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EDITORIAL

Mortality among elderly patients with COVID-19 ARDS—age still does matter

Mortality rates in elderly coronavirus disease 2019 (COVID-19) patients have been a major concern throughout the COVID-19 pandemic. According to data from the World Health Organization,[1] the overall mortality rate for COVID-19 is estimated to be around 2%, but the mortality rate increases dramatically for elderly patients. For example, the mortality rate for patients over the age of 80 has been estimated to be as high as 15—20%. This is at least in part due to the fact that elderly patients are more likely to have underlying health conditions such as heart disease, diabetes, and respiratory illness, which can increase the severity of COVID-19 symptoms. In addition to age, other factors that may increase mortality risk in elderly COVID-19 patients include sex, obesity, and the presence of certain comorbidities such as hypertension or chronic kidney disease. The mortality rate increases drastically for patients who require admission to an intensive care unit (ICU), especially for those who need mechanical ventilation.

In this issue of *Pulmonology*, Cilloniz et al. report on an analysis of the conveniently-sized observational study in critically ill COVID-19 patients in 55 ICUs in Spain, named the CIBERESUCICOVID study.[2] In this analysis she studied risk factors for mortality in a cohort of 5090 ventilated patients of which 1525 (27%) were aged ≥70 years. Overall in-hospital mortality in patients aged ≥70 years was twice that in patients aged <70 years: 50 versus 23%. Factors that had an independent association with higher in-hospital mortality in patients aged ≥70 years were ventilation at ICU admission, age, chronic heart disease, chronic renal failure, platelet count, and previous admission within the last 30 days. Of note, use of systemic steroids had an independent association with lower in-hospital mortality.

It is worth noting that mortality rates for COVID-19 can vary widely between countries and regions, depending on factors such as healthcare infrastructure and access to treatment. The could also be true for patients that require admission to an ICU. However, one recent analysis of the PRoVENT-COVID study, a nationwide multicenter observational study in the 22 ICUs in the Netherlands, performed in the first three months of the national outbreak of COVID-19, showed a remarkably similar pattern for mortality in elderly patients.[3,4] The PRoVENT-COVID study focused on key ventilator parameters, including tidal volume, positive end-expiratory pressure, driving pressure, and respiratory system compliance, and the use of rescue therapies for refractory hypoxemia in the first days of mechanical ventilation, but also reported on pulmonary and extrapulmonary complications, hospital- and ICU stay, and mortality amongst four age groups (<58, 58—65, 66—72, and >72 years). No meaningful differences were found in ventilation parameters and in the use of rescue therapies in the first days of ventilation. Older patients, however, received more often a tracheostomy, developed more frequently acute kidney injury and myocardial infarction, stayed longer in the ICU and in the hospital, and had higher mortality rates, e.g., in-hospital mortality increased from 16.6, to 27.7, 44.3, and 55.6%. The mortality rate in the oldest group in the Dutch study was fairly comparable to that in the Spanish study, on which Cilloniz et al. report in this issue of *Pulmonology*.[2]

It is also worth noting that we may be looking at the results of 'triage'.[5] Indeed, the decision to admit an elderly patient to an ICU for e.g., ventilation is often individualized, based on the specific clinical situation, in collaboration with the patient and their family, and with input from a multidisciplinary team of healthcare providers. ICU triage for elderly patients involves assessing the patient's overall health status, the severity of their illness, and the potential benefits and risks of ICU care.[6,7] Some factors to consider when triaging elderly patients to an ICU include:

1. overall health status—elderly patients with multiple comorbidities or poor functional status may have a lower chance of benefiting from ICU care; however, patients who are otherwise healthy and have a good baseline functional status may be good candidates for ICU admission;
2. severity of illness—severity of illness is a key factor in determining whether ICU care is necessary; however,

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patients with severe illness, such as respiratory failure, may benefit from ICU care regardless of age;
3. potential benefits and risks—elderly patients may be at higher risk of complications, such as delirium or infection, and may have a longer recovery time; however, ICU care may also provide life-saving interventions and improve outcomes; and
4. goals of care—the patient's goals of care should also be taken into consideration; quality of life may be more important than prolonging life for some elderly patients, and they may prefer to forego aggressive interventions.

Could there have been a policy early in the COVID-19 pandemic to keep elderly patients away from ICUs? Hospitals worldwide were confronted with surges of patients with an at that time unknown disease, with initially reportedly extremely high mortality rates. We also may have selected patients with the best survival rates, excluding older patients from ICU care more than usual. And if this is true, could it be that there are differences between countries and regions? The PRoVENT-COP investigators will use individual patient data from four recently published large observational COVID-19 studies,[8] including the Spanish study reported on in this issue of Pulmonology[2] and the Dutch study mentioned above,[3,4] and 2 large observational studies of ARDS from the pre-COVID era to answer this question.[7]

Mortality rates for elderly ICU patients in general can vary depending on a variety of factors, including the underlying medical conditions of the patient, the severity of their illness, and the quality of care they receive. However, research has consistently shown that advanced age is a significant predictor of mortality in ICU patients. One study found that ICU mortality rates increased with age, with patients over the age of 80 having a significantly higher risk of death than younger patients.[6,7] The study also found that elderly patients who required ventilation had a higher mortality risk than those who did not. Another study published found that the mortality rate for elderly ICU patients was high, with nearly half of patients over the age of 80 dying within 1 year.[9] Elderly patients who have pre-existing health conditions, such as heart disease or dementia, are at an even higher risk of mortality. And again, it is important to note that mortality rates for elderly ICU patients can vary depending on the specific ICU and hospital setting, as well as the quality of care provided. In some countries, elderly patients may easier, or earlier choose to forego aggressive medical interventions like ventilation, which definitely affects the overall mortality risk, but also the outcome of ICU care due to changes in case-mixes.[10]

Is COVID-19 ARDS different from other forms of ARDS, and does this translate in differences in outcomes among the elderly? While the pathophysiology of ARDS in COVID-19 patients is similar to 'classic' ARDS, there are some differences:

1. time course—COVID-19 ARDS may have a more prolonged course than non-COVID ARDS, with some patients requiring ventilation for several weeks;
2. hypoxemia—COVID-19 ARDS is associated with more severe hypoxemia than non-COVID ARDS, even in patients with relatively preserved lung compliance;
3. lung compliance—in COVID-19 ARDS, the lungs may be stiffer than in non-COVID ARDS, albeit that this was recently challenged;[11,12]
4. blood clotting—COVID-19 ARDS is associated with a higher risk of blood clotting in the lungs and other organs;
5. inflammatory response—COVID-19 ARDS is associated with a particularly strong inflammatory response, with elevated levels of cytokines and other inflammatory mediators, which may contribute to other complications; and
6. treatment response—studies showed that COVID-19 ARDS responds well to steroids; of note, this was confirmed in the CIBERESUCICOVID study, wherein patients that used corticosteroids had a 39% decrease in the risk of death?

In the current analysis of the CIBERESUCICOVID study a multivariable analysis was performed to determine which factors had an independent association with outcome.[2] The CIBERESUCICOVID-investigators could have considered doing a propensity matched analysis, a statistical method used to compare two or more groups of individuals with similar characteristics in order to draw conclusions about the effects of e.g., age or steroid use. This method is increasingly used in observational studies, as this type of analysis can help to control for potential confounding factors and reduce bias in a study, allowing for more accurate conclusions about the effects of the intervention being studied.

The findings of this analysis of CIBERESUCICOVID study are an important part of the information surrounding COVID-19. Even now that the pandemic appears to be over, at least in many countries, this information remains important: the world will face more frequent outbreaks of (respiratory) infections, and lessons from previous epidemics help guide steps to take in the next epidemic.[13]

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COMMENT

A new gambler at the table of management of COVID-19 associated acute respiratory failure. Changing position to do it better?

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The COVID-19 pandemic has led to an increase in publications (with high percentages of retractions),[1] nevertheless, after three years, we still need reproducible randomised controlled trials (RCTs) on several issues, especially to evaluate strategies and tools to manage individuals with COVID-19-associated acute hypoxaemic respiratory failure such as non-invasive respiratory support (NRS), high flow nasal cannula or awake prone positioning.[2-5] This latter has gained attention as a potential intervention since the early phase of the pandemic, and despite the limited RCTs evidence, it has been widely used as a co-intervention even in mild hypoxaemia.[6,7] It has been reported that awake prone positioning has been used in one in six critically ill individuals with COVID-19, has been started early, and sessions lasted long but were often discontinued because of need for intubation.[8]

Prone positioning may promote more homogeneous ventilation, improving the ventilation-to-perfusion ratio by "recruiting" dorsal non-aerated but perfused lung units, reducing ventral hyperinflation, and increasing airway clearance resulting in relevant improvement in oxygenation.[9] Early observational studies, with relatively small sample sizes, showed conflicting results with beneficial effects on oxygenation not sustained over time.[10] However, due to the limited treatment option, many clinicians have used this modality as a tool to improve oxygenation. Several predictors of its success have been proposed, including duration of intervention $>$ 8 h/day, respiratory rate at enrollment $\leq$ 25 breaths/min, improvement in ROX index $>$ 1.25 and lung ultrasound score $\geq$ 2 within the first 3 days.[11-13]

A meta-trial by Ehrmann et al.[14] combining six independent RCTs, with 1126 participants with $PaO_2/FiO_2 \leq 300$ mm Hg in mixed settings, showed significant improvements in the composite outcome of intubation or death rate within 28 days using awake proning as compared to standard treatment, with a number needed to treat (NNT) of 15 to avoid treatment failure. This outcome was primarily driven by a decrease in the need for tracheal intubation and awake proning did not reduce mortality as compared with usual care. However, uncertainty remains about the magnitude of a survival benefit left by the included studies that were underpowered for this outcome and heterogeneous in the severity of study population, settings, and type of NRS used.[15]

Another RCT failed to show a reduction in endotracheal intubation rate at 30 days using awake proning compared to usual care.[16] Musso et al. showed that this modality, combined with NRS strategies, reduced the intubation rate.[17]

