals, the odds of female first authorship were higher in Thorax, while Lancet Respiratory Medicine, JAMA, and NEJM had lower odds. For Journal of Heart and Lung Transplantation, the odds were lower for the first and last authorship.

Evaluation of female authorship in biomedical journals

The proportions of female authorship in different disciplines of clinical medicine varied (Table 3). Using the aggregated data published between 2012 and 2021 to generate the overall proportion of female authorship in different disciplines, the top three disciplines ranked by the percentages of female first authorship were nursing (83.0%), obstetrics and gynecology (60.3%), rheumatology (51.5%). Furthermore, the top three disciplines ranked by the female last authorship were nursing (72.0%), obstetrics and gynecology (41.7%), dermatology (35.6%). There were increasing proportions of female first and last authors in most disciplines, such as oncology, pediatric surgery, and anesthesiology (eFigs. 9 and 10).

Discussion

In this study, we found that the percentages of female first and last authors increased slightly between 2012 and 2021, especially a significant increase during the COVID-19 pandemic periods. Parity was foreseen in 2046 for the first authors and 2059 for the last authors. Articles with male-male pairs were cited more than articles with female-female pairs. Male-male pairs decreased significantly from 2012 to 2021, whereas female-female pairs increased significantly.

Our findings are consistent with several recent studies illustrating gender disparities in academic publications.[13,15-17] Our findings were not surprising considering the low number of female physicians in pulmonary medicine (12.3%) and critical care medicine (26.8%) in the United States, according to AAMC.[32] That said, the percentage of

Table 2 Multivariable analyses.

	Odds of female first authorship (95% CI)	*P*	Odds of female last authorship (95% CI)	*P*
Year				
2012	Reference		Reference	
2013	1.161 (1.001−1.346)	*0.048*	0.944 (0.790−1.128)	*0.525*
2014	1.150 (0.987−1.338)	*0.072*	1.145 (0.958−1.367)	*0.136*
2015	1.195 (1.028−1.390)	*0.021*	1.151 (0.964−1.374)	*0.119*
2016	1.212 (1.039−1.415)	*0.014*	1.093 (0.911−1.312)	*0.340*
2017	1.297 (1.110−1.515)	*0.001*	1.070 (0.890−1.287)	*0.474*
2018	1.179 (1.006−1.380)	*0.041*	1.188 (0.989−1.428)	*0.066*
2019	1.149 (0.981−1.346)	*0.086*	1.193 (0.993−1.433)	*0.059*
2020	1.333 (1.147−1.548)	*<0.001*	1.367 (1.150−1.625)	*<0.001*
2021	1.347 (1.165−1.559)	*<0.001*	1.403 (1.186−1.660)	*<0.001*
Article type				
Original research	Reference		Reference	
Review	0.903 (0.800−1.018)	*0.095*	0.927 (0.807−1.064)	*0.280*
Region				
North America	Reference		Reference	
Europe	1.115 (1.030−1.207)	*0.007*	0.891 (0.813−0.977)	*0.014*
Asia	0.650 (0.569−0.743)	*<0.001*	0.563 (0.475−0.667)	*<0.001*
Oceania	1.453 (1.222−1.726)	*<0.001*	1.060 (0.869−1.292)	*0.564*
South America	1.479 (1.060−2.064)	*0.021*	0.803 (0.520−1.242)	*0.325*
Africa	0.975 (0.659−1.442)	*0.897*	0.861 (0.544−1.363)	*0.523*
Journal				
European Respiratory Review	Reference		Reference	
Thorax	1.307 (1.050−1.627)	*0.017*	1.234 (0.959−1.588)	*0.102*
Chest	0.986 (0.801−1.213)	*0.890*	0.890 (0.699−1.133)	*0.346*
Journal of Heart and Lung Transplantation	0.748 (0.595−0.939)	*0.012*	0.716 (0.549−0.935)	*0.014*
Journal of Thoracic Oncology	1.058 (0.852−1.314)	*0.610*	0.973 (0.757−1.252)	*0.834*
ERJ	1.183 (0.961−1.457)	*0.113*	1.131 (0.889−1.439)	*0.318*
AJRCCM	0.969 (0.782−1.200)	*0.771*	0.896 (0.699−1.150)	*0.390*
Lancet Respiratory Medicine	0.629 (0.487−0.813)	*<0.001*	0.870 (0.649−1.164)	*0.348*
BMJ	0.958 (0.652−1.408)	*0.826*	1.145 (0.745−1.759)	*0.536*
JAMA	0.706 (0.501−0.993)	*0.046*	0.744 (0.499−1.109)	*0.146*
Lancet	0.783 (0.571−1.073)	*0.128*	1.061 (0.746−1.510)	*0.741*
NEJM	0.632 (0.461−0.865)	*0.004*	1.217 (0.871−1.701)	*0.249*

Abbreviations: CI, confidence interval; ERJ, European Respiratory Journal; AJRCCM, American Journal of Respiratory and Critical Care Medicine; BMJ, British medical journal; JAMA, Journal of the American Medical Association; NEJM, New England Journal of Medicine.

female first authors (37.0%) in our study is relatively high among all the medical specialties (Table 3).

In many specialties, including emergency medicine, internal medicine, and surgery, the COVID-19 pandemic reduced female researchers' productivity,[33,34] due to family responsibility, childcare needs,[33,35] and the lack of patients or research materials.[36] In contrast, we found a significant increase in publications with females as the first and last authors. This might be explained by the fact that pulmonary medicine was directly impacted by the COVID-19 pandemic. In general, the lack of childcare support and flexible working hours might explain the reduced output of female researchers.

In our study, the percentage of female first authors was nearly double that of female last authors and might be explained by the lack of female senior research mentors.[37] According to the 2021 AAMC report, the percentages of female faculty in the ranks of assistant professors and instructors is similar to that of male faculty (29% vs 29%),[32] while the percentages of female faculty in higher ranks (Associate and full Professors) is lower than that of male faculty (13% vs 26%).[32] Our study suggests that this disparity might eventually be resolved, but this will take 20-30 years at the current rate of change. However, efforts to promote female authorship, grant awards, and academic leadership positions might accelerate the process.[29] We also found a growth in female-female pairs and a decline in male-male pairs, which might be explained by the feminization of the workforce[38] and the increasing numbers of female senior researchers in the field.[39]

Table 3 Percentages of female first and last authors in publications from 2012 to 2021 and percentages of female physicians and faculty reported by AAMC.

Specialties	Percentage of Female First Authors From 2012 to 2021	Percentage of Female First Authors in 2019	Percentage of Female Last Authors From 2012 to 2021	Percentage of Female Last Authors in 2019	Percentage of Female Physicians in 2019 Reported by AAMC	Percentage of Female Faculty in 2021 Reported by AAMC
Nursing	83.0%	83.5%	72.0%	NR	NR	NR
Obstetrics and Gynecology	60.3%	NR	41.7%	NR	58.9%	67.3%
Rheumatology	51.5%	NR	35.3%	NR	46.3%	NR
Dermatology	50.6%	NR	35.6%	NR	51.0%	52.5%
Psychiatry	49.6%	49.5%	35.9%	35.7%	40.2%	55.6%
Family Medicine	49.3%	NR	42.3%	NR	41.3%	54.1%
Pediatrics	44.7%	54.4%	34.8%	37.7%	64.3%	60.3%
Stomatology	41.9%	44.7%	25.7%	NR	NR	NR
Ophthalmology	37.5%	41.3%	25.0%	28.6%	26.7%	41.7%
Pulmonary Disease[a]	**37.0%**	**36.2%**	**22.2%**	**23.0%**	**12.3%**	**NR**
Oncology	36.0%	34.7%	27.6%	30.1%	34.3%	NR
Gastroenterology	33.7%	31.7%	18.7%	19.3%	18.9%	NR
Internal Medicine	32.9%	34.3%	19.1%	16.2%	38.7%	41.9%
Otolaryngology	32.5%	36.4%	22.1%	24.6%	18.3%	36.5%
Critical Care Medicine	31.5%	32.6%	18.5%	21.4%	26.8%	NR
Radiology	30.6%	NR	19.8%	NR	NR	29.9%
Emergency Medicine	30.3%	30.2%	20.4%	22.7%	28.3%	38.5%
Anesthesiology	30.3%	40.6%	16.3%	17.6%	25.9%	37.0%
Cardiovascular Disease	28.0%	38.6%	15.8%	7.9%	14.9%	NR
Surgery Medicine	22.1%	26.9%	13.7%	15.4%	22.0%	27.7%
Neurology	20.3%	20.6%	12.2%	11.6%	30.9%	42.7%
Sports Medicine	17.5%	NR	NR	NR	27.2%	NR

Abbreviations: AAMC, Association of American Medical Colleges; NR, Not Reported; **a**, Data from Our Research Results.

Regarding citations of articles authored by females and males, we found articles with female first authors were cited fewer times than articles with male first authors within four years of publication. These findings agree with results from research by Chatterjee and Werner, who found that articles by women as primary authors had fewer citations within four years of publication.[29] Interestingly, we found that the difference in citations between female and male first authors was not significantly different after four years of publication. Compared to females, males tend to have more opportunities to present at conferences, participate in clinical practice guideline development, serve as content experts, and share their research findings,[40-43] which may result in more citations shortly after study publication.[27] In the long term, citations might be more dependent on the content and relevance of the publication, thus the citations become similar.

Finally, we found lower percentages of female first and last authors in Asian countries, in contrast to high percentages of female authors in European countries. In particular, we found that among the developed countries, the Netherlands has the highest percentages of female authorship in contrast to the lowest proportions in Japan, this finding agrees with research in critical care medicine[44] and transplantation research.[45] The discrepancy between Asian and European countries might be explained by differences in cultural expectations and roles/responsibilities of women in society and family,[45] the overall lack of research training/opportunities, and the lack of female mentors and academic leaders in educational institutions.[14,44,46] Likewise, the only two journals that exceeded the average percentage of overall female first authorship among the 12 journals were Thorax and ERJ, which both belonged to European scientific/medical societies, and both societies made rules or policies on female representations and participation,[47,48] with an endeavor to achieve gender equality. To what extent these rules or policies contribute to female authorship remains unclear. Recently, Chest journal starts to collect authors' gender during manuscript submission and whether these data help improve gender equality requires more investigation.

Our findings suggest that female researchers should have the same opportunities to disseminate the findings of their research as their male counterparts. Solutions may include increasing mentorship and sponsorship opportunities, encouraging and inviting women to pursue formal research training, and for senior investigators to invite early-career women onto their teams. Further studies are needed to identify factors that influenced our findings.

Strengths of our study include the large sample size and comprehensive analyses of gender distribution in different geographic areas, journals, trends over time, collaborations between first and last author genders, and article citations in high-impact journals of pulmonary medicine. Notably, the journal impact factor is just one measure of scientific output as highlighted and advocated by the Declaration on Research Assessment (DORA), thus high-impact journals included in this study might not represent their true academic reputation and scientific influence. Additionally, we conducted a thorough literature search and performed an evaluation of female authorship. This study also has limitations. First, we only included original research and review articles published by pulmonary medicine journals with the highest impact factors, thus our findings may not be generalizable to all journals in academic medicine. Second, gender was determined by an online web tool, which may have resulted in misclassification, even though genders that were assigned with a low probability of accuracy were manually evaluated. Third, there was a risk of misclassifying publication types. Fourth, single-author articles were excluded. Lastly, the exact number of female researchers (the denominator) in academic pulmonary medicine worldwide is unknown.

Conclusion

In conclusion, this study demonstrates a significant difference between female and male authorship in medical journals pertaining to pulmonary medicine. These findings appear to differ between countries and continents, suggesting that some regions and academic environments might be more supportive of female researchers. We suggest that efforts be made by academic institutions globally to ensure equal opportunities for any individual pursuing research.

Author contributions

JL and BD designed this project. YR and FG conducted the screening and data extraction for the study of academic literature in pulmonary medicine, while YR and HJH performed literature search, screening, and data extraction for the evaluation. FG performed the data analysis. BD participated in the resolution of discrepancies on data extraction. FG and YR had full access to the data and verified the data. JBS, SLS, and SM interpreted the data and provided critical edits and comments on the manuscript. JL, BD, YR, FG, and HJH attended bi-monthly web meetings. JL drafted the manuscript, all authors reviewed the manuscript for important intellectual content, and approved the final manuscript. FG, YR, HJH, and BD equally contributed to the overall project described in this article. JL was responsible for the decision to submit the manuscript.

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Data Sharing Statement

Data will be available immediately after article publication to researchers who provide a proposal for any purpose of analysis.

Conflict of Interest

JL discloses research funding from Fisher & Paykel Healthcare Ltd, Aerogen Ltd, and Rice Foundation, and speaker fees from American Association for Respiratory Care, Aerogen Ltd, Heyer Ltd, and Fisher & Paykel Healthcare Ltd. JL also serves as section editor for *Respiratory Care*. JBS

discloses research funding from Teleflex and speaker fees from Aerogen and Medline Industries, LP.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2023.03.005.

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REVIEW

Endotypes in bronchiectasis: moving towards precision medicine. A narrative review

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Abstract Bronchiectasis is a highly complex entity that can be very challenging to investigate and manage. Patients are diverse in their aetiology, symptoms, risk of complications and outcomes. "Endotypes"- subtypes of disease with distinct biological mechanisms, has been proposed as a means of better managing bronchiectasis. This review discusses the emerging field of endotyping in bronchiectasis.

We searched PubMed and Google Scholar for randomized controlled trials (RCT), observational studies, systematic reviews and meta-analysis published from inception until October 2022, using the terms: "bronchiectasis", "endotypes", "biomarkers", "microbiome" and "inflammation". Exclusion criteria included commentaries and non-English language articles as well as case reports. Duplicate articles between databases were initially identified and appropriately excluded.

Studies identified suggest that it is possible to classify bronchiectasis patients into multiple endotypes deriving from their co-morbidities or underlying causes to complex infective or inflammatory endotypes. Specific biomarkers closely related to a particular endotype might be used to determine response to treatment and prognosis. The most clearly defined examples of endotypes in bronchiectasis are the underlying causes such as immunodeficiency or allergic bronchopulmonary aspergillosis where the underlying causes are clearly related to a specific treatment. The heterogeneity of bronchiectasis extends, however, far beyond aetiology and it is now possible to identify subtypes of disease based on inflammatory mechanisms such airway neutrophil extracellular traps and eosinophilia. In future biomarkers of host response and infection, including the microbiome may be useful to guide treatments and to increase the success of randomized trials.

Advances in the understanding the inflammatory pathways, microbiome, and genetics in bronchiectasis are key to move towards a personalized medicine in bronchiectasis.

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Introduction

Bronchiectasis is a complex and heterogenous disease with multiple aetiologies and comorbidities.[1] Differences in the aetiology, epidemiology and microbiology of bronchiectasis can be observed across countries and continents which may influence the pathogenesis in this disease, by different molecular pathways — the endotypes — which converge in airway inflammation and permanent dilation of the bronchi.[2,3] Endotypes refer to subtypes of a disease which have distinct biological mechanisms that may link to phenotype, clinical outcomes or treatment response.

Treatment of bronchiectasis primarily consists of airway clearance therapies/techniques and antibiotic therapy, whether for maintenance or during exacerbations.[4] Responses to treatment in bronchiectasis are inconsistent as illustrated by the failure of inhaled antibiotics and mucoactive drugs to show benefits in several randomized trials.[5,6] Thus, there is an urgent need to better understand the underlying inflammatory and microbiological contributions for the pathogenesis, to better stratify patients in different endotypes prone to target therapies.[7] A treatable traits approach, based on the recognition of endotypes, might guide us towards precision medicine and, subsequently, converge in better clinical outcomes.[8,9]

It is now possible to integrate and analyse extensive novel biological data from patients to identify relevant disease biomarkers and associations - known as "multi-omics" (which includes genomics, transcriptomics, proteomics, metabolomics, lipidomics, and glycosomics).[10] Multi-omics is significantly advancing our understanding of the pathophysiology of bronchiectasis and has generated a number of new potential biomarkers.

The objective of this review was to review recent advances in understanding the pathophysiology bronchiectasis (excluding cystic fibrosis) with a specific focus on data identifying subtypes of disease with therapeutic implications, also known as endotypes.

Methods

We searched PubMed and Google Scholar for randomized controlled trials (RCT), observational studies, systematic reviews and meta-analysis published from inception until October 2022, using the terms: "bronchiectasis", "endotypes", "biomarkers", "microbiome" and "inflammation". Exclusion criteria included commentaries and non-English language articles as well as case reports. Duplicate articles between databases were initially identified and appropriately excluded.

Results

The search process yielded 2131 articles. After a careful analysis of the title and abstract, we included 118 articles. This information was summarized in a narrative review.

The identification of candidate endotypes involves the integration of clinical patient data, underlying cause, microbiology and inflammatory data to classify patients into meaningful subgroups. In considering endotyping in bronchiectasis we will discuss these factors in isolation followed by efforts to understand how they link together to identify candidate subtypes of disease.

We will first discuss the major co-morbidities and underlying causes of bronchiectasis and what data supports their role within bronchiectasis endotypes (Table 1).

Main comorbidities and underlying causes

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) and bronchiectasis (BE) are two diseases with overlapping clinical presentation, and increased susceptibility to exacerbations. Both entities are defined by different criteria but simultaneous diagnosis still occurs, termed as the COPD-BE association.[11] Poorer outcomes have been widely reported but the underlying biological mechanisms leading to those outcomes have not been studied until recently.[11]

Analysis from sputum microbiome (using 16 s rRNA amplicon sequencing) and protein profiling revealed that patients with the COPD-BE association had a higher abundance of Proteobacteria (microbiome phylum containing the pathogenic Gram-negative organisms such as *Pseudomonas aeruginosa)*, higher expression of the pro-inflammatory mucin MUC5AC, and proteins from the "neutrophil degranulation" pathway. Instead, patients with COPD had an elevated expression of several peptidase inhibitors, higher abundance of common commensal taxa, and greater microbiome diversity.[12] Although patients with COPD-BE association were most likely to have these more infected and inflammatory endotypes, compared to BE or COPD alone, disease labels did not perfectly classify patients.

Five endotypes have been proposed with differential inflammatory, mucin, and microbiological features (Fig. 1). This information may be used for biological classification of COPD—BE association endotypes (III to V) and have potential therapeutic implications.[12]

Asthma

Asthma is one of the most frequent BE-associated comorbidities, and this association may increase airways inflammation and exacerbation rates.[13]

According to Sheng et al., the coexistence of bronchiectasis predicts more severe disease in terms of asthma and chronic rhinosinusitis (CRS) and a higher incidence rate of nasal polyps.[14] Furthermore, in patients with severe asthma, bronchiectasis is associated with longer asthma history and chronic airflow obstruction.[15]

These findings are still insufficient to consider features of asthma-BE endotypes but could possibly contribute to early recognition and targeted treatment of this patient group. Underlying asthma as an endotype is limited by two important considerations. First, asthma itself is a heterogeneous disease with multiple endotypes and is increasingly categorised into Th2 high and Th2 low subgroups, with further subdivisions based for example on the presence of specific allergy and eosinophilia. Second, the diagnosis of asthma is challenging and is sometimes inaccurate. Consequently, while it is possible to say that asthma and bronchiectasis frequently

Table 1 Endotypes in bronchiectasis according to main co-morbidities or underlying causes.

Co-morbidity or underlying cause	Clinical features	Underlying biological features	Current and future treatment implications
COPD	Smoking history Airflow obstruction Emphysema Severe disease	Endotypes based on proteome and microbiome (Fig. 2)	Targeting NET-associated proteins and Th2 inflammation
Asthma	Bronchial hyperresponsiveness Variable airflow obstruction Wheezing Frequent exacerbations	Th2-driven inflammation or less commonly neutrophilic	Targeting Th2-inflammation
GORD	Episodic bronchitis Frequent exacerbations Isolation of Gram-negative pathogens	Neutrophilic inflammation Proteobacteria dysbiosis	Proton pump inhibitors Prokinetics Azithromycin
IBD	Large airway involvement Large sputum volumes with negative sputum cultures	Lung-gut axis determining a shared lymphocytic inflammation	Inhaled corticosteroid therapy
Primary immunodeficiency	Frequent infections since childhood Non-pulmonary infections	Multiple genes involved Neutrophilic inflammation	Immunoglobulin replacement Prophylactic antibiotics Future gene therapies
Secondary immunodeficiency	Frequent infections with onset at any age	Iatrogenic immunosuppression or autoimmune mechanisms	Altering treatment Immunoglobulin replacement Prophylactic antibiotics
Systemic autoimmune diseases	Rapidly progressive disease Frequent exacerbations	Autoimmune features and enhanced infection risk due to immunomodulating therapy	Prophylactic antibiotic therapy
PCD	Early age of onset Chronic rhinosinusitis Congenital cardiac defects or dextrocardia/*situs inversus* Otitis media	Multiple genes involved Usually neutrophilic inflammation	Gene-targeted therapy
AATd	Chronic bronchitis Frequent exacerbations Emphysema	Abnormal AAT genotypes Neutrophilic inflammation	Smoking cessation Augmentation therapy in some countries
Allergic bronchopulmonary aspergillosis	Wheezing Mucus plugging Steroid responsiveness	Elevated IgE Eosinophilic inflammation	Systematic corticosteroids +/- antifungal therapy
Non-tuberculous mycobacterial infection	Variable clinical picture but may be dry with slowly progressive dyspnoea and weight loss	Impaired mucociliary clearance Immunosuppression Immunosenescence	Improve mucociliary clearance. Combination antibiotic treatment

co-exist there are limited data on how this translates into underlying biology.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is a common comorbidity in bronchiectasis with a prevalence ranging from 26% to 75%. Two mechanisms are thought to contribute to bronchiectasis pathogenesis in GORD context: vagally mediated reflex bronchoconstriction and pulmonary microaspiration.[16] The pathogenic role of *Helicobacter pylori* infection in bronchiectasis is still not fully understood, but once the microbiome in bronchiectasis is frequently dominated by enteric Gram-negative organisms, it is plausible to

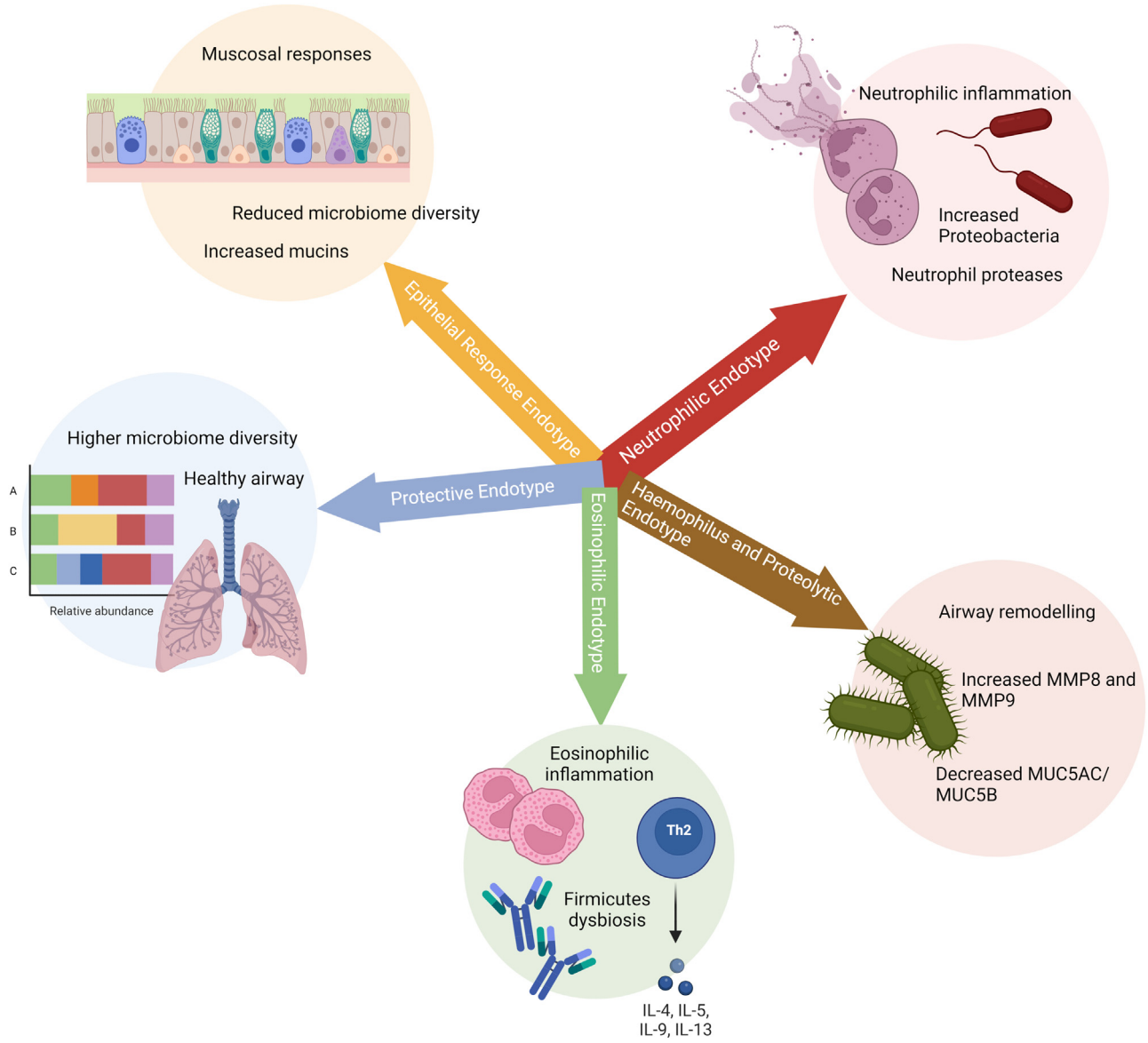

Fig. 1 Disclosed endotypes for patients with chronic obstructive pulmonary disease (COPD), bronchiectasis and COPD-bronchiectasis association. The five groups are based on: 1) neutrophilic inflammation associated to NETosis; 2) proteolytic remodelling; 3) Th2 high responses associated to eosinophilic inflammation; 4) regulated inflammation; 5) mucus hypersecretion.

there be a link between the gut, the upper airway and the lung.[17] Patients with co-existing bronchiectasis and GORD have increased disease severity and mortality, more frequent exacerbations, greater radiological extent, with reduced pulmonary function and quality of life.[16]

Identifying GORD in bronchiectasis patients may have important therapeutic and prognostic implications, although clinical trial evidence that treatment targeted at GORD can improve outcomes in bronchiectasis is currently lacking.

Inflammatory bowel diseases

Pulmonary manifestations of inflammatory bowel disease (IBD) like bronchiectasis are increasingly recognized in patients with ulcerative colitis and Crohn's disease.

Although the pathogenic mechanisms are still poorly understood, evolving data suggest that there is a "lung-gut axis" and a shared antigen hypothesis behind these shared disease states. The lungs and the intestines are derived from the same embryonic cell line, the foregut region of the endoderm. Since they share a common epithelium, they may develop similar inflammatory reactions.[18] On the other hand, the shared antigen theory, notes that gut and lung epithelia are exposed to the same antigens and this shared exposure may induce similar lymphoid inflammation in both systems.[19]

Of patients with large airways disease, about two-thirds will have bronchiectasis, which are more frequently associated to ulcerative colitis and female gender.[20] As both diseases are based on lymphoid inflammation, management

typically includes corticosteroid therapy, making IBD associated disease a relevant endotype with a specific treatment.[21]

Immunodeficiency syndromes

Immunodeficiency syndromes, both primary and secondary forms, are an important and underdiagnosed cause of bronchiectasis. Primary immune deficiencies, in particular, are increasingly identified and defined as contributors, most commonly common variable immunodeficiency (CVID).[22]

According to Patrawala et al., more than half of the CVID patients were reported to have airway disease, including bronchiectasis.[23] This is associated to low CD4+ levels, late age diagnosis and severe disease measured by pathogenic organisms such as *P. aeruginosa* and NTM.[22,24,25]

Hyper-IgE syndromes (HIESs) require gene sequencing for diagnosis once they are associated to specific gene mutations and they associate to recurrent pyogenic pneumonias during childhood culminate in structural lung abnormalities, namely bronchiectasis.[26] In other immune deficiency such as X-linked agammaglobulinemia (XLA), once bronchiectasis has developed, it progresses despite IgG replacement therapy.[27]

Secondary forms of immunodeficiency result in bronchiectasis through a complex network of autoinflammatory and autoimmunity mechanisms.

Undoubtedly, all patients with idiopathic bronchiectasis should be screened for possible immunodeficiency. Its identification impacts therapeutic management and provides an opportunity to improve clinical outcomes.

Connective tissue diseases and other systemic autoimmune diseases

Bronchiectasis is a common extra-articular feature in rheumatoid arthritis (RA), with a prevalence of approximately 20%, and it may precede articular manifestations but it is most often seen as a delayed complication of RA.[28]

Several hypotheses have been exposed to explain the pathogenesis of RA-bronchiectasis, including a link between autoimmunity in RA leading to airway damage, as well as recurrent infections leading to bronchiectasis.[29] The later seems less likely the main mechanism as patients with other connective tissue diseases such as systemic sclerosis only very rarely develop free standing bronchiectasis.[30] Risk factors for RA-bronchiectasis include older age, longer RA duration, and genetics.[28] Current literature also suggests that anti-CCP antibodies (ACPA) levels are higher in patients with RA-bronchiectasis are associate with more severe lung disease.[30]

The frequency of bronchiectasis in Sjögren syndrome, as assessed by HRCT, varies from 7% to 54%.[31] Sjögren's syndrome patients with bronchiectasis are older at the time of diagnosis, are more likely to have hiatal hernia, have a higher frequency of anti-smooth muscle antibody and a lower frequency of anti-SSA antibody than those without bronchiectasis.[32]

More research is needed to identify proper biomarkers to personalize treatment in systemic autoimmune diseases.

Primary ciliary dyskinesia

Primary ciliary dyskinesia (PCD) is a genetically and clinically heterogeneous disease, and an underdiagnosed cause of bronchiectasis.[33] This syndrome is caused by genetic mutations, usually inherited in an autosomal recessive pattern, affecting motile cilia, causing disease of the upper and lower airways.[34]

Recent advances in genomics allowed the discovery of new primary ciliary dyskinesia genes over the past decade, and >50 genes are now reported to cause PCD.[35]

Mutations in the gene *DNAH5* result in the most frequent defect reported in individuals with primary ciliary dyskinesia.[34] Genetic defects evolving MNS1, ENKUR, CFAP53 and DNAH9 genes have been recognised in individuals with motile ciliopathies that result in randomisation of left−right body asymmetry and male infertility or both, but presenting subtle or no respiratory disease.[35] Reduced generation of multiple motile cilia occurs in patients with mutations in MCIDAS and CCNO resulting in a severe respiratory phenotype.[36,37] DNAH11 mutations cause a shared abnormality in ciliary ultrastructure previously undetectable by transmission electron microscopy (TEM).[38]

As a result of the heterogeneity of PCD genetically, patients may present with classical PCD in childhood with laterality defects, whereas other patients may be missed even in adulthood because of atypical presentation and a lack of awareness.

As multidisciplinary and holistic approach to diagnostic testing is required, remarkable progress in genomics is improving diagnostic capabilities and has the potential to lead to new personalised therapeutic options.

Alpha-1 antitrypsin deficiency

Alpha-1-antitrypsin deficiency (AATd) is a hereditary disease, mainly characterized by early onset and lower lobes' predominant panlobular emphysema. Bronchiectasis is also frequently observed in patients with AATd.[39]

Augmentation therapy is licensed in several countries, particularly in cases of severe disease with airway obstruction. However, there is not a clear recommendation to screen for bronchiectasis in AATd.[40] The European Respiratory Society guidelines for the management of adult bronchiectasis suggest that only the presence of lower lobes emphysema or early onset airways' obstruction could represent an indication to screen for AATd.[1]

Routine screening for AATd shows variable detection rates according to geographical location perhaps reflecting variable prevalence of AATd across Europe.[39,41] Protease-antiprotease balance is important in the pathophysiology of bronchiectasis and with antiprotease therapies now in development it is likely it will become an even more important topic in future. Further studies are required in different geographical regions, which may have a higher prevalence of AATd, allowing personalised therapy that may improve the management in targeted patients.