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Conversely, Qian et al. showed no clinical benefit and a potential detrimental effect with progression of lung damage and worsening in oxygenation.[18] Li et al. showed a significant effect in reducing the need for intubation in the overall population with a 16% relative risk reduction (especially in the subgroup of individuals receiving NRS or treated in ICU settings) but not in mortality rate.[19] However, the interpretation of subgroup analyses in meta-analyses requires caution since estimates of treatment effect for clinically relevant subgroups of participants are observational, not accounting for the distribution of confounders and should be considered hypothesis-generating rather than confirmatory results. Weatherald et al. concluded that awake proning reduces the intubation rate with a NNT of 18 to prevent intubation without any benefit on mortality, ICU or hospital length of stay, ventilator-free days or escalation of oxygen strategies, with consistent results using both frequentistic and bayesian analytical methods.[20] Therefore, it seems reasonable to assume that awake proning also may have little or no indirect effects on critical care beds availability, a crucial aspect to consider for the response to the pandemic. Even though a cause-effect relationship cannot be established with certainty, the current best evidence is consistent in conferring no benefit to awake proning in reducing mortality risk. However, the lack of individual data, differences in the definition and reporting of outcomes and variability in duration of intervention among studies may limit any definitive conclusion. Despite treated people's overall negative attitude towards the position, with low tolerance along the prescribed intervention time, participants would highly recommend this modality, perceiving a potential benefit.[21] Moreover, very recently, despite moderate quality of evidence Rapid Practice Guidelines strongly recommended a trial of awake proning under different NRS strategies, suggesting that awake proning may be considered a valid clinical strategy.[22]

Despite the amount of literature on the management of COVID-19-associated acute respiratory failure (also Pulmonology has contributed to, see the reference list), in the future, large international registries, multicenter cohort studies and adequately powered prospective RCTs are needed to improve our understanding of the role of awake proning as well as of other diagnostic and therapeutic options in the comprehensive management of these individuals.[23,24] Based on the current evidence, there is still no firm conclusion on the clinical role of awake proning in spontaneously breathing individuals with COVID-19-related acute respiratory failure, even if this tool has been shown to improve oxygenation for these individuals and appears to be safe. However, the benefits of reducing intubation rates have been only seen in moderate-to-severe individuals undergoing high-flow nasal cannula. Awake prone position should be initiated early and with a target of at least 8 h/day duration. Pillows under the body and an accurate search of individualised position are essential to enhance adherence. Oxygenation improvement and changes in the lung ultrasound findings may help to identify those individuals more likely to avoid intubation.[25]

So, where should we go from here? Although awake proning is challenging for healthcare workers and cared people, the growing body of literature provides several promising results to be evaluated in more depth also in non-COVID scenarios. A more nuanced understanding regarding the type and severity of the population most likely to benefit from awake proning, its safety profile and the best daily duration and timing of its initiation, implementation, and interruption is required to avoid delayed intubation and to assess its long-term clinical efficacy. To move forward and provide definitive evidence, accurate and methodical recordings of awake proning and objective measures of adherence and compliance should be considered for the design of future research. Until then, awake proning should be a selected and tailored choice of physicians after a judicious clinical evaluation and warranted close monitoring for adherence, clinical response and need for intubation. Indeed, like any other medical intervention, awake prone positioning should not be considered a "better than nothing" strategy, even in resource-limited settings and it should be applied in locations adequate for number, and quality of trained caregivers, with dedicated structures and devices.

Conflicts of interest

The authors declare no conflict of interests.

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COMMENT

Regulations on e-cigarettes: China is taking action

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Invented in China in 2003, electronic nicotine delivery systems (ENDS), commonly known as electronic cigarettes (e-cigarettes), are battery-powered devices that convert a mixture containing nicotine into an inhalable aerosol.[1] They structurally comprise four components: a battery, a reservoir with the liquid formulation, a vaporizing chamber with a heating element, and a mouthpiece for inhalation.[2] In recent years, China has issued dozens of regulations to control the e-cigarette industry due to the increasing use of e-cigarettes along with their significant health risks.

The use of e-cigarettes has gained great popularity, especially among youngsters. An online survey in China showed that 89.52% of adolescents aged between 12 and 18 years were aware of e-cigarettes while the ever-use rate was 26.44%.[3] Another survey in China showed that 88.40% of young Chinese adults aged between 19 and 29 years were aware of e-cigarettes and 24.45% of them have used e-cigarettes.[4] Among Chinese adults, the weighted prevalence of past 30-day e-cigarette use among Chinese adults increased from 1.3% in 2015–2016 to 1.6% in 2018–2019, indicating that e-cigarette use in China has increased substantially.[5] Reasons why e-cigarettes have attracted millions of people are (1) their variety of flavors; (2) convenience in smoking and purchasing; (3) similar satisfaction to conventional cigarettes; (4) the popular belief that e-cigarettes help in quitting smoking and are less harmful to the body.

However, a variety of studies have still confirmed the harmful effects of e-cigarettes. Firstly, nicotine, as the main bioactive component in e-cigarettes, can easily lead to addiction. Furthermore, unlike nicotine replacement treatment (NRT), which was believed to have a safe and low-addictive nicotine content to help smokers quit, the unregulated amount of nicotine in e-cigarettes combined with the reinforcement of smoking behavior may generate a more addictive product. Secondly, the most commonly used organic solvent of e-cigarette oil, propylene glycol (PG), is identified to function in altering physiological processes and producing acute toxicity and airway irritation. Additionally, in the process of aerosol generation, it can be oxidized to form carcinogens such as formaldehyde and acetaldehyde. Thirdly, flavors added to e-cigarettes have varied degrees of cytotoxicity and can cause oxidative stress reactions. Fourthly, the components of e-cigarettes contain a variety of carcinogenic metals, the most common of which are chromium, nickel, and aluminum. When heated, these metals can be released into the liquid, entering the user's body along with the smoke. In conclusion, the inhaled toxic and carcinogenic ingredients will result in impaired physiological function of corresponding tissues and organs and lead to a variety of acute and chronic diseases, and even cause cancer. Among these hazards, smoking is particularly harmful to the respiratory system, since the respiratory tract is directly exposed to e-cigarette aerosol, which causes individuals to

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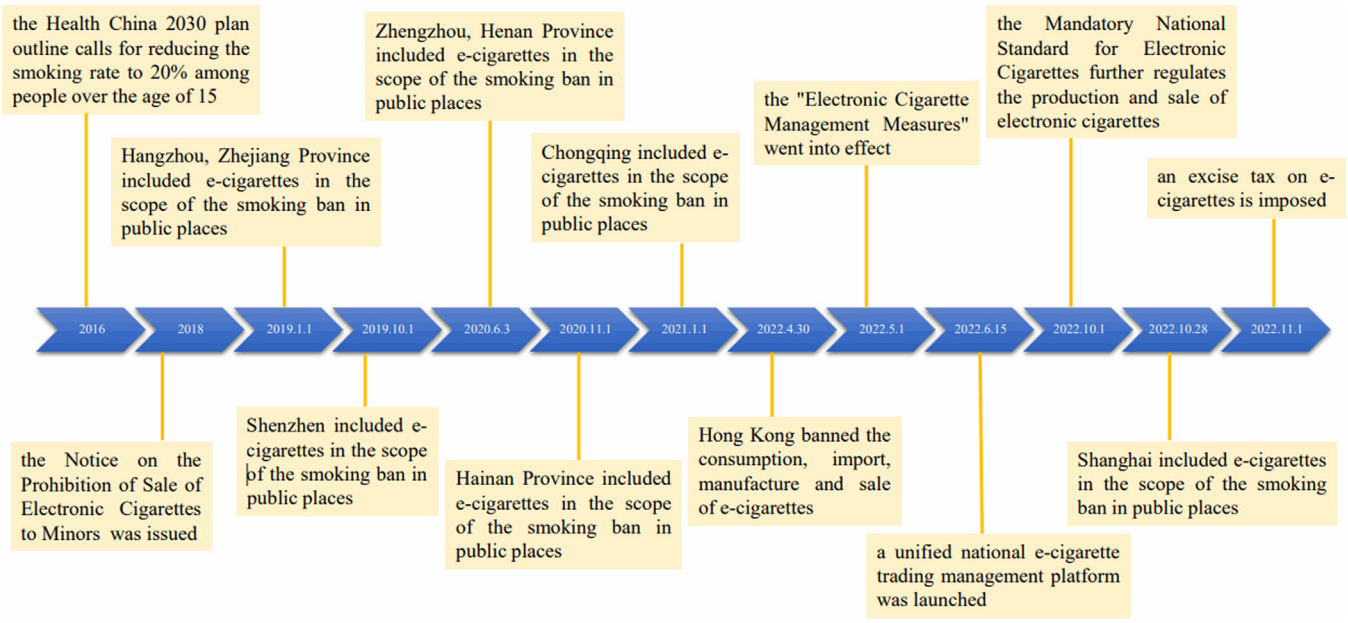

Fig. 1 The timeline of China's actions in regulating e-cigarettes.

become more sensitive to asthma, COPD, and lung cancer.[1] Besides, there is not a single type of e-cigarette, but several different types of e-cigarettes, which further complicates the harmful effects of e-cigarettes. In addition, e-cigarettes increase the risk of starting and relapsing smoking conventional cigarettes and do not increase smoking cessation, and results are more favorable in clinical settings.[6,7] This may cause a combination of health damage from two or more products.

Since the harm of smoking became clearer and the World Health Organization Framework Convention on Tobacco Control came into force, an increasing number of countries have adopted effective measures to control tobacco use. From 2007 to 2017, the prevalence of smoking among people over the age of 15 dropped to 19.2%.[8] However, there are more than 300 million smokers in China. In 2018, the smoking rate among people over the age of 15 was 26.6%, higher than the global average, with the rate of e-cigarette smoking increasing yearly.[9] Tobacco kills more than 1 million people in China annually and is expected to rise to 2 million a year by 2030 and 3 million a year by 2050 if no effective action is taken.[10]

To regulate the e-cigarette industry and reduce the smoking-related disease burden, China has taken a series of measures (Fig. 1). As a significant first step, the Outline of the Healthy China 2030 Plan released in October 2016 has called for comprehensive strengthening of tobacco control to reduce the smoking rate to 20% among people over the age of 15 by 2030.[11] Subsequently, to enhance the protection of teenagers, the Notice on the Prohibition of Sale of Electronic Cigarettes to Teenagers, issued on August 28, 2018, bans the sale of e-cigarettes to teenagers and requires the withdrawal of e-cigarette advertisements on the Internet.[12] As a step further, on May 1, 2022, the ``Electronic Cigarette Management Measures'' went into effect, explicitly prohibiting the sale of flavored e-cigarettes other than tobacco flavors and reducing the number of young people interested in e-cigarettes merely because of their taste. To better implement the previous regulations, the Mandatory National Standard for Electronic Cigarettes, implemented on October 1, 2022, further regulates the production and sale of electronic cigarettes.[13] On October 28, Shanghai, following Shenzhen, Hangzhou, etc., integrated e-cigarettes into the scope of the smoking ban in public places.[14] Lately, an excise tax on e-cigarettes was imposed on November 1, 2022, to reduce e-cigarette consumption through high taxes that affect sales prices.[15]

It is believed that with tightening regulations, the rate of e-cigarette users will gradually decrease, which will lower the electronic cigarette-related disease burden and greatly benefit public health. We are glad to see the sale of e-cigarettes has been banned on major online shopping platforms in China, and vendors selling e-cigarettes to teenagers have also been heavily punished. However, there is still a lot to be done. At present, illegally produced e-cigarettes are still sold to people, especially teenagers, through illegal selling channels. Firstly, to strengthen the regulation of e-cigarette sales, the government should eliminate illegal e-cigarette manufacturers and punish those who are still producing e-cigarettes without licenses. Secondly, the circulation of illegal e-cigarettes could be reduced by limiting the number of related products posted per person per day. Thirdly, to reduce e-cigarette purchasing, the government is supposed to conduct health education about the danger of e-cigarettes. It is strongly believed that, through the joint efforts of the government and all citizens, the goal of the Outline of the Healthy China 2030 Plan will be realized steadily.

Conflicts of interest

The authors have no conflicts of interest to declare.

CRediT authorship contribution statement

Y. Cao: Conceptualization, Data curation, Formal analysis, Investigation, Writing — original draft. **H. Yi:** Conceptualization, Data curation, Formal analysis, Investigation, Writing — original draft. **J. Zhou:** Writing — original draft, Writing — review & editing. **Y. Cheng:** Conceptualization, Writing — review & editing. **Y. Mao:** Conceptualization, Writing — review & editing.

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ORIGINAL ARTICLE

Risk factors associated with mortality among elderly patients with COVID-19: Data from 55 intensive care units in Spain

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KEYWORDS
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Abstract
Introduction and objectives: Critically-ill elderly ICU patients with COVID-19 have poor outcomes. We aimed to compare the rates of in-hospital mortality between non-elderly and elderly critically-ill COVID-19 ventilated patients, as well as to analyze the characteristics, secondary outcomes and independent risk factors associated with in-hospital mortality of elderly ventilated patients.
Patients and Methods: We conducted a multicentre, observational cohort study including consecutive critically-ill patients admitted to 55 Spanish ICUs due to severe COVID-19 requiring mechanical ventilation (non-invasive respiratory support [NIRS; include non-invasive mechanical

Abbreviations: NIRS, non-invasive respiratory support; IMV, invasive mechanical ventilation; sHRs, sub-distribution hazard ratios; CIs, confidence intervals; ICU, intensive care unit; REDCap, Research Electronic Data Capture; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; CDC, Center for Disease Control and Prevention; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health disease Classification System II; NIMV, non-invasive mechanical ventilation; HFNC, high-flow nasal cannula; PEEP, positive end-expiratory pressure; CIF, cumulative incidence function; Q1, first quartile; Q3, third quartile; VIF, variance inflation factor.

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ventilation and high-flow nasal cannula] and invasive mechanical ventilation [IMV]) between February 2020 and October 2021.

Results: Out of 5,090 critically-ill ventilated patients, 1,525 (27%) were aged ≥70 years (554 [36%] received NIRS and 971 [64%] received IMV. In the elderly group, median age was 74 years (interquartile range 72−77) and 68% were male. Overall in-hospital mortality was 31% (23% in patients <70 years and 50% in those ≥70 years; $p<0.001$). In-hospital mortality in the group ≥70 years significantly varied according to the modality of ventilation (40% in NIRS vs. 55% in IMV group; $p<0.001$). Factors independently associated with in-hospital mortality in elderly ventilated patients were age (sHR 1.07 [95%CI 1.05−1.10], $p<0.001$); previous admission within the last 30 days (sHR 1.40 [95%CI 1.04−1.89], $p = 0.027$); chronic heart disease (sHR 1.21 [95%CI 1.01−1.44], $p = 0.041$); chronic renal failure (sHR 1.43 [95%CI 1.12- 1.82], $p = 0.005$); platelet count (sHR 0.98 [95% CI 0.98−0.99], $p<0.001$); IMV at ICU admission (sHR 1.41 [95% CI 1.16-1.73], $p<0.001$); and systemic steroids (sHR 0.61 [95%CI 0.48- 0.77], $p<0.001$).

Conclusions: Amongst critically-ill COVID-19 ventilated patients, those aged ≥70 years presented significantly higher rates of in-hospital mortality than younger patients. Increasing age, previous admission within the last 30 days, chronic heart disease, chronic renal failure, platelet count, IMV at ICU admission and systemic steroids (protective) all comprised independent factors for in-hospital mortality in elderly patients

Introduction

By 5 September 2022, the COVID-19 pandemic saw 615 million confirmed cases and had claimed the lives of more than 6.5 million people globally.[1] Underlying medical conditions and older age have been identified as strong predictors of death in patients with COVID-19 in general population.[2] Analyzing data from 540,667 adults hospitalized with COVID-19, Kompaniyets et al. reported that underlying medical conditions such as obesity, diabetes with complications, chronic cardiovascular disease and chronic lung disease had the strongest association with death especially in elderly patients (≥70 years old) in overall population.[3] The higher likelihood of presenting poor outcomes amongst elderly patients also appears to apply to those with severe COVID-19 requiring intensive care unit (ICU) admission.[4,5] A recent systematic review and meta-analysis pooling data from 57,000 COVID-19 patients that required mechanical ventilation, reported an overall case-fatality rate of 45% (95% CI: 39−52%), which increased according to age group, being 84% (95% Confidential Interval (CI): 83.3−85.4%) in patients over 80 years.[6] A multicenter cohort study from Japan reported that the mortality rates in patients received invasive mechanical ventilation (IMV) were 8.6%, 20.7%, 34.9%, 49.7% and 83.3% for patients in the age group 50, 60, 70, 80, and 90 years old, respectively. The multivariable analysis showed that the odds ratio of death was 7 times higher in patients aged 70 years old (OR, 6.92. 95% CI 4.23 to 11.31; $p < 0.01$), 13 times higher in patients aged 80 years old (OR, 13.17, 95% CI 7.21 to 24.06; $p < 0.01$), and 92 times higher in patients aged 90 years old (OR, 92.63, 95% CI 16.66 to 514.98; $p < 0.01$), compared with those aged <60 years.[7] However, available evidence on critically-ill elderly patients with COVID-19 admitted to the ICU needing mechanical ventilation (non-invasive and invasive ventilation) is widely variable across countries and some relevant aspects regarding management and prognosis remain poorly known.

We hypothesized that crude mortality of very elderly mechanically-ventilated COVID-19 patients was higher and the risk factors different as compared to those of younger patients. Thus, we aimed to assess the clinical characteristics, therapy, management, complications and risk factors associated with mortality amongst critically ill elderly patients with COVID-19 who were admitted to ICU and received non-invasive respiratory support (NIRS) and/or IMV at hospital and ICU admission.

Methods

Study design and patients

We retrospectively analysed patients from the CIBERESUCI-COVID study (NCT04457505),[8,9] which had prospectively included patients aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection from across 55 Spanish hospitals between 5 February 2020 and 7 October 2021 (participating sites are listed in the S-Table 1 in the Supplementary Material). All consecutive patients admitted to ICU were enrolled if the reason for admission was COVID-19. Exclusion criteria for patients included: (1) unconfirmed SARS-CoV-2 infection; (2) lack of data at baseline or hospital discharge; (3) lack of information about age; (4) lack of data about ventilation requirement or conventional oxygen therapy at hospital and ICU admission. The study received first approval by Hospital Clínic of Barcelona, Spain IRB (Comité Ètic d'Investigació Clínica, registry number HCB/2020/0370), and ulterior approval by local IRBs in the rest of participating hospitals. Either patients or their relatives provided informed consent. De-identified data were collected and stored in Research Electronic Data Capture (REDCap). Trained local researchers incorporated data from patients' medical records into a separate database. Prior to statistical analyses, three

independent and experienced data collectors trained in critical care (PC, AM, CS) reviewed the data; in cases of query, site investigators were contacted. Missing analyses were performed, and site investigators were approached to obtain as much reliable and complete data as possible. Results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[10]

Data collection

We recorded data on demographics, comorbidities, illness severity and organ damage (APACHE-II and SOFA scores), and previous treatment. Standard laboratory and clinical data were collected at hospital and ICU admission. Data on pharmacologic treatments and non-pharmacological interventions during index admission were collected. Main complications during hospital stay, including pulmonary complications (acute respiratory distress syndrome-ARDS); septic shock, bacteraemia, hyperglycaemia, nosocomial infections, thromboembolic events, gastrointestinal bleeding, acute kidney injury and acute hepatic failure were also collected.

Primary and secondary outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included length of ventilation, recovery from ICU admission, ICU-mortality, 90-day mortality, lengths of ICU and hospital stay.

Definitions

Patients were divided in two groups: 1.- Patients that received non-invasive respiratory support (NIRS) which included patients that received non-invasive mechanical ventilation (NIMV) and/or high-flow nasal cannula (HFNC) at the ICU admission, and 2.- Patients that received invasive mechanical ventilation (IMV) at the ICU admission. Patients who received NIRS before but needed intubation at the ICU admission were included in the IMV group. The start dates of the first respiratory support with NIRS or IMV were recorded whether it was provided in the general ward or in the ICU. Length of ICU and hospital stay was calculated from ICU admission and hospitalization, respectively. Nosocomial pneumonia was defined according to international guidelines.[11] Hyperglycaemia was defined as a consistent blood glucose level above 126 mg/dL. Hemorrhage referred to any type of clinically significant bleeding. Further details are reported in a previous publication.[12] Driving pressure was defined as plateau pressure minus plateau pressure (PEEP). Static compliance of the respiratory system was calculated as tidal volume/ (plateau pressure − PEEP). Ventilatory ratio was calculated as follows: (minute ventilation × $PaCO_2$) − (PBW × 100 × 37.5).

Statistical analysis

We report the number and percentage of patients as categorical variables, and the median (first quartile [Q1]; third quartile [Q3]) as continuous variables. Categorical variables were compared using the chi-squared test or Fisher's exact test, whereas continuous variables were compared using the nonparametric Mann-Whitney U test.

First, we compared patients according to age group (<70 years and ≥70 years). Then, a comparison of patients according to study group (i.e., NIRS and IMV) in patients aged ≥70 years was performed. We also explored the clinical characteristics and outcomes in the subgroup of patients aged 80 years and older.