There are many other underlying causes of bronchiectasis some of which have very important clinical implications. Next, we will discuss topics on airway inflammation and infection. Tuberculosis is an important cause of bronchiectasis

globally but data are limited on whether this has a specific clinical presentation or endotype.

Infective endotypes

Microbiome

Understanding the contribution of airway infection to the pathogenesis of bronchiectasis is pivotal. The Cole's "vicious cycle" has been recently replaced by the "vortex cycle" model, which suggests a similar group of factors and consequences, but no sequential manner to their incitement or perpetuation in developing bronchiectasis.[42] Reflecting the increasingly complexity of our understanding of bronchiectasis pathophysiology, the idea that patients are chronically infected with pathogenic bacteria has been replaced with an understanding that microbial dysbiosis, in which loss of microbial diversity and dominance of the microbiome with specific organisms contributes to disease progression. Woo et al. suggests that the lung microbiome in bronchiectasis is relatively stable over time, being highly individualized, and that lung microbial diversity may be an important contributor to clinical course.[43]

Present knowledge on lung microbiome in bronchiectasis is growing due to the use of next-generation sequencing (NGS) techniques in lung samples, with 16S rRNA amplicon sequencing the most commonly used technique in bronchiectasis.[44] Changes in the bacteriome are associated with raised inflammatory parameters in sputum and impaired lung function.[45] Studies of the sputum microbiome uncover a complex milieu of organisms including bacteria, viruses, and fungi that potentially interact within the bronchiectasis airway, which explains the inherent heterogeneity and contrasting clinical course observed between patients.[46]

Total airway bacterial load can classify patients depending on their response to antibiotic treatment, with high bacterial load being associated with greater lung inflammation and a greater response to inhaled antibiotics.[47] Furthermore, recurrent antimicrobial use might influence microbial homoeostasis, not only disrupting the microbes and current microbial interaction networks but also increasing the emergence of microbial resistance leading into a complex and dynamic microbiological paradigm.[48]

The characterization of the microbiome is vital for disentangling a clinically heterogenous endotype that converges in a mutual structural airway damage.[49] It incorporates the bacteriome, virome, mycobiome and also lesser common pathogens as non-tuberculous mycobacteria (NTM).

Bacteriome

The dominant genera in a healthy airway include *Prevotella, Veillonella, Fusobacterium, Streptococcus, Porphyromonas* and *Neisseria*, all thought to be seeded into the lower airway through microaspiration from the upper respiratory tract. However, the most common organisms that chronically infect the airways of bronchiectasis patients are the Gram-negative pathogens from the Proteobacteria phylum such as *Pseudomonas aeruginosa, Haemophilus influenzae, Moraxella catarrhalis*, and Enterobacteriaceae, or pathogens from the Firmicutes phylum such as *Staphylococcus aureus* and *Streptococcus pneumoniae*.[46] Proteobacteria dysbiosis of the microbiome, defined as dominance of these taxa, most commonly *Pseudomonas* and *Haemophilus*, is associated with more severe disease and worse clinical outcomes, indicating microbial targets for interventions.[50] (Fig. 2).

An antagonist relationship has been observed, in both culture-based and culture-independent studies, between *H. influenzae* and *P. aeruginosa*.[43]. These are also the two most dominant taxa identified by 16S rRNA sequencing and isolation of mucoid *P. aeruginosa* or *H. influenzae* have been shown to have the greatest influence on community structure as a whole.[51] In fact, patients with *P. aeruginosa*– and

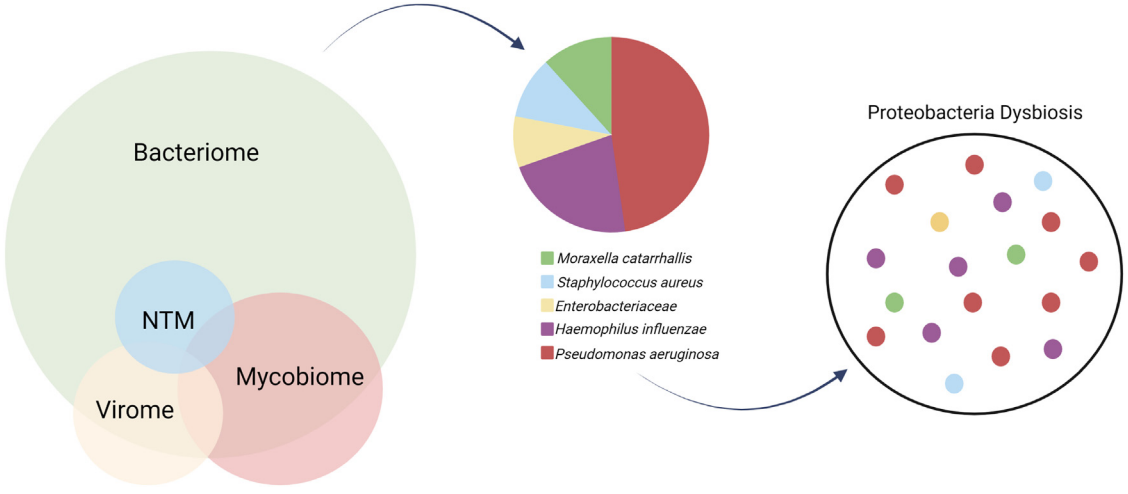

Fig. 2 The microbiome in bronchiectasis in composed by the bacteriome, mycobiome and virome. Respectably to the bacteriome, culture-based microbiology results from European cohorts show predominance for *Haemophilus influenzae* and *Pseudomonas aeruginosa*. Multiple factors might lead to Proteobacteria dysbiosis and loss of diversity in the bronchiectasis lung microbiota.

H. influenzae— dominated communities had significantly higher serum levels of C-reactive protein (CRP), and higher sputum levels of interleukin (IL)—1β and IL-8.[52]

Pseudomonas aeruginosa

P. aeruginosa is the most commonly identified pathogen in bronchiectasis patients worldwide. It has been associated with increased exacerbation frequency, increased hospital admission risk and worse quality of life.[53] It is associated to a nearly threefold increased risk of death, with the risk strongly associated with exacerbations.[54]

Higher levels of active neutrophil elastase are associated to low microbiome diversity and specifically to *P. aeruginosa* infection.[55] The induction of neutrophil extracellular traps (NETs) formation gives *P. aeruginosa* a survival advantage: NETs inhibit and kill competitor microorganisms, and *P. aeruginosa* persists by degrading NETs and evading killing by inflammatory cells.[56,57] Moreover, *P. aeruginosa* relies on the quorum sensing (QS) signalling system as a central regulator mechanism of virulence expression that contributes to the formation and maintenance of biofilms and tolerance to conventional antimicrobials. Therefore, the persistence of this pathogen is associated with biofilm formation, innate antimicrobial resistance and resistance to host cell clearance. Consequently, *P. aeruginosa* infected patients are considered a distinct and stable phenotype with poor outcomes.[58]

Other bacteria

H. influenzae is a common but less well studied pathogen in bronchiectasis.[44] It has been associated with a loss of microbial diversity and the formation of NETs as well as specific increases in matrix metalloproteinases MMP2 and MMP8.[56,59]

The relationship between *S. aureus* and non-CF bronchiectasis is yet not well established.[60] Metersky et al. reported a frequency of infection similar to prior studies and that *S. aureus* does not appear to be an independent risk factor for severe disease in patients with bronchiectasis.[61]

As for *S. aureus*, scarce information is available about *Stenotrophomonas maltophilia* in patients with bronchiectasis. Metersky et al. also concluded that bronchiectasis patients with *S. maltophilia* may have worse outcomes than patients without this organism or without *P. aeruginosa*.[62]

Virome

Few actual studies exist that can illustrate the true extent of the virome in the setting of bronchiectasis. Respiratory viruses are commonly detected in patients with stable bronchiectasis, with elevated burdens over winter comparing to summer season.[63] Respiratory viruses play crucial roles in triggering bronchiectasis exacerbations, particularly coronavirus, rhinovirus and influenza A and B.[64] Despite high viral burden in stable-state bronchiectasis, it was not detected significant association between common respiratory viruses and clinical outcomes.

Whether some patients with bronchiectasis who experience frequent exacerbations have increased susceptibility to viral infection or exacerbation upon viral infection, as has been demonstrated in asthma, is unknown.

Mycobiome

Fungi might have a pathogenic role in bronchiectasis related to immune dysregulation and a sharp allergic response following exposure. The major clinical manifestations of fungal disease in bronchiectasis is ABPA, which affects up to 10% of the patients, being dominated by a Th2-driven response with elevated levels of total and specific IgE and eosinophilic inflammation.[65]

Máiz et al. showed high rates of fungal isolation and persistence in respiratory secretions of bronchiectasis patients.[66] In a study using molecular methods to profile the "mycobiome", it was determined that, while the *Aspergilli* remain the best characterized fungi in the bronchiectasis airway, *Candida* species are the most widely detected in bronchiectasis patients.[67] Additionally, Poh et al. described that systemic chitinase activity, an important innate immune defence mechanism against infection, may represent a useful clinical tool for the identification of fungal-driven "frequent exacerbators" with bronchiectasis in South-East Asian populations.[68]

More recently, the Cohort of Matched Asian and European Bronchiectasis (CAMEB) study was the first report on the pulmonary mycobiome in bronchiectasis across continents and in age and sex-matched populations from distinct geographical regions. It provided key insights into *Aspergillus*-associated disease in bronchiectasis since it identifies distinct dominant mycobiome profiles according to a geographic region.[69] Moreover, compared with those *Aspergillus* colonized and/or sensitized, patients with serological ABPA (sABPA) had more severe disease, greater exacerbations, and poorer lung function.[2,69]

To date, it is clear that sensitization to fungi leads to a clinically relevant and treatable endotype of disease. From a mycobiome standpoint, research suggests there are detectable fungi within the airway but their clinical correlates and usefulness in patient stratification are not yet clear.

Non-tuberculous mycobacteria

NTM can be a cause or a consequence of bronchiectasis and despite its heterogeneous prevalence due its distinct geographic distribution, it is settled that the incidence of NTM pulmonary disease (NTM-PD) is increasing worldwide.[70,71]

Bronchiectasis patients have a higher risk of NTM-PD compared with age- and sex-matched populations and particular phenotypic characteristics are also associated to NTM infection as pectus excavatum, scoliosis, mitral valve prolapse and lower fat mass index.[72,73,74] This suggests a distinct endotype although the genetics are complex and suggest a combination of cilia and connective tissue related genes may be involved.

Patients with NTM often have coinfection with *P. aeruginosa* and *Aspergillus*-related lung disease, which suggests there may be a shared susceptibility across different infections.[73]

Inflammatory endotypes

Neutrophilic inflammation

Neutrophils, the major cell type identified in bronchiectasis airway secretions, are mobilized to the airways via a variety of

chemokines including leukotriene B4, IL-8, IL-1β and TNF-α.[75] Neutrophils in bronchiectasis are dysfunctional, and predisposed to increased protease release, overwhelming anti-protease defence and failure of pathogen clearance.[76]

NET formation has been identified as a key mechanism of neutrophil dysfunction in bronchiectasis. NETs function is to eliminate pathogenic microorganisms, but an excess of its production leads to tissue damage and persistent airway inflammation.[77]

NETs release webs of neutrophil DNA into the airway with large amount of enzymes including neutrophil elastase (NE). NE is a key driver of disease in bronchiectasis with links to tissue degranulation, impaired bacterial clearance and mucus hypersecretion. Increased NE sputum levels in patients with bronchiectasis is associated with decline in FEV1, chronic infection by *P. aeruginosa*, high exacerbations rate and risk of mortality.[56,78,79,80] As NE is one the molecules contributing to NETosis and NETs increased production is a recognised negative predictor of clinical outcomes, endotypes based on NETs or NE are promising, pointing to potential targetable therapy.[81]

Cathepsin C, also known as dipeptidyl peptidase-1 (DPP1), is responsible for the activation of serine proteases, like NE, in neutrophils precursors.[76] Due to the fundamental role of DPP1 in serine protease activation, DPP1 inhibitors have recently been developed. Brensocatib reduced neutrophil elastase activity and prolonged the time to next exacerbation in a recent phase 2 trial.[82]

MMPs are proteases responsible for degrading the extracellular matrix and, so far, 28 MMPs have been described.[83] Elevated sputum levels of MMP-8 and MMP-9, expressed by neutrophils, associate to more severe disease, *P. aeruginosa* infection as well as higher risk of future exacerbations.[84]

PZP is a glycoprotein and one of the molecules released by the neutrophils as part of the NET formation. Elevated sputum levels of PZP were found in exacerbator patients with severe bronchiectasis disease. Microbiome analysis revealed the predominance of pathogenic Proteobacteria, supporting that neutrophil-associated proteomic signatures predict dysbiosis.[85]

Overall, there are now multiple markers demonstrating the importance of neutrophilic inflammation and protease anti-protease balance in bronchiectasis. Patients with higher levels of NETs have a distinct prognosis and response to treatment suggesting a true "endotype". Macrolides have been shown to reduce NETs and may be a marker of response.[56] In addition, as NETs are strongly associated with bacterial infection, higher levels of neutrophilic inflammation may be an indication for antibiotic treatment.[56]

Eosinophilic inflammation

Th2-driven responses have been increasingly recognized in bronchiectasis. This endotype, defined by the presence of either eosinophils blood count$\geq$300 cells/μL or oral FeNO$\geq$25 dpp, has been described in 20$-$30% of the bronchiectasis patients without asthma.[86,87]

Recent sputum protein profiling results disclosed that eosinophil peroxidase (EPX) is significantly elevated in severe disease and severe exacerbations. Moreover, correlation analysis confirmed EPX as an eosinophil-specific inflammatory marker.[88]

Blood eosinophil counts of $>$300 cells/μl were associated with both *Streptococcus*- and *Pseudomonas*-dominated microbiome profiles and, after controlling for infection status, Shoemark et al. showed that raised blood eosinophil counts associated with shorter time to exacerbation.[87] In fact, one study suggested that 5% of non-asthmatic bronchiectasis patients with a T2-high endotype are frequent exacerbators, despite therapeutic optimization, and might be ideal candidates for anti-IL5 and anti-IL5rα treatments.[86] Some observational studies have also observed the positive effect from biological therapies such as mepolizumab or benralizumab in patients with clinically relevant severe bronchiectasis and eosinophilia with both concomitant and non-concomitant asthma, with a reduction in blood eosinophils accompanied by a clinical and functional improvement in the quality of life.[89,90]

It is not only high levels of eosinophils which are a useful biomarker. Blood eosinophils counts of $<$100 cells/μl are associated with bronchiectasis severity and increased mortality, suggesting that low blood eosinophils could be a good biomarker of severity of bronchiectasis.[87,91] One potential mechanism for the above is that patients with low blood eosinophils are those with more severe neutrophilic disease and this reflected in a switch in granulocyte production towards neutrophils and away from eosinophils.

The evidence accumulated on the role of bronchial and eosinophils in bronchiectasis is still very scarce, but it has already been suggested that inhaled corticosteroids (ICs) might reduce the exacerbation rate and improve quality of life in patients with bronchiectasis not related to COPD.[92,93]

In the context of Th2-driven responses, Mac Aogáin et al. focused their research on atopy and sensitization. The CAMEB study concluded that sensitization rates in bronchiectasis exceed those of an atopic comparator (allergic rhinitis).[69] Following a comprehensive airway immune profiling, two "immunoalergotypes" were disclosed.[94] One of these immunoalergotypes associates to significant worse lung function, implicating fungal exposure as a potentially treatable endotype in the implicated sub-populations.[95]

In summary, there is Th2-endotype of bronchiectasis which is distinguished from asthma and may be identified through blood eosinophils, raised FeNO and/or sensitization to *Aspergillus* or other aeroallergens. There is preliminary evidence that biomarkers such as blood eosinophils can identify responders to ICS or anti-IL5 therapies in a precision medicine approach.

Antimicrobial peptides associated inflammation

Antimicrobial peptides (AMPs) are a diverse group of molecules that are important in host defence against microbes but can be proinflammatory in chronic lung disease. Sibila et al. concluded that frequent exacerbators with bronchiectasis showed dysregulated sputum AMP levels, characterised by elevated LL-37 and reduced secretory leucocyte peptidase inhibitor (SLPI). High levels of LL-37 and low levels of SLPI levels in sputum have an independent association to disease severity, *P. aeruginosa* infection and risk of future exacerbation.[96]

Recent cluster analysis allowed the identification of three endotypes based on different sputum levels of AMPs. These endotypes display distinct inflammation profiles and might

hold different disease severity and risk of exacerbation.[97] Still, SLPI is degraded by NE and some AMPs including LL-37 are released from neutrophils during NETosis so whether this represents distinct endotypes or alternative biomarkers of the severe NET associated endotype has not been fully established.

Systemic inflammation

The inflammatory response present in bronchiectasis is predominantly located at the pulmonary level. Nevertheless, different studies report elevated levels of systemic inflammatory markers whether in clinical stability or exacerbations and that systemic inflammation itself is a feature that has been associated with a greater degree of local inflammation and severity.[98,99]

White blood cells, erythrocyte sedimentation rate (ESR) and serum TNF-α all have a well-established and significant association between systemic inflammation and bronchiectasis severity.[99,100] The strengths of these associations are weak and do not allow decision making at an individual patient level, particularly as systemic inflammatory markers are non-specific.

Higher CRP value is associated with a greater risk of future severe exacerbations in patients with steady-state bronchiectasis and interestingly patients were more responsive to macrolides in bronchiectasis if they had higher levels of CRP at baseline.[101,102]

Platelets represent a cheap and easy-to-evaluate biomarker. In stable state bronchiectasis, thrombocytosis is associated with disease severity, hospital admissions, poor quality of life, and mortality.[103] Soluble P-selectin (sP-selectin), which is released from platelet membrane, plays an essential role in platelet activation. sP-selectin levels were higher in exacerbated patients compared to those in the stable state, and also higher in stable state patients compared to controls, suggesting a baseline increased platelet activation in bronchiectasis patients.[104]

Patients with bronchiectasis have an increased risk of mortality, particularly mortality related to cardiovascular disease.[105] The associated cardiovascular risk further increases around the time of exacerbation.[106] Endothelial progenitor cells (EPCs) are inversely correlated with cardiovascular risk factors and deficiencies in their number and function are present in patients with bronchiectasis, which relate to disease severity.[107] Additionally, serum desmosine (sDES), which represents systemic elastic degradation and vascular ageing, is a particular predictor of cardiovascular mortality in bronchiectasis since elastin degradation may be plausible link between airway inflammation and cardiovascular risk.[108]

According to gender, Wang et al. reported that female patients had lower levels of inflammatory parameters except for ESR (normal ranges in both genders but slightly greater in female).[109] Rather than the evaluation of a single biomarker, these authors also believe that clustering analysis of systemic parameters offers a powerful tool to better characterize patients with bronchiectasis. Using a data mining approach, they were able to define three clusters which significantly correlated to disease severity, indicating that these results have clinical implications in the management of the complexity and heterogeneity of bronchiectasis patients.[110]

Mucus, mucins and mucociliary dysfunction

Mucus is a protective coating secreted in the healthy airways, composed of water, salt and proteins. Mucins are glycoproteins responsible for the protective and clearance properties of the mucus. MUC5AC and MUC5B are most abundant and important airway mucins.[111]. Mucin concentration is significantly higher in patients with bronchiectasis than healthy individuals and it related to osmotic pressure, greater viscosity and inflammation, and infection.[112]

Mucus and cilia form the mucociliary escalator, ensuring that airway's foreign agents are transported and either swallowed or expelled by coughing.[113] Factors that may cause reduced ciliary beating include cyanide produced by *P. aeruginosa* and neutrophil proteases.[114] Recently, it has been proposed that impairment of mucociliary clearance might result from both Th1 (IL-1β, IL-8) and Th2 (IL-4 and IL-5) inflammatory cytokines.[115] MUC5AC release is also closely related to airway inflammation. Therefore, while impaired mucociliary clearance may contribute to some endotypes, they are closely linked to the inflammatory endotypes described above with both NET associated and Th2 high endotypes causing ciliary dysfunction and mucus hypersecretion.

Genetics

It is likely in the coming years that whole genome sequencing will identify new genetic causes of bronchiectasis. Although most patients will be diagnosed with idiopathic bronchiectasis, reviewing conditions with well-known genetics-based pathways offers insights into understanding the underlying mechanisms of bronchiectasis pathogenesis.[42]

Mannose-binding lectin (MBL) is a key component of innate immunity involved in clearance of bacteria and apoptotic cells. Genetic *MBL* deficiency is common in the general population and related to disease severity in bronchiectasis, including quality of life and frequency of exacerbations and admission to hospital.[116]

Secretion of α(1,2)fucosylated glycans elicits a dichotomous effect on host—microbe interactions, making the secretor genotype (*FUT2)* a risk factor underlying variation in infection type and disease severity in bronchiectasis. Homozygous secretors exhibit lower lung function, higher exacerbation rate and more frequent *P. aeruginosa*-dominated infection.[117]

Telomere attrition is an established ageing biomarker. Lim et al. reported that shortened telomere length was significantly relevant in sputum immune cells of bronchiectasis patients and that gene *GBP5* upregulation, a positive regulator of the NLRP3 inflammasome, led to exaggerated immune response upon bacterial infections.[118]

Most studies of genetics in bronchiectasis to date are limited to a few hundred patients whereas breakthroughs in the genetics of other complex diseases have required studies of several thousand patients. As large cohorts are increasingly established with associated biobanks it should be possible to gain a deeper understanding of the contribution of genetics to endotype in bronchiectasis.

Conclusion

The heterogenous nature of the bronchiectasis in underlined by multiple endotypes which may represent different treatable traits. It is essential to define the biological pathways leading to airway inflammation and disease progression, by using the available "omics" technologies, so that novel biomarkers are identified and personalized therapies are developed.

Future results from international multi-omics studies such as the Bronchiectasis Research Involving Databases, Genomics and Endotyping (BRIDGE) study (ClinicalTrials.gov Identifier: NCT03791086), promoted by EMBARC, will allow us to identify and characterize subpopulations of patients with bronchiectasis, through stable state or exacerbation, in order to obtain meaningful outcomes.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2023.03.004.

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REVIEW

Impact of acute exacerbations of COPD on patients' health status beyond pulmonary function: A scoping review

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Abstract This scoping review summarized the evidence regarding the impact of acute exacerbations of COPD (AECOPD) on patients' health status beyond pulmonary function.

PubMed, Embase, and Web of Science were searched. Prospective cohort studies assessing the health status of patients with COPD in a stable phase of the disease and after a follow-up period (where at least one AECOPD occurred) were included. An integrated assessment framework of health status (i.e., physiological functioning, complaints, functional impairment, quality of life) was used.

Abbreviations: 6MWD, six-minute walking distance; 95%CI, 95% confidence interval; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; CAT, COPD assessment test; CCQ, clinical COPD questionnaire; CES-D, centre for epidemiological studies depression scale; COPD, chronic obstructive pulmonary disease; CRQ, chronic respiratory disease questionnaire; EQ-5D, EuroQoL 5-dimension questionnaire; FACIT-F, functional assessment of chronic illness therapy-fatigue; FEV_1, forced expiratory volume in one second; FFM, fat-free mass; GOLD, global initiative for chronic obstructive lung disease; mMRC, modified Medical Research Council dyspnoea questionnaire; PRISMA-ScR, preferred reporting items for systematic reviews and meta-analysis extension for scoping reviews; QMVC, quadriceps maximum voluntary contraction; QoL, quality of life; SF-12, 12-item short form health survey; SF-36, 36-item short form health survey; SGRQ, Saint George's respiratory questionnaire; VMU, vector magnitude units.

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Twenty-two studies were included. AECOPD acutely affected exercise tolerance, quadriceps muscle strength, physical activity levels, symptoms of dyspnoea and fatigue, and impact of the disease. Long-term effects on quadriceps muscle strength, symptoms of dyspnoea and depression, and quality of life were found. Repeated exacerbations negatively impacted the fat-free mass, levels of dyspnoea, impact of the disease and quality of life. Conflicting evidence was found regarding the impact of repeated exacerbations on exercise tolerance and physical activity levels.

AECOPD have well-established acute and long-term adverse effects on health status beyond pulmonary function; nevertheless, the recovery trajectory and the impact of repeated exacerbations are still poorly studied. Further prospective research is recommended to draw firm conclusions on these aspects.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by the onset of acute exacerbations (AECOPD), defined as an acute worsening of respiratory symptoms that result in additional therapy.[1] On average, patients with COPD experience 1 to 4 AECOPD per year,[2,3] which account for 50—70% of all COPD related-costs and increase their susceptibility to new AECOPD, hospitalization, and death.[1,4,5] These events are associated with increased dyspnoea that usually lasts for 7 to 10 days, although in some cases there is no full recovery after weeks or months.[1,6] Even a single AECOPD results in accelerated lung function decline and disease progression.[7-9] Evidence also suggests that AECOPD lead to declines in exercise performance, functional status and quality of life (QoL), thus harming health status beyond pulmonary function.[1,10-12] In addition, AECOPD are not random events but cluster together in time with a high-risk period for recurrent AECOPD in the 8-weeks following an initial exacerbation.[1,13] Some patients are particularly susceptible to these (repeated) exacerbations and are known as the frequent exacerbator phenotype, which can be found across all disease severity groups.[1,11] These frequent exacerbators seem to suffer from even more significant declines in lung function and QoL, potentially experiencing a further negative impact on health status.[1,11,14-16]

Health status can be defined as the impact of health on a person's ability to perform and derive fulfilment from daily life activities.[17] Given its complexity, an integrated assessment framework of health status in COPD has been developed, which encompasses four sub-domains: physiological functioning, complaints, functional impairment and QoL.[18] These subdomains are relatively independent, and therefore a comprehensive assessment is essential to understand the impact of AECOPD on all health status domains and tailor interventions to counteract the detrimental effects that each person experiences.[16,18-20] However, to date there are no reviews of the available evidence on the impact of AECOPD on the different health status domains. A scoping review to outline the existing evidence on this topic would provide the basis for future research to guide clinical practice on this matter.

Thus, this scoping review aimed to summarize and critically appraise the existing scientific evidence of the impact of AECOPD on the different sub-domains of health status in patients with COPD. Accordingly, our review question was: what do we know about the impact of AECOPD on the different sub-domains of health status in patients with COPD?

Methods

This review followed the updated methodological framework to conduct scoping reviews proposed by Peters and colleagues,[21] and is reported according to the Preferred Reporting Items for Systematic reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR) checklist guidelines.[22]

Database and search strategy

One researcher (AM) performed an electronic literature search on PubMed, Embase and Web of Science from inception until January 2021. The following search strategy was used: ((COPD [title/abstract] OR chronic obstructive pulmonary disease [title/abstract/MeSH]) AND (hospital*[title] OR exacerbation [title/abstract])). The search results were imported to EndNote X9 (Clarivate Analytics, Philadelphia, PA, United States of America) and the duplicates were identified and removed.

A single researcher (AM or MSBG or CB) performed the title screening conservatively, i.e., excluding studies which clearly did not fulfil the criteria. Abstract and consequent full-text screening were performed independently by two out of three researchers (AM and CB or MSBG and CB). A consensus-based decision was made after discussion when discrepancies were present.

Selection criteria

Studies were included if they (i) studied patients with COPD that suffered from at least one AECOPD throughout the study; (ii) were prospective cohort studies; (iii) performed at least one type of health status assessment; and (iv) were written in English. Patients had to be assessed at baseline (in a stable phase of the disease) and after a follow-up period. The follow-up assessment(s) could have been conducted immediately after an AECOPD, during the course of a single AECOPD, or over a more extended period of time with the onset of AECOPD during the follow-up period being recorded (e.g., to compare changes in health status in

frequent exacerbators vs. non-frequent exacerbators). Given the variability of used definitions of AECOPD in the literature, for the purpose of this review, AECOPD could be defined using symptom-based (i.e., patient-reported worsening of respiratory symptoms either to a healthcare professional or using a diary or tool) or event-based (i.e., change in treatment – medication and/or hospitalization) definitions, or a combination of both.[23]

Studies reporting on the short-, mid- or long-term effects of any intervention were excluded, unless it was possible to retrieve the data of a control group receiving only standard of care. Abstracts in conference proceedings were also excluded.

Based on the sub-classification of health status previously proposed for patients with COPD,[18] we included measures of physiological functioning (exercise tolerance, muscle function and body composition), complaints (subjective complaints, expected dyspnoea and dyspnoea emotions), functional impairment (subjective impairment, behavioural impairment and actual physical activity) and QoL (general QoL, health-related QoL, satisfaction and relations). Measures of pulmonary function were not included.

Data extraction

A customized data collection tool in Microsoft® Excel (Microsoft, Redmond, Washington, United States of America) and a data extraction table in Microsoft® Word (Microsoft, Redmond, Washington, United States of America) were developed to extract the most relevant information from the included studies and facilitate their subsequent analysis and interpretation. Data extraction was performed by AM and MSBG. Information on study design and timing of assessment, sample size, baseline characteristics (age, gender, body mass index (BMI), forced expiratory volume in one second (FEV_1)), definition of (frequent) exacerbations used, AECOPD management and setting, measures of health status and main results regarding health status was collected.

Data synthesis

Data are presented in a tabularized format with a narrative summary linking the review results with the aim and review question. Key findings were categorized according to the sub-domains of health status proposed by Vercoulen and colleagues.[18] In addition, whenever possible, results synthesis were grouped on acute vs. long-term effects of AECOPD, and on single vs. repeated AECOPD. For the purposes of this review, acute effects combined the results found regarding the onset and first days of an AECOPD, long-term effects combined the data on recovery/sustained changes over time, i.e., data from post-AECOPD periods, annual changes and follow-up times. Numerical summaries for the definition of (frequent) exacerbations, AECOPD characteristics and management, and measures of health status were collated. Schematic overviews were further developed to provide a visual synthesis of the results.

Results

Search results

The literature search provided a total of 23,677 records. After the removal of duplicates, 12,662 records were screened for relevant content using titles and abstracts. From these, 12,199 were excluded through title screening and 388 through abstract screening. Thus, the full text of 74 potentially relevant reports was assessed. Twenty-two studies were included in the review. The screening process is visualized in a flow chart (Fig. 1).

General characteristics

Characteristics of the included studies are shown in Table 1. Studies were conducted between 2004 and 2020.

Most studies (n = 14) defined AECOPD based on an increase in respiratory symptoms[24-37] leading to changes in medication (n = 12) (e.g., treatment with antibiotics or systemic steroids)[26,28,30,31,33-35,37-41] or to hospitalization (n = 4).[35,38,39,41] Follow-up time varied from six weeks up to eight years. Ninety-one percent (n = 20) of the studies[25,26,28-45] involved a sample combining patients that suffered a single exacerbation and patients that suffered repeated exacerbations. Severity of exacerbations was usually not reported. Nevertheless, 80% of the studies reporting this information were focused on moderate to severe AECOPD.[24,26,28,29,37,40,41,45] Most reported treatment was composed by antibiotics, oral steroids or a combination of both (n = 10).[25,26,28,29,34,37-41] Twelve studies included a sample combining patients treated at home with patients treated in the hospital.[26-29,33,36-42]

Tools used to assess health status

Physiological functioning was assessed in five studies with the six-minute walking distance (6MWD),[24,26,28,29] the quadriceps maximum voluntary contraction (QMVC)[24,30] and the fat-free mass (FFM).[30]

Complaints were assessed in nine studies with the modified Medical Research Council dyspnoea questionnaire (mMRC),[26,28,44] the COPD assessment test (CAT),[35,37-39] the clinical COPD questionnaire (CCQ)[35,36] and the functional assessment of chronic illness therapy-fatigue (FACIT-F).[24]

Functional impairment was assessed in five studies via physical activity levels.[24,25,27,40,42] Physical activity was objectively assessed by daily step count[25,40] and the time spent in light[24] or higher intensity (i.e., >3000 vector magnitude units (VMU))[42] activities. The time spent indoors/outdoors[25,27] was quantified based on a diary.

Finally, QoL was assessed in twelve studies with the Saint George's respiratory questionnaire (SGRQ),[27-29,31-34,43-45] the chronic respiratory disease questionnaire (CRQ),[28,34] the 36-item short form health survey (SF-36),[35,43] the 12-item short form health survey (SF-12),[33] the EuroQoL 5-dimension questionnaire (EQ-5D)[35] and the centre for epidemiologic studies depression scale (CES-D).[41]

Fig. 2 provides an overview of the outcome measures used to assess each health status subdomain. No study assessed all the domains that compose health status.

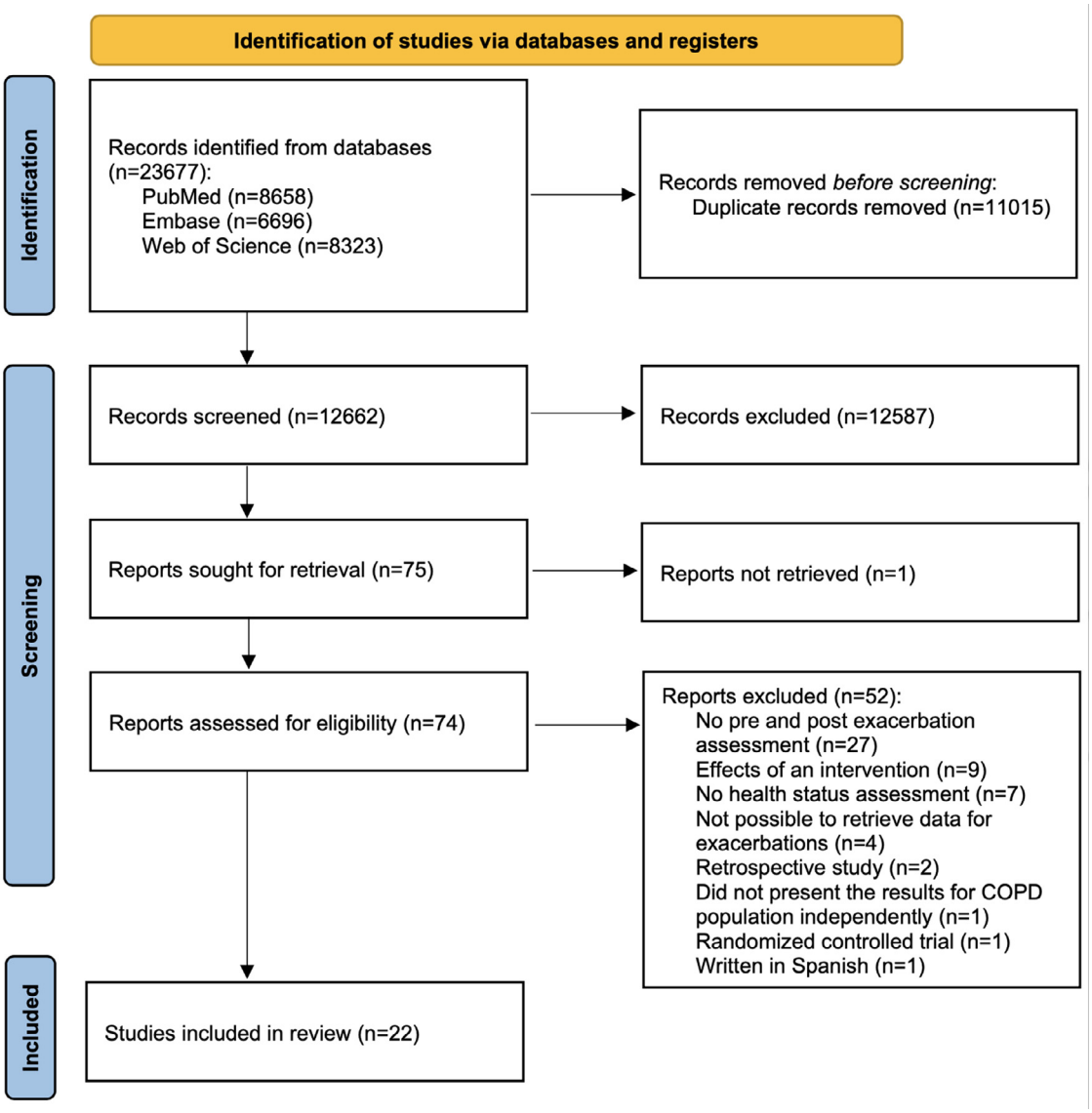

Figure 1 PRISMA flowchart of the included studies.

Instead, the majority of studies[25,30-34,36-43,45] (n = 15) focused on a single health status domain.

Influence of exacerbations on physiological function

Two studies[24,26] reported a significant reduction in the 6MWD in the first two to three days after the onset of an AECOPD, which was found to be more pronounced in patients with severe to very severe disease (GOLD stages 3 and 4).[24] In addition, studies exploring the effects of repeated AECOPD[26,28,29] also found a consistent decline in the 6MWD however, the recovery trajectory was conflicting. One study[24] reported that the 6MWD increased back to the pre-exacerbation status after seven days, whereas more extended studies[26,28] found that the observed decrease in 6MWD was maintained up to two years of follow-up, with inconsistent results regarding a lower 6MWD in frequent exacerbators (i.e., two or more AECOPD per year).[26,28]

QMVC was significantly reduced three and seven days after the onset of AECOPD symptoms.[24] A decline in QMVC over a 1-year follow-up was also observed but with no correlation with having frequent exacerbations (i.e., two or more per year).[30] Yet, frequent exacerbators had a more pronounced decline in FFM.[30]

Influence of exacerbations on complaints

A consistent worsening of complaints at the onset of an AECOPD was found across all outcome measures.[24,26,36,37]

There was an increase (worsening) in the mMRC score within 48 h of the onset of an AECOPD, which was more pronounced in patients suffering from repeated exacerbations.[26] Furthermore, this increase was sustained at 1- and 2-years follow-up in frequent exacerbators (i.e., two or more AECOPD per year), but not in single exacerbators.[26] A second study also corroborated these findings by reporting higher mMRC scores in frequent exacerbators.[28]

Similarly, a significant increase (worsening) in the CAT total score was found at the onset of an AECOPD, which was already noticeable one day before and was sustained for up

Table 1 Influence of exacerbations on changes in health status over time in patients with COPD (n=22).

Author(s), year	Study design/ Time of assessment	Population	Exacerbation – definition, treatment & setting	Health status assessment measure	Main results

Miravitlles et al., 2004[33]	**Observational prospective study**
	
	Time points:
	- Baseline
	- Every 6 months during 2 years
		Total sample:
		n=336; 98% male;
		66±8 years;
		FEV_1 33.0±8.0 %predicted; BMI 27.4±4.0 kg/m^2
		
		Frequent exacerbators (≥3 AECOPD in 2 years)**:**
		n=158; 98% male;
		66±9 years;
		FEV_1 31.8±8.0 %predicted; BMI 27.0±4.1 kg/m^2
		
		Infrequent exacerbators (<3 AECOPD in 2 years)**:**
		n=178; 98% male;
		67±8 years;
		FEV_1 34.2±8.0 %predicted; BMI 27.8±3.9 kg/m^2
		
		AECOPD treated with oral steroids: n=189 (41.4%)
		
		Patients admitted to the hospital for AECOPD: n=103 (30.7%)
			- Defined as a sustained worsening of patient's condition from the stable state characterized by the increase of any combination of three cardinal symptoms: dyspnoea, sputum purulence, and sputum volume, that is acute in onset and necessitates a change in regular medication
			- Antibiotics and/or oral steroids and/or increased doses of inhaled steroids and bronchodilators
			- Home or hospital
				SGRQ symptoms score
				
				SGRQ activity score
				
				SGRQ impact score
				
				SGRQ total score
				
				SF-12 physical component score
				
				SF-12 mental component score
					Baseline vs. 6 months vs. 1 year vs. 18 months vs. 2 year
					Frequent exacerbators: 52±20 vs. 44 vs. 49 vs. 43 vs. 47±19
					Infrequent exacerbators: 45±20 vs. 33 vs. 38 vs. 31 vs. 34±19
					Frequent exacerbators vs. Infrequent exacerbators: p<0.001
					
					Frequent exacerbators: 67±19 vs. 65 vs. 69 vs. 66 vs. 68±19
					Infrequent exacerbators: 59±22 vs. 57 vs. 59 vs. 58 vs. 60±20
					Frequent exacerbators vs. Infrequent exacerbators: p<0.001
					
					Frequent exacerbators: 42±17 vs. 38 vs. 39 vs. 38 vs. 38±18
					Infrequent exacerbators: 36±18 vs. 29 vs. 30 vs. 28 vs. 30±18
					Frequent exacerbators vs. Infrequent exacerbators: p<0.001
					
					Frequent exacerbators: 51±16 vs. 47 vs. 50 vs. 48 vs. 49±16
					Infrequent exacerbators: 44±18 vs. 38 vs. 40 vs. 38 vs. 39±17
					Frequent exacerbators vs. Infrequent exacerbators: p<0.001
					Patients with moderate COPD
					Influence of frequent exacerbations in SGRQ change (compared to infrequent exacerbators): 5.5, p=0.013
					Annual rate of change: Frequent exacerbators -0.6 vs. Infrequent exacerbators -2.6, p<0.05
					Influence of hospital admission in SGRQ change (compared to no hospital admission): 1.4, p=0.563
					Patients with severe COPD
					Influence of frequent exacerbations in SGRQ change (compared to infrequent exacerbators): 3.0, p=0.169
					Influence of hospital admission in SGRQ change (compared to no hospital admission): 5.5, p=0.007
					
					Frequent exacerbators:
					Baseline: 37±8 vs. 2 year: 37±9
					Infrequent exacerbators:
					Baseline: 40±10 vs. 2 year: 40±9
					Frequent exacerbators vs. Infrequent exacerbators: p<0.05
					
					Frequent exacerbators:
					Baseline: 49±13 vs. 2 year: 50±12
					Infrequent exacerbators:
					Baseline: 51±12 vs. 2 year: 51±12
					Frequent exacerbators vs. Infrequent exacerbators: p>0.05

Donaldson et al., 2005[27]	**Observational prospective study** **Time points:** - Baseline: 8-14 days preceding exacerbation onset - Day of the exacerbation onset - Recovery: 3 day moving average equal or better than baseline - Every year up to 8 years	**Total sample:** n=147; 69% male; 68±8 years; FEV_1 40.9±15.7 %predicted **Patients with data recorded during exacerbations:** n=136 **AECOPD leading to hospital admission:** n=90 (6.2%)	- Recorded in a diary - Defined as an increase in respiratory symptoms for 2 consecutive days, with at least one major symptom (dyspnoea, sputum purulence or sputum volume) plus either another major or a minor symptom (wheeze, cold, sore throat, and cough) - Home or hospital	Days spent indoors (%) Days/week spending all day indoors (n) Time spent outdoors (hours/day) SGRQ symptoms score SGRQ activity score SGRQ impact score SGRQ total score	Baseline: 34.1% vs. AECOPD onset: 44.4% vs. Post AECOPD: 39.7% Baseline: 2 [1; 4] vs. Post AECOPD 3 [1; 5], ¤0 [0; 1], p<0.001 Baseline vs. AECOPD: ¤, p=0.021 Baseline vs. Post AECOPD: ¤, p=0.024 Annual decline: -0.1 (95%CI: -0.2 to -0.1) hours/year, p<0.001 Annual decline: -1.3 (95%CI: -2.0 to -0.7), ¤2.0%/year, p<0.001 Annual decline: 1.5 (95%CI: 1.0 to 1.1), ¤2.1%/year, p<0.001 Annual decline: 1.5 (95%CI: 0.9 to 2.1), ¤3.8%/year, p<0.001 Annual decline: 1.0 (95%CI: 0.6 to 1.5), ¤1.9%/year, p<0.001
Cote et al., 2007[26]	**Observational prospective study** **Time points:** - Baseline - At exacerbation: within 48h of the onset of symptoms - Follow-up: 6 months, 1 and 2 years after exacerbation	**Total sample:** n=130; 94% male; 67±9 years; FEV_1 39.5±15.0 %predicted; BMI 27.4±5.9 kg/m^2 **Subgroups:** **Single exacerbators** (1 exacerbation/year): n=48 **Frequent exacerbators** (≥2 exacerbations/year): n=82 **Patients admitted to the hospital for AECOPD (during follow-up period):** n=50	Defined as an event characterized by a sustained worsening of respiratory symptoms for at least 2 days, requiring: - a visit to a doctor or the emergency department - treatment with antibiotics or systemic steroids or both - no need for hospitalization	6MWD (m) mMRC grade	**Total sample:** Baseline: 354±119 vs. AECOPD: ¤72 (20.4%) vs. 6 months: ¤37 (10.5%) vs. 1 year: ¤49 (13.9%) vs. 2 years: ¤74 (21.0%), p<0.001 **Single exacerbators:** Baseline: 385±116 vs. AECOPD: ¤77 (20.0%) vs. 1 year: ¤51 (13.0%) vs. 2 years: ¤81 (21.0%) **Frequent exacerbators:** Baseline: 334±117 vs. AECOPD: ¤69 (21.0%) vs. 1 year: ¤49 (15.0%) vs. 2 years: ¤67 (20.0%) **Total sample:** Baseline: 2.3±0.9 vs. AECOPD: ¤0.5 (20.6%) vs. 6 months: ¤0.2 (10.5%) vs. 1 year: ¤0.3 (11.0%) vs. 2 years: ¤0.3 (14.5%), p=0.009 **Single exacerbators:** Baseline: 2.1±1.1 vs. AECOPD: ¤0.4 (19.2%) vs. 1 year: ¤0.2 (10.0%) vs. 2 years: ¤0.2 (7.9%) **Frequent exacerbators:** Baseline: 2.4±0.9 vs. AECOPD: ¤0.5 (21.5%) vs. 1 year: ¤0.3 (11.0%) vs. 2 years: ¤0.4 (16.0%)

Table 1 (*Continued*)

Author(s), year	Study design/ Time of assessment	Population	Exacerbation – definition, treatment & setting	Health status assessment measure	Main results
Hopkinson et al., 2007[30]	**Observational prospective study** **Time points:** - Baseline - 1 year follow-up	**Total sample:** n=64; 66% male; 62±9 years; FEV_1 36.0±18.4 %predicted; BMI 24.3±5.2 kg/m^2 **Frequent exacerbators** (≥2 exacerbations/year): n=36	- Defined as episodes of worsening of respiratory symptoms leading to treatment with antibiotics - Antibiotics	QMVC (kg) QMVC (%predicted) Fat-free mass (kg)	Baseline: 35±2 vs. 1 year: 33±2, p=0.04 Not associated with having frequent AECOPD Baseline: 66±18 vs. 1 year: 62±18, p=0.009 Not associated with having frequent AECOPD Baseline: 48±8 vs. 1 year: 47±8, p>0.05 Correlated with having frequent AECOPD: r=-0.3, p=0.006

Llor et a., 2008[32]	**Observational prospective study**
	
	Time points:
	- Baseline
	- Every 6 months during 2 years
		Total sample:
		n=136; 96% male;
		70±10 years;
		FEV_1 48.7±14.5 %predicted
		
		Patients with one or more exacerbations:
		n=90; 97% male;
		69±10 years;
		FEV_1 47.7±14.6 %predicted
			Defined by the symptoms: an increase in dyspnoea, expectoration and/or in the purulence of the sputum	SGRQ total score	**Total sample:**
					Baseline: 40±19 vs. 2 years: 38±20, ▫2, p=0.181
					Patients with exacerbations:
					Baseline: 41±18 vs. 2 years: ▫0, p=0.781
					Patients with one exacerbation (n = 32):
					Baseline vs. 2 years: ▫ 4, p=0.023
					Patients with two or more exacerbations (n = 58)
					Baseline vs. 2 years: ▫ 2, p=0.13

Esteban et al., 2009[43]	**Observational prospective study** **Time points:** - Baseline - 5 years after the initial assessment	**Total sample:** n=391 **No hospitalizations during 5 years follow-up:** n=287; 65±9 years; FEV_1 53.9±13.7 %predicted; BMI 27.8±4.0 kg/m^2 **1-2 hospitalizations during 5 years follow-up:** n=76; 67±7 years; FEV_1 49.5±13.7 %predicted; BMI 28.6±5.4 kg/m^2 **3 or more hospitalizations during 5 years follow-up:** n=28; 65±9 years; FEV_1 44.6±13.3 %predicted; BMI 28.6±4.6 kg/m^2	- Information on hospital admissions due to AECOPD was obtained by analysing the database of the hospital, which is the benchmark hospital for the patients enrolled in the study - Hospital	SGRQ symptoms score SGRQ activity score SGRQ impact score SGRQ total score SF-36 physical component score SF-36 mental component score	**No hospitalizations:** Baseline: 38±21 vs. 5 years: 39±22, p>0.05 **1-2 hospitalizations:** Baseline: 47±21 vs. 5 years: 50±21, p>0.05 **3 or more hospitalizations:** Baseline: 47±18 vs. 5 years: 62±19, p<0.05 **No hospitalizations:** Baseline: 48±20 vs. 5 years: 44±24, p<0.05 **1-2 hospitalizations:** Baseline: 57±23 vs. 5 years: 55±25, p>0.05 **3 or more hospitalizations:** Baseline: 58±21 vs. 5 years: 69±22, p<0.05 **No hospitalizations:** Baseline: 29±19 vs. 5 years: 29±21, p>0.05 **1-2 hospitalizations:** Baseline: 34±20 vs. 5 years: 38±21, p>0.05 **3 or more hospitalizations:** Baseline: 35±18 vs. 5 years: 50±22, p<0.05 **No hospitalizations:** Baseline: 36±18 vs. 5 years: 35±20, p>0.05 **1-2 hospitalizations:** Baseline: 43±19 vs. 5 years: 45±20, p>0.05 **3 or more hospitalizations:** Baseline: 44±16 vs. 5 years: 58±20, p<0.05 **No hospitalizations:** Baseline: 46±8 vs. 5 years: 41±9, p<0.05 **1-2 hospitalizations:** Baseline: 44±8 vs. 5 years: 37±9, p<0.05 **3 or more hospitalizations:** Baseline: 45±6 vs. 5 years: 35±8, p<0.05 **No hospitalizations:** Baseline: 50±11 vs. 5 years: 52±11, p<0.05 **1-2 hospitalizations:** Baseline: 50±11 vs. 5 years: 51±12, p>0.05 **3 or more hospitalizations:** Baseline: 50±10 vs. 5 years: 46±13, p>0.05

Nishimura et al., 2009[34]	**Observational longitudinal study**
	
	Time points:
	- Baseline
	- After 6 months. If an exacerbation is present: 6 week exacerbation-free period
		Total sample:
		n=156; 96% male;
		71±6 years;
		FEV_1 38.1 %predicted
		
		Patients with exacerbations:
		n=48; 96% male;
		71±7 years;
		FEV_1 40.7±10.9 %predicted
		Patients with ≥2 AECOPD: n=12
			- Defined as a worsening of the respiratory symptoms that required treatment with oral corticosteroids or antibiotics or both
			- Oral corticosteroids or antibiotics or both
				SGRQ symptoms score
				
				SGRQ activity score
				
				SGRQ impact score
					Patients with exacerbations:
					Baseline: 54±21 vs. 6 months: ▫5±2, p<0.05
					Patients with 2 or more exacerbations:
					Baseline vs. 6 months: ▫12±6, p<0.05
					
					Patients with exacerbations:
					Baseline: 54±20 vs. 6 months: ▫2±1, p>0.05
					Patients with 2 or more exacerbations:
					Baseline vs. 6 months: ▫5±2, p<0.05
					
					Patients with exacerbations:
					Baseline: 33±19 vs. 6 months: ▫1±1, p>0.05
					Patients with 2 or more exacerbations:
					Baseline vs. 6 months: ▫4±2, p<0.05

Table 1 (*Continued*)

Author(s), year	Study design/ Time of assessment	Population	Exacerbation – definition, treatment & setting	Health status assessment measure	Main results
				SGRQ total score	**Patients with exacerbations:** Baseline: 45±18 vs. 6 months: ¤2±1, p>0.05 **Patients with 2 or more exacerbations:** Baseline vs. 6 months: ¤6±2, p<0.05
				CRQ fatigue score	**Patients with exacerbations:** Baseline: 19±5 vs. 6 months: ¤0.4±0.2/question, p<0.05 **Patients with 2 or more exacerbations:** Baseline vs. 6 months: ¤0.5±0.2/question, p<0.05
				CRQ emotion score	**Patients with exacerbations:** Baseline: 37±9 vs. 6 months: ¤0.3±0.1/question, p<0.05 **Patients with 2 or more exacerbations:** Baseline vs. 6 months: ¤0.5±0.3/question, p<0.05
				CRQ mastery score	**Patients with exacerbations:** Baseline: 22±4 vs. 6 months: ¤0.4±0.2/question, p<0.05 **Patients with 2 or more exacerbations:** Baseline vs. 6 months: ¤0.6±0.3/question, p<0.05
					Patients with exacerbations: Baseline: 104±20 vs. 6 months: ¤0.3±0.1/question, p<0.05
				CRQ total score	
Trappenburg et al., 2010[36]	**Prospective cohort study** **Time points:** - Baseline - Every week for 6 weeks	**Patients with AECOPD:** n=69; 60% male; 67±10 years; FEV_1 46.0±18.4 %predicted	- Defined as an increase in any two major symptoms (dyspnoea, sputum purulence, sputum volume), or increase in one major and the presence of at least one minor symptom for at least two consecutive days - Increase in inhaled medication, corticosteroids or antibiotics - Home or hospital	CCQ total score	Mean changes in score **Stable:** -0.0 (95%CI -0.1 to 0.0) vs. **AECOPD onset:** 0.3 (95%CI 0.1 to 0.4), p<0.001 **Stable:** -0.0 (95%CI -0.1 to 0.0) vs. **Post-AECOPD:** -0.3 (95%CI -0.4 to -0.0), p=0.001
				CCQ symptoms score	**AECOPD onset:** 0.2 (95%CI 0.0 to 0.4)
				CCQ functional state score	**AECOPD onset:** 0.2 (95%CI 0.0 to 0.4)
				CCQ mental state score	**AECOPD onset:** 0.3 (95%CI 0.1 to 0.5)
Ferrari et al., 2011[29]	**Observational longitudinal study** **Time points:** - Baseline - After 3 years	**Total sample:** n=95; 66% male; 64±9 years; FEV_1 59.3±23.2 %predicted; BMI 25.9±5.8 kg/m^2 **Patients that suffered at least one exacerbation:** 72 (75.8%)	- Defined as an increase in dyspnoea, sputum purulence, and increased sputum volume - Antibiotics or systemic steroids or both - Home or hospital	6MWD (m)	Baseline: 438±86 vs. 3 years: 412±100, p=0.001
				SGRQ activity score	Baseline: 52±21 vs. 3 years: 60±22, p<0.001
				SGRQ total score	Baseline: 42±19 vs. 3 years: 44±19, p=0.041 Number of AECOPD during the 3 years included in the multiple regression model to predict SGRQ total score: 1.3 (95%CI: 0.1 to 2.5), p=0.031
Ehsan et al., 2013[42]	**Observational longitudinal study** **Time points:** - Baseline - Every month up to 4 weeks after an AECOPD	**Total sample:** n=17; 53% male; 63±12 years; FEV_1 52.0±20.0 %predicted; BMI 25.0±5.0 kg/m^2 **AECOPD leading to hospital admission:** n=2	- Recorded in a diary - Defined as an increase greater than 9 points sustained for 3 days or 12 points sustained for 2 days, from baseline score, in the 14-item EXACT; or clinically reported - Home or hospital	PAL (minutes per day in higher level activities, i.e., >3000VMU)	Stable: 157±14 vs. AECOPD 131±13, 26 (17%) p<0.0001
Alahmari et al., 2014[25]	**Observational prospective study** **Time points:** - Baseline: starting 2 weeks before the onset of an AECOPD - During AECOPD: starting at the onset - Recovery: 3 day moving average equal or better than baseline	**Total sample:** n=73; 70% male; 71±9 years; FEV_1 52.9±16.5 %predicted; BMI 26.8±5.6 kg/m^2 **Subgroups:** **Infrequent exacerbators** (0-1 exacerbations in the preceding year): n=33 **Frequent exacerbators** (≥2 exacerbations in the preceding year): n=40 **AECOPD management:** **Antibiotics:** n=11 **Oral corticosteroids:** n=7 **Antibiotics and oral corticosteroids:** n=39 **Untreated:** n=22	- Recorded in a diary - Defined as an increase in respiratory symptoms for 2 consecutive days, with at least one major symptom (i.e., dyspnoea, sputum purulence or sputum volume) plus either another major or a minor symptom (i.e., wheeze, cold, sore throat, and cough) - Antibiotics, oral corticosteroids or both - Home	Daily step-count (steps/day) Time outdoors (hours/day) Days on which patients went outdoors (%) Daily step-count (steps/day)	**Total sample** (stable vs. AECOPD, change from baseline, p-value): 4154±2586 vs. 3673±2258, ¤480±1408, p=0.045 Days to return to baseline levels: 4 [1; 8] 3.4±1.8 vs. 3.2±1.8, ¤0.1±1.1, p=0.51 Days to return to baseline levels: 1 [0; 5] 84.4±24.2 vs. 79.6±26.1, ¤4.8±18, p=0.13 **Infrequent vs. frequent exacerbators**: -338 (95%CI: -504 to -170) vs. -708 (95%CI: -867 to -549), p=0.002
Liang et al., 2014[31]	**Prospective cohort study**	**Total sample:** n=450; 69% male;	- Defined either by a worsening of at least one of three key symptoms	SGRQ symptoms score	Baseline: 61±19 vs. 1 year: 55±20, p<0.001

Table 1 (*Continued*)

Author(s), year	Study design/ Time of assessment	Population	Exacerbation – definition, treatment & setting	Health status assessment measure	Main results
	Time points: - Baseline - 1 year follow-up	65±11 years; FEV_1 48.3±15.8 %predicted; BMI 24.0±4.2 kg/m^2 **No of patients with AECOPD:** 0: n=161 1: n=38 2: n=43 ≥3: n=208	(increased sputum amount, changed sputum colour or purulence, and increased dyspnoea), for at least 48h; or by a worsening of at least one key symptom plus a change in at least one of three medications (antibiotics, corticosteroid, and bronchodilator) - Antibiotics and/or corticosteroid and/or bronchodilator	SGRQ activity score SGRQ impact score SGRQ total score	Baseline vs. 1 year: p=0.914 Baseline: 35±22 vs. 1 year: 30±22, p<0.001 Baseline: 46±19 vs. 1 year: 42.±19, p<0.001 **Influence of AECOPD in SGRQ change at 1 year** (compared to no AECOPD): p<0.001 1 AECOPD: OR 0.9 (95%CI 0.3 to 2.5), p=0.865 2 AECOPD: OR 0.9 (95%CI 0.4 to 2.4), p=0.896 ≥3 AECOPD: OR 2.9 (95%CI 0.7 to 4.8), p<0.001
Dreyse et a., 2015[28]	**Observational prospective study** **Time points:** - Baseline - Every 6 months until 2 years follow-up	**Total sample:** n=100; 58% male; 69±8 years; FEV_1 52.6±20.6 %predicted; BMI 26.6±3.7 kg/m^2 **Subgroups:** **Infrequent exacerbators** (<2 exacerbations/year): n=51 **Frequent exacerbators** (≥2 exacerbations/year): n=49 **AECOPD leading to hospital admission:** 4%	- Defined as a sustained worsening of the patient's condition from the stable state and beyond normal day-to-day variation, that has an acute onset and necessitates a change in regular medication - Antibiotics or systemic corticosteroids or both - Home or hospital	6MWD (m) CRQ score mMRC grade SGRQ score	6MWD and CRQ are lower in frequent exacerbators without differences across time mMRC and SGRQ are higher in frequent exacerbators without differences across time

Alahmari et al., 2016[24]	**Observational prospective study**
	
	Time points:
	- Baseline
	- At exacerbation (0 day)
	- 3 and 7 days post exacerbation
		Total sample:
		n=78
		
		Protocol 1 (PAL + 6MWD):
		n=50; 72% male;
		73±8 years;
		FEV_1 50.7±15.1 %predicted; BMI 26.6±5.6 kg/m^2
		
		Protocol 2 (QMVC):
		n=47; 60% male;
		72±8 years;
		FEV_1 50.1±17.2 %predicted; BMI 25.9±5.6 kg/m^2
		
		Subgroups:
		Infrequent exacerbators (0-1 exacerbations in the preceding year)
		Frequent exacerbators (≥2 exacerbations in the preceding year)
		
		AECOPD management:
		Antibiotics: n=18
		Oral corticosteroids: n=10
		Antibiotics and oral corticosteroids: n=68
		Increased inhaled corticosteroids: n=1
			- Recorded in a diary
			- Defined as an increase in respiratory symptoms for 2 consecutive days, with at least one major symptom (i.e., dyspnoea, sputum purulence or sputum volume) plus either another major or a minor symptom (i.e., wheeze, cold, sore throat, and cough)
			- Antibiotics, oral corticosteroids or both, increase in inhaled corticosteroids
			- Home
				6MWD (m)
				
				QMVC (kg)
				
				Functional Assessment of Chronic Illness Therapy-Fatigue score
				
				Time spent in light activities (hours/day)
					Total sample - protocol 1:
					Baseline: 422 [337; 500] vs. day 3: 373 [265; 450], ¤49 (13.1%), p=0.001
					Baseline: 422 [337; 550] vs. day 7: 415 [290; 490], ¤7 (1.7%), p=0.103
					Day 3: 373 [265; 450] vs. day 7: 415 [290; 490], p<0.001
					GOLD stage 1-2 vs. 3-4 (change from baseline to onset of AECOPD):
					¤24±14 vs. ¤81±22, p=0.034
					
					Total sample - protocol 2:
					Baseline: 33±3 vs. day 3: 30±3, ¤3 (8.9%), p=0.026
					Baseline: 33±3 vs. day 7: 29±3, ¤4 (10.7%), p=0.019
					Day 3: 30±3 vs. day 7: 29±3
					Total sample:
					Baseline: 36±2 vs. day 0: 31±2, ¤5 (13.8%), p<0.001
					
					Baseline: 36.0±1.5 vs. day 0: 31.0±1.7, ¤5, p<0.001
					Baseline: 36.0±1.5 vs. day 3: 35.0±1.5, ¤2 (5.4%), p=0.037
					
					Total sample - protocol 1:
					Week 1: 2.2±0.2 vs. week 2: 2.0±0.2, p=0.009
					Infrequent vs. frequent exacerbators:
					¤0.1±0.1 vs. ¤0.4±0.1, p=0.048

Rubinsztajn et al., 2016[44]	**Observational prospective study** **Time points:** - Baseline - After 12 months - After 24 months	**Total sample:** n=445; 66±9 years; FEV_1 50.2±15.8 %predicted; BMI 26.6±5.6 kg/m^2 **Completer after 24 months:** n=261 **Subgroups:** **0-1 exacerbations/year:** n=190 **≥2 exacerbations/year:** n=71	Self-reported and recorded in a diary	mMRC grade SGRQ symptoms score SGRQ activity score SGRQ impact score	**Total sample:** Baseline: 2.1±1.1 vs. 12 months: 2.0±1.0 vs. 24 months: 2.1±1.0, p>0.05 **Total sample:** Baseline: 56±22 vs. 12 months: 59±21 vs. 24 months: 58±22, p>0.05 **Patients with 0-1 vs. ≥2 exacerbations/year:** 0-1: 49±20 vs. ≥2: 61±25, p<0.001 **Total sample:** Baseline: 66±2 vs. 12 months: 62 ±3 vs. 24 months: 601±20, p>0.05 **Patients with 0-1 vs. ≥2 exacerbations/year:** 0-1: 62±21 vs. ≥2: 76±17, p<0.001 **Total sample:** Baseline: 41±20 vs. 12 months: 40±21 vs. 24 months: 40±19, p>0.05 **Patients with 0-1 vs. ≥2 exacerbations/year:** 0-1: 36±18 vs. ≥2: 53±17, p<0.001