To describe in-hospital mortality, we utilized a competing risk model,[13] considering recovery (i.e., discharge from hospital) as competing risk for mortality. First, we obtained the estimate of the cumulative incidence function (CIF) for the marginal probability of in-hospital mortality and recovery. Gray's test was used to compare equality of cumulative incidence curves across groups.[14] To explore the risk factors associated with in-hospital mortality, a Fine-Gray competing risks model stratified on the center variable was used. A list of candidate predictors was established a priori based on previous findings and clinical constraints: age, sex, previous 30 days admission, chronic heart disease, chronic lung disease, chronic renal failure, confusion; the following parameters at ICU admission: APACHE-II score, SOFA score, PaO_2/FiO_2 ratio, pH, lymphocyte count, platelet count, D-dimers, C-reactive protein, serum creatinine, ferritin, septic shock, MV, and vasopressor treatment, continuous neuromuscular blockers, corticosteroids administered during ICU admission, and COVID-19 wave. Single collinearity was evaluated using the Pearson correlation (r) and multicollinearity was examined by means of the variance inflation factor (VIF). Several variables were excluded from the analysis due to collinearity (see Supplementary Material). Sub-distribution hazard ratios (sHRs) and their 95% confidence intervals (CIs) were calculated. The proportional hazards assumption was checked by an evaluation of the Schoenfeld residuals, as shown in Supplementary S-Figure 1. Patients who were transferred to another hospital were censored in the survival analyses. We used the multiple imputation method[15] for missing data in the multivariable analysis (S-Table 1).

The level of significance was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Description of the cohort

5090 patients requiring ventilation due to COVID-19 were enrolled in the CIBERESUCICOVID dataset (55 Spanish ICUs) from February 2020 to October 2021. The comparison of characteristics and outcomes between patients aged <70 years and those aged ≥70 years are summarized in S-Tables 2-4 and S-Figures 2-3. Remarkably, 3565 (63%) were aged <70 years (1529 [43%] received NIRS and 2036 [57%] received IMV) and 1525 (27%) were aged ≥70 years (554 [36%] received NIRS and 971 [64%] received IMV) (Fig. 1). Overall in-hospital mortality was 31% (23% in patients <70 years and 50% in those ≥70 years; $p<0.001$).

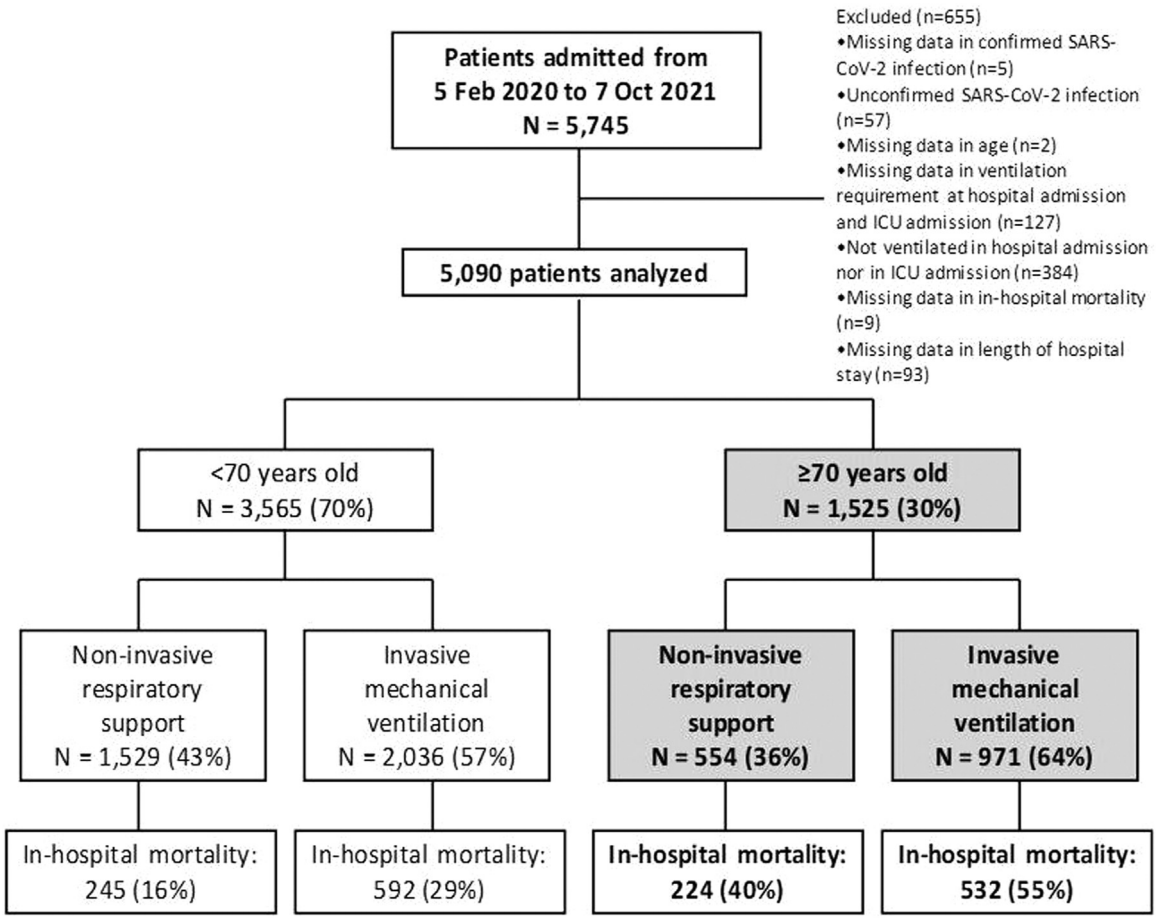

Fig. 1 Flow diagram of the study population.

Mechanical ventilation modality in patients ≥70 years

The overall baseline characteristics and ventilation features in patients aged ≥70 years and the comparison between the group receiving NIRS and IMV are shown in Table 1. Notably, patients received NIRS presented higher proportion of patients aged ≥80 years old, have higher rate of chronic lung disease, chronic renal disease and immunosuppression that patients received IMV. They also presented longer day from hospital admission to ICU admission, lower rate of septic shock, lower levels of CRP, D-dimer, neutrophils-lymphocytes ratio and lower SOFA score compared with patients who received IMV.

Main interventions and treatments are displayed in Table 2

Table 3 shows the complications and outcomes according to the type of MV in patients ≥70 years. Medians for ICU and hospital length of stay were 17 (9; 30) and 26 (16; 44) days for NIRS and IMV respectively. The mortality rate of patients that failed to NIRS and required IMV was 52% (149/288), whereas the mortality rate of patients that only required NIRS was 26% (55/214). ICU, in-hospital and 90-day mortality rates were 46%, 50% and 52% respectively, in all three cases being significantly higher in the IMV subgroup. The main cause of in-hospital mortality in IMV group was multi-organic failure (41%), while, respiratory failure was the main cause of death in NIRS group (51%). The CIF curves for in-hospital mortality and recovery are depicted in Fig. 2A. Furthermore, the CIF curves show that patients with IMV had a higher likelihood of death ($p<0.001$) than patients with NIRS, and patients with NIRS had a higher likelihood of recovery ($p<0.001$) than patients with IMV (Fig. 2B).

The characteristics of patients aged ≥70 years that survived the index admission vs. those of patients who died are shown in S-Tables 5 to 7. In-hospital mortality significantly increased per 5-year blocks age groups ($p<0.001$) (Fig. 3A). Meanwhile, there was a decreasing trend in in-hospital mortality across COVID-19 waves ($p = 0.006$) (Fig. 3B).

Sub-analysis of patients ≥80 years

There were 136 patients ≥80 years old, of these 84 (62%) patients received NIRS (28 with initial NIRS, required IMV during hospitalization) and 52 (38%) received IMV. Median APACHE II and SOFA scores were 14 (12; 17) and 4 (4; 7), respectively (S-Table 8). Interestingly, prone position was implemented in 35% of patients and renal replacement therapy was used in 7% of patients (4% in NIRS and 12% in IMV patients; $p = 0.085$) (S-Table 9). The mortality rate of patients that failed to NIRS and required IMV was 61% (17/28), whereas the mortality rate of patients that only

Table 1 Demographic and clinical characteristics of the study population ≥70 years old by type of respiratory support.[a]

Variables	All patients (*N* = 1525)	Non-invasive respiratory support (*N* = 554)	Invasive mechanical ventilation (*N* = 971)	*p*-value
Age, median (Q1; Q3), years	74 (72; 77)	74 (72; 78)	74 (72; 76)	0.055
Age ≥80 years, n (%)	136 (9)	84 (15)	52 (5)	<0.001
Male sex, n (%)	1037 (68)	372 (67)	665 (69)	0.639
BMI, median (Q1; Q3), kg/m^2	27.8 (25.5; 31.1)	28 (25.3; 31)	27.8 (25.6; 31.1)	0.810
BMI, n (%)				0.679
Underweight (<18.5 kg/m^2)	8 (1)	4 (1)	4 (0.5)	–
Normal weight (≥18.5 - <25 kg/m^2)	268 (20)	103 (22)	165 (20)	–
Pre-Obese (≥25 - <30 kg/m^2)	636 (48)	227 (47)	409 (48)	–
Obese (≥30 kg/m^2)	410 (31)	144 (30)	266 (32)	–
Comorbidities, n (%)				
Active smoker	60 (4)	20 (4)	40 (5)	0.535
Hypertension	1063 (70)	385 (69)	678 (70)	0.869
Diabetes mellitus	501 (33)	187 (34)	314 (32)	0.571
Dyslipidemia	561 (37)	206 (37)	355 (37)	0.822
Chronic heart disease	330 (22)	134 (24)	196 (20)	0.069
Chronic liver disease	44 (3)	13 (2)	31 (3)	0.343
Chronic lung disease	273 (18)	116 (21)	157 (16)	0.019
Chronic renal failure	157 (10)	74 (13)	83 (9)	0.003
Immunosuppression	51 (3)	31 (6)	20 (2)	<0.001
Nursing-home, n (%)	39 (3)	19 (3)	20 (2)	0.117
Previous 30 days admission, n (%)	69 (5)	28 (5)	41 (4)	0.450
Days from first symptoms to hospital admission, median (Q1; Q3)	7 (4; 9)	6 (4; 9)	7 (4; 9)	0.692
Days from hospital admission to ICU admission, median (Q1; Q3)	2 (0; 4)	2 (0; 5)	2 (0; 4)	0.002
Symptoms at hospital admission, n (%)				
Fever	1168 (78)	417 (76)	751 (79)	0.120
Dry cough	871 (58)	312 (57)	559 (59)	0.461
Productive cough	219 (15)	82 (15)	137 (14)	0.781
Dyspnoea	1043 (69)	373 (68)	670 (70)	0.309
Fatigue	629 (42)	232 (42)	397 (42)	0.899
Muscle pain	381 (26)	134 (25)	247 (26)	0.485
Diarrhoea	277 (18)	99 (18)	178 (19)	0.746
Confusion	107 (7)	24 (4)	83 (9)	0.002
Characteristics on ICU admission				
Glasgow Coma Scale, median (Q1; Q3)	15 (15; 15)	15 (15; 15)	15 (14; 15)	<0.001
APACHE-II score, median (Q1; Q3)	14 (12; 18)	13 (11; 15)	15 (12; 21)	<0.001
APACHE-II APS component, median (Q1; Q3)	8 (6; 12)	7 (5; 9)	10 (6; 15)	<0.001
SOFA score, median (Q1; Q3)	5 (4; 8)	4 (3; 5)	7 (4; 8)	<0.001
SOFA hemodynamic component, median (Q1; Q3)	0 (0; 4)	0 (0; 0)	4 (0; 4)	<0.001
SOFA renal component, median (Q1; Q3)	0 (0, 1)	0 (0, 0)	0 (0, 1)	0.005
Temperature, median (Q1; Q3), °C	36.5 (36; 37.3)	36.5 (36; 37.1)	36.6 (36; 37.5)	0.020
Respiratory rate, median (Q1; Q3), breaths per min	25 (20; 30)	27 (23; 32)	24 (20; 30)	<0.001
Arterial blood gasses at ICU admission				
PaO_2/FiO_2 ratio, median (Q1; Q3)	107.8 (79; 154.1)	96 (73.8; 141)	113.8 (82; 162)	<0.001
PaO_2/FiO_2 ratio, n (%)				<0.001
Severe (<100)	553 (45)	202 (54)	351 (42)	<0.001
Moderate (≥100 - <200)	504 (41)	146 (39)	358 (42)	0.233
Mild (≥200 - <300)	126 (10)	20 (5)	106 (13)	<0.001
No ARDS (≥300)	39 (3)	9 (2)	30 (4)	0.285
pH, median (Q1; Q3)	7.40 (7.33; 7.45)	7.45 (7.41; 7.47)	7.36 (7.29; 7.43)	<0.001
$PaCO_2$, median (Q1; Q3), mmHg	40 (34; 47)	35.3 (32; 40)	42.7 (36; 50)	<0.001
Laboratory findings at ICU admission				
Haemoglobin, median (Q1; Q3), g/dL	13 (11.6; 14.2)	13.3 (11.8; 14.3)	13 (11.5; 14.1)	0.044
Leucocyte count, median (Q1; Q3), 10^9/L	9.5 (6.8; 13.1)	8.5 (6.1; 11.6)	10.1 (7.4; 13.9)	<0.001