Table 1 (*Continued*)

Author(s), year	Study design/ Time of assessment	Population	Exacerbation – definition, treatment & setting	Health status assessment measure	Main results
					Total sample: Baseline: 51±18 vs. 12 months: 50±19 vs. 24 months: 49±17, p>0.05 **Patients with 0-1 vs. ≥2 exacerbations/year:** 0-1: 46±19 vs. ≥2: 62±14, p<0.001
Kardos et al., 2017[38]	**Observational prospective study** **Time points:** - Baseline - 1 year follow-up - 2 years follow-up	**Total sample:** n=3137; 59% male; 66±10 years; FEV_1 62.9±24.4 %predicted; BMI 27.3±5.6 kg/m^2 **Patients with AECOPD:** **1 Year:** 26.2%; AECOPD rate 0.4 **2 Year:** 23.2%; AECOPD rate 0.3 **Patients admitted to the hospital for AECOPD: 1 Year 1:** n=111 (3.5%) **Year 2:** n=108 (3.4%)	- Defined by prescription of oral steroids and/or antibiotics or hospitalization - Oral steroids and/or antibiotics - Home or hospital	SGRQ total score CAT total score	Baseline: 20±8 vs. 1year: ▫2±6 vs 2 years: ▫2±7 **Improvement ≥MCID, number (%) of patients:** 1 year = 1554 (49.5%) patients 2 years = 1701 (54.2%) patients **Worsening ≥MCID, number (%) of patients:** 1 year = 918 (29.3%) patients 2 years = 710 (22.6%) patients AECOPD rate was lower in patients with a sustained improvement than in those with a sustained worsening: 0.3 (95%CI 0.3 to 0.4) vs. 0.5 (95%CI 0.4 to 0.6)
Yohannes et al., 2017[41]	**Observational prospective study** **Time points:** - Baseline - 1 year follow-up - 2 years follow-up - 3 years follow-up	**Total sample:** n=2059; 64% male; 63±7 years; FEV_1 48.0±15.6 %predicted; BMI 26.6±5.7 kg/m^2	- Defined as events that led a care provider to prescribe antibiotics or corticosteroids (or both) or that led to hospitalization - Antibiotic or corticosteroid or both - Home or hospital	Centre for epidemiologic studies depression scale	**No exacerbations in the first year:** Baseline vs. 3 years follow-up: 0.7 (95%CI: -0.1 to -1.4) **1 exacerbation in the first year:** Baseline vs. 3 years follow-up: 2.1 (95%CI: 1.2 to -3.0) **2 exacerbations in the first year:** Baseline vs. 3 years follow-up: 2.8 (95%CI: 1.7 to 3.9) **3+ exacerbations in the first year:** Baseline vs. 3 years follow-up: 3.7 (95%CI: 2.5 to 4.8)
Rodrigues et al., 2019[35]	**Observational prospective study** **Time points:** - Baseline - After 1 year - After 2 years - After 3 years - After 6 years	**Total sample:** n=61; 74% male; 64±7 years; FEV_1 85.0±16.0 %predicted; BMI 27.0±4.0 kg/m^2 **Completers after 6 years:** n=42 **Patients that suffered ≥1 AECOPD:** n=25	Defined as a variation on respiratory symptoms which required a change in medication or hospitalization	CCQ total score CAT total score SF-36 physical component score SF-36 mental component score EQ-5D index score EQ-5D visual analog scale score	Yearly change: 0.1 (0.0), p<0.05 **Exacerbators vs. non-exacerbators:** Yearly change: 0.1 (0.0) vs. 0.0 (0.0), p=0.63 Yearly change: 0.3 (0.2), p>0.05 **Exacerbators vs. non-exacerbators:** Yearly change: 0.9 (0.2) vs. -0.3 (0.3), p<0.01 Yearly change: -1.0 (0.4), p<0.05 **Exacerbators vs. non-exacerbators:** Yearly change: -1.5 (0.5) vs. -0.5 (0.5), p=0.16 Yearly change: -0.5 (0.4), p>0.05 **Exacerbators vs. non-exacerbators:** Yearly change: -1.2 (0.5) vs. 0.0 (0.5), p=0.16 Yearly change: 0.0 (0.0), p<0.05 **Exacerbators vs. non-exacerbators:** Yearly change: 0.0 (0.0) vs. 0.0 (0.0), p=0.66 Yearly change: -0.6 (0.3), p<0.05 **Exacerbators vs. non-exacerbators:** Yearly change: -0.8 (0.5) vs. -0.4 (0.4), p=0.48
Sievi et al., 2019[40]	**Observational prospective study** **Time points:** - Baseline - Once per year until up to 7 years follow-up	**Total sample:** n=181; 65% male; 64 [59; 69] years; FEV_1 46.0 [33.0; 65.0] %predicted; BMI 25.8 [22.6; 28.3] kg/m^2 **Subgroups:** **Infrequent exacerbators** (0-1 exacerbations/ year) **Frequent exacerbators** (≥2 exacerbations/year) **AECOPD leading to hospital admission:** n=55	- Defined as an event that led to prescription of antibiotics and/or corticosteroids - Antibiotics and/or corticosteroids - Home or hospital	Daily step-count (steps/day)	**Total sample:** Annual decline: -479 (95%CI: -634 to -324), p<0.001 **Frequent vs Infrequent exacerbators:** Annual decline: -137 (95%CI: -750 to 473), p=0.660
Esteban et al., 2020[45]	**Observational prospective study** **Time points:** - Baseline - After 1 year - After 2 years - After 5 years	**Total sample that completed 5 years:** n=324; 95% male; 66±8 years; FEV_1 54.3±14.8 %predicted; BMI 27.6±4.8 kg/m^2 **No of patients with hospitalization for AECOPD:** 0: n=234	Data on hospitalization for AECOPD was retrieved from the personal electronic clinical record of each patient at every visit - Hospital	SGRQ score SGRQ symptoms score	Previous hospitalizations for AECOPD were related to 5 to 45% poorer SGRQ scores **Influence of hospitalizations for AECOPD in SGRQ annual change** (compared to no AECOPD): 1 AECOPD: 0.2±0.1, p<0.001, OR 1.2 2 AECOPD: 0.3±0.1, p<0.001, OR 1.3 >2 AECOPD: 0.2±0.1, p=0.003, OR 1.2

Table 1 (*Continued*)

Author(s), year	Study design/ Time of assessment	Population	Exacerbation – definition, treatment & setting	Health status assessment measure	Main results
		1: n=40 2: n=23 3: n=14 >3: n=13		SGRQ activity score	1 AECOPD: 0.1±0.0, p=0.021, OR 1.1 2 AECOPD: 0.3±0.1, p<0.001, OR 1.3 3 AECOPD: 0.3±0.1, p=0.004, OR 1.3 >3 AECOPD: 0.3±0.1, p<0.001, OR 1.4
				SGRQ impact score	1 AECOPD: 0.0±0.0, p=0.294, OR 1.0 2 AECOPD: 0.3±0.1, p<0.001, OR 1.2 >2 AECOPD: 0.2±0.1, p=0.004, OR 1.2

Kardos et al., 2020[39]	**Observational prospective study**
	
	Time points:
	- Baseline
	- 1 year follow-up
	- 2 years follow-up
		Total sample:
		n=6075; 59% male;
		66±10 years;
		FEV_1 61.6±20.3 %predicted
		
		Patients with frequent (≥2) or severe (≥1 hospitalization) AECOPD:
		n=285; 62% male;
		67±10 years;
		FEV_1 47.3±17.0 %predicted
		
		No of patients with AECOPD: n=1697
			- Defined by prescription of oral corticosteroids and/or antibiotics or hospitalization
			- Antibiotic and/or corticosteroid
			- Home or hospital
				CAT total score	**Patients with frequent or severe AECOPD:**
					Baseline vs. 1 year vs. 2 year: no overall change
					Worsening ≥MCID: 1 year = 37.5%, 2 year = 37.2%
					No change: 1 year = 23.2%, 2 year = 22.5%
					Improvement ≥MCID: 1 year = 39.3%, 2 year = 40.4%
					Remaining patients:
					Baseline vs. 1 year vs. 2 year: clinically relevant improvements
					Worsening ≥MCID: 1 year = 19.1%, 2 year = 20.5%
					No change: 1 year = 26.0%, 2 year = 20.5%
					Improvement ≥MCID: 1 year = 54.9%, 2 year = 59.0%
					Patients with frequent or severe AECOPD vs. Remaining patients: p<0.001

Zimmermann et al., 2020[37]	**Observational prospective study** **Time points:** - Baseline - Every day for 8-9 months	**Total sample:** n=15; 73% male; 69±10 years; FEV_1 39.0±10.0 %predicted; BMI 22.4±4.8 kg/m^2 **Patients with AECOPD:** n=13 **AECOPD management:** **Antibiotics:** n=17 **Oral corticosteroids:** n=16 **AECOPD leading to hospital admission:** n=4	- Defined by an increase in respiratory symptoms requiring oral corticosteroids and/or antibiotics, with or without medical review and/or hospitalization - Antibiotic and/or corticosteroid - Home or hospital	CAT total score	Mean change from baseline **1 day before AECOPD:** 1±0, p=0.020 **AECOPD onset:** 1±0, p<0.001 **Up to 7-days after AECOPD onset:** p<0.001

Data are presented as mean±standard deviation, median [quartile 1; quartile 3] or mean (standard error), unless otherwise stated.
6MWD, 6-min walk distance; 95%CI, 95% confidence interval; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; CAT, COPD assessment test; CCQ, Clinical COPD questionnaire; COPD, chronic obstructive pulmonary disease; CRQ, chronic respiratory disease questionnaire; EQ-5D, EuroQoL 5-dimension questionnaire; EXACT, exacerbations of chronic pulmonary disease tool; FEV_1, forced expiratory volume in 1 s; GOLD, global initiative for chronic obstructive lung disease; MCID, minimal clinically important difference; mMRC, modified Medical Research Council dyspnoea questionnaire; OR, odds ratio; PAL, physical activity level; QMVC, quadriceps maximum voluntary contraction; SF-12, 12-item short form health survey; SF-36, 36-item short form health survey; SGRQ, Saint George's respiratory questionnaire; VMU, vector magnitude units.

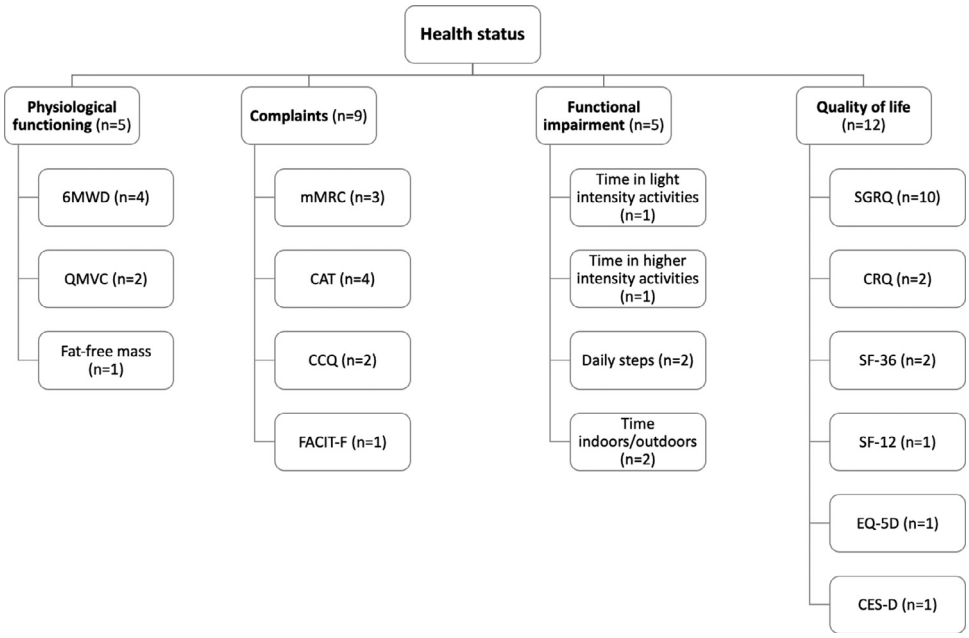

Figure 2 Schematic overview of the outcome measures used to assess each health status subdomain. *, activities >3000 vector magnitude units; 6MWD, six-minute walking distance; CAT, COPD assessment test; CCQ, clinical COPD questionnaire; CES-D, centre for epidemiological studies depression scale; CRQ, chronic respiratory disease questionnaire; EQ-5D, EuroQoL 5-dimension questionnaire; FACIT-F, functional assessment of chronic illness therapy-fatigue; mMRC, modified Medical Research Council dyspnoea questionnaire; QMVC, quadriceps maximum voluntary contraction; SF-12, 12-item short form health survey; SF-36, 36-item short form health survey; SGRQ, Saint George's respiratory questionnaire.

to seven days after the onset of the exacerbation.[37] Consistently, a faster deterioration in the CAT score (yearly change) was found in patients with exacerbations in comparison to non-exacerbators.[35] In addition, patients presenting a sustained worsening on CAT score (i.e., increase ≥2 points) had a higher number of exacerbations.[38,39]

An increase (worsening) in the CCQ total score was found at the onset of an AECOPD, which recovered in the post-AECOPD assessment.[36] This worsening was consistent across all CCQ domains.[36] The CCQ score also deteriorated over time but without differences between exacerbators and non-exacerbators.[35]

A significant reduction (worsening) of 5 points in the FACIT-F score was observed at the onset of an AECOPD, which recovered to a 2 points reduction at day 3 in comparison to stable phase.[24]

Influence of exacerbations on functional impairment

Daily step count was reduced during the first 7 days of an AECOPD compared to a stable week.[25] Further analysis of these data showed that it took a median of 3.5 days return to baseline levels, and patients with the largest falls in daily step count during the exacerbation were the ones taking longer to recover.[25] Conflicting results were found regarding the annual decline, with one study[25] finding a significantly faster decline in frequent exacerbators (i.e., two or more AECOPD per year) in comparison to infrequent exacerbators, and another study[40] finding no differences between the decline of steps in frequent and infrequent exacerbators.

Time spent in activities >3000 VMU was reduced during AECOPD in comparison to the preceding or subsequent weeks.[42] This decline was significant during the first week of exacerbation, with no further decline on the second week, and tended to increase back to baseline levels in the two subsequent weeks.[42] In line with these results, time spent in light activities was higher during the first week post-exacerbation than the second week, with frequent exacerbators (i.e., two or more AECOPD in the preceding year) presenting a more considerable reduction in time spent in light activities from week 1 to week 2 in comparison to infrequent exacerbators.[24]

There was an increase in time spent indoors during exacerbations, which was sustained in the post-exacerbation period (days 1 to 35 after the onset) in comparison to the stable phase.[27] A decrease in outdoors time during AECOPD that continues in the post-exacerbation period was also found, with frequent exacerbators (i.e., at least 2.5 AECOPD per year) presenting a faster annual decline in daily time outdoors than infrequent exacerbators.[27] However, inconsistent results were found as in another study,[25] in patients with a similar severity of AECOPD but better baseline lung function, the fall in time and percentage of days outdoors during exacerbations did not reach statistical significance.

Influence of exacerbations on quality of life

A consistent increase (worsening) in the SGRQ score with exacerbations[27,29,34,43,45] was reported, with frequent exacerbators presenting faster and more pronounced declines in QoL.[28,29,31,33,34,43-45] In a study with a 2-year follow-up,

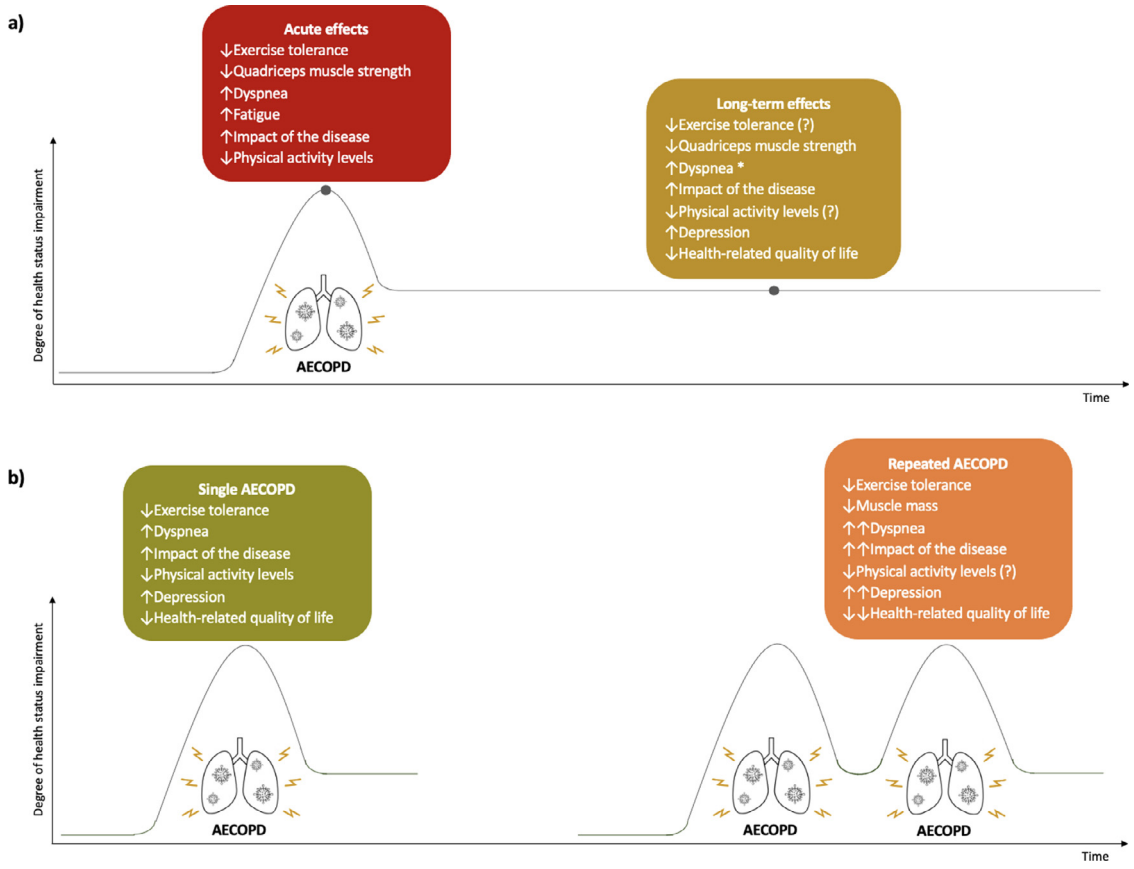

Figure 3 Effects of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) on patients' health status. (**a**) acute and long-term effects of AECOPD on health status. (**b**) effects of single and repeated AECOPD on health status. ↑, increase; ↓, decrease; ↑↑, greater increase than in single AECOPD; ↓↓, greater decrease than in single AECOPD; *, only in repeated AECOPD; (?), conflicting results found.

patients who suffered a single AECOPD improved in SGRQ score by −3.8 points while frequent exacerbators (i.e., two or more AECOPD per year) worsened +2.4 points.[32]

A similar pattern for QoL has also been found in the CRQ, SF-36 and SF-12. Patients with AECOPD presented a decline in CRQ, SF-36 and SF-12 scores, which was more pronounced in frequent exacerbators across all CRQ domains and in the physical component of SF-36 and SF-12.[28,33-35,43] The EQ-5D was found to decline annually in exacerbators and non-exacerbators, similarly.[35]

A strong relationship between the number of AECOPD during the first year of follow-up and the change in depression score (i.e., CES-D) over 3-years has been found, with patients who suffered from more exacerbations presenting the most significant declines.[41]

A summary of the acute and long-term effects of AECOPD and the impact of single and repeated exacerbations on health status can be found in Fig. 3.

Discussion

This scoping review summarized the acute and long-term effects of AECOPD and the impact of repeated exacerbations on the health status of patients with COPD. Acute effects included a worsening of symptoms and impact of the disease, and a reduction of exercise capacity, quadriceps muscle strength and physical activity levels. Long-term negative effects were reported on complaints, quadriceps muscle strength and quality of life. Repeated exacerbations negatively impacted FFM and resulted in further worsening of complaints (i.e., dyspnoea and impact of the disease) and QoL (i.e., health related QoL and depression). The impact of repeated exacerbations on exercise tolerance and physical activity levels is less clear.

Impact of exacerbations on complaints

An AECOPD is defined by an acute worsening of respiratory symptoms and it is usually characterized by increased airway inflammation, mucus production and air trapping.[1] A recent proposal on an updated definition of AECOPD states that these events are characterized by dyspnoea and/or cough and sputum that worsens over up to 14 days, possibly accompanied by tachypnoea and/or tachycardia, and often associated with increased local and systemic inflammation.[46] Not surprisingly, an acute worsening of complaints (i.e., dyspnoea and fatigue) during exacerbations was found.[24,26] During this period, the worsening of airway obstruction results in increased work of breathing, dynamic

hyperinflation and hypoxaemia, leading to symptoms of dyspnoea and fatigue.[47-49] These symptoms usually recover following the exacerbation,[47,49] yet persistent (up to 2 years) and higher increases in dyspnoea levels were found in frequent exacerbators,[26,28] emphasizing the high impact of these events on patients' life. In fact, the impact of the disease, as assessed by the CAT, has been found higher during either single or repeated exacerbations and on the long-term,[35,37-39] and associated to the worsening of lung function, systemic inflammation and functional status.[50,51]

Impact of exacerbations on physiological function

Exacerbations result in physiological impairment. There is an immediate reduction in QMVC three and seven days after the onset of exacerbation symptoms.[24] The increased systemic inflammation appears to contribute to this, as QMVC has been correlated with systemic levels of IGF-I and CXCL8 in AECOPD[52]; and pro-inflammatory cytokines activate pathways leading to atrophy and inflammation-induced muscle dysfunction.[53,54] The reduced physical activity levels and medication used (e.g., corticosteroids) during this period seem to also play a role in QMVC reduction.[53,55] Moreover, the increased cost of ventilation during exacerbations increases resting energy expenditure, with negative consequences on body weight and muscle mass,[55] highlighting a potential role of nutritional support in these patients.[56] Over the 1-year follow-up, one study found that frequent exacerbations were associated with FFM decline,[30] possibly indicating a cumulative effect of AECOPD on muscle mass depletion – the main constituent of FFM.[57] Furthermore, the same study found that the decline in FFM was also associated with the use of maintenance oral corticosteroids,[30] which has been described in steroid-induced myopathy.[58,59] Given the known relationship between reduced muscle mass and muscle strength impairment,[58,60,61] one could expect that frequent AECOPD would also be associated with QMVC decline. Nevertheless, no association was found,[30] showing that muscle mass and muscle strength are not always reduced in the same proportion.[62] Further research is therefore needed to enhance our understanding on the impact of AECOPD on muscle dysfunction.

Exacerbations (single or repeated) also result in an acute decrease in functional exercise tolerance, which was expected since the breathing load is acutely increased and patients experience breathlessness even when performing low-intensity activities.[47,63] Moreover, fatigue and quadriceps muscle weakness also play a role as limiting factors of exercise performance.[64] Surprisingly, although it is often assumed that AECOPD leads to a permanent impairment on exercise performance, it is still unclear if the decrease in exercise tolerance recovers after a few days,[24] alongside with symptomatic recovery,[6,47,65] or whether it is sustained on a long-term, with studies[26,28] even suggesting a sustained impairment 2 years after the exacerbation. It is known that (i) different types of AECOPD result in distinct clinical findings, prognosis and responses to treatment[66,67]; (ii) hospitalized patients with AECOPD are the ones presenting worse prognosis[68]; and (iii) the use of antibiotics and corticosteroids presents inconsistent benefits depending on the clinical setting and severity of AECOPD.[68] Since in one study[24] only community managed AECOPD were included and patients were mostly treated with a combination of antibiotics and oral corticosteroids, while the other two studies[26,28] involved a percentage of AECOPD that resulted in hospital admission and did not report the exact number of patients treated with each medications, it is likely that these factors may have contributed to the disparity of the findings. Moreover, the six-minute walk test presents a significant learning effect and evidence shows the necessity of conducting the test twice in AECOPD.[69,70] Therefore, differences in the methodology regarding the frequency and timing of assessments and the number of tests performed, might have also contributed to the inconsistency in the results. Future studies with robust methodologies are needed to clarify the long-term effects of AECOPD on exercise tolerance.

Impact of exacerbations on functional impairment

Exacerbations lead to functional impairment observed by reduced physical activity levels,[24,25,27,42] which seems to be more accentuated in repeated AECOPD. An acute decrease in physical activity levels is associated with the severe inactivity and low amount of time spent in weight-bearing activities during hospitalization for AECOPD, general immobility and tendency to become housebound.[16,71,72] The worsening of symptoms - particularly dyspnoea at rest - hypoxaemia, muscle weakness and loss of exercise capacity might also reduce physical activity levels.[71,73,74] In turn, reduced physical activity levels lead to further skeletal muscle deconditioning and reduction of exercise capacity, bringing patients into a vicious cycle of symptoms and inactivity.[74-77] It has been hypothesized that this vicious cycle could explain the long-term effect of AECOPD on physical activity levels.[74] Nevertheless, conflicting evidence was found,[74,78] with studies showing that physical activity levels can either recover in a few days/weeks or may not return to pre-exacerbation levels, especially in the case of frequent exacerbators.[25,27,40,42,79] The differences in the time-points of assessment and outcome measures used (e.g., objective vs. subjective measures) might have contributed to the heterogeneity in the results found.[80] Further studies, following the international recommendations on how to measure physical activity in patients with COPD,[81] are needed to better understand the impact of AECOPD on physical activity over time.

Impact of exacerbations on quality of life

The effects of exacerbations on QoL were the most studied. A long-term decline (up to 8 years) in QoL due to AECOPD was found,[27,29,33,34,43,45] which was more pronounced in frequent exacerbators,[28,29,31,33-35,43-45] suggesting a cumulative effect of repeated exacerbations in this domain. It is known that AECOPD have a huge impact on patients' everyday activities (e.g., walking, sleeping, work) and, consequently, they feel unable to maintain their lifestyle and make plans.[82-84] Given these reasons and all the consequences of AECOPD mentioned above on complaints, physiological functioning and functional impairment, the decline on QoL was expected.

Implications of the findings for research

In sum, heterogeneity amongst the presentation and trajectory of recovery of exacerbations was found, and there is at least a subset of patients presenting a sustained worsening of health status after (repeated) exacerbations. This heterogeneity might have been influenced by the variety of AECOPD definitions found, as it is known that even small changes in the definition used affect the incidence rate, type and classification of exacerbations, with event-based AECOPD being usually considerably less identified and in specific groups of patients.[23,85,86] The underlying cause of the AECOPD (e.g., viral exacerbations are known for being more severe and taking a longer recovery time),[87] its severity, treatment setting (e.g., hospital vs. home), the standard of care provided (i.e., pharmacological treatment), presence of comorbidities, socioeconomic status and/or knowledge about the disease, might have also contributed to the heterogeneity found.[67,87-93] A more accurate definition of AECOPD and understanding of its aetiology and diagnosis is, therefore, critical to better recognise exacerbations' clinical impacts and improve treatment strategies. Despite this heterogeneity, AECOPD are usually treated uniformly (i.e., bronchodilators, systemic corticosteroids and/or antibiotics) without considering the different underlying outcomes and treatment needs.[94] Since one size does not fit all, comprehensive health status assessments that allow the identification of distinct treatable traits amongst individuals are crucial to personalize treatments, contributing to improved AECOPD recovery and prevention.[95] In this review, we have found that no study assessed all the domains that compose health status, thus future studies should explore the effects of AECOPD on patients' health status using comprehensive measures. Moreover, early pulmonary rehabilitation is a safe intervention for the management of patients with AECOPD that has been shown to improve QoL, and reduce the length of hospitalization, hospital readmissions and mortality in these patients, while targeting several treatable traits (e.g., physical activity, exercise capacity, muscle weakness, dyspnoea) that are associated with exacerbation recurrence.[4,96-98] Evidence suggests that pulmonary rehabilitation may be offered to patients with AECOPD to recover their pre-exacerbation health status.[99] Pulmonary rehabilitation seems particularly important to those presenting a late recovery or who never recover to pre-exacerbation levels.[90] Future studies should focus on personalizing pulmonary rehabilitation programs to target the different identified treatable traits during AECOPD.[94,95]

Methodological considerations

This scoping review has some strengths and limitations that need to be acknowledged. To our knowledge, this is the first review of the impact of AECOPD in the different sub-domains of health status in patients with COPD. A thorough search and screening were performed, and rigorous methodological and reporting frameworks (JBI and PRISMA-ScR) were followed. Nevertheless, we did not publish a protocol of the study before conducting this scoping review, thus the methods were not peer-reviewed prior to our search. Several concepts have been used to define health status and numerous tools were designed to assess the different aspects of this comprehensive measure. To ensure clarity, this work followed a previously published assessment framework for health status in patients with COPD.[18] Additionally, the summary of the impacts of AECOPD on the different domains of health status was challenging due to the diversity in exacerbation definition and diagnosis, timepoints of assessment, outcome measures used, and lack of clarity of some results found. Most studies included a population combining different AECOPD severities, treatments and/or treatment settings, which prevented the presentation of these results separately. All these aspects have hampered results synthesis. Lastly, since most of the studies included were focused on moderate to severe AECOPD, the findings of this review cannot be translated to mild AECOPD.

Conclusion

Exacerbations of COPD result in both acute and long-term impairments in all health status domains. Acutely, there is a worsening of symptoms and impact of the disease, and a reduction in exercise capacity, quadriceps muscle strength and physical activity levels. Long-term negative effects are noticed on complaints, quadriceps muscle strength and quality of life. Repeated exacerbations result in a reduction of FFM and further worsening of complaints and QoL. However, the impact of repeated exacerbations on exercise tolerance and physical activity levels, and the trajectory of patients' recovery, is less clear due to the lack of studies and conflicting evidence found. Future research focused on these aspects is therefore warranted.

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Conflicts of Interest

None.

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LETTER TO THE EDITOR

Long-term sequelae of TB and COVID-19 co-infection: Prospective cohort evaluation after 1 year

Dear Editor,

The coronavirus disease 2019 (COVID-19) pandemic has shown negative effects on tuberculosis (TB) control. Disruptions to the access to TB services have been reported. In fact, the World Health Organization data show that the pandemic has had a substantial effect on TB trends, with an overall decrease in the number of new TB cases, and an increase in the number of deaths between 2019 and 2020.[1]

TB and COVID-19 coinfection may be associated with more severe clinical conditions than either disease on its own, leading to greater morbimortality during the acute phase.[2–4] Additionally, post-TB lung disease (PTLD) and post-COVID-19 disorders account for substantial consequences on the health of survivors and often require rehabilitation.[5,6] Pulmonary impairment after TB is identified in more than 50% of patients, and post-COVID-19 sequelae may affect up to 80% of COVID-19 survivors.[5,7] However, the sequelae of TB and COVID-19 co-infected individuals are largely unknown, and there are no studies so far that have evaluated long-term lung function in these patients.

We conducted a prospective cohort study at Hospital de Clínicas de Porto Alegre, Brazil in collaboration with Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Maugeri, Tradate, Italy. The study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre (number 200188). All participants gave their written consent to participation. The study objectives were to assess pulmonary functions tests (PFT, including 6-minute walk test- 6MWT) and quality of life (QoL) in patients with COVID-19 and TB, one year after COVID-19, and to evaluate factors associated with mortality.