Table 1 (*Continued*)

Variables	All patients (*N* = 1525)	Non-invasive respiratory support (*N* = 554)	Invasive mechanical ventilation (*N* = 971)	*p*-value
Lymphocyte count, median (Q1; Q3), 10^9/L	0.6 (0.4; 0.88)	0.62 (0.45; 0.9)	0.6 (0.4; 0.87)	0.040
Neutrophil count, median (Q1; Q3), 10^9/L	8.2 (5.6; 11.7)	7.3 (5.1; 10)	8.8 (6.1; 12.7)	<0.001
Neutrophil-to-lymphocyte ratio, median (Q1; Q3)	13 (7.8; 22)	11.1 (6.6; 18)	14.7 (8.8; 24.8)	<0.001
Monocyte count, median (Q1; Q3), 10^9/L	0.37 (0.2; 0.57)	0.34 (0.2; 0.55)	0.39 (0.21; 0.59)	0.096
Platelet count, median (Q1; Q3), 10^9/L	224 (172; 291)	220 (173; 293)	225 (172; 290)	0.713
D-dimers, median (Q1; Q3), ng/mL	1278 (697; 3800)	1049 (580; 2250)	1525 (780; 5131)	<0.001
Ferritin, median (Q1; Q3), ng/mL	1033 (578; 1714)	977 (528; 1643)	1095 (620; 1750)	0.256
C-reactive protein, median (Q1; Q3), mg/L	138 (69; 230)	109 (61; 197)	152 (73; 249)	<0.001
C-reactive protein ≥150 mg/L, n (%)	652 (46)	198 (38)	454 (51)	<0.001
C-reactive protein-to-lymphocyte ratio, median (Q1; Q3)	213 (92; 395)	174 (71; 343)	237 (106; 429)	<0.001
IL-6, median (Q1; Q3), pg/mL	94.2 (37; 202)	82 (27.5; 175.8)	105 (39.3; 222)	0.069
Serum creatinine, median (Q1; Q3), mg/dL	0.91 (0.71; 1.2)	0.86 (0.7; 1.12)	0.95 (0.73; 1.24)	0.001
LDH, median (Q1; Q3), U/L	485 (377; 657)	424 (342; 554)	540 (411; 709)	<0.001
Evolution of type of respiratory support, n (%)[a]				–
Non-invasive respiratory support at ICU admission & Conventional oxygen therapy at day 3 of ICU admission or end of MV	15 (1)	15 (3)	0 (0)	–
Non-invasive respiratory support at ICU admission & Non-invasive respiratory support at day 3 of ICU admission or end of MV	214 (14)	214 (41)	0 (0)	–
Non-invasive respiratory support at ICU admission & Invasive MV at day 3 of ICU admission or end of MV	288 (19)	288 (56)	0 (0)	–
Invasive MV at ICU admission & Conventional oxygen therapy, Non-invasive respiratory support or Invasive MV at day 3 or end of MV	971 (65)	0 (0)	971 (100)	–
Ventilatory setting and pulmonary mechanics at MV start				
Tidal volume/PBW, median (Q1; Q3), mL/kg	7.1 (6.4; 7.9)	6.9 (6.3; 7.8)	7.1 (6.5; 7.9)	0.024
Respiratory rate, median (Q1; Q3), breaths per min	20 (18; 24)	21 (18; 24)	20 (18; 24)	0.862
PEEP, median (Q1; Q3), cmH_2O	12 (10; 14)	12 (10; 14)	12 (10; 14)	0.064
FiO_2, median (Q1; Q3),%	80 (60; 100)	80 (60; 100)	80 (60; 100)	0.291
Peak inspiratory pressure, median (Q1; Q3), cmH_2O	31 (28; 35)	30 (28; 34)	31 (28; 35)	0.392
End-inspiratory plateau pressure, median (Q1; Q3), cmH_2O	24 (21; 28)	24 (21; 28)	25 (21; 28)	0.323
Driving pressure, median (Q1; Q3), cmH_2O[b]	12 (10; 15)	12 (9; 15)	12 (10; 15)	0.972
Compliance, median (Q1; Q3), mL/cmH_2O[c]	35.7 (28; 46.2)	35.2 (27.6; 43.3)	35.7 (28.2; 47.2)	0.443
Ventilatory ratio, median (Q1; Q3)[d]	1.69 (1.38; 2.12)	1.67 (1.37; 2.03)	1.7 (1.39; 2.15)	0.416
Position, n (%)				0.044
Supine	630 (62)	182 (87)	448 (60)	0.029
Prone	362 (36)	83 (31)	279 (37)	0.053
Lateral	12 (1)	4 (1)	8 (1)	0.529
Other	11 (1)	0 (0)	11 (1)	0.071
Septic shock at ICU admission[e]	125 (9)	6 (1)	119 (15)	<0.001

Abbreviations: ICU indicates intensive care unit; Q1, first quartile; Q3, third quartile; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; APS, acute physiology score; SOFA, sequential organ failure assessment; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen; LDH, lactate dehydrogenase; MV, mechanical ventilation. Percentages calculated on non-missing data. *p*-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit.

[a] Patients who received non-invasive respiratory support but needed intubation were included in the invasive mechanical ventilation group.

[b] Defined as plateau pressure − PEEP.

[c] Defined as tidal volume/(plateau pressure − PEEP).

[d] Defined as (minute ventilation × PaCO2) − (PBW × 100 × 37.5).

[e] Criteria for the Sepsis-3 definition of septic shock include vasopressor treatment and a lactate concentration >2 mmol/L.

Table 2 Main interventions and treatments of the study population ≥70 years old by type of respiratory support.[a]

Variables	All patients (*N* = 1525)	Non-invasive respiratory support (*N* = 554)	Invasive mechanical ventilation (*N* = 971)	*p*-value
COVID-19 therapies during ICU admission, n (%)				
Ribavirin	4 (0.3)	0 (0)	4 (0.4)	0.303
Lopinavir/ritonavir	659 (43)	146 (26)	513 (53)	<0.001
Remdesivir	229 (15)	127 (23)	102 (11)	<0.001
Interferon alpha	5 (0.3)	0 (0)	5 (1)	0.166
Interferon beta	322 (21)	58 (10)	264 (27)	<0.001
Chloroquine	54 (4)	18 (3)	36 (4)	0.641
Hydroxychloroquine	686 (45)	149 (27)	537 (55)	<0.001
Tocilizumab	574 (38)	213 (39)	361 (37)	0.625
Darunavir/cobicistat	27 (2)	6 (1)	21 (2)	0.124
Pharmacological adjunctive therapies during ICU admission				
Continuous furosemide, n (%)	775 (51)	224 (41)	551 (57)	<0.001
Immunoglobulins, n (%)	27 (2)	11 (2)	16 (2)	0.645
Subcutaneous heparin, n (%)	1357 (96)	504 (97)	853 (96)	0.162
≤1 mg/kg/day, n (%)	1065 (70)	428 (78)	637 (66)	<0.001
>1 mg/kg/day, n (%)	497 (33)	174 (32)	323 (34)	0.426
Convalescent plasma, n (%)	47 (3)	27 (5)	20 (2)	0.002
Vasopressor treatment, n (%)	1161 (76)	271 (49)	890 (92)	<0.001
Continuous neuromuscular blockers, n (%)	1037 (68)	245 (44)	792 (82)	<0.001
Corticosteroid, n (%)	1300 (86)	509 (93)	791 (83)	<0.001
Length of treatment, median (Q1; Q3), days	10 (7; 13)	10 (7; 15)	10 (6; 13)	<0.001
Total equivalent dexamethasone dose, median (Q1; Q3), mg/day	15 (6; 29.4)	12.6 (6; 25.6)	15.8 (7.5; 33.8)	<0.001
Other adjunctive treatments during ICU admission				
Tracheostomy, n (%)	517 (34)	129 (23)	388 (40)	<0.001
Recruitment manoeuvres, n (%)	626 (43)	133 (25)	493 (53)	<0.001
Prone position, n (%)	971 (64)	249 (45)	722 (75)	<0.001
Prone length, median (Q1; Q3), hours	48 (24; 90)	48 (24; 96)	48 (24; 85)	0.764
ECMO support, n (%)	3 (0.2)	0 (0)	3 (0.3)	0.558
ECMO length, median (Q1; Q3), hours	25 (1; 49)	–	25 (1; 49)	–
Renal replacement therapy, n (%)	158 (10)	28 (5)	130 (13)	<0.001

Abbreviations: ICU indicates intensive care unit; Q1, first quartile; Q3, third quartile; ECMO, extracorporeal membrane oxygenation. Percentages calculated on non-missing data. *p*-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit.

[a] Patients who received non-invasive respiratory support but needed intubation were included in the invasive mechanical ventilation group.

required NIRS was 55% (24/44). Remarkably, ICU, in-hospital and 90-day mortality rates were 51%, 61% and 65% respectively; and respiratory failure (52% in the NIRS group vs. 43% in the IMV group) and multi-organic failure (33% in the NIRS group vs. 24% in the IMV group) were the main causes of in-hospital mortality without differences between groups. Medians for ICU and hospital length of stay were 13 (7; 23) and 29 (17; 45) days, respectively (S-Table 10).

Predictive factors for in-hospital mortality and recovery in patients aged ≥70 years

Results of the multivariable analysis are reported in Table 4. The following factors were associated with in-hospital mortality: age, previous admission within the last 30 days, chronic heart disease, chronic renal failure, platelet count, MV, and corticosteroids. Firstly, with every year increase in age, the risk of death increased with 7% (sHR 1.07, 95% CI 1.05 to 1.10), and the chances of recovery decreased with 6% (sHR 0.94, 95% CI 0.91 to 0.96). In other words, if in two patients all variables except for age are the same, the patient who is one year older has a 7% higher risk of dying. Furthermore, patients with previous admission within the last 30 days had a 40% increased risk of death (sHR 1.40, 95% CI 1.04 to 1.89). Moreover, patients with chronic heart disease had a 21% increase in risk of death (sHR 1.21, 95% CI 1.01 to 1.44), while patients with chronic renal failure had a 43% increase in risk of death (sHR 1.43, 95% CI 1.12 to 1.82),

Table 3 Complications and outcome variables of the study population ≥70 years old by type of respiratory support.[a]

Variables	All patients (*N* = 1525)	Non-invasive respiratory support (*N* = 554)	Invasive mechanical ventilation (*N* = 971)	*p*-value
Complications, n (%)				
Bacterial pneumonia[b]	481 (32)	140 (25)	341 (35)	<0.001
Pneumothorax	156 (10)	41 (7)	115 (12)	0.006
Pleural effusion	203 (13)	63 (11)	140 (14)	0.088
Organizing pneumonia	94 (6)	50 (9)	44 (5)	0.001
Tracheobronchitis	19 (1)	7 (1)	12 (1)	0.959
Pulmonary embolism	132 (9)	54 (10)	78 (8)	0.267
Cardiac injury[c]	266 (17)	80 (14)	186 (19)	0.018
Bacteraemia	444 (29)	116 (21)	328 (34)	<0.001
Stroke	32 (2)	7 (1)	25 (3)	0.084
Delirium	298 (20)	82 (15)	216 (22)	<0.001
Coagulation disorder[d]	399 (26)	146 (26)	253 (26)	0.903
Disseminated intravascular coagulation[e]	93 (24)	20 (14)	73 (30)	<0.001
Anaemia[f]	991 (65)	331 (60)	660 (68)	0.001
Rhabdomyolysis	58 (4)	19 (3)	39 (4)	0.564
Acute renal failure[g]	680 (45)	193 (35)	487 (50)	<0.001
Pancreatitis	15 (1)	3 (1)	12 (1)	0.187
Liver dysfunction	418 (27)	147 (27)	271 (28)	0.547
Hyperglycaemia	1054 (69)	375 (68)	679 (70)	0.333
Haemorrhage	149 (10)	44 (8)	105 (11)	0.067
Outcomes				
Length of hospital stay, median (Q1; Q3), days				
All patients	26 (16; 44)	22 (15; 41)	27 (16; 47)	0.002
Surviving patients	37 (21; 59)	27.5 (17; 46)	43 (28; 68)	<0.001
Length of ICU stay, median (Q1; Q3), days				
All patients	17 (9; 30)	12 (6; 26)	19 (11; 32)	<0.001
Surviving patients	18 (10; 37)	12 (6; 27)	25 (13; 42)	<0.001
Invasive mechanical ventilation length, median (Q1; Q3), days	16 (9; 28)	16 (9; 31)	16 (9; 27)	0.550
In-hospital mortality, n (%)	756 (50)	224 (40)	532 (55)	<0.001
ICU mortality, n (%)	708 (46)	211 (38)	497 (51)	<0.001
90-day mortality, n (%)[h]	757 (52)	231 (44)	526 (57)	<0.001
Ventilator free days, median (Q1; Q3)	0 (0; 6)	0 (0; 5)	0 (0; 6)	0.176
ICU free days, median (Q1; Q3)	0 (0; 10)	0 (0; 18)	0 (0; 1)	<0.001

Abbreviations: ICU indicates intensive care unit; Q1, first quartile; Q3, third quartile. Percentages calculated on non-missing data. *p*-values marked in bold indicate numbers that are statistically significant on the 95% confidence limit.

[a] Patients who received non-invasive respiratory support but needed intubation were included in the invasive mechanical ventilation group.

[b] Clinically or radiologically diagnosed bacterial pneumonia managed with antimicrobials. Bacteriological confirmation was not required.

[c] Cardiac injury include cardiac arrest, myocardial infarction, endocarditis, myocarditis/pericarditis, cardiomyopathy, heart failure and cardiac ischemia.

[d] Abnormal coagulation was identified by abnormal prothrombin time or activated partial thromboplastin time.

[e] Disseminated intravascular coagulation was defined by thrombocytopenia, prolonged prothrombin time, low fibrinogen, elevated D-dimer and thrombotic microangiopathy.

[f] Hemoglobin consistently below 120 g/L for non-pregnant women and 130 g/L for men.

[g] Acute renal injury was defined as an increase in serum creatinine by ≥0.3 mg/dL within 48 h or an increase in serum creatinine to ≥1.5 times baseline.

[h] Calculated only for patients with 90-day follow-up (526 in the non-invasive respiratory support group and 921 in the invasive mechanical ventilation group).

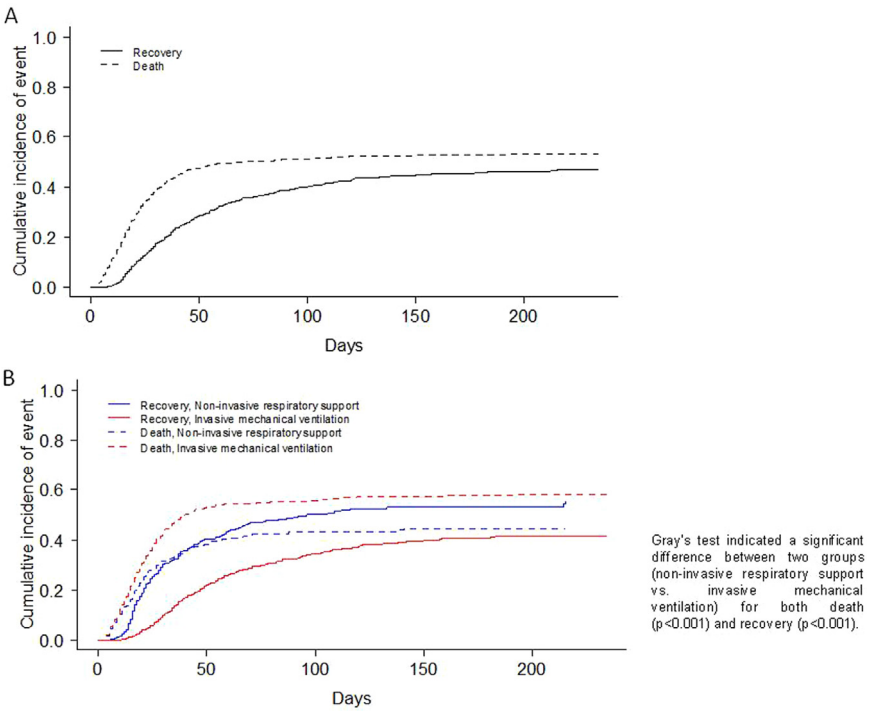

Fig. 2 Cumulative incidence plot of in-hospital mortality and recovery in the overall population of patients ≥70 years old (*N* = 1525) (A) and according to type of respiratory support group (B).

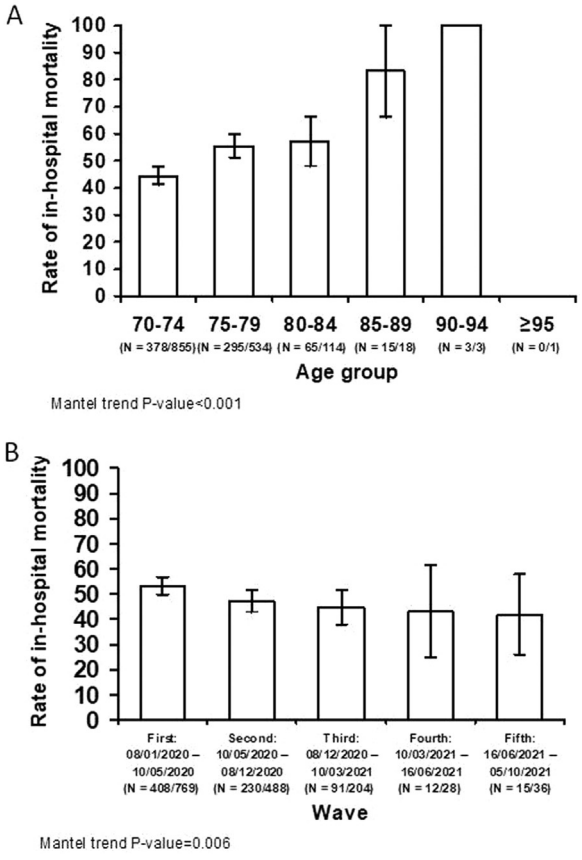

Fig. 3 In-hospital mortality per age group (A), and during the five COVID-19 pandemic waves (B). Study population ≥70 years old (*N* = 1525).

and 33% decrease in chances of recovery (sHR 0.67, 95% CI 0.49 to 0.92). In terms of arterial blood gasses, a ten-fold increase in APACHE-II score at ICU admission, the risk of death increased 1% (sHR 1.01, 95% CI 1.00 to 1.03). In terms of laboratory parameters, a ten-fold increase in platelet count at ICU admission was associated with a 2% decrease in risk of death (sHR 0.98, 95% CI 0.98 to 0.99), and a 2% increase in chances of recovery (sHR 1.02, 95% CI 1.01 to 1.03). Moreover, patients with IMV at ICU admission had a 41% increase in risk of death (sHR 1.41, 95% CI 1.16 to 1.73), and 42% decrease in chances of recovery (sHR 0.58, 95% CI 0.47 to 0.72). Finally, patients that used corticosteroids had a 39% decrease in the risk of death (sHR 0.61, 95% CI 0.48 to 0.77).