Patients $\geq$18 years of age hospitalized with a concomitant diagnosis of COVID-19 and TB (active or sequelae) were evaluated one year after discharge. Patients underwent PFT: spirometry, plethysmography, d*iffusing capacity* of the lung for *carbon monoxide (DLCO)*, and 6MWT. To assess QoL, the EuroQol-5D scale (EQ-5D) was used. In addition, patients were asked about persistent post-COVID-19 symptoms. Categorical comparisons were performed by chi-square test using Yates's correction if indicated, or Fisher's exact test. Continuous variables were compared using the *t*-test or Wilcoxon test. A two-sided *p* value <0.05 was considered significant.

We included 106 patients with COVID-19 and active TB (n = 24) or TB sequelae (n = 82), from March 2020 to December 2022. Forty (37.7%) patients died from COVID-19 during the study period. Of the 66 patients who survived COVID-19, 23 underwent PFT (and 6MWT), and were assessed for QoL and persistence of symptoms. Table 1 shows the cohort characteristics. The most common post-COVID-19 ventilatory impairment was restrictive. A large percentage of patients had impaired QoL in the usual activities, anxiety/depression, mobility and pain/discomfort dimensions. All patients reported at least one persistent post-COVID-19 symptom. Active TB patients were younger and had a higher prevalence of current smoking.

Ten patients had PFT pre- and post-COVID-19. There was a reduction in all lung function parameters, but not statistically significant ($p > 0.05$ for all comparisons; data not shown). The 6MWT final test was in average 39.4 m lower than the initial test (although not significant, patients lost about 10% of the performance).

Table 2 shows the factors associated with mortality. TB sequelae patients who were older, needed supplemental oxygen and invasive ventilation, and those who had lower total lung capacity (TLC) (%) and DLCO (%) had higher mortality. Active TB patients who needed invasive ventilation had higher mortality.

In this prospective cohort study, we demonstrated that, one year after COVID-19, patients with TB and COVID-19 had abnormal PFT, reduced 6MWT performances, impaired QoL, and persistent symptoms. Furthermore, the mortality of these patients was high (almost 40%).

In the largest cohort of patients with TB and COVID-19,[2] mortality was 11%, and the factors associated with death were older age, male gender and invasive ventilation. In a previous study,[3] the case fatality rate was 12.3% and deaths were mostly in patients >60 years, with at least one comorbidity. Older age and invasive ventilation were also risk factors for mortality in the present study. However, we identified a higher mortality, probably because we included only hospitalized patients.

Patients with TB sequelae and COVID-19 who died had lower TLC (%) and DLCO (%) pre-COVID-19, emphasizing the mortality related to PTLD. In fact, PTLD patients have twice the risk of spirometry abnormalities than the general

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Table 1 General characteristics of patients.

Demographic data	Active TB (*n* = 24)	TB sequelae (*n* = 82)	*p* value
Age (years)	51.3 ± 16.3	60.3 ± 14.9	0.013
Male sex	15 (62.5)	45 (54.9)	0.668
Smoking status			
Current smoker	9 (37.5)	8 (9.8)	0.005
Former smoker	9 (37.5)	48 (58.5)	
Never smoker	6 (25.0)	26 (31.7)	
Alcohol abuse	7 (29.2)	20 (24.4)	0.837
Intravenous drug user	5 (20.8)	7 (8.5)	0.137
HIV positive	9 (37.5)	15 (18.3)	0.089
TB data			
CXR at TB diagnosis			
Unilateral pulmonary cavitary lesions	1 (4.2)	3 (3.7)	0.999
Bilateral pulmonary cavitary lesions	1 (4.2)	0	0.226
Unilateral pulmonary infiltrates (no cavities)	4 (16.7)	38 (46.3)	0.017
Bilateral pulmonary infiltrates (no cavities)	14 (58.3)	32 (39.0)	0.149
PFT pre-COVID-19 (*n* = 29)			
Post-BD FEV_1 (L)	2.23 ± 0.21	2.13 ± 0.98	0.892
Post-BD FEV_1 (%)	97.0 ± 37.8	71.0 ± 29.5	0.248
Post-BD FVC (L)	2.97 ± 0.64	2.88 ± 0.95	0.902
Post-BD FVC (%)	92.9 ± 32.0	77.1 ± 25.4	0.410
Post-BD FEV_1/FVC	83.6 ± 1.13	72.6 ± 18.2	0.007
TLC (L)	–	4.93 ± 1.52	–
TLC (%)	–	82.8 ± 24.8	–
RV (L)	–	2.17 ± 1.13	–
RV (%)	–	90.6 ± 33.8	–
DLCO (L)	–	4.76 ± 2.61	–
DLCO (%)	–	54.1 ± 25.2	–
6MWT (m)	–	385.3 ± 119.7	–
Desaturation in 6MWT	–	6 (35.3)	–
Ventilatory defect pre-COVID-19			
Obstructive	0	6 (23.1)	
Restrictive	1 (33.3)	10 (38.5)	0.541
Normal	2 (66.7)	10 (38.5)	
COVID-19 data			
CXR at COVID-19 diagnosis			
Unilateral pulmonary cavitary lesions	1 (4.2)	1 (1.2)	0.403
Bilateral pulmonary cavitary lesions	1 (4.2)	0	0.226
Unilateral pulmonary infiltrates (no cavities)	0	9 (11.0)	0.204
Bilateral pulmonary infiltrates (no cavities)	8 (33.3)	27 (32.9)	0.999
CT at COVID-19 diagnosis			
Typical ground glass opacity, unilateral	4 (16.7)	7 (8.5)	0.265
Typical ground glass opacity, bilateral	7 (29.2)	20 (24.4)	0.837
Atypical	12 (50.0)	35 (42.7)	0.688
Supplemental oxygen during COVID-19	16 (66.7)	53 (64.6)	0.999
Type of ventilation used during COVID-19			
Invasive	9 (37.5)	28 (34.1)	0.436
Non-invasive	2 (8.3)	16 (19.5)	
No ventilation	13 (54.2)	38 (46.3)	
COVID-19 outcome			
Discharge	18 (75.0)	48 (58.5)	0.221
Death	6 (25.0)	34 (41.5)	
PFT post-COVID-19 (*n* =23)[a]			
Post-BD FEV_1 (L)	3.10 ± 0.74	2.24 ± 1.09	0.156
Post-BD FEV_1 (%)	83.1 ± 9.1	70.6 ± 30.1	0.149
Post-BD FVC (L)	3.61 ± 0.81	3.02 ± 1.22	0.370
Post-BD FVC (%)	78.6 ± 8.9	76.3 ± 26.8	0.767
Post-BD FEV_1/CVF	85.9 ± 2.3	73.6 ± 15.7	0.004
TLC (L)	4.88 ± 0.35	5.38 ± 1.15	0.410

Table 1 (*Continued*)

Demographic data	Active TB (*n* = 24)	TB sequelae (*n* = 82)	*p* value
TLC (%)	77.8 ± 10.7	93.5 ± 20.3	0.155
RV (L)	1.54 ± 0.41	2.24 ± 0.85	0.133
RV (%)	84.4 ± 30.8	113.9 ± 43.9	0.222
DLCO (L)	5.79 ± 0.57	4.76 ± 2.41	0.175
DLCO (%)	57.5 ± 7.4	54.8 ± 21.4	0.709
6MWT (m)	416.7 ± 77.1	384.2 ± 107.6	0.627
Desaturation in 6MWT	0	6 (35.3)	0.521
Ventilatory defect post-COVID-19			
Obstructive	0	3 (15.8)	
Restrictive	4 (100)	9 (47.4)	0.074
Normal	0	7 (36.8)	
EuroQol-5D mobility			
I have no problems walking	4 (36.4)	16 (59.3)	0.494
I have slight problems walking	2 (18.2)	3 (11.1)	
I have moderate problems walking	4 (36.4)	4 (14.8)	
I have severe problems walking	1 (9.1)	3 (11.1)	
I am unable to walk	0	1 (3.7)	
EuroQol-5D self-care			
I have no problems washing or dressing myself	9 (81.8)	19 (70.4)	0.783
I have slight problems washing or dressing myself	1 (9.1)	2 (7.4)	
I have moderate problems washing or dressing	1 (9.1)	4 (14.8)	
I have severe problems washing or dressing	0	1 (3.7)	
I am unable to wash or dress myself	0	1 (3.7)	
EuroQol-5D usual activities			
I have no problems doing my usual activities	4 (36.4)	15 (55.6)	0.507
I have slight problems doing my usual activities	2 (18.2)	6 (22.2)	
I have moderate problems doing my usual activities	3 (27.3)	3 (11.1)	
I have severe problems doing my usual activities	2 (18.2)	2 (7.4)	
I am unable to do my usual activities	0	1 (3.7)	
EuroQol-5D pain and discomfort			
I have no pain or discomfort	4 (36.4)	16 (59.3)	0.194
I have slight pain or discomfort	5 (45.5)	4 (14.8)	
I have moderate pain or discomfort	0	3 (11.1)	
I have severe pain or discomfort	1 (9.1)	1 (3.7)	
I have extreme pain or discomfort	1 (9.1)	3 (11.1)	
EuroQol-5D anxiety/depression			
I am not anxious or depressed	5 (45.5)	14 (51.9)	0.687
I am slightly anxious or depressed	2 (18.2)	4 (14.8)	
I am moderately anxious or depressed	0	2 (7.4)	
I am severely anxious or depressed	2 (18.2)	2 (7.4)	
I am extremely anxious or depressed	2 (18.2)	5 (18.5)	
EuroQol-5D - your health today	68.5 ± 17.7	66.7 ± 22.3	0.818
Persistent symptoms post-COVID-19 (most common)			
Olfactory disorders	2 (40.0)	11 (52.4)	0.999
Dyspnea	1 (20.0)	10 (47.6)	0.356
Arthralgia	2 (40.0)	7 (33.3)	0.999
Mylagia	0	7 (33.3)	0.278
Fatigue	0	6 (28.6)	0.298

[a] Among the 66 survivors, 21 patients could not undergo PFT due to contraindications: 13 due to active respiratory infection; 3 due to tracheostomy; 3 due to recent myocardial infarction; 1 due to aortic aneurysm and 1 due to a recent surgical procedure in the eye region.

Table 2 Factors associated with mortality in TB-COVID-19 patients.

Demographic data	Active TB		*p* value	TB Sequelae		*p* value
	Survivors (*n* = 18)	Non-survivors[a] (*n* = 6)		Survivors (*n* = 48)	Non-survivors[a] (*n* = 34)	
Age (years)	49.6 ± 13.9	56.3 ± 22.9	0.393	55.1 ± 15.4	67.5 ± 10.9	<0.0001
Male sex	11 (61.1)	4 (66.7)	0.999	24 (50.0)	21 (61.8)	0.407
Smoking status						
Current smoker	8 (44.4)	1 (16.7)	0.230	4 (8.3)	4 (11.8)	0.189
Former smoker	5 (27.8)	4 (66.7)		25 (52.1)	23 (67.6)	
Never smoker	5 (27.8)	1 (16.7)		19 (39.6)	7 (20.6)	
Alcohol abuse	5 (27.8)	2 (33.3)	0.999	12 (25.0)	8 (23.5)	0.999
Intravenous drug user	3 (16.7)	2 (33.3)	0.568	4 (8.3)	3 (8.8)	0.999
HIV positive	7 (38.9)	2 (33.3)	0.999	7 (14.6)	8 (23.5)	0.458
TB data						
PFT pre-COVID-19						
Post-BD FEV_1 (L)	2.23 ± 0.21	–	–	2.29 ± 1.09	1.91 ± 0.84	0.358
Post-BD FEV_1 (%)	97.0 ± 37.8	–	–	75.2 ± 30.8	65.7 ± 28.4	0.436
Post-BD FVC (L)	2.97 ± 0.64	–	–	3.04 ± 0.96	2.69 ± 0.94	0.373
Post-BD FVC (%)	92.9 ± 32.0	–	–	80.9 ± 26.4	72.2 ± 24.4	0.398
Post-BD FEV_1/FVC	83.6 ± 1.1	–	–	75.3 ± 19.6	69.2 ± 16.4	0.418
TLC (L)	–	–	–	5.57 ± 1.49	4.39 ± 1.43	0.179
TLC (%)	–	–	–	99.1 ± 25.1	68.9 ± 14.6	0.020
RV (L)	–	–	–	2.55 ± 1.42	1.84 ± 0.76	0.279
RV (%)	–	–	–	94.4 ± 35.0	86.9 ± 35.5	0.721
DLCO (L)	–	–	–	5.50 ± 3.08	4.12 ± 2.12	0.325
DLCO (%)	–	–	–	68.4 ± 21.5	41.7 ± 22.2	0.035
6MWT (m)	–	–	–	394.1 ± 131.4	377.4 ± 115.8	0.786
Desaturation in 6MWT	–	–	–			
Ventilatory defect post-TB						
Obstructive	–	–	–	4 (28.6)	2 (16.7)	0.148
Restrictive	–	–		3 (21.4)	7 (58.3)	
Normal	2 (66.7)	–		7 (50.0)	3 (25.0)	
COVID-19 data						
CXR at COVID-19 diagnosis						
Unilateral pulmonary cavitary lesions	0	1 (16.7)	0.250	1 (2.1)	0	0.999
Bilateral pulmonary cavitary lesions	0	1 (16.7)	0.250	–	–	–
Unilateral pulmonary infiltrates (no cavities)	–	–	–	5 (10.4)	4 (11.8)	0.999
Bilateral pulmonary infiltrates (no cavities)	4 (22.2)	4 (66.7)	0.129	17 (35.4)	10 (29.4)	0.740
CT at COVID-19 diagnosis						
Typical ground glass opacity, unilateral	4 (22.2)	0	0.539	3 (6.3)	4 (11.8)	0.441
Typical ground glass opacity, bilateral	4 (22.2)	3 (50.0)	0.307	12 (25.0)	8 (23.5)	0.999
Atypical	10 (55.6)	2 (33.3)	0.640	18 (37.5)	17 (50.0)	0.368
Supplemental oxygen during COVID-19	10 (55.6)	6 (100)	0.066	22 (45.8)	31 (91.2)	<0.0001
Type of ventilation used during COVID-19						
Invasive	4 (22.2)	5 (83.3)	0.003	8 (16.7)	20 (58.8)	<0.0001
Non-invasive	1 (5.6)	1 (16.7)		6 (12.5)	10 (29.4)	
No ventilation	13 (72.2)	0		34 (70.8)	4 (11.8)	

Median time do death: Active TB group (13 days [5—27.8 days]) and TB sequelae group (15.5 days [6.8—29.3 days], $p = 0.691$.

[a] Causes of death: Active TB group (3 deaths for COVID-19 and 3 deaths for TB + COVID-19); TB sequelae group (all 34 deaths for COVID-19).

population, and patients surviving COVID-19 may have persistent abnormalities in PFT, such as restrictive ventilatory defects and diffusion impairment.[5] In the present study, a large percentage of patients had restrictive ventilatory pattern, although part of this may be due to sequelae from TB. Although not significant, the loss in 6MWT performances in the final test (about 10%) was relevant.

This study has some limitations. We did not evaluate COVID-19 radiological sequelae, nor pre-COVID-19 QoL. The relatively small sample size of patients with pre- and post-COVID-19 PFT (several patients had severe clinical conditions contraindicating PFT) may have prevented us from finding statistically significant differences.

In conclusion, this study describes the combination of PTLD and post-COVID-19 sequelae, evaluated through PFT (including 6MWT) and QoL. Further studies should evaluate comprehensive strategies to assessment/follow-up and determine the need for pulmonary rehabilitation to improve lung health of patients with these two diseases overlapping.

Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

Will smoking on beaches become a thing of the past? Bibione: The first smoke-free beach in Italy

Dear Editor,

Tobacco consumption has been consistently declared as the main preventable cause of morbidity and mortality in the world. Numerous scientific studies have documented the adverse health effects of second-hand smoke (SHS).[1,2] The dangers of SHS, even for those exposed to it outdoors, are well known,[3,4] but outdoor smoking bans are rare.[5]

In order to protect people and the environment, the Municipality of Bibione, a popular seaside tourist destination near Venice (Italy), introduced a smoking ban for the whole beach, except for specially designated smoking areas. This pioneering initiative in Italy, and one of the few in Europe to ban tobacco on beaches, was acknowledged by the WHO.[6]

Demonstrating a significant improvement in air quality following the introduction of the Bibione beach smoking ban presented significant challenges: to accurately evaluate the air quality before and after the ban, it would have been necessary to install several fixed pollution monitoring stations along kilometers of beach with hundreds of parasols and this was not technically possible. Each monitoring station would have needed an electrical power supply with electrical cables laid all along the beach where people normally walk barefoot presenting an unacceptable safety risk.

Therefore, we engineered an alternative solution: "hunting" for cigarette smoke pollution on beaches using personal portable analyzers. Fixed instruments were deployed on a terrace and on a roundabout for comparison.

The measurement of Black Carbon (BC) was used to detect the level of outdoor SHS pollution because previous studies had demonstrated a very high sensitivity to biomass combustion when measurements are performed at 370 nm, whereas fossil combustion is measured at 950 nm.[7]

The instruments we used were:

- **portable aethalometer model AE51** (Aethlab), factory calibrated to measure BC at 370 nm, programmed with 1 s sampling time carried by the researcher at nose level;
- **fixed aethalometer model AE31** (Magee Scientific), factory calibrated to measure BC on seven channels from 370 to 950 nm programmed with 2 min sampling time, installed at 10 m height on a terrace at about 50 m from a roundabout at the entrance of the Bibione town, which represents a sort of background.
- **fixed sensor for wind direction and velocity** model Kestrel 4500 programmed, with 2 min sampling time, battery supplied, installed at the seashore.

The BC measurements on the beach and on the roundabout were performed before and after the ban. After the installation of the fixed instruments (on a terrace and at a roundabout), the researchers equipped with the portable BC analyzer started wandering among the beach parasols, stopping only when they perceived the smell of cigarette smoke, trying to locate the source, and identify the distance and number of smokers. Considering that the cigarettes diffusion plume, with the measured wind speed of 2.7 ± 1.0 m/s is almost horizontal, and that one average cigarette emission rate is about 1.43 mg/min,[8] we estimated that the Black Carbon Ultra Violet (BCUV) measurements would detect SHS even at several meters downwind from smokers.

Averages of BCUV were calculated for the different sites and periods of measurements, and *t*-test was applied to evaluate the differences.

Before the ban SHS concentrations generated by smokers under parasols were detected at variable distances between 3 and up to 4—15 m downwind and were characterized by short, frequent, and also some extremely high BCUV peaks, detected simultaneously with the SHS odour . Fig. 1a shows an example of the BCUV measurement where it is possible to count the smoker puffs (each peak corresponds to one puff).

Since the distance between umbrellas is four meters, all those under three to four umbrellas located downwind are exposed to SHS. As can be seen in Fig. 1b, in all tests the mean BCUV concentration levels measured downwind of the smokers is higher than those measured at the traffic crossing site within the same time window (8.1 ± 5.4 vs 2.0 ± 2.0 $\mu g/m^3$, p-value = 0.02).

After the ban no SHS was detected by the BCUV and by olfactory sensation during the wandering of the researchers on the beach, with the exception of downwind to the four special smoking sites located far away from the umbrellas zone, and therefore there are no data to report.

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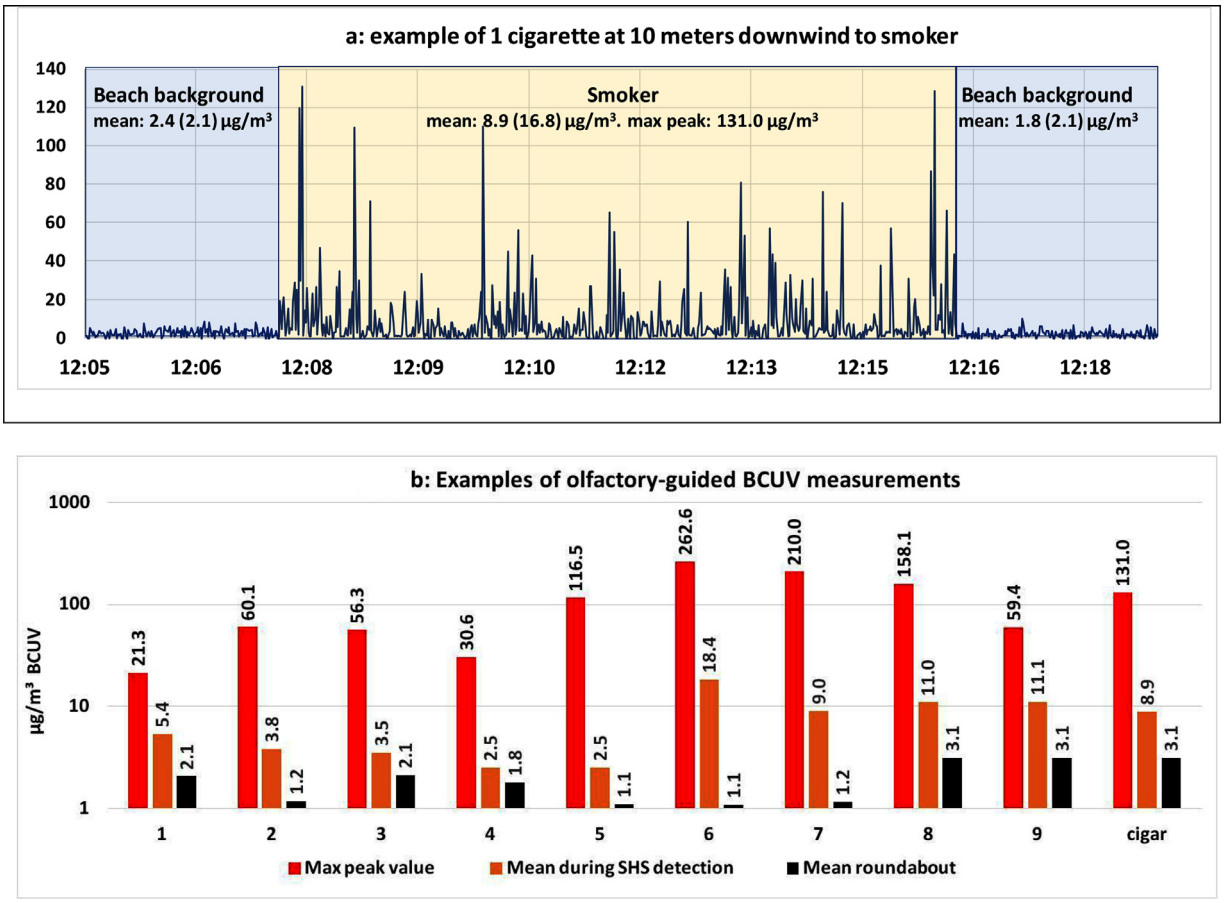

Fig. 1 (a) Examples of one cigarette at ten meters downwind to smoker. (b) Examples of olfactory-guided BCUV measurements. Despite the limited number of BCUV measurements, the results of our study demonstrate that, a significant improvement in the air quality was achieved on the beach after the introduction of the smoking ban.

Conflicts of interest

The authors have no conflicts of interest to declare.

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LETTER TO THE EDITOR

A real-life study of elexacaftor-tezacaftor-ivacaftor therapy in people with cystic fibrosis in Brazil

Cystic fibrosis (CF) is a monogenic inherited disease caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. The disease has a multiorgan involvement, but primarily affects the respiratory and gastrointestinal tracts, and leads to high morbidity and mortality.[1] Brazil currently is the sixth highest country worldwide for the number of people diagnosed with CF (PwCF)[1] and an incidence of 1 in ~7,500 newborns.[2]

Over the last decade, modulator drugs rescuing mutant CFTR traffic and function were developed, thus targeting the fundamental cause of CF.[1,3] Recently, a triple combination of two CFTR correctors (elexacaftor and tezacaftor) and a CFTR potentiator (ivacaftor) demonstrated safety and remarkable effectiveness in PwCF carrying the most prevalent F508del mutation.[3–5] In phase III trials, the elexacaftor-tezacaftor-ivacaftor (ETI) combination remarkably improved lung function, body mass index (BMI), CF quality of life scores, and sweat chloride concentration (SCC) in either F508del-homozygous or F508del-heterozygous PwCF.[4,5] It is estimated that the introduction of ETI into clinical practice will increase the life expectancy of PwCF to >50 years in the United States,[6] although it is much lower in countries where ETI is not available.[7] This report aimed to assess the real-life efficacy of ETI in Brazilians with CF who earned the right to receive this therapy through court rulings.

After ethics committee approval (CAAE: 15748619.8.1001.0068), written informed consent was obtained from all participants. Twenty-two PwCF were followed by specialized pulmonology physicians at a single CF center in Sao Paulo. All data were documented and processed anonymously, and obtained at baseline, 3 and 6 months after ETI initiation. Lung function (as forced expiratory volume in 1s [FEV1]) was measured according to the recommendations of the American Thoracic Society[8] using Brazilian Predictive Values.[9] Computed tomography (CT) scan was performed with thin slices (1 mm) in volumetric multi-detector instruments, which allow for analysis of the whole lung parenchyma in high resolution. The SCC was measured by colorimetric method with a reference value for CF as >60 mmol.L^{-1}. The usage of oxygen therapy, frequency of pulmonary exacerbations, BMI, and adverse effects were also included. The quality of life score was assessed using the CF Questionnaire-Revised (CFQ-R).[10] For statistical analysis, the Kolmogorov-Smirov test was performed to assess the data normality. Thereafter, paired Student's T-test was used to compare SCC, pulmonary exacerbations, and CFQ-R values, while differences in parameters between F508del-homozygous and F508del-heterozygous cohorts were assessed by unpaired Student's T-test. Finally, General Linear Model for repeated measurements was performed to compare BMI and FEV1 at different time points. A *P*-value <0.05 was considered significant.

The mean age of the 22 participants was 26.6 (± 9.2) years, all had pancreatic insufficiency and 14 were male (63.6%). All had the F508del mutation on at least one allele, 10 being (45.4%) homozygous for this mutation. Other mutations present in heterozygosis were: 2184delA (1), Q220X (1), A349P (1) G542X (3), R1066H (1), R1066S (1), and R1162X (4). Fifteen individuals (68.2%) had advanced lung disease (FEV1 <40% predicted) and 12 (54.5%) were under continuous home oxygen therapy. The baseline mean of BMI, FEV1, and SCC were 19.9 kg.m^{-2}, 41.4% predicted, and 102.7 mmol.L^{-1}, respectively (Table 1).

After 3 and 6 months of ETI initiation, the mean improvement of FEV1 was 10.3% and 14.2% points (Table 1). CT scans revealed a marked improvement in lung abnormalities, although bronchiectasis persisted (Fig. 1). Only one individual remained under continuous home oxygen therapy after ETI therapy, representing a 91.6% reduction in supplementary oxygen necessity. The annualized number of pulmonary exacerbations per individual after ETI initiation (mean 0.22 ± 0.42) was significantly lower (p<0.0001) compared to the frequency in the year before ETI initiation (mean 2.96 ± 1.77).

Triple therapy improved BMI with a mean increase of 1.1 and 2.1 kg.m^{-2} in 3 and 6 months, respectively, from baseline. Similar findings were observed for the mean of SCC, which dropped 49.7 mmol.L^{-1} after 3 months of ETI, indicating the rescue of CFTR function. Regarding the quality of life questionnaire (CFQ-R), the mean values increased significantly in both physical activity (+54 points) and respiratory (+46.7 points) domains after 6 months of ETI.

Overall, ETI therapy was well tolerated and 13 individuals (59.1%) demonstrated no adverse effects. There was no ETI discontinuation and adverse effects observed in the remaining individuals were classified as mild or moderate and

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Table 1 Clinical data of 22 participants at baseline, 3 and 6 months after ETI initiation. Data were presented as mean ± standard deviation. Significant results were considered significant when $p<0.05$.

		BMI ($kg.m^{-2}$)	FEV1 predicted (%)	SCC ($mmol.L^{-1}$)	Physical CFQ-R domain	Respiratory CFQ-R domain
	Baseline	19.9 ± 0.57^a	41.4 ± 22.38^a	102.7 ± 16.96	38.5 ± 22.51	39.6 ± 19.44
ETI	3 months	21.0 ± 0.64^b	51.7 ± 27.12^b	44.9 ± 11.50	NP	NP
	6 months	22.0 ± 0.57^c	55.6 ± 27.24^c	NP	92.5 ± 3.55	86.3 ± 12.26
P value		<0.0001¥	<0.0001¥	<0.0001*	<0.0001*	<0.0001*
Homozygous (n=10)	Baseline	19.4 ± 2.70	38.1 ± 21.24	104.6 ± 19.27	33.9 ± 22.60	26.2 ± 19.42
Heterozygous (n=12)		20.7 ± 2.20	45.7 ± 22.57	108.7 ± 27.07	42.08 ± 24.44	50.1 ± 13.80
P-value		0.248	0.441	0.756	0.505	0.012#
Homozygous (n=10)	6 months	21.8 ± 2.86	51.8 ± 22.88	NP	90.7 ± 3.8	83.9 ± 16.62
Heterozygous (n=12)		20.1 ± 7.33	59.0 ± 32.68	NP	94.0 ± 3.00	88.1 ± 9.23
P value		0.496	0.599	NP	0.073	0.533

BMI: body mass index; CFQ-R: cystic fibrosis questionnaire-revised; ETI: elexacaftor-tezacaftor-ivacaftor; FEV1: forced expiratory volume in one second; SCC: sweat chloride concentration; NP: not performed.
¥ General Linear Model Test for repeated measurements.
* Paired Student's T-test.
# Unpaired Student's T-test.

included: rash (1), diarrhea (2), abdominal pain (2), and altered values in liver enzymes (CPK and ALT) (4).

This is the first real-life study in Brazil to demonstrate an association of ETI therapy with the significant improvement of predicted FEV1, BMI, and quality of life scores in PwCF in Brazil. Triple therapy also reduced SCC, the need for oxygen therapy, and the frequency of pulmonary exacerbations in a 6-month follow-up. Furthermore, ETI therapy was safe and well tolerated, which aligns with other clinical studies in PwCF carrying at least one F508del-CFTR that demonstrated a rapid clinical improvement after ETI initiation[3,11] and a low discontinuation rate (<2%).[4,5]

Although F508del-homozygous participants exhibited the worst CFQ-R scores in the respiratory domain at baseline, similar clinical effectiveness was observed in the F508del-homozygous and F508del-heterozygous cohorts after ETI therapy (Table 1). Additionally, the improvements in lung function and structure, and nutritional status were sustained for up to 6 months in both cohorts. Similar results were found in a post-approval trial, although the mean of FEV1 increased 9.76% points after 6 months of ETI,[12] compared to 14.2% points increase in this study. Lung function changes may have been larger in our report since PwCF were naïve to modulators, while half of the participants in the former study were already using other modulators before switching to ETI.[12]

Pulmonary exacerbations are deleterious events that frequently lead to accelerated decline in lung function, hospitalization, and worse quality of life.[4,5] Following lung function improvement in this study, a significant reduction of pulmonary exacerbation occurrence was also associated with the usage of ETI therapy, which may have contributed

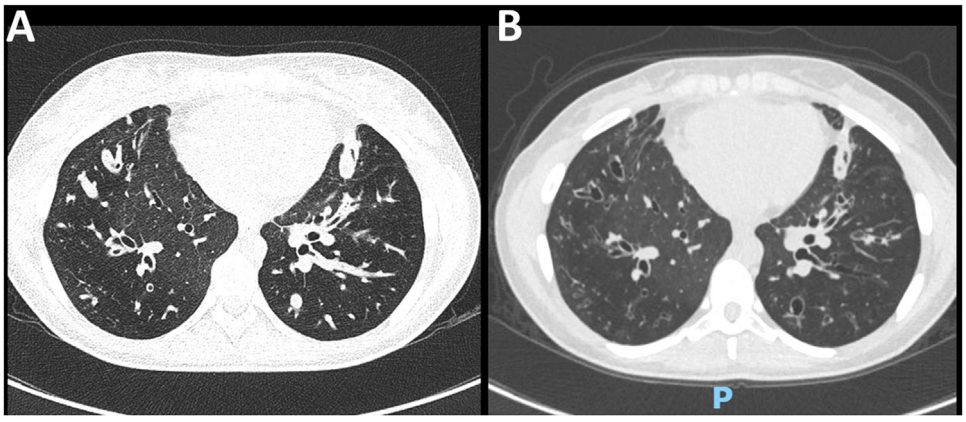

Fig. 1 Chest CT scan of a 22-year-old female with CF (F508del/F508del genotype). (**A**) At baseline, diffuse bronchial thickening, intrabronchial mucus plugging, and bilateral bronchiectasis in lower lobes were evidenced. (**B**) After 6 months of ETI therapy, there was a significant reduction in mucus plugging and bronchial thickening.

to the decreased respiratory symptoms and increased self-perceived quality of life.