Discussion

In a cohort of 5090 critically ill patients admitted to 55 Spanish ICUs for severe COVID-19 we found: 1) 30% of the overall cohort were aged ≥70 years old, and this group presented significantly higher rates of in-hospital mortality rates than younger patients; 2) patients aged ≥70 years receiving IMV presented significantly worse outcomes than those receiving NIRS; and 3) risk factors for in-hospital mortality in patients aged ≥70 years included increasing age, previous 30 days admission, chronic cardiovascular disease and chronic renal failure as baseline variables, and platelet count and IMV as ICU-related variables, whereas corticosteroid therapy conferred a beneficial effect on in-hospital mortality.

Mortality of critically-ill patients with COVID-19 varies widely across countries worldwide ranging from 30% to 80%, being highest in ventilated patients.[16–20] The high mortality

Table 4 Multivariable model assessing predictors of in-hospital mortality and recovery of the study population ≥70 years old (*N* = 1525).

Variables	In-hospital mortality		Recovery	
	sHR (95% CI)	*p*-value	sHR (95% CI)	*p*-value
Age (+1 year)[a]	1.07 (1.05 to 1.10)	<0.001	0.94 (0.91 to 0.96)	<0.001
Male sex	0.89 (0.75 to 1.06)	0.18	1.14 (0.95 to 1.37)	0.17
Previous 30 days admission	1.40 (1.04 to 1.89)	0.027	0.77 (0.48 to 1.25)	0.29
Chronic heart disease	1.21 (1.01 to 1.44)	0.041	0.80 (0.63 to 1.00)	0.054
Chronic lung disease	1.16 (0.95 to 1.41)	0.14	0.96 (0.76 to 1.21)	0.74
Chronic renal failure	1.43 (1.12 to 1.82)	0.005	0.67 (0.49 to 0.92)	0.014
Confusion	1.19 (0.90 to 1.57)	0.23	0.81 (0.56 to 1.15)	0.23
APACHE-II score at ICU admission (+1)[a]	1.01 (1.00 to 1.03)	0.063	0.99 (0.98 to 1.01)	0.39
PaO_2/FiO_2 ratio at ICU admission (+10)[b]	1.00 (0.98 to 1.01)	0.47	1.01 (1.00 to 1.03)	0.037
Lymphocyte count at ICU admission (+1 × 10^9/L)[a]	0.92 (0.83 to 1.03)	0.14	1.07 (0.95 to 1.20)	0.25
Platelet count at ICU admission (+10 × 10^9/L)[b]	0.98 (0.98 to 0.99)	<0.001	1.02 (1.01 to 1.03)	<0.001
D-dimers at ICU admission (+1000 ng/mL)[c]	1.00 (1.00 to 1.01)	0.54	0.99 (0.98 to 1.00)	0.056
Ferritin at ICU admission (+1000 ng/mL)[c]	1.01 (0.98 to 1.04)	0.59	0.96 (0.89 to 1.04)	0.34
C-reactive protein at ICU admission (+10 mg/L)[b]	1.00 (1.00 to 1.01)	0.31	0.99 (0.98 to 1.00)	0.056
Septic shock at ICU admission[d]	1.15 (0.93 to 1.41)	0.19	0.83 (0.64 to 1.09)	0.18
Invasive mechanical ventilation at ICU admission	1.41 (1.16 to 1.73)	<0.001	0.58 (0.47 to 0.72)	<0.001
Corticosteroids	0.61 (0.48 to 0.77)	<0.001	1.15 (0.85 to 1.56)	0.35

Abbreviations: sHR indicates subdistribution hazard ratio; CI, confidence interval; APACHE, acute physiology and chronic health evaluation; ICU, intensive care unit; PaO_2, partial pressure of arterial oxygen; FiO_2, fraction of inspired oxygen. Data are shown as estimated HRs (95% CIs) of the explanatory variables in the in-hospital mortality group and the recovery group. Fine-Gray competing risks model stratified on the center variable and adjusted by COVID-19 wave. The *p*-value is based on the null hypothesis that all HRs relating to an explanatory variable equal unity (no effect).

[a] "+1" means a one-unit increase on the scale in the predictor variable (i.e., going from 1 to 2, 2 to 3, etc.).

[b] "+10" means a ten-unit increase on the scale in the predictor variable (i.e., going from 10 to 20, 20 to 30, etc.).

[c] "+1000" means a one thousand-unit increase on the scale in the predictor variable (i.e., going from 1000 to 2000, 2000 to 3000, etc.).

[d] Criteria for the Sepsis-3 definition of septic shock include vasopressor treatment and a lactate concentration >2 mmol/L.

rate observed in our study is consistent with studies from various countries, in which older age and underlying frailty were identified as risk factors strongly associated with severe COVID-19 infection.[3,16,21–25] A report on COVID-19-related deaths issued by the CDC showed that the mortality rate in individuals aged ≥65 years was more than 65-fold times higher than that in patients aged 18−29 years.[21] Similarly, individuals with underlying medical conditions such as chronic renal or heart failure have increased risk of severe COVID-19 and mortality.[26] Nevertheless, the limitation of life-sustaining treatments, which was more frequent in older and more severe patients, may hugely influence this high crude mortality.[27] Moreover, meta-analyses had previously found lower platelet counts being associated with an increased risk of in-hospital mortality in overall population.[28,29]

Several studies have shown that increasing age is associated with a lower likelihood of being intubated in critically-ill COVID-19 elderly patients.[23,30–35] Interestingly, a meta-analysis comprising 21 studies with a combined population of 37,359 patients with COVID-19 (5800 receiving IMV) from 7 countries did not find an association between increasing age and the likelihood of receiving IMV, yet in line with our findings decreasing mortality rates amongst ventilated patients across waves were found.[33] Another recent posthoc analysis of the PRoVENT-COVID study showed that in a cohort of invasively ventilated critically ill COVID-19 patients, age had no effect on ventilator management. However greater age was associated with more complications and higher mortality.[23] It is also worth mentioning that prior studies found much higher mortality rates in ventilated elderly patients. In a recent meta-analysis pooling data from 57,000 COVID-19 patients that required mechanical ventilation, the overall case-fatality rate was 45% (95% CI: 39−52%), which increased according to age group, being 84% (95% CI: 83.3−85.4%) in patients over 80 years.[6] Andrei and colleagues found even higher mortality rates in patients very elderly ventilated patients with COVID-19, as in 1666 patients with a median age of 83 years ICU mortality was 78%, reaching 97% amongst those receiving mechanical ventilation.[34] In a prospective cohort of 3.719 severe CAP patients (mean age of 70 years old) from Spain previous to the COVID-19 pandemic,[35] the authors reported a higher 30-day mortality in mechanical ventilated patients compared with patients received non-invasive ventilation (33% vs. 18%, $p<0001$). They also reported that IMV was an independently predicted of 30-day mortality in patients with severe CAP. Meanwhile, in-hospital mortality was 61% amongst patients ≥80 years in our study, and although the difference did not reach statistical significance, patients receiving NIRS presented a notably lower mortality rate than those receiving IMV (55% vs. 71%, $p = 0.057$).

A major strength of our study is the large multicentre nature, the consecutive inclusion of all patients from each

center, and the detailed information on ICU-related features provide great value for all healthcare professionals treating COVID-19 in the setting of critically ill patients. On the other hand, our findings are constrained by a lack of sub-analyses assessing the impact of the type of steroid, time of initiation, dosing and length of treatment. Limitations of our study include different waves of the pandemic (S-Table 11), which could have influenced our results. We have however adjusted our multivariable analysis for this confounder. We also do not have data on restrictions of care, and not systematically collected the time point in which patients transitioned from one ventilation modality to another. Finally, as we examined real-world data, limitations associated to the observational nature and missing data should be considered.

In conclusion, patients aged $\geq$70 years constituted a significant proportion of ventilated patients with COVID-19 across 55 Spanish ICUs, presenting high mortality rates. Age, previous admission within the last 30 days, chronic heart disease, chronic renal failure, platelet count, IMV at ICU admission and systemic steroids (protective) were independent factors associated with in-hospital mortality in critically ill patients aged $\geq$70 years. Administering systemic steroids could have beneficial effects on in-hospital mortality.

Author contributions

Study concept and design: CC, AM, AT; data collection: CC, AM, AP, TC, AC statistical analysis: AG; analysis and interpretation of data: CC, AM, JP, TC, AT; drafting of the manuscript: CC, AM, JP, AT; critical revision of the manuscript for important intellectual content: CC, AM, JP, and AT; and study supervision: AT. AT had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. CiberesUCICOVID consortium participated in data collection.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration Competing Interests

The authors declare that they have no competing interests.

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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.2023.01.007.

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ORIGINAL ARTICLE

Impact of self-reported environmental mould exposure on COPD outcomes

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Abstract
Background: Indoor and outdoor mould exposure can affect respiratory symptoms, but its contribution to COPD outcomes such as exacerbation rates or antibiotics courses is not well defined. Some patients with COPD develop chronic pulmonary aspergillosis (CPA), but the contribution of environmental exposure is not known.
Methods: We correlated activities or exposures related to mould with COPD outcomes in patients with COPD with or without CPA using a questionnaire.
Results: One hundred and forty patients were included and 60 had CPA in addition to COPD. Seventy-six were male and mean age was 66.9 years (range 40—87). Thirty-nine (28%) were active cigarette smokers. On multivariate analysis, occupational contact with agricultural resources (p = 0.017), vacuuming once weekly or more often (p = 0.026) and not asking visitors to remove shoes on home entry (p = 0.035) were significantly more common in participants reporting $\geq$ 4 office visits for COPD symptoms in the last year. Living within one mile of industrial composting sites (p = 0.013), vacuuming once weekly or more often (p = 0.016) and not asking visitors to remove shoes on home entry (p = 0.028) were significantly more common in participants reporting $\geq$4 antibiotics courses in the last year. Patients with CPA showed a trend for residence within one mile of farms or agricultural areas (P = 0.088, OR 2, 95% CI 0.9—4.4).

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Conclusion: Activities potentially leading to mould exposure were common in a population with COPD with or without CPA and were associated with adverse COPD outcomes. Environmental mould exposure may play a role in the development of CPA in patients with COPD.