In summary, this report demonstrated the safety and efficacy of ETI in PwCF in a real-life setting in Brazil. Despite the small sample size, ETI had remarkably positive effects on all clinical outcomes evaluated in the 6 months follow-up, highlighting its impact not only on symptoms and complications but also on individuals' physical and social well-being. Therefore, the introduction of ETI into clinical practice in Brazil may represent a life-changing therapy for many PwCF.

Conflicts of interest

RA Athanazio and SZ Rached has received lectures honoraria from Vertex.

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LETTER TO THE EDITOR

Poor sleep quality and nocturnal home noninvasive ventilation: Prevalence, risk factors and impact

Chronic respiratory diseases deteriorate sleep, impacting total sleep time, sleep efficiency, and sleep architecture.[1] Nocturnal noninvasive ventilation (NIV) can restore sleep quality, as documented by polysomnography (PSG).[1] Therefore, current guidelines stipulate that NIV should be initiated under PSG guidance.[2] This is not done in practice because of resources limitation. Some evidence supports the hypothesis that, in the absence of PSG guidance, sleep quality can be poor under NIV.[3] To further explore this hypothesis, we prospectively administered the Pittsburgh sleep quality index (PSQI)[4] to unselected patients placed under NIV without PSG guidance. In addition to prevalence data, we aimed to evaluate risk factors of poor sleep quality under NIV and to assess its impact on quality of life (QoL).

Over 90 days, we consecutively enrolled patients previously established on nocturnal home NIV without PSG guidance, clinically stable for at least 3 months and attending our NIV clinic for a scheduled follow-up. Study received ethics approval (*CERNI,* Rouen, E2018—06).

Patients answered the PSQI, the Severe Respiratory Insufficiency questionnaire (SRI; 0: poorest QoL; 100: best), and Epworth Sleepiness Scale. NIV side effects were graded from 0 —absent— to 4 —unbearable— according to an in-house questionnaire (eye irritation, rhinorrhea, dry mouth, hoarseness, bloating, mask or harness-related pain, pressure sores, leaks, deventilation dyspnea and perceived patient-ventilator asynchrony). NIV usage was assessed from 30-days ventilator logs. Leaks were considered abnormal if >2 L/min for Resmed® ventilators, >10 L/min for Philips Respironics® ventilators. A PSQI above 5 defined a "poor sleep quality group",[4] mirrored by a "good sleep quality" one.

Results are expressed as number and percentages, median and interquartile range (IQR). Mann-Whitney's *U* test, the chi-square test and Spearman's test were used for comparisons and correlations. Multivariate analysis (binomial logistic regression) incorporated clinically relevant variables with $p < 0.15$ on univariate analysis. All tests were two-sided with 0.05 significance threshold (GraphPad Prism 6® and IBM SPSS® v26.0).

One hundred and fifty-nine patients attended the clinic during the study period; 32 declined to participate or could not be included (mostly because of staff unavailability), leaving 127 for analysis. The "poor sleep quality" group comprised 64 patients (50.5%) (Table 1). NIV indications, settings, effect on PaCO2 and adherence did not differ between groups (Table 2). Poor sleep quality patients more frequently reported grade 3—4 mouth dryness (59 vs 40% s, $p = 0.033$) and overnight NIV interruptions: 0.3 [0.0 — 1.1] breaks/night vs 0.1 [0.0 — 0.3], $p = 0.026$). Multivariate analysis evidenced 3 variables associated with poor sleep quality: benzodiazepine use (OR= 6.83 [1.53—30.65], $p = 0.012$), airway secretions (OR= 4.66 [1.06—20.43], $p = 0.041$), and abnormal leaks (OR= 4.52 [1.25—16.39], $p = 0.022$). SRI-evaluated QoL was lower in poor sleep quality patients (50.0 [39.7 — 62.5] vs. 62.0 [50.0 — 76.3] out of 100, $p<0.001$). PSQI inversely correlated with SRI (rho = —0.410, $p < 0.001$).

Patients receiving benzodiazepines more often had a PSQI above 5 (71 vs. 41%, $p = 0.004$), had been on NIV for shorter durations (18 [4—50] months vs. 41 [12 — 83], $p = 0.014$), had poorer daytime $PaCO_2$ control (6.39 [5.89 — 6.99] kPa vs. 6.09 [5.45 — 6.89], $p = 0.038$), and lower SRI scores (50 [38 — 64] vs. 59 [47 — 72], $p = 0.030$).

In this real-life study, half of a cohort of patients under long-term NIV initiated without PSG guidance reported poor sleep quality according to the PSQI, irrespective of NIV indication. This was associated with lower QoL, in line with literature.[5]

The three variables independently associated with poor sleep quality in this study can all be subject to medical intervention . Our data emphasize the known importance of controlling leaks during home nocturnal NIV. Indeed, leaks can fragment sleep and promote mouth dryness, as in our poor sleep quality group. Our observations also highlight the known importance of trying to control airway secretions in NIV patients (e.g., in-exsufflation in neuromuscular patients). Interestingly, 27% of

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Table 1 Clinical characteristics according to group (COPD: chronic obstructive pulmonary disease; IQR: interquartile range; mMRC: modified medical research council; OSA: obstructive sleep apnea; NIV: non-invasive ventilation; PSQI: Pittsburgh sleep quality index).

	Patients with good sleep quality ($n = 63$)	Patients with poor sleep quality ($n = 64$)	
	Median [IQR] / n (%)	Median [IQR] / n (%)	p
Demographic data			
Age at NIV initiation (years)	63 [54−68]	63.5 [53−74]	0.308
Time since NIV initiation (months)	36 [12−82]	34 [7−71]	0.215
Gender (male)	35 (56%)	25 (39%)	0.076
Body mass index (kg/m^2)	32.4 [25.6−40.7]	30.8 [24.1− 41.5]	0.250
Comorbidities			
Apnea-hypopnea index before NIV setup (/h)	17 [7−44.25]	17 [6.75−34]	0.665
Active or former smoker	37 (79%)	31 (74%)	0.624
Ischemic heart disease	7 (11%)	7 (11%)	1.000
Depression	12 (20%)	21 (33%)	0.105
Mental illness	0 (0%)	3 (5%)	0.240
Drug intake			
Benzodiazepines and "Z-drugs"	10 (16%)	25 (40%)	0.005
Antipsychotics	3 (5%)	12 (19%)	0.025
Underlying respiratory disease			
Neuromuscular disease	15 (25%)	17 (27%)	0.972
Obesity hypoventilation syndrome	16 (27%)	16 (25%)	
COPD-OSA	17 (27%)	14 (25%)	
COPD	11 (17%)	12 (19%)	
Chest wall disease	4 (6%)	5 (8%)	
Daytime symptoms			
Airway secretions (yes)	4 (8%)	26 (41%)	<0.001
Dyspnea mMRC $\geq$ 2	40 (64%)	51 (80%)	0.050
Chronic cough (yes)	22 (36%)	26 (41%)	0.586
Self-reported daytime sleepiness (yes)	16 (25%)	30 (47%)	0.014
Epworth Sleepiness Scale (/24)	3 [1−6]	5 [2−9]	0.001
Sleep			
PSQI (/28)	3 (1−5)	10 (6−20)	<0.001
Reported sleep latency (min)	10 [5−15]	20 [5−60]	0.062
Reported nighttime awakenings	1 [0.5−2]	2 [1−3]	0.002
Reported snoring ($\geq$ occasional)	13 (21%)	24 (38%)	0.037
Unrefreshing sleep (yes)	9 (16%)	19 (29%)	0.036
Daytime nap (yes)	39 (61%)	24 (38%)	0.010

our patients received benzodiazepines or "Z-drugs" that are contra-indicated in chronic respiratory failure where they heighten the risks of respiratory related hospitalization.[6] They also increase upper airway resistance during sleep,[7] which is deleterious during nocturnal NIV. NIV which may be inappropriately viewed as a "safety net" against deleterious effects of benzodiazepines on breathing control. We could not ascertain the motivation and timing of benzodiazepine prescriptions and causality between benzodiazepines and poor sleep quality cannot be inferred. Nevertheless, our observations call for a reminder that benzodiazepines are inadvisable in chronic respiratory insufficiency: their prescription in this context should systematically be questioned.

We acknowledge study limitations (single-center, observational design, lack of evaluation of the effect of NIV initiation on sleep quality) and the need for larger trials. However, we propose that evaluation of NIV efficacy should not be confined to currently recommended "hard" criteria (e.g. arterial carbon dioxide), but should incorporate the easy and costless evaluation of sleep quality (*e.g.* PSQI) and QoL (*e.g.* SRI) that should trigger more in-depth assessments.

Table 2 NIV settings, effect on PaCO2, tolerance, and data from built-in software according to group (BUR: back-up respiratory rate; EPAP: expiratory positive airway pressure; IQR: interquartile range; IPAP: inspiratory positive airway pressure; NIV: noninvasive ventilation; PaCO2: partial arterial pressure of carbon dioxide; PVA: patient-ventilator asynchrony).

	Patients with good sleep quality ($n = 63$)	Patients with poor sleep quality ($n = 64$)	
	Median [IQR] / n (%)	Median [IQR] / n (%)	p
NIV settings			
Spontaneous timed mode	52 (84%)	55 (87%)	0.620
IPAP (cmH_2O)	19 [16 – 22]	20 [16 – 22]	0.862
EPAP (cmH_2O)	6 [5 – 9]	6 [4 – 8]	0.083
BUR (/min)	14 [12 – 14]	14 [12 – 14]	0.801
Full face mask (yes)	55 (87%)	51 (80%)	0.248
Arterial blood gasses			
$PaCO_2$ during unsupported breathing (kPa)	6.02 [5.48 – 6.82]	6.21 [5.67 – 7.07]	0.437
$PaCO_2$ on NIV (kPa)	5.36 [4.71 – 6.11]	5.76 [4.99 – 6.51]	0.206
Change in $PaCO_2$ after 1 hour on NIV (kPa)	−0.51 [−0.16 −1.24]	−0.58 [−0.22 −1.15]	0.649
NIV tolerance			
Dry mouth ≥ moderate	25 (40%)	38 (59%)	0.033
Perceived leaks ≥ occasional	21 (33%)	32 (50%)	0.072
Persistent skin damage related to mask	9 (15%)	9 (14%)	1.000
Mask-related pain ≥ moderate	3 (5%)	5 (8%)	0.718
Self-reported PVA ≥ occasional	3 (5%)	6 (9%)	0.492
Deventilation dyspnea ≥ moderate	3 (5%)	9 (14%)	0.073
Data from NIV built-in software			
Adherence (h/day)	8.2 [7.3 – 9.4]	7.7 [5.9 – 9.7]	0.309
Adherence > 4 h/night	97 [94 – 100]	96 [77 – 100]	0.093
Number of NIV interruptions overnight	0.1 [0 – 0.3]	0.3 [0 – 1.1]	0.026
Abnormal leaks (n)	22 (51.2%)	34 (66.7%)	0.144
Expired tidal volume (ml)	520 [365 – 602]	464 [368 – 653]	0.813
Respiratory rate (/min)	16.2 [15 – 18]	16 [14 – 18.3]	0.800
Percentage of triggered breaths	54 [22 – 81]	50 [20 – 78]	0.641
Estimated residual events (/hour)	2 [0.8 – 5]	2.5 [1.138 – 5.05]	0.456

Data availability statement

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

Authors contribution

JS, AC, IA, TS, MP: conception, acquisition, analysis, interpretation, drafting the work, revising critically.

RL, JM: acquisition, interpretation, revising critically.

Conflict of interest

MP reports personal fees from ANTADIR, SOS Oxygène, Air Liquide Medical personal fees and non-financial support from Asten Santé, personal fees and non-financial support from Philips Respironics, grants, personal fees and non-financial support from ResMed, grants, personal fees and non-financial support from Fisher & Paykel, personal fees and non-financial support from Chiesi, grants from B&D Electromedical, stock from Kernel Biomedidical outside the submitted work.

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IA reports speaker fees from UCB Pharma and consultant fees from Idorsia Pharma, Roche Pharma and Onco Pharma outside the submitted work.

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LETTER TO THE EDITOR

"Gallia est omnis divisa in partes tres": Is it time to divide Pleuroparenchymal Fibroelastosis in three different forms?

Pleuroparenchymal fibroelastosis (PPFE) is a clinicopathological and radiological entity characterized by dense pleural and subpleural fibrosis, and elastic fibers deposition[1,2] which, in a certain percentage of cases, manifests with additional changes which can be coexisting IP-like patterns[3-5] or chronic infectious disease.[6] We investigated if this different radiological presentation of PPFE could be at the basis of peculiar clinical profiles.

A retrospective, single-center, observational analysis (approved by the Ethical Review Board of AUSL Romagna Nr. 30/2020 I.5/284) was carried out. Patients with radiological diagnosis of a definite PPFE or with histological evidence of PPFE biopsy plus compatible CT scan, in the period between 2008 and 2018, were analyzed. The inclusion criteria were: age above 18, availability of volumetric CT scan, complete pulmonary function tests and autoimmunity panel. Data on vital status were collected up to the end 2018 with a follow-up of at least 4 years. Thereafter all patients were contacted in December 2022 to certify the survival status and/or lung transplant.

Radiological analysis, performed in consensus by a chest radiologist (SP) and a pulmonologist expert on imaging (LSF), consisted of the visual scoring of each CT finding.[7] Furthermore, patients were subclassified into three groups: CT evidence of standalone PPFE (group I); PPFE plus CT evidence of a coexisting ILD (group II); PPFE plus signs of airway disease (group III) (Fig. 1). Clinical data collected and visual CT analysis are reported in the supplemental materials.

Fifty-three patients (34 women, 19 men, median age 59 years, IQR: 51-72 years), mostly nonsmokers (73.6%), were included in the study. Sixteen of them (30.2 %) with histologic confirmation (7 surgical lung biopsy; 9 transbronchial cryobiopsy). Bronchoalveolar lavage revealed presence of infection in eleven cases: *Aspergillus Niger* (*n*=1), *Aspergillus Terreus* (*n*=1), *Mycobacterium tuberculosis* (*n*=4); *Mycobacterium avium-intracellulare* (*n*=2); *Haemophilus Influenzae* (*n*=2); and *Nocardia abscessus* (*n*=1).

Systemic/autoimmune disorders were demonstrated in nine cases: Hashimoto's thyroiditis (*n*=2; one in group I and one in group II); Sjogren's disease (*n*=3), two in group III, one case in group II); undifferentiated collagen vascular disease (n=1, group II); scleroderma (*n*=1, group II); and rheumatoid arthritis (*n*=1, group II). Sarcoidosis was present in one (*n*=1, group II). History of hematologic disorders was present in five cases and, in two of them, PPFE was the manifestation of a chronic graft-versus-host disease.

The radiological analysis revealed that in the standalone PPFE (*n*= 22) the dense pleural fibrosis was mainly in the upper to middle lung regions (77.3%; *n*= 17) and only in 22.7% of cases extended to lower lobes (*n*=5).

PPFE-ILD group (*n*=19) showed features of PPFE plus: definite UIP (52.6%, n=10), probable UIP (15.8%, *n*=3), indeterminate UIP (10.5%, *n*=2), definite HP pattern (15.8%, *n*=3), and sarcoidosis (5.3%, *n*=1).

Among these, six patients received a final MDT diagnosis of IPF (with excessive PPFE manifestation); six of familial pulmonary fibrosis; three of fibrosing hypersensitivity pneumonitis, one patient of sarcoidosis, one of diffuse scleroderma, one of RA-ILD, and one of Sjogren's syndrome.

The last group, PPFE-airways disease, had CT findings including signs of bronchiolitis and/or bronchial inflammation. Findings included respectively: centrilobular nodules along with tree-in-bud (50.0%, *n*= 6) or bronchiectasis, mucus plugging and tree-in-bud (50.0%, *n*=6).

The three groups showed significant differences in the semiquantitative radiological score, as well.

First, standalone PPFE had significantly higher dense-subpleural fibrosis score (median: 100, IQR: 60-100) compared to group III (median: 90, IQR: 50-100) and group II (median: 56.7, IQR: 40-80) ($p = 0.004$).

Second, PPFE-ILD had the highest traction bronchiectasis score [median: 7 (IQR: 4-10), compared to 0.5 (IQR 0-2.5) in group III and 0 (IQR: 0-6) the group I ($p < 0.001$)] and fissural elastotic thickening [(median: 211.4; IQR: 87.7-441.4) compared to group I (median: 64.6; IQR: 13.7-245.2) or group III (median: 103.8; IQR: 19.0-282.4) ($p = 0.001$)]. Also, the clinical features showed different profiles.

Standalone PPFE patients were younger (mean age: 47.7) than those with PPFE and airways disease (mean: 67.2) and those with PPFE-ILD (mean: 65.2) ($p < 0.001$).

BMI of the whole group was in the lower normal limits (median value: 20.4; 18.9-23.6); however, comparing the three groups (Group I: 17 IQR 16-21.5; Group II: 21.6 IQR 20.2-26.0; Group III: 20.4 IQR 14.1-22.7), a significant difference was evident between the group I and the group II ($p = 0.049$): subjects with standalone PPFE were

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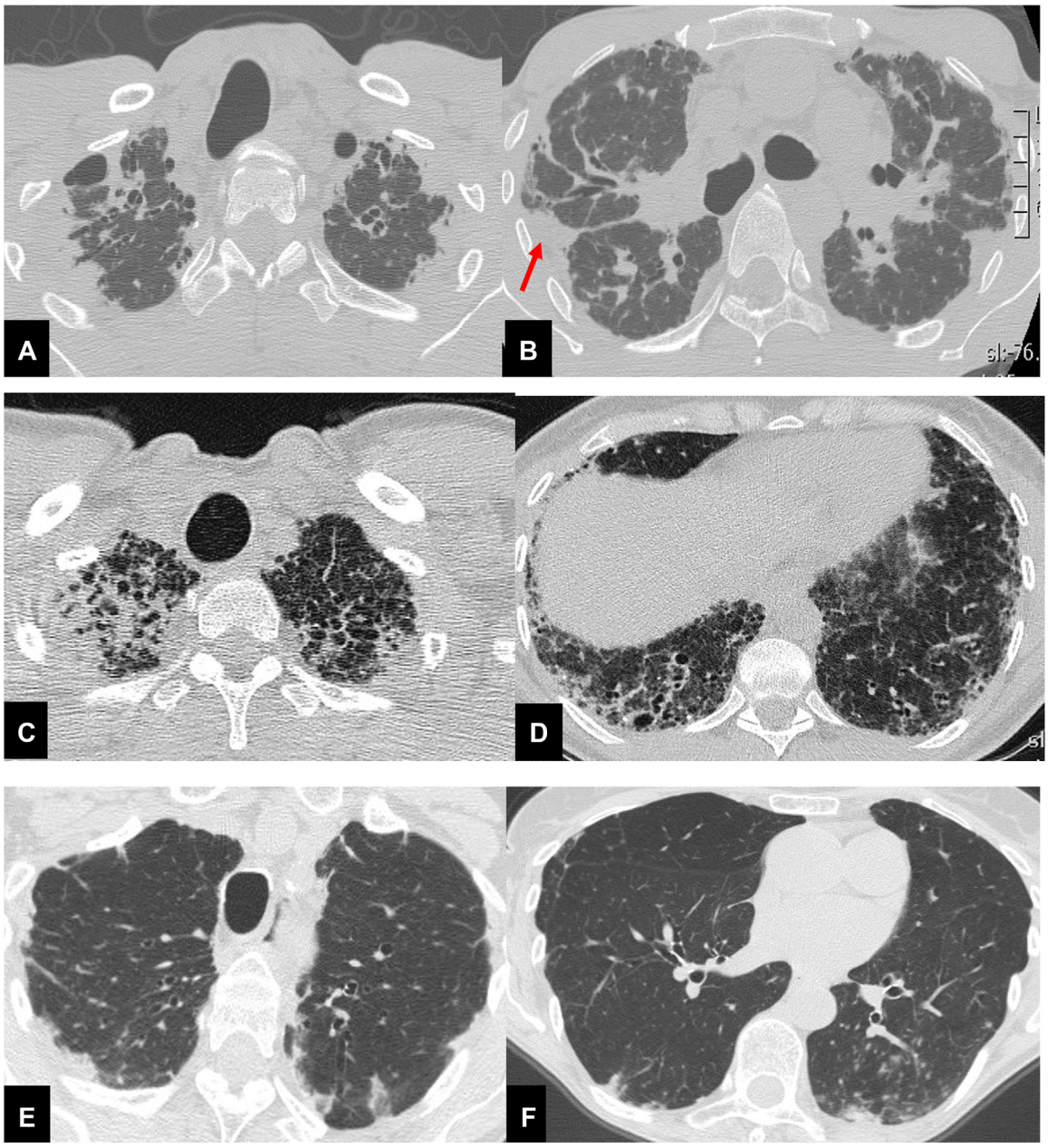

Fig. 1 Thirty-seven year-old male (A,B), with surgical biopsy-proven PPFE and severe impairment of PFT (FVC 27% FEV1 25% DLCO 31%). CT scan shows bilateral, dense pleural and subpleural fibrosis suggestive of PPFE, in the upper and mid lung regions. The elastotic tissue is also present in the fissures, with particular evidence for the right one (red arrow). Scattered traction bronchiectasis are present in the surrounding dense elastotic fibrosis.
Sixty-seven year-old female (C,D), with diagnosis of familial pulmonary fibrosis. Surgical lung biopsy documented: PPFE + UIP pattern. CT scan shows brobable UIP pattern in both lower lobes, mainly on the right associated with pulmonary ossifications e traction bronchiectasis.
Seventy-eight-year-old female (E,F), affected by Sjogren disease, with diagnosis of bronchiolitis Nocardia abscessus related. PPFE is present in both upper lobes associated with centrilobular nodules and mucus plugging in the bronchi in the left lower lobe.

slimmer than those with PPFE-ILD. Moreover, patients in Group I, with BMI $\leq$17 died (median value 16, IQR 16-17), (n=6), suggesting that a low BMI can be a prognostic determinant.

Median survival was 9 years (95%CI: 7-13 years), with the shortest one documented in the PPFE-ILD group (median 4 years, 95%CI: 3-8 years), followed by the PPFE airways diseases (median 9 years, 95%CI: 7-13 years) and finally the standalone PPFE group (median 9 years, 95%CI: 9-13 years) (log-rank test chi2(2) = 9.93, p = 0.0070).

In conclusion, quoting the incipit of *De Bello Gallico*, we may start to consider PPFE as a complex entity divisible into three main particular clinical profiles, based on the radiological appearance.

Table 1 Clinical summary of patients' characteristics.

	Overall (n = 53)		PPFE (n = 22)		PPFE-ILD (n = 19)		PPFE-airways disease (n = 12)		p-value
Age (years)									
Mean (SD)	59.0	(15.1)	47.7	(13.3)	65.2	(9.1)	67.2	(15.2)	< 0.001
Median (IQR)	59.5	(51.0—72.0)	51.0	(37-0 - 56.0)	66.0	(57.0—74.0)	70.5	(58.5—78.0)	
BMI									
Median (IQR)	20.4	(18.9-23.6)	17.0	(16.0-21.6)	21.6	(20.2—26.0)	20.4	(14.1—22.7)	0.049
Smoking, n (%)									
None	39	(73.6)	15	(68.2)	15	(79.0)	9	(75.0)	0.323
Current Smoker	8	(15.1)	3	(13.6)	4	(21.1)	1	(8.3)	
Former Smoker	6	(11.3)	4	(18.2)	0	(0.0)	2	(16.7)	
Professional exposure, n (%)									
None	39	(73.6)	17	(77.3)	13	(68.4)	9	(75.0)	0.869
Chemical	2	(3.8)	1	(4.6)	1	(5.3)	0	(0.0)	
Inorganic	5	(9.4)	2	(9.1)	1	(5.3)	2	(16.7)	
Organic	7	(13.2)	2	(9.1)	4	(21.1)	1	(8.3)	
Familiarity, n (%)	7	(13.2)	1	(4.6)	6	(31.6)	0	(0.0)	0.012
Previous pneumothorax, n (%)	3	(5.7)	2	(9.1)	1	(5.3)	0	(0.0)	0.368
Exordium, n (%)									
Acute	2	(3.9)	1	(4.8)	0	(0.0)	1	(8.3)	0.119
Chronic	36	(69.2)	11	(52.4)	15	(79.0)	10	(83.3)	
Asymptomatic	11	(21.2)	8	(38.1)	2	(10.5)	1	(8.3)	
Subacute	3	(5.8)	1	(4.8)	2	(10.5)	0	(0.0)	
Cough, n (%)	37	(69.8)	12	(54.6)	16	(84.2)	9	(75.0)	0.368
Relapsing Fever, n (%)	18	(34.0)	9	(40.9)	2	(10.5)	7	(58.3)	0.115
Dyspnea, n (%)	31	(58.5)	6	(27.3)	17	(89.5)	8	(66.7)	0.036
PH, n (%)	5	(9.4)	0	(0.0)	4	(21.1)	1	(8.3)	0.074
Weight Loss, n (%)	14	(26.4)	4	(18.2)	8	(42.1)	2	(16.7)	0.135
Arthralgia, n (%)	4	(12.1)	1	(8.3)	2	(12.5)	1	(20.0)	0.779
Myalgia, n (%)	1	(3.1)	1	(8.3)	0	(0.0)	0	(0.0)	0.368
Cyanosis, n (%)	3	(10.0)	0	(0.0)	3	(21.4)	0	(0.0)	0.050
Comorbidities, n (%)	23	(43.4)	9	(40.9)	8	(42.1)	6	(50.0)	0.738
MRC, n (%)									
0	17	(36.2)	13	(68.4)	2	(10.5)	2	(22.2)	0.005
1	13	(27.7)	3	(15.8)	7	(36.8)	3	(33.3)	
2	12	(25.5)	2	(10.5)	6	(31.6)	4	(44.4)	
3	5	(10.6)	1	(5.3)	4	(21.1)	0	(0.0)	
Mean (SD)	1.1	(1.0)	0.5	(0.9)	1.6	(0.9)	1.2	(0.8)	0.002
Median (IQR)	1.0	(0-2)	0	(0—1)	2	(1—2)	1	(1—2)	
IPF Stage, n (%)									
I	33	(75.0)	13	(72.2)	13	(68.4)	7	(100.0)	0.297
II	11	(25.0)	5	(27.8)	6	(31.6)	0	(0.00)	
Antifibrotics, n (%)	10	(21.3)	3	(15.8)	7	(36.8)	0	(0.00)	0.025

Table 1 (*Continued*)

	Overall (n = 53)		PPFE (n = 22)		PPFE-ILD (n = 19)		PPFE-airways disease (n = 12)		p-value
Therapy, n (%)	19	(35.9)	4	(18.2)	10	(52.6)	5	(41.7)	0.196
Asthma, n (%)	3	(5.66)	2	(9.1)	0	(0.0)	1	(8.3)	0.368
HSCT, n (%)	2	(3.8)	1	(4.6)	0	(0.0)	1	(8.3)	0.607
Pulmonary Function Test									
FVC%									
Mean (SD)	74.42	(21.2)	74.00	(23.7)	69.05	(19.7)	83.67	(17.0)	0.051
Median (IQR)	85.0	(60.0—85.0)	85.0	(63.0—85.0)	67.0	(56.0—80.0)	86.0	(72.5.0—95.5.0)	
DLCO%									
Mean (SD)	61.08	(21.4)	67.27	(23.6)	54.74	(17.3)	59.75	(21.3)	0.121
Median (IQR)	61.0	(43.0 -80.0)	80.0	(53.0—80.0)	48.0	(43.0—66.0)	64.5	(40.0—80.0)	
FEV1%									
Mean (SD)	75.28	(22.1)	73.32	(22.3)	74.21	(23.1)	80.58	(21.2)	0.587
Median (IQR)	80.0	(64.0—84.0)	80.0	(22.0—80.0)	71.0	(52.0—91.0)	80.0	(68.0—88.5.0)	
Follow-up									
Mean (SD)	6.5	(3.3)	7.2	(3.1)	5.9	(4.0)	5.9	(1.8)	0.169
Median (IQR)	7.0	(4-8)	7.0	(6-9)	4.0	(3-8)	6.0	(4-7)	
Death	25	(49.0)	6	(27.3)	15	(83.3)	4	(36.4)	0.001

The standalone PPFE is mainly paucisymtomatic and affects mainly middle-aged non-smoker females with a low BMI. The PPFE-ILD, manifests mainly in males with a familial predisposition, in their mid-sixties, with significant restrictive impairment, severe symptoms, and the lowest survival. The PPFE-airway diseases affect older non-smoking females, manifesting with relapsing fever and an underlying infection (Table 1).

Conflicts of interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2023.04.001.

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LETTER TO THE EDITOR

Optimizing the use of systemic corticosteroids in severe asthma (ROSA II project): a national Delphi consensus study

Dear Editor,

Although the prevalence of severe asthma is not high (5—10% of patients), it is responsible for a large part of the overall disease burden and costs (50—60% of total costs), especially if the condition remains uncontrolled (which occurs in around 40% of cases).[1] Currently, for patients without disease control or presenting frequent exacerbations despite optimal therapy, add-on treatments, traditionally long-acting anticholinergics, oral corticosteroids (OCS) or biologic agents (monoclonal antibodies) are recommended.[2] Nonetheless, the long-term use of oral/systemic corticosteroids (CS) is significantly associated with adverse effects, acute and chronic complications that may decrease health-related quality of life and worsen prognosis, thus requiring additional monitoring and management. Conversely, target therapies (i.e., omalizumab, mepolizumab, reslizumab, benralizumab and more recently, dupilumab) have been developed grounded on the different phenotypes and endotypes of severe asthma, and are gradually reducing the reliance on OCS (i.e., greater specificity for achieving disease control by reducing the risk of exacerbations and requirements for rescue medication and OCS, with limited adverse events).[3,4]

In 2020, our research group performed a Delphi consensus in Portugal that showed a favorable perception among physicians for using biologic agents in severe asthma[5]; however, several questions including drugs availability, costs, patient eligibility and when to start therapy, remained to be clarified.[6,7] This is especially important as therapeutic approaches can vary widely among clinical settings, which broadens the gap between real-world practices and intensifies the discussions on therapeutic optimization. Thus, with the goal of optimizing the use of systemic CS in adults with severe asthma in Portugal, including eligible and ineligible patients for biological therapy, we performed a nationwide consensus among pulmonology and immunoallergology experts.

This study was a 3-phase modified Delphi exercise consisting of a pre-round for developing the statements and two sequential rounds of anonymous questionnaires (1st and 2nd rounds) done online (May-July 2021). A total of 58 statements were developed by the scientific committee based on a literature search in PubMed using the keywords “severe asthma”, “corticosteroids” and “biologics” combined with the Boolean Operators AND and OR ($n = 2.757$ reviewed papers published between 2010 and 2020). These statements were grouped into three topics: (1) CS in severe asthma ($n = 32$ items); (2) CS in patients eligible for biological therapy ($n = 17$ items); (3) CS in patients not eligible for biological therapy ($n = 9$ items). A five-point Likert-type scale was used (1-‘strongly disagree’; 5-‘strongly agree’) to individually rate the statements in each round; consensus threshold was established as a percentage of agreement among participants ($\geq$90% in the 1st round; $\geq$85% in the 2nd round). The level of consensus achieved by the participants was discussed by the scientific committee. Detailed methods have been previously published[5]; procedures followed standards for scientific research and were performed according to the Declaration of Helsinki. The scientific committee comprised six experts with experience in the treatment of severe asthma. The expert panel selected by the scientific committee consisted of 48 physicians (female:male 28:20; 26 pulmonologists and 22 immunoallergologists) with clinical and academic expertise in the management of severe asthma in Portugal (median H-index: 7.5 [IQR 2.75—13.25; minimum-maximum: 1—45], summing over 990 published articles indexed in PubMed), working in public or private institutions distributed at national level to capture regional specificities.

Overall, 45 experts participated in the study (93.8% response rate) (Fig. 1A). Around 75% ($n = 44$) of statements obtained positive consensus by the end of the 1st round. Most statements ($n = 37$; 84.1%) had a concordance over 95%, with seventeen of them (around 40%) presenting an agreement rate equal to 100%. Fourteen remaining items were iterated in the 2nd round, where 12 (85.7%) reached

The Portuguese ROSA Group is composed by: Ana Arrobas, Ana Luísa Ferreira, Ana Mafalda Van Zeller, Ana Mendes, Ana Todo Bom, Anna Sokolova, Beatriz Fernandes, Carlos Lopes, Catarina Teles Martins, Cecilia Pardal, Célia Costa, Claudia Chaves Loureiro, Claudia Pinto, Cristina Lopes Abreu, Emilia Faria, Estrella Alonso, Fernanda S. Tonin, Filipa Duarte-Ramos, Filipa Todo Bom, Frederico Regateiro, Inês Belchior, Ivone Fernandes, João Cordeiro Costa, João Marques, José Ferreira, José Manuel Silva, José Placido, Ligia Fernandes, Luís Amaral, Luis Taborda, Lurdes Ferreira, Manuel Branco Ferreira, Marta Drummond, Natacha Lopes, Natália André, Nuno Neuphart, Nuno Pires, Nuno Sousa, Paula Leiria Pinto, Paula Rosa, Pedro Martins, Ricardo Lima, Rita Boa Ventura, Rita Gerardo, Rodrigo Alves, Sofia Campina, Ulisses Brito.

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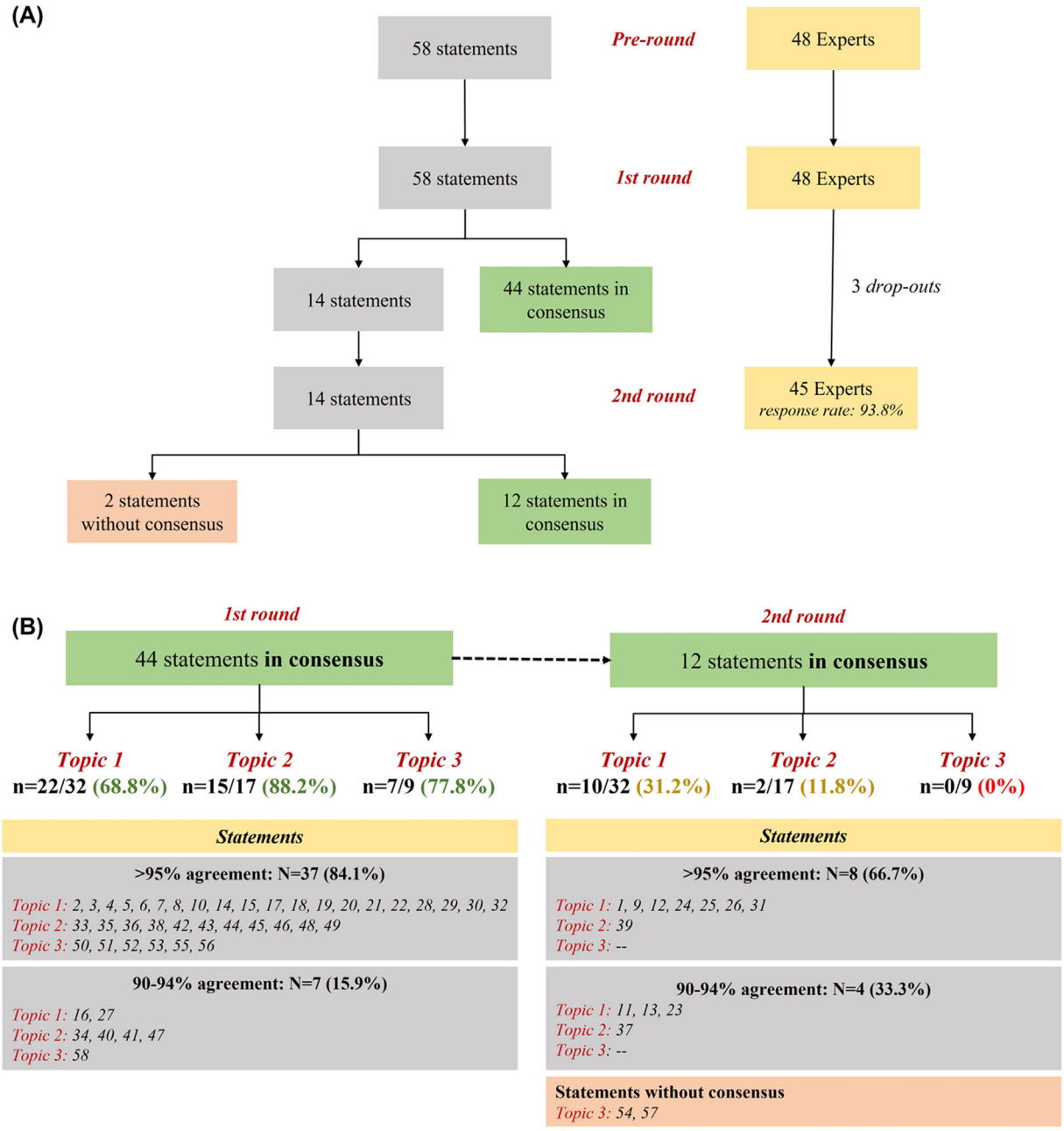

Fig. 1 (A) Flowchart of the Delphi exercise and (B) summary of findings.

positive consensus (Fig. 1B). Table 1 summarize all rounds of consensus. These findings reinforce the conclusions from our previous Delphi study[5] on the need for best practices in severe asthma management during the entire journey of the patient, including early specialist referral, phenotyping evaluation, risk factors/comorbidities assessment, therapeutic selection and rational use of OCS (e.g. patients' eligibility, tailored tapering, early start of biologics) aiming at reducing or avoiding its related-risks (e.g. adverse events, toxicity), especially during chronic use. Conversely, by the end of the study, two statements (3.4%) [items 54 and 57 - both from Topic 3], were not consensual. In fact, statements from this topic focusing on the use of systemic CS in patients not eligible for biological therapy, were significantly less consensual compared to the other two topics ($p = 0.02$). One possible explanation for this is the lack of data for therapeutic decisions when biological therapy is unavailable.[8]

One of the most relevant conclusions of our study was related to the overall consensus obtained on statement 38 ('The reduction of CS therapy should be tailored according to its dose and duration, symptoms control, exacerbations, side effects and assessment of the HPA axis in order to evaluate secondary adrenal insufficiency'), which is aligned with the updated recommendations from GINA 2023 related to adrenal insufficiency in patients taking maintenance OCS or high dose ICS.[2]

Available biologic drugs for severe asthma usually target T2-high inflammatory pathways. Nonetheless, T2-low asthma is often a severe asthma subtype (associated with CS

Table 1 Results of the Delphi exercise.

Item	Statements	Round of consensus	Positive agreement	Neutral opinion	Negative agreement	N. answers
Topic 1: Systemic corticosteroids in severe asthma						
1	Chronic therapy with oral CS is only indicated in patients with severe asthma in step 5 in uncontrolled patients and for those with no indication for other therapies (i.e. biological therapies).	1st	89.6%	6.3%	4.2%	48
		2nd	97.8%	0.0%	2.2%	45
2	In patients under maximized inhalation therapy and controlled comorbidities who are awaiting to start other therapies, it is acceptable to begin chronic treatment with oral CS at the lowest possible dose, which should be discontinued as soon as possible after the initiation of other therapies	1st	97.9%	2.1%	0.0%	48
3	The referral of patients with severe asthma to specialized centers is essential for optimizing the management of cases.	1st	95.8%	0.0%	4.2%	48
4	The history of exacerbations and response to therapy, age at disease onset and biomarkers (eosinophils, IgE, FeNO, among others) are key factors for the identification of severe asthma phenotypes.	1st	100.0%	0.0%	0.0%	48
5	In patients with severe asthma for whom biological therapy are not indicated and in whom the start of chronic therapy with oral CS is intended, the effectiveness of this therapy should be evaluated, including recording of usual medications, number of exacerbations, frequency and doses of medication relief, respiratory function, asthma control measured by standardized questionnaires, and quality of life.	1st	100.0%	0.0%	0.0%	48
6	In patients with severe asthma for whom biological therapy are not indicated and in whom the start of chronic therapy with oral CS is intend, active monitoring of this therapy safety profile (adverse effects) should be performed, including the assessment of the number of infections, BMI and abdominal perimeter, bone densitometry, blood pressure, analytical parameters (e.g. fasting blood glucose, HbA1c, total cholesterol, LDL, HDL, triglycerides, serum protein electrophoresis, serum IgG) and ophthalmological evaluation for early identification of glaucoma or cataracts.	1st	95.8%	4.2%	0.0%	48
7	In patients with severe asthma for whom biological therapy are not indicated and in whom the start of chronic therapy with oral CS is intend, the benefit/risk ratio should be discussed and integrated with each patient's goals, disease status and comorbidities.	1st	97.9%	2.1%	0.0%	48
8	After starting oral CS therapy and for deciding its continuation, effectiveness should be evaluated within 6 months, with an optimal schedule of 1 month and 3 months and adapted to each case (no longer than 6 months).	1st	95.8%	2.1%	2.1%	48
9	The safety criteria for oral CS should be periodically reassessed according to each adverse effect within 12 months. The exception is bone densitometry assessment.	1st	83.3%	4.2%	12.5%	48
		2nd	97.8%	0.0%	2.2%	45
10	The benefits and potential adverse effects of chronic therapy with oral CS should always be discussed with the patient	1st	100.0%	0.0%	0.0%	48
11	Given the significant risk of fracture with oral CS initiation, baseline bone densitometry is recommended for patients using CS for more than 3 months according to NOC 001/2010	1st	85.4%	8.3%	6.3%	48
		2nd	93.3%	0.0%	6.7%	45
12	According to the bone densitometry results (normal or osteopenia) and FRAX index, a supply of calcium and vitamin D (diet or supplement) must be ensured within the beginning of chronic oral CS therapy.	1st	79.2%	12.5%	8.3%	48
		2nd	95.6%	2.2%	2.2%	45
13	Given the significant risk of fracture with the beginning of chronic oral CS, bisphosphonates should be started as soon as some degree of osteoporosis is identified and as long as no contraindication exists.	1st	77.1%	16.7%	6.3%	48
		2nd	93.4%	2.2%	4.4%	45

Table 1 (*Continued*)

Item	Statements	Round of consensus	Positive agreement	Neutral opinion	Negative agreement	N. answers
14	In patients with osteoporosis, referral to specialized medical consultations are recommended, aiming at providing patients with target treatments (i.e. biological therapies) that are currently available.	1st	97.9%	2.1%	0.0%	48
15	The need for concomitant initiation with PPIs, or others that are considered adequate to prevent gastric complications, should be evaluated in all patients, being mandatory in those with risk factors for gastric hemorrhage or pre-existing gastric pathology.	1st	97.9%	0.0%	2.1%	48
16	Before starting chronic therapy with oral CS, patients over 18 years of age must be vaccinated with antipneumococcic vaccine and must maintain the annual flu vaccination, unless contraindicated, according to Vaccination Guidelines.	1st	91.7%	6.3%	2.1%	48
17	Asthma risk factors and comorbidities are responsible for the difficulty in controlling the disease, which is why it is important to promote their reduction/control as a strategy to minimize the use of oral CS.	1st	100.0%	0.0%	0.0%	48
18	Patient's lack of adherence to treatment and the abusive use of relief medication are common problems that should be regularly evaluated to reduce the use of oral CS in severe asthma.	1st	100.0%	0.0%	0.0%	48
19	Improving adherence to therapy and inhalation technique (assessment and teaching) should be considered as strategies for better asthma control and to reduce crises and avoid as possible the use of oral CS.	1st	100.0%	0.0%	0.0%	48
20	All available and feasible therapies for patients with severe asthma (i.e. optimization of inhalation therapy or biological therapy) should be considered to reduce the use of oral CS.	1st	100.0%	0.0%	0.0%	48
21	The timely and early initiation of biological therapy in eligible patients should be one of the strategies to reduce the use of oral CS.	1st	100.0%	0.0%	0.0%	48
22	The use of oral CS is recommended in an asthma exacerbation only if it meets the criteria of moderate to severe exacerbation.	1st	95.8%	4.2%	0.0%	48
23	A dose of 1 mg/kg/day of prednisolone or equivalent weight during 5—7 days in adults and of 1—2 mg/kg/day for 3—5 days in children is recommended for treating asthma exacerbation. This should not exceed the maximum dose of 50 mg/day; there is no need for further progressive dose reduction.	1st 2nd	89.6% 91.1%	4.2% 2.2%	6.3% 6.7%	48 45
24	If a patient with asthma, regardless of the degree of severity attributed by the treating physician, has been subjected to a cumulative dose equal to or greater than 500 mg of prednisolone or equivalent per year (corresponds, on average, to 2 cycles of oral CS in a 70 kg adult), he/she should be referred to a specialist (pneumologist or immunoallergist).	1st 2nd	72.9% 95.6%	12.5% 2.2%	14.6% 2.2%	48 45
25	In addition to other referral criteria, all patients who exceed a cumulative dose of oral CS of 500 mg/year of prednisolone or equivalent, corresponding to an average of 2 or more moderate to severe exacerbations/year, should be referred to a specialist (pneumologist or immunoallergist).	1st 2nd	87.5% 95.6%	6.3% 2.2%	6.3% 2.2%	48 45
26	In patients who have received a cumulative dose greater than 500 mg of prednisolone or equivalent in the last 12 months, an active search for CS' side effects should be considered. This is mandatory in patients with previous comorbidities or at greater risk for the occurrence of these effects.	1st 2nd	85.4% 97.8%	10.4% 0.0%	4.2% 2.2%	48 45
27	The transition from a time-limited CS use regimen for the treatment of an acuteness to chronic use of oral CS or frequent repetition of oral CS should be avoided.	1st	93.8%	6.3%	0.0%	48

Table 1 (*Continued*)

Item	Statements	Round of consensus	Positive agreement	Neutral opinion	Negative agreement	N. answers
28	For a patient with severe asthma presenting two or more severe exacerbations requiring CS in the previous 12 months (and after excluding other causes of asthma exacerbation), the use of biological therapy in phenotypically eligible cases is recommended.	1st	95.8%	0.0%	4.2%	48
29	Adverse effects of chronic CS therapy are cumulative dose dependent and may arise even with daily doses of prednisolone less than 5 mg or equivalent.	1st	100.0%	0.0%	0.0%	48
30	Given the toxicity/adverse effects of CS, their use - even in short cycles, should be carefully balanced.	1st	100.0%	0.0%	0.0%	48
31	The use of CS even in a single cycle (5—7 days in adults) or in short cycles is not free of risks for the patient, and may led to loss of bone density, hypertension, gastrointestinal ulcers/hemorrhages, risk of infections, neuropsychiatric signs/symptoms. The risk-benefit of this therapy must be always considered.	1st 2nd	89.6% 95.6%	6.3% 0.0%	4.2% 4.4%	48 45
32	The prolonged use of oral CS in patients with severe asthma should be balanced and avoided whenever possible, given the cumulative dose impact on the development of adverse effects, which results in increased use of the therapy and health care costs.	1st	100.0%	0.0%	0.0%	48
Topic 2: Systemic corticosteroids in patients eligible for biological therapy						
33	To define eligibility for biological therapy, patients should be evaluated for: 1) asthma control, ideally assessed using standardized questionnaires; 2) number of severe exacerbations (which imply the need to resort to the ER/hospitalization or the need to use CS for treatment); 3) use of therapy with oral CS; 4) respiratory function and 5) type 2 inflammation parameters such as eosinophilia, FeNO and total IgE.	1st	97.9%	2.1%	0.0%	48
34	The timely initiation of biological therapy is recommended considering its potential benefits in airway remodeling mechanisms.	1st	93.8%	6.3%	0.0%	48
35	Detailed phenotyping within different dimensions (clinical, inflammatory, functional) should be used aiming at targeting treatments to improve the effectiveness of the various therapeutic options (e.g. biological therapy, bronchial thermoplasty, bariatric surgery, among others).	1st	97.9%	2.1%	0.0%	48
36	In patients with severe asthma who are eligible for different biological therapies, detailed phenotyping is recommended to guide the selection among the available options.	1st	97.9%	2.1%	0.0%	48
37	In case of exacerbation and considering the available resources, pathophysiological mechanisms (infection, increased inflammation, and predominant inflammatory type) should be determined using: 1) clinical parameters (infection parameters, exposure to allergens or irritants/pollutants); 2) type 2 biomarkers (FeNO, eosinophils); 3) inflammatory markers of infection (such as CRP and neutrophilia) and 4) cell count and microbiological examination of sputum. The aim is to decide on the use of oral CS, regardless of the concomitant use of a biological agent.	1st 2nd	83.3% 91.1%	12.5% 4.4%	4.2% 4.4%	48 45
38	The reduction of CS therapy should be tailored according to its dose and duration, symptoms control, exacerbations, side effects and assessment of the HPA axis in order to evaluate secondary adrenal insufficiency.	1st	100.0%	0.0%	0.0%	48
39	If an evidence of patients' global improvement and satisfactory control of asthma is observed, corticotherapy tailored reduction regimen should be started ideally within 4 weeks after the first dose of the monoclonal antibody.	1st 2nd	77.1% 95.6%	12.5% 2.2%	10.4% 2.2%	48 45

Table 1 (*Continued*)

Item	Statements	Round of consensus	Positive agreement	Neutral opinion	Negative agreement	N. answers
40	The reduction of CS therapy after the beginning of biological therapy should be carried out considering the combination of symptoms control, quality of life, rate and severity of exacerbations, respiratory function, evaluation of side effects, risk of adrenal insufficiency and type 2 biomarkers.	1st	93.8%	4.2%	2.1%	48
41	The reduction regimen of oral CS should consider the basal dose and treatment duration (over 6 months), which can be further accelerated up to a dose of 7.5 mg (i.e. physiological dose according to the literature) of prednisolone or equivalent.	1st	91.7%	6.3%	2.1%	48
42	Corticotherapy reduction regimen from a dose of 7.5 mg of prednisolone or equivalent should be tailored to each patient and consider the periodic assessment of HPA axis and monitoring of signs and symptoms associated with adrenal insufficiency.	1st	95.8%	4.2%	0.0%	48
43	When reducing CS therapy, the risk of developing adrenal insufficiency should be early assessed and continuously monitored using laboratory (e.g. decrease in serum cortisol, ACTH, hypoglycemia, hyponatremia) and clinical (fatigue, weakness, weight loss, nausea, vomiting, diarrhea or hypotension) parameters.	1st	97.9%	0.0%	2.1%	48
44	When adrenal insufficiency is detected, referral to endocrinology should be made.	1st	100.0%	0.0%	0.0%	48
45	The effectiveness of biological therapy should be evaluated within 4—12 months after therapy beginning depending on the drug.	1st	95.8%	2.1%	2.1%	48
46	The complete assessment of the biological therapy effectiveness should consider the identification of patients' comorbidities or risk factors that may contribute to disease worsening and reduce the response to therapy.	1st	100.0%	0.0%	0.0%	48
47	Insufficient adherence to inhaled treatment in patients undergoing biological therapy is a common problem that must be identified and solved.	1st	93.8%	4.2%	2.1%	48
48	In case of failure with biological therapy, and considering patient's inflammatory profile, evolution and reassessment, a possible modification to another biological therapy (from similar or different classes) or treatments (e.g. azithromycin, bronchial thermoplasty or bariatric surgery) should be evaluated.	1st	97.9%	2.1%	0.0%	48
49	If an overlap in eligibility for several biological therapies exist and in the absence of effectiveness of one of them, a therapeutic trial with an alternative biological therapy should be carried out to reduce/avoid the use of oral CS.	1st	95.8%	4.2%	0.0%	48
Topic 3: Systemic corticosteroids in patients not eligible for biological therapy						
50	Patients with severe uncontrolled type 2 asthma are not currently eligible for the available biological therapies, thus other treatment alternatives should be considered.	1st	95.8%	0.0%	4.2%	48
51	For patients with severe asthma undergoing oral CS and who are not eligible for biological therapy, the existing therapeutic options (e.g. chronic treatment with azithromycin, bronchial thermoplasty or bariatric surgery, where applicable) should be considered in an attempt to improve asthma control and reduce/discontinue oral CS.	1st	97.9%	2.1%	0.0%	48
52	To identify non-type 2 asthma, the maximum combination of clinical parameters (e.g. adult onset of disease, obesity, infections' history, poor response to systemic CS therapy, absence of nasal polyposis or respiratory disease exacerbated by NSAIDs or atopy) and the absence of biomarkers suggestive of type 2 inflammation (e.g. elevated FeNO values, blood eosinophilia, induced sputum or bronchoalveolar lavage) should be considered.	1st	100.0%	0.0%	0.0%	48

Table 1 (*Continued*)

Item	Statements	Round of consensus	Positive agreement	Neutral opinion	Negative agreement	N. answers
53	As severe non-type 2 asthma typically does not respond effectively to systemic CS, this should not be used as chronic treatment unless improvements in previously defined efficacy parameters are noted and no other effective therapy is available.	1st	95.8%	4.2%	0.0%	48
54*	The use of systemic corticosteroid therapy in patients with severe non-type 2 asthma may contribute to worsening its control, considering the usual side effects (e.g. weight gain, sleep interference, gastric symptoms), and should therefore be avoided.	1st 2nd	87.5% 84.4%	12.5% 8.9%	0.0% 6.7%	48 45
55	In patients with severe non-type 2 asthma presenting acute signs and symptoms of disease severity after therapy failure, short cycle of oral CS should be considered, but always evaluating the risk/benefit ratio.	1st	100.0%	0.0%	0.0%	48
56	In patients with severe non-type 2 asthma undergoing treatment with chronic systemic CS, the dose of CS should be reduced until its suspension (as referred in statements 41 and 42) when clinically possible (safeguarding control of asthma) and with side effects monitoring.	1st	100.0%	0.0%	0.0%	48
57*	Whenever available, bronchial thermoplasty should be considered as an additional therapeutic option in selected patients with non-type 2 inflammation and in patients with type 2 inflammation with insufficient response to targeted therapies (uncontrolled symptoms and frequent exacerbations).	1st 2nd	72.9% 82.2%	18.8% 15.6%	8.3% 2.2%	48 45
58	In patients with severe, uncontrolled, type 2 asthma, chronic treatment with azithromycin in an immunomodulation scheme, rather than chronic systemic CS, should be considered for a period of 6–12 months after evaluating the potential risks of this therapy and by periodically reassessing its benefits.	1st	93.8%	6.3%	0.0%	48

* Statements without consensus during the Delphi exercise.

resistance) with limited treatment options (biologics are lacking for this indication) or scarce overall clinical evidence on their benefit or otherwise. The European Medicines Agency has recently approved tezepelumab (anti-TSLP, an alarmin) for the treatment of severe asthma without limiting a specific type of condition, although it is still not reimbursed in several countries; results regarding the use of this drug in patients previously non-eligible for biological therapy are promising.[9] Yet, as mentioned in statement n. 53, physicians agreed that systemic CS should not be used in these patients as chronic treatment unless improvements in previously defined efficacy parameters are noted, and no other effective therapy is available. Conversely, no consensus regarding the use of CS in non-type 2 asthma patients or on the selection of alternatives for type 2 inflammation with insufficient response to targeted therapies were obtained (statement n. 54 '*the use of systemic corticosteroid therapy in patients with severe non-type 2 asthma may contribute to worsening its control, considering the usual side effects (*e.g. *weight gain, sleep interference, gastric symptoms), and should therefore be avoided*'). Although speculative, it is possible that some experts might still consider the use of systemic CS in this population due to the lack of current therapeutic options in the country for non-type 2 asthma. Current available GINA recommendations also consider the use of dupilumab for adults or adolescents requiring treatment with maintenance OCS, although available evidence for this indication is still scarce.[2]

Another controversial item among experts is related to the benefits of using bronchial thermoplasty for severe asthma (statement n. 57 '*whenever available, bronchial thermoplasty should be considered as an additional therapeutic option in selected patients with non-type 2 inflammation and in patients with type 2 inflammation with insufficient response to targeted therapies (uncontrolled symptoms and frequent exacerbations)'*). Yet, recent studies show that this technique may improve lung function and both asthma control and asthma quality of life scores in selected patients but with increased frequency of unscheduled doctor-visits and rescue courses of OCS and antibiotics.[10]

Although our study has some limitations related to the study design, relatively small sample, and large number of raw statements, it was strictly conducted according to a widely recognized method for achieving consensus and reflects the clinical practice challenges in severe asthma at a national level among selected key opinion leaders. These findings can support clinical decisions on oral/systematic CS use and tapering, adverse effects screening, and biologics initiation in severe asthma, while areas of that did not reach consensus, namely on the effects of CS for non-type 2 asthma and alternative approaches for non-responders to target therapies should be further investigated.

Conflicts of interest

None.

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Role of the funding source

The funding source had no role in study design, data collection, analysis and interpretation, nor in the writing and submitting decision of the article.

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LETTER TO THE EDITOR

PI*ZQ0$_{Attikon}$ genotype discovery in severe alpha-1 antitrypsin deficiency

A_1Antitrypsin (AAT), the major protease inhibitor in serum and severe AAT deficiency (AATD) worldwide, relates mainly to the homozygous state of the PI*Z variant.[1] However, the genetic repertoire of severe AATD is constantly expanding far beyond the homozygous PI*Z variant to a multitude of rare alleles decoding for deficient, dysfunctional or non (null-alleles) producing AAT.[2] In recent years a geographical trend towards South Europe also began to appear regarding severe AATD related to rare variants.[3] Recently, we described that by genotyping AATD in Greece, a multiplicity of rare and ultra-rare variants and a diversity of rare combinations were observed in two-thirds of patients, confirming an established North-South European geographical trend in rare variants.[4] The Greek rare variants embraced the null PI*Q0$_{Bellingham}$, PI*Q0$_{Amersfoort}$, PI*Q0$_{Granite\ Falls}$, PI*Q0$_{Saint\text{-}Etienne}$, PI*Q0$_{Mattawa}$; and the deficient variants PI*M$_{Heerlen}$, PI*M$_{Procida}$, PI*M$_{Malton}$, PI*M$_{Würzburg}$, and PI*N$_{Hardfordcity}$; PI*O$_{Feyzin}$ and PI*P$_{Lowell.}$(p.Asp280Val).[4] The epitome of rarities in AATD in Greece was the discovery of a novel variant named as Q0$_{Attikon}$(c.1A>G; p.Met1?), herein described in detail.

A 56 year-old non-smoker male, BMI=27.1 kg/m^2, with no family history of lung disease or toxic environmental and occupational exposures was referred to our center for repetitive exacerbations upon overlapping early-age-emphysema, bronchiectasis and eosinophilic asthma. He had dyspnea on exertion which had progressively deteriorated in the last 3 years (MRC=3) and cough. The patient had severe panlobular emphysema with bronchiectasis (Fig. 1a,b,c), de-oxygenated on exertion from SpO_2=94% to 80% and presented values of forced expiratory volume at 1 sec (FEV_1)% predicted, FEV_1/ Forced vital capacity (FVC) %, diffusion capacity of the lung for carbon monoxide (DLCO)% predicted and transfer coefficient for the diffusion of carbon monoxide (CO) [DLCO/alveolar volume (VA)] % predicted of 37, 34.8, 53 and 72 respectively. More precisely in the last 2 years, the FEV_1 value deteriorated from 1520 ml to 1300 ml, corresponding to an accelerated decline of 110 ml per year. AAT serum levels by nephelometry were 0.14 g/L (0.9—2.0 g/L) with normal values of CRP at 2.7 mg/L(0—5 mg/L).

Genetic analysis was performed at the German AAT Laboratory at the University of Marburg. The laboratory methods are described in detail elsewhere.[4] After informed consent, the patient's dried blood spot samples were tested using the Progenika AAT genotyping kit (Progenika Biopharma, S,A, Derio, Spain) on the Luminex 200 (Luminex, Austin, TX, USA). This multiplex PCR (polymerase chain reaction) and hybridization test allows the simultaneous identification of 14 alleles. The test confirmed the presence of Z allele in heterozygosity. Phenotyping was performed by isoelectric focusing (IEF). IEF is used for samples that indicate other mutations may be present. On IEF only the Z-protein was identified, suggesting an additional null mutation given the discrepancy between the very low levels of AAT and the genotype- phenotype findings so far. Whole *SERPINA1* gene sequencing in a reference laboratory in Spain followed identifying a (c.1A>G) heterozygous mutation. This new variant, identified by Next Generation Sequencing (NGS) and confirmed by Sanger sequencing (Fig. 2), affected the translation initiation codon (Met1) completely inhibiting AAT production. The case was discussed in a web-based multidisciplinary meeting dedicated to AATD (www.respifil.fr) confirming the above findings. Family members were investigated (Fig. 2) and augmentation therapy was recommended. The patient presented no findings compatible with liver disease both in liver biology blood examination and in hepatic ultrasound and shear wave elastography (S0 steatosis and F0 fibrosis staging) and had no history of alcohol abuse.

The new variant was named by the University-Clinic and Hospital of discovery Pi*Q0$_{Attikon}$. In this case the new variant proved clearly pathogenic and seriously deleterious. In the absence of functional studies, this was demonstrated mostly from a high REVEL score of 0.759 (range 0—1)[5] in association with the clinical presentation of the patient, a never smoker. We have shown that in Greece the great majority of patients with severe AATD relates to rare variants instead of the Pi*ZZ phenotype that prevails worldwide.[4] Therefore, the discovery of a novel, never reported and clearly pathogenic variant constitutes the epitome of rarities in severe AATD in Greece.

Rare variants are increasingly reported in recent years, by genotyping, mainly in south Europe and surprisingly as reported by us in Greece, the epicenter of rarities in severe AATD.[2,4,6] A significant proportion were homozygous Q0 variants in a multiplicity of different genotype combinations with very low AAT levels, almost imperceptible in fact. Another significant proportion of variants were in compound

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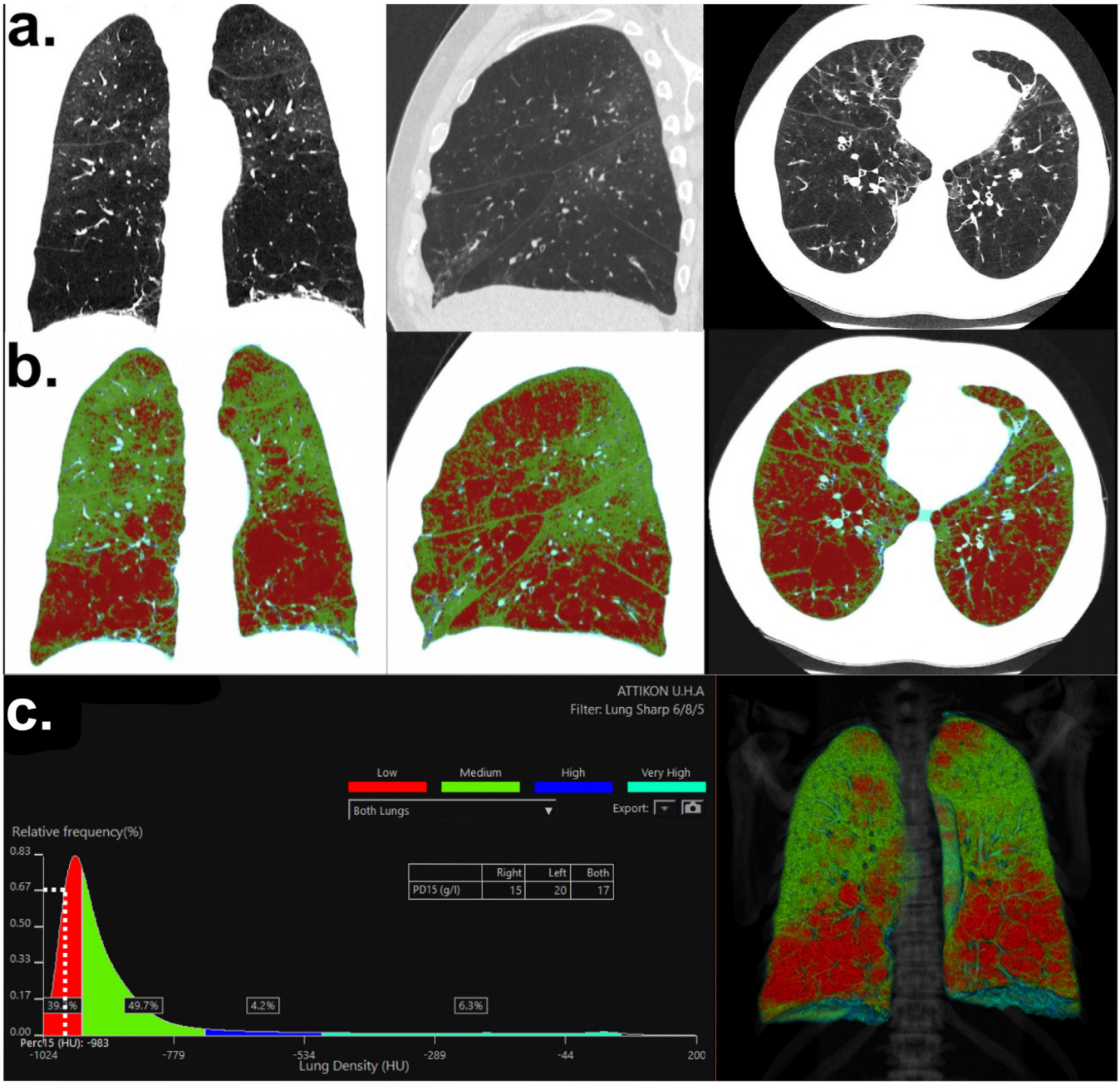

Fig. 1 a. High-resolution chest computed tomography of the proband. Normal lung parenchyma distortion due to emphysema. Frontal, sagittal and axial views (from left to right), b: Color-coded visual map on lung density analysis to assess lung emphysema. Red-colored pixels represent attenuation lower than <-950HU, c: Lung density distribution graph. PD15 = -983HU shows an estimated pulmonary density of 17 g/L (for both lungs). The percentage of emphysema (areas of low-attenuation) was estimated ~ 44,2% for both lungs.

heterozygous state with the Z variant as in the case described herein and another significant proportion were Mdeficient variants in different combinations with null (Q0) or Z variants not always identifiable without genotyping.[4] From the above observation concern may arise regarding the dose-effectiveness of current dose recommendation of augmentation treatment in zero or almost zero carrying AAT levels, since previous international protocols included exclusively ZZ homozygous phenotypes. Furthermore, additional investigation is necessary regarding the clinical history and fate of these patients as well as the clinical phenotype expressed from carriers of rare variants; a project that fulfills the European Alpha-1 Research Collaboration (EARCO) consortium.[7]

In conclusion, the characterization of a new null variant of *SERPINA1* named by the University-Clinic and Hospital of discovery Pi*$Q0_{Attikon}$ associated with a Pi*Z variant, leading to severe AATD is described. This rare mutation c.1A>G has

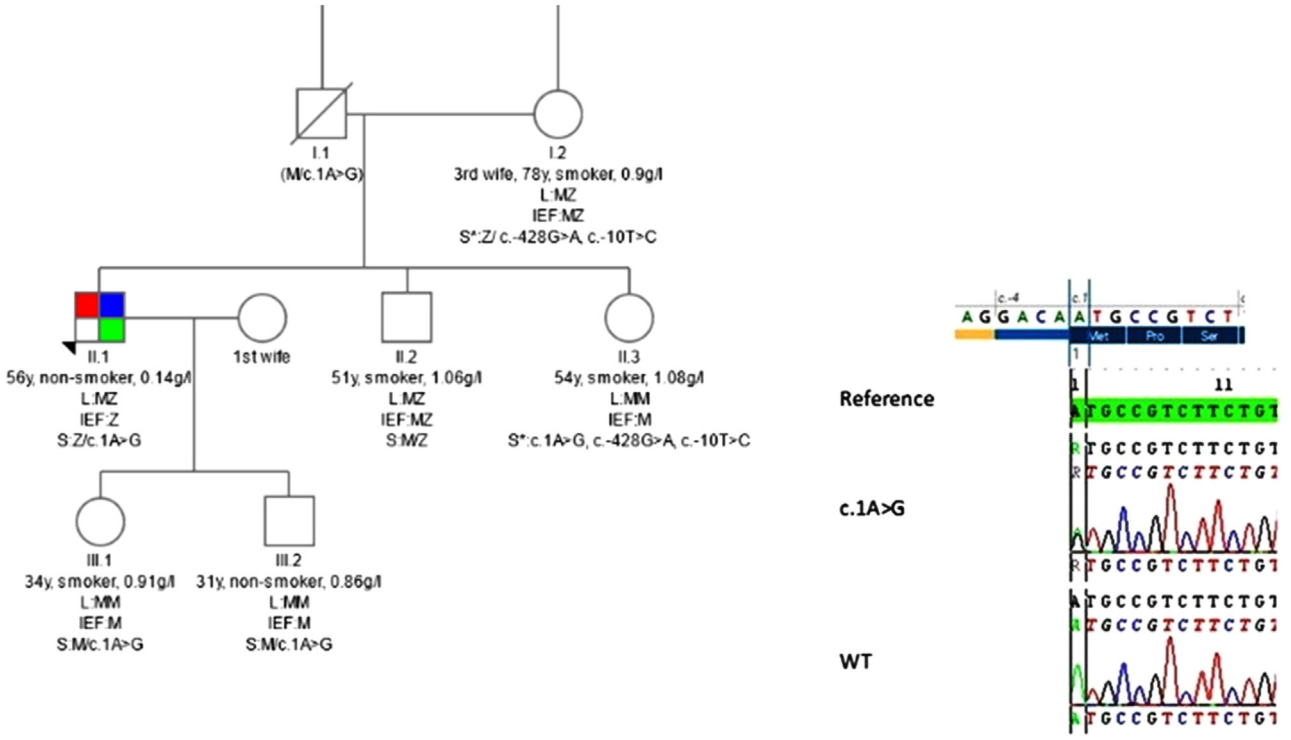

Fig. 2 Three-generation pedigree of the proband. Numbers below individual symbols are age at inclusion in the study. Smoking status (pack/years) and levels of alpha-1 antitrypsin in serum (g/l) are also depicted. In details shown for each individual [parents I1, I.2, the proband, sister and brother II.1, II.2, II.3 from the third marriage of the father of the proband and children III.1, III.2 first marriage of the proband], the results of the analysis including LUMINEX (L), Isoelectric focusing (IEF) and gene sequencing (S). *The variant c.-428G>A; c.-10T>C found in individuals I.2 and II.3 seems to be like a M variant in the IEF. c.1A>G corresponding to $QO_{Attikon}$newly described mutation is depicted at the proband II.1 in compound heterozygous state with PI*Z as well as at his sister II.3 and his children III.1 and III.2 at heterozygous state. (M/c.1A>G) for individual I.1 indicates an obligate carrier status. All members of the bloodline are reportedly asymptomatic except the proband which presents emphysema (red), bronchiectasis (blue) and asthma (green). In the insert the$QO_{Attikon}$ mutation confirmed by Sanger sequencing: sequencing results of proband compared with wild type and reference sequence. Translation initiation codon (Met1) is affected by this mutation (top of the insert figure).

never been identified before. Gene sequencing was necessary for genetic diagnosis. In the future the detection of rare genotypes by widening AATD spectrum and geographic distribution of variants may add to understanding of the anthropologic evolution of its mutations and probably help to personalize preventive and therapeutic measures.

Author's contributions

SAP made a major contribution to the concept and design of the study, to the acquisition, analysis and interpretation of data, and wrote the final version of the manuscript with EDM; MV performed the genetic analysis of the patient, made a major contribution to the interpretation of data regarding the new variant and wrote part of the manuscript; AL had major role in the clinical management of the patient, the acquisition and interpretation of data for all family members and critically revised this work for important intellectual content; MB, CL, MD, MFO made major contributions to the interpretation of data for the new variant and revised this work critically for very important intellectual content; EE, LO performed the NGS for the identification of the new variant, provided the figure for Sanger analysis and revised this work critically for important intellectual content; MK, VA had a major role in the management of the patient upon hospitalization and revised this work critically for important intellectual content; SP, CK prepared the radiology figures and figure legends of the manuscript and revised this work critically for important intellectual content; LK, IF, JFM had major contribution in the interpretation of data for the new variant and revised this work critically for very important intellectual content; CVF and TG had major contribution in the genetic analysis of the patient in their expert laboratory, played a major role in the interpretation of all data and revised this work critically for important intellectual content; EDM made a major contribution to the concept and design of the study, to the acquisition, analysis and interpretation of data, had access to all data, supervised the accuracy and integrity of all parts of the work and wrote the final version of the manuscript with SAP. All authors read and approved the final version of the submitted publication.

Declaration of Competing Interest

EE and LO are working at the Progenika Biopharma, a Grifols Company, Derio, Vizcaya, Spain. All authors have provided

an ICMJE statement regarding any other conflict of interest related and un-related to this work.

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LETTER TO THE EDITOR

Is there a place for mechanical in-exsufflator in the emergency department?

A seventy-nine-year-old man presented to the emergency department (ED) with dyspnea, cough and bronchial secretions that he was unable to mobilize.

He had a right hemiparesis and dysphagia due to intracerebral haemorrhage, and was a long-term bedridden patient, without cognitive deficits, and with good social support. No previous history of pulmonary diseases.

On admission, he was hemodynamically stable and afebrile, but presented tachypnoea with accessory muscle use. Pulmonary auscultation revealed decreased breath sounds on the left and scattered rhonchi on both sites.

Blood work revealed leucocytosis (24,15 × 10E3/uL leukocytes) and a C Reactive Protein of 3.57 mg/dL. Arterial blood gas showed isolated type 1 respiratory insufficiency (FiO2 35%, pH 7.468, pO2 36.2 mmHg, pCO2 39.9 mmHg, HCO3- 28.7 mmol/L).

The X ray revealed an opacified white left lung (Fig. 1). Chest tomography scan showed the left airways filled with mucoid material, with atelectasis of the entire left lung and mediastinal shift to the ipsilateral side. Evaluation of the pulmonary parenchyma did not show any suspicious alterations, including consolidations or expansive lesions.

The patient was put on an empiric antibiotic therapy with ceftriaxone 2mg once a day and dual bronchodilation (ipratropium bromide 60 μg every 6 hours, and salbutamol 200 μg every 6 hours).

Since the patient was not deemed eligible for admission to the Intensive care unit (ICU), emergency bronchoscopy was protracted. Instead, and although it wasn't possible to quantify the peak cough flow (PCF) in the ED, the medical team attempted using Mechanical in-exsufflator (MI-E) to clear the tracheobronchial airway.

We used the following parameters for MI-E therapy: oronasal interface, automatic mode with cough track, inspiratory pressure of +40 cmH2O for 3 seconds, with low inspiratory flow rate, expiratory pressure of -40cmH2O for 2,5 seconds. We progressively adjusted the pressures with +/- 5cmH2O increments every 2 or 3 cycles, starting with expiration pressure, until +50cmH2O and -60cmH2O, with which we got a MI-E PCF $>$ 280 L/min. The secretions were still hard to expel, so, we added an oscillation on both phases 10Hz, 10cmH2O.

After 8 treatments consisting of 2 series of 5 cycles of MIE, there was a significant increase in vesicular murmur in the left apical region of the thorax and the patient's oxygen saturation increased to 93% with a Ventimask at 31% FiO2. We continued the treatment for an additional two days, six times per day.

A follow-up Chest X-ray (48h hours later) revealed a significant improvement, with complete resolution of the left lung atelectasis (Fig. 2).

As the patient kept ineffective cough, with PCF less than 60L/min, we instructed the patient's daughter on how to use the MI-E. At discharge, the patient's oxygen saturation was 94% in air.

The elderly and bedridden population is increasing. Neurological diseases and immobility are associated with respiratory dysfunction, due to weakness of inspiratory and/or expiratory muscles (essential to an effective cough), lung volume changes (a combination of muscle weakness and alterations of the mechanical properties of the lungs and chest wall) and bulbar dysfunction, with loss of the ability to cough and swallow (that may result in pooling of saliva and mucus in the pharynx, predisposing to aspiration). Even so, there aren't any studies on respiratory function, quality of cough, prevalence of respiratory infections, atelectasis, acute or chronic respiratory failure, and their repercussions on morbidity and mortality in elderly people who are bedridden for a long time.

Cough augmentation techniques aim to improve cough efficiency, with potential for both short— and long—term effects on pulmonary morbidity. During episodes of acute respiratory exacerbation, cough augmentation techniques could clear impacted secretions to prevent the progression to respiratory failure. In the long-term, the regular use of cough augmentation is intended to reduce the incidence and/or severity of respiratory tract infections requiring unscheduled hospitalization.

MI-E therapy is a cough augmentation technique that increases inspiratory and expiratory flow to restore cough quality and improve secretion mobilization.[1] Experts suggest that using MI-E in very weak patients is a priority.[2] However, the overall quality of evidence on the efficacy and safety of MI-E is very low. Most of the research on cough augmentation techniques has been carried out in chronic neuromuscular disease (NMD) and in extubation or weaning of critically-ill patients.[3,4] The author couldn't find any studies on the efficacy and safety of the technique in long-term bedridden patients

The author presents a case of pulmonary atelectasis in a long-term bedridden patient, which highlights the

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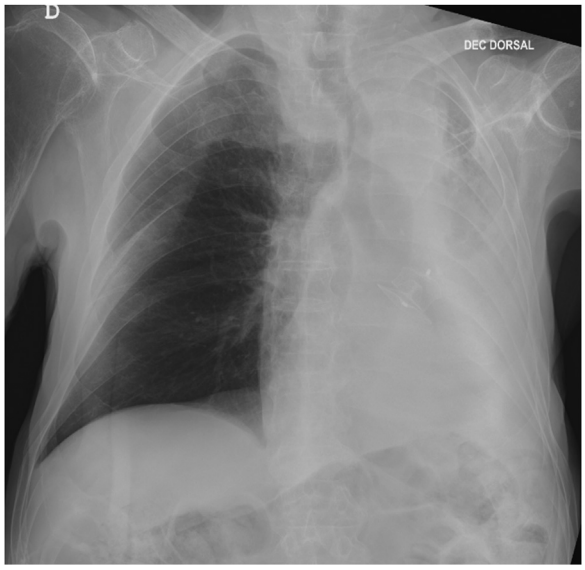

Figure 1 Admission chest X-ray.

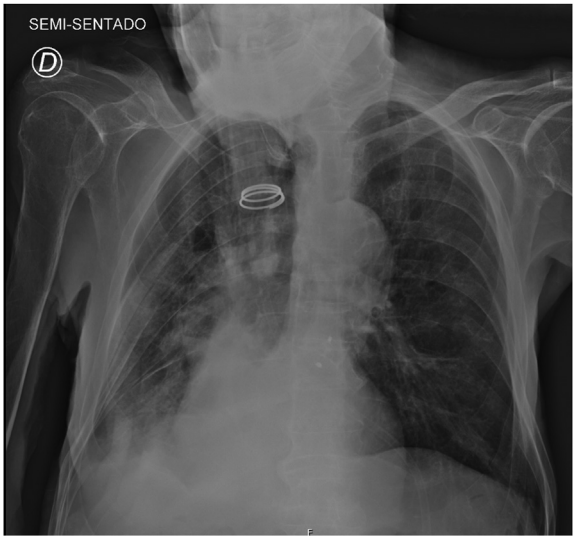

Figure 2 Chest X-ray 48h hours later.

effectiveness of a non-invasive, generally safe and relatively inexpensive technique (the MI-E), even in the context of an ED, for patients not eligible for ICU or broncoscopy.

Future research is needed to evaluate the effectiveness, potential adverse effects, precautions and contraindications of MI-E in the long-term bedridden patients. In addition to clinical outcomes, factors such as patient tolerance, adherence, treatment burden, knowledge of the technique, confidence, availability of devices, and cost should be considered by clinicians, patients, and caregivers.

Declarations of Competing Interest

None.

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LETTER TO THE EDITOR

An investigation of TB infection and reinfection among stone quarry workers

Stone quarry workers are considered at increased risk from tuberculosis (TB) mainly because of their prolonged exposure to silica.[1] They are considered a vulnerable population group for TB in Portugal, especially in the municipalities of *Penafiel* and *Marco de Canaveses*.[2,3]

Understanding transmission patterns is essential for developing prevention strategies and prioritising resources.[4] Whole-genome sequencing (WGS) is an important tool to identify clusters.[5,6]

Data from all cases of TB in stone quarry workers from 2015 to 2019, for whom *M. tuberculosis* (MTB)-positive specimens were available for complementary laboratory testing (n = 35, 47.9% of the eligible sample) was analysed. The data was collected by the local public health services during their routine surveillance and public health authority duties. TB clusters were identified using WGS (single nucleotide polymorphism [SNP]-based approach[7]), and the largest cluster identified was investigated to distinguish potential exposure settings and propose strategies to reduce transmission.

Six clusters were found. The largest cluster included 12 MTB isolates from 2015 to 2019. Five of the 12 cases (41.7%) had already had at least one previous episode of TB, six (50.0%) had silicosis and alcohol dependence, and eight (66.7%) were smokers (Fig. 1). Out of the 12 cases, who lived in seven different parishes of the *Penafiel* and *Marco de Canaveses* municipalities, nine (75.0%) were employed in seven companies, and nine (75.0%) reported frequently attending seven different coffee shops (Fig. 2).

Cases C1.2 and C1.5 were identified as close contacts of a co-worker from the same company that had had active TB in 2014 (a non-genotyped case that was considered the primary case for this cluster - X). The three worked in the central region of Portugal during the week and returned to three different parishes for the weekend. C1.2 shared the same room, and C1.5 shared transport and meals with the primary case. C1.2 had active TB in 2015, diagnosed during screening; C1.5 only had active TB in 2017 (a reinfection, previous treatment in 1999). C1.5 was identified for screening but the follow-up cannot be traced, and the screening result is not known. Failure to attend or incomplete screening was previously reported in this population,[2] with active TB cases identified late among those considered close contacts.

Case C1.5, who also had silicosis and was a smoker, had a cough for three months before the diagnosis (Fig. 1); he was the suspected primary case of a community outbreak that included another six cases of TB in the first six months of 2017 in the parish where he lives. None of the other six cases were genotyped.

The primary case of this genotyped cluster (X) was considered cured in 2015 but had a second episode of active TB in 2017 at 33 years old. The new strain was genotyped and found to be associated with a different cluster suggesting that X was re-infected two years after his cure.

Case C1.9 was working abroad at the time of diagnosis and reported attending a bar also attended by C1.12 and two previous non-genotyped cases (Fig. 2).

These 12 stone quarry workers had identical strains of *Mycobacterium tuberculosis* (with less than six differences in SNP), which suggests that they belong to the same chain of transmission. Nevertheless, it is probable that missing intermediary cases exist both in the general community and in other non-genotyped cases among stone quarry workers. The importance of household contact was not assessed in this study, but the epidemiological enquiry did not find any relatives who previously had TB.

Based on epidemiological investigation data, only close contacts in the workplace were identified. Social connections such as those occurring in coffee shops and not identified by the case, are difficult to find. However, these social contacts seem to be important in maintaining the ongoing active transmission in this high-risk population.

Active transmission of TB among stone quarry workers in this cluster was driven by multiple factors, including those related to occupation, but also those related to social habits. We highlight that this outbreak probably spread to different regions of the country and possibly to other countries. Stone quarry workers' vulnerability, mainly due to silicosis, probably makes them more prone to TB infection and reinfection.

To better understand TB transmission dynamics in this high-risk population and the community, it would be beneficial if all the cases occurring in the country or region were genotyped. That would allow us to understand the transmission chains and different exposure settings better.

It is paramount that the local public health services explore all possible exposure settings during the epidemiological investigation whenever a new case is notified. Strategies to protect the most vulnerable should be enhanced: not

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Case	Silicosis	Tobacco	Alcohol	Previous TB
C1.1	Yes	Yes	No	Yes
C1.2	No	No	Yes	No
C1.3	Yes	Yes	Yes	Yes
C1.4	No	Yes	Yes	Yes
C1.5	Yes	Yes	No	Yes
C1.6	Yes	No	No	Yes
C1.7	No	No	No	No
C1.8	No	Yes	No	No
C1.9	No	Yes	Yes	No
C1.10	Yes	No	No	No
C1.11	No	Yes	Yes	No
C1.12	Yes	Yes	Yes	No

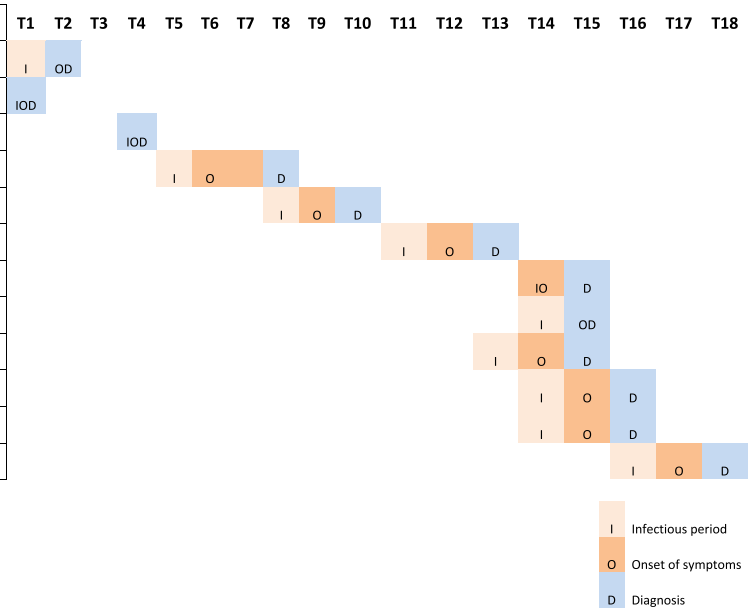

Fig. 1 Detailed analysis of the 12 cases of Cluster 1 by trimester (T) regarding risk factors and time of diagnosis. Infectious period was considered for three months before symptoms onset if positive sputum smear or for one month before symptoms onset if negative sputum smear.

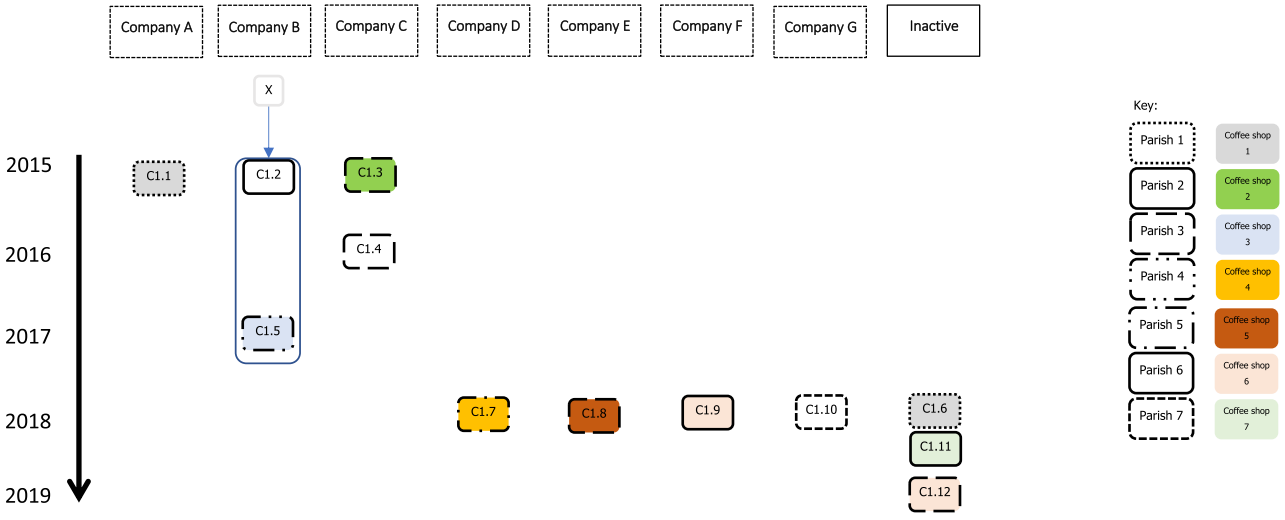

Fig. 2 Detailed analysis of the 12 cases of Cluster 1.

only strategies addressing individuals such as promoting screening and health literacy to recognize symptoms and decrease diagnosis delay, but also environmental level strategies such as improving the ventilation conditions of the sites at which exposure occurs.

Ethical approval for this study was obtained (Ethics Boards of the Northern Regional Health Administration, 134/2022).

No funding was obtained for this study.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgments

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CORRESPONDENCE

Underestimated asthma prevalence in Guarda's district leads to overestimated hospitalizations

Dear Editor,

As pulmonologists in Guarda's Local Health Unit, we cannot avoid commenting on the editorial published in March 2023 in Pulmonology Journal[1] as it greatly concerns us.

The article states that, in mainland Portugal, the Guarda district has the most prevalence-adjusted asthma hospital admissions. These results are based on an asthma prevalence in the Guarda district of 1.7%. That estimated prevalence is, by far, the lowest in mainland Portugal. The lowest after Guarda is the Braga district, with 4.2% (2.5 times higher than in our district).

The reference for this data is the Portuguese National Asthma Survey,[2] published in 2010. However, there is no detailed data on asthma prevalence by district in that study. The results are presented by region, with a prevalence of asthma of 6.2% in the centre of Portugal (location of Guarda). This prevalence includes our neighbouring districts, where patients have similar characteristics:

- 5.2% in Viseu (more than three times higher than the estimated prevalence in Guarda)
- 4.95% in Castelo Branco (2.9 times higher than the estimated prevalence in Guarda).

It is therefore impossible to know where the data for the Guarda district was found.

According to the Portuguese census of 2021, the population in Guarda's Local Health Unit area is 137,788 inhabitants.

In our hospital, we conduct severe asthma consultations. In 2022, we observed a total of 238 patients. GINA estimates that 3.7% of asthma patients worldwide have severe asthma. This statistic allows us to infer that, given our consultation data compared to the Guarda district population, we obtained circa 6432 patients with asthma in the Guarda district. This number gives us an estimated asthma prevalence in the Guarda district of 4.67% - a significantly higher percentage than the one mentioned in the editorial abovementioned. Moreover, that is a low estimate since not all patients with severe asthma in the Guarda district have medical records in our hospital.

Therefore, the prevalence of asthma in the Guarda district is underestimated and distorts the prevalence-adjusted asthma hospital admissions, skewing the study's conclusions.

Conflicts of interest

The authors have no conflicts of interest to declare.

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PHOTO

A rare case of pulmonary malignant peripheral nerve sheath tumor

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Malignant peripheral nerve sheath tumors (MPNSTs) are extremely rare tumors (0,001% incidence in the general population, less than 10% of all soft tissue sarcomas) and, in adulthood, they are associated with neurofibromatosis type 1.[1] Primary pulmonary MPNSTs can mimic lung cancer but there are few literature case reports.[2,3]

A 53-year-old non-smoker male, with no relevant past medical history, went to the emergency department complaining of chest discomfort over several days. The patient had no family history of neurofibromatosis or café-au-lait spots on physical examination. The electrocardiogram and cardiac markers were normal, but the x-ray showed a left hypotransparency. The chest computed tomography (CT) presented a homogeneous spindle-shaped mass (100 × 70 mm), with no signs of invasion of mediastinal structures or lymphadenopathies.

The positron emission tomography (PET) revealed a high accumulation of fluorodeoxyglucose (FDG) in the mass (Fig. 1A). Bronchofibroscopy did not show endobronchial lesions. Two transbronchial lung biopsies were performed: the first one had a small amount of material but revealed a probably neuroendocrine tumor; the second biopsy showed only necrosis. The patient underwent an upper left lobectomy and systematic lymph node dissection by thoracotomy; no evidence of invasion of the thoracic wall was found.

Surgical specimen histology revealed a spindle cell tumor, with infiltration of bronchial structures (Fig. 1B), and atypical neoplastic cells, with frequent mitotic figures (Fig. 1C). On immunohistochemical study, tumoral cells expressed vimentin and B-cell lymphoma 2 (BCL2). There was loss of tri-methylation of lysine 27 on histone H3 protein (H3K27me3) expression in the tumoral cells. Pancytokeratins (AE1-AE3), S100 protein, desmin, cluster of differentiation 34 (CD34) and Melan A were negative. There was no translocation t(x,18). MPNST was the suggested diagnosis.

After 3 months, the patient started chemotherapy (doxorubicin). At this time, he already presented metastatic lesions on the pectoralis major. He died after 3 years, with a hilar mass with invasion of the mediastinum, which caused complete occlusion of the left main bronchus (LMB). In his last two years, the patient was submitted to at least 5 rigid bronchoscopies, for mechanical release, and one prosthesis was placed at the LMB one year before he died.

Immunohistochemical and molecular studies are essential to diagnose of MPNSTs.[2,3]

MPNSTs are highly invasive, with a low survival rate, but surgery significantly improves disease-free survival.[4] Chemotherapy is most used in unresectable or metastatic

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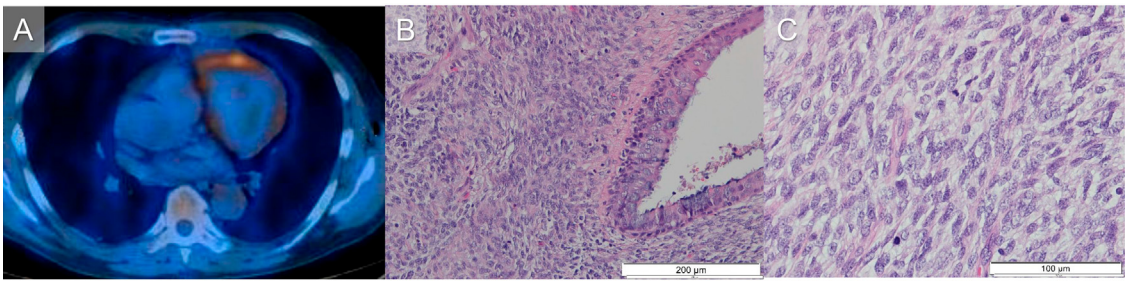

Fig. 1 (A) PET scan image showing high accumulation of FDG in the pulmonary mass. (B) Spindle cell tumor with infiltration of bronchial structures (HE 200X). Magnification bar = 200 μm.(C) Atypical neoplastic cells with frequent mitotic figures (HE 400x). Magnification bar = 100 μm.

malignancies, like in our patient, but there are no formal treatment or palliative care guidelines.[5] Rare tumors are associated with difficulties in diagnosis and evidence-based treatments are lacking. Therefore, every case is a challenge. Despite being rare, MPNSTs must be kept in mind.

Ethical considerations

Written informed consent was obtained from the patient guardian for publication of the article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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