Introduction

Environmental exposure to mould has been shown to have detrimental effects on people with lung conditions. The association has been well documented in children, adolescents and adults with asthma, with less evidence available for other chronic lung conditions.[1–3] Indoor vs. outdoor exposure, and rural vs. urban surroundings, may have different contributions in various settings.[4,5] Amongst the multitude of environmental fungi, Aspergillus has been linked with pathology in patients with chronic lung disease, in the forms of invasive, chronic and allergic pulmonary aspergillosis.[6,7]

Aspergillus is a common environmental mould, prevalent in most surroundings, but existing in higher concentrations in damp or dusty environments, such as decaying vegetation, compost, or as visible mould indoors. In addition, some occupations may lead to more fungal exposure than others, as has been documented in cases of allergic bronchopulmonary aspergillosis.[8,9] Fungal exposure may have additional detrimental effects besides the respiratory system, such as constitutional or neurological symptoms, and real or perceived exposure to mould can be a source of distress for patients and healthy individuals alike.[10,11]

In contrast to the links between fungal exposure and asthma, the effect of environmental mould on the symptoms and course of chronic obstructive pulmonary disease (COPD) is not clear. COPD is associated with significant morbidity and mortality: in addition to chronic progression of respiratory decline, acute exacerbations result in outpatient or hospital visits, admissions to hospitals and frequent antibiotic use, which promotes antimicrobial resistance. Multiple hospital admissions with exacerbations are associated with substantial mortality; therefore, preventing them is a key COPD treatment target.[12–14]

Patients with COPD have a higher frequency of Aspergillus sensitisation than smokers without COPD, and Aspergillus-sensitised patients are more likely to have worse lung function and bronchiectasis than the non-sensitised.[15] It is possible that fungal sensitisation in COPD is caused by substantial fungal exposure in the environment. There is evidence that Aspergillus-specific T-lymphocytes are more abundant in the blood of people who have been exposed to Aspergillus through specific indoor or outdoor activities.[16] In addition, the same resistant Aspergillus strains were cultured from respiratory secretions of COPD patients and from patients with invasive aspergillosis and their homes.[17,18] In a small number of COPD patients, quantity of fungi in floor dust was associated with poorer lung function.[19] If specific activities linked to mould exposure can be shown to affect COPD symptoms or outcomes, this information can inform advice on avoidance of certain high-risk exposures which in turn can lead to a reduction in the number of exacerbations and prevention of deterioration of lung function.

Chronic pulmonary aspergillosis (CPA) is a slowly progressive debilitating condition affecting mainly patients with chronic lung disease like COPD or previous tuberculosis. Unless recognised and treated, it can progress and lead to poor quality of life. It is not clear why some patients with COPD develop CPA; genetic associations have been suggested.[20] The importance of the environment in the development of CPA has not been investigated, although it has been shown that immunocompromised patients with self-reported domestic fungal exposure were more likely to develop invasive aspergillosis.[21] Therefore, it is possible that particular high-risk exposures may predispose to CPA in patients with COPD.

The aim of this study is to describe the effect of self-reported indoor, outdoor, and occupational fungal exposure on COPD outcomes such as exacerbations, antibiotics courses and hospital visits and to explore the connection between fungal exposure and the development of CPA.

Methods

Participants and recruitment methods

Patients with COPD attending the clinics of the North West Lung Centre, Manchester University NHS Foundation Trust, were eligible. Recruitment started in June 2019. Consecutive participants were approached after their clinic appointment and asked to complete a questionnaire after written consent. Recruitment was from a specialist COPD clinic and a specialist CPA clinic. The patient populations attending the two clinics are different and distinct, as the specialist CPA clinic is a national CPA referral centre (National Aspergillosis Centre). The diagnosis of CPA was confirmed with the treating physician and from the medical notes after the clinic appointment.

The standardised questionnaire included questions on potential exposure to mould at work, at home or outdoors (Table 1). For all categories, current as well as prior, exposure was recorded. In addition, COPD outcomes included self-reported number of General Practitioner (GP) appointments for respiratory symptoms, numbers of antibiotics courses received, numbers of Emergency Department visits and number of hospital admissions for respiratory complaints over the previous 12 months. Participants with more than four visits or antibiotics courses were recorded as 'five or more' rather than the exact number to reduce recall bias. Smoking history and number of years with COPD diagnosis were documented. The full questionnaire is provided in the Appendix. During development, the questionnaire was shown to 10 patients with COPD and changes made according to feedback.

Information recorded from the medical notes included demographics, the most recent lung function tests including

Table 1 Activities included in questionnaire.

Category	Activity
Occupational exposure	Visible mould, mouldy smell, or water damage
	Contact with organic waste or agricultural resources
	Processing of wood or wood products
	Renovation work
	Handling of plants/gardening
	Handling of air-conditioning or cooling systems
Exposure at home	Visible mould, mouldy smell, or water damage
	Humidifier use
	Pets and type of pet
	Drying clothes indoors
	Frequency of vacuuming
	Asking visitors to remove shoes when entering
	Number of rooms that have carpets
Outdoor exposure	Gardening/composting
	Residence in city/town/village/countryside
	Proximity to farms or industrial composting sites
	Hobbies related to fungal exposure

FEV1 and FVC, peripheral eosinophil count, Aspergillus serology when available, and presence of concomitant CPA.

In March 2020, face-to-face recruitment ceased due to the COVID-19 pandemic. At that stage, we reverted to recruitment using the Research for the Future Programme (NIHR Clinical Research Network, North West E Health, Health Innovation Manchester and Northern Care Alliance NHS Group). From that point on, recruitment was through online questionnaire.

The study received ethical approval from the NHS Health Research Authority (REC Reference 19/SC/0103).

Statistical analysis

The association of all types of activities, clinical information, and demographics with each of the COPD outcomes was performed with chi square test for categorical variables, with *T*-Test for continuous normally distributed variables and Mann-Whitney *U* test for not normally distributed variables. Normality was checked with the Shapiro-Wilk test. All parameters with a p value < 0.1 were included in further analysis (binary logistic regression when the outcomes were considered as < 4 or ≥ 4 events per year, and linear regression when the outcomes were considered as a continuous variable). A p value of < 0.05 was considered statistically significant. All patients with COPD were included in the analysis for COPD outcomes. Patients with COPD/CPA were compared to those with COPD without CPA for the analysis of risk factors associated with CPA. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Results

One hundred and four patients were recruited face-to-face and 36 through online questionnaire. Seventy-six (54%) were male and mean age was 66.9 years (range 40−87). The mean time (±SD) since the diagnosis of COPD was 11.5 (±9.4) years. Thirty-nine (28%) were active cigarette smokers, 13 (9%) were active e-cigarette smokers and four (3%) were active cannabis smokers.

Mean FEV1 (±SD) was 60.5% (±29) predicted. One hundred and twenty-one (87%) saw their GP in the preceding year for respiratory complaints and 64 (46%) attended four times or more. One hundred and ten (81%) received antibiotics for a chest infection in the last year, and 54 (40%) had four or more courses. Forty-four (32%) visited the emergency department with respiratory symptoms and 38 (18%) were admitted to hospital in the last 12 months. Sixty (43%) had the diagnosis of CPA in addition to COPD. Table 2 shows GP visits and antibiotics courses in relation to demographics, lung function, smoking status, and laboratory parameters. Emergency department visits in relation to these parameters are shown in the Appendix (Table 1A).

Seventeen patients were working at the time of the interview, 25 did not disclose their occupation status and 98 were retired or unemployed. Occupational exposures, either present or previous, reported by participants were: gardening (40%), handling plants (37%), mouldy smell at workplace (37%), visible mould at workplace (36%), renovation work in old buildings (34%), water leakage (31%), contact with organic waste (29%), contact with agricultural resources (21%), processing wood and wood products (21%) and handling air-conditioning and cooling systems (12%). Table 3 shows the association between COPD outcomes and occupational mould exposures.

Area of residence was reported as ‘town’ in 67 (48%), ‘city’ in 30 (21%), ‘village’ in 28 (20%) and ‘countryside’ in 15 (11%). Eighty-eight (63%) lived in a home built more than 40 years ago. The most frequent form of accommodation was house (n = 88, 63%), followed by flat (n = 28, 20%) and bungalow (n = 21, 15%). Reported potential mould exposures at home were: having a garden (85%), vacuuming weekly or more often (85%), not asking visitors to remove shoes when entering the property (83%), drying clothes indoors (64%), gardening (55%), living within one mile of farms or agricultural areas (51%), having carpets in most rooms (49%), using compost when gardening (41%), visible mould in the home (39%), owning pets (38%), composting of garden waste (23%), mouldy smell at home (18%), water damage (15%), living within one mile of an industrial composting site (16%) and use of a humidifier (11%).

Among pet owners, 59 (42%) had dogs and 46 (33%) had cats. Fifty-five participants reported visible mould in the home, specifically: 31 (22%) in the bedroom, 26 (19%) in the bathroom, nine (6%) in the kitchen and seven (5%) in the living room. Hobbies exposing to mould were reported by 14 (9%); these included walking in parks, farming, gardening, golf, decorating, renovating and animal breeding. Tables 4

Table 2 COPD outcomes in relation to demographics and pertinent clinical information.

	Number of GP visits in last 12 months					Number of antibiotics courses in last 12 months				
	med	P^1	< 4	≥ 4	P^2 (OR, 95%CI)	med	P^1	< 4	≥ 4	P^2 (OR, 95%CI)
Gender		0.119			0.231		0.687			0.725
Male	4		37 (48.7)	39 (51.3)	(1.56, 0.79−3.07)	3		47 (62.7)	28 (27.3)	(0.86, 0.43−1.71)
Female	2.5		37 (59.7)	25 (40.3)		3		36 (59)	25 (41)	
Age, mean±SD			66.0 ± 8.8	67.9 ± 9.5	0.213 (1.02, 0.97−1.06)			66.4 ± 9.6	67.8 ± 8.2	0.41 (1.02, 0.98−1.06)
Current smoker		0.781			1.00		0.871			0.438
Yes	3		21 (53.8)	18 (46.2)	(1.01, 0.48−2.13)	3		21 (55.3)	17 (44.7)	(1.37, 0.64−2.94)
No	3		53 (54.1)	45 (45.9)		3		61 (62.9)	36 (37.1)	
FEV1 (% predicted), mean± SD			57.3 ± 26.5	63.6 ± 29.4	0.457 (1.01, 0.99−1.03)			61.4 ± 28.4	61.78±27.6	0.961 (1.00, 0.98−1.02)
Peripheral eosinophils ($x10^9$/L), mean±SD			0.22±0.24	0.23±0.20	0.850 (1.20, 0.18−7.86)			0.23±0.23	0.23±0.20	0.874 (1.16, 0.18−7.34)
Bronchiectasis		0.413			0.458		**0.049**			**0.016**
Yes	5		3 (42.9)	4 (57.1)	(1.85, 0.39−8.79)	4.5		1 (16.7)	5 (83.3)	(11.35,
No	3		50 (58.1)	36 (41.9)		3		59 (69.4)	26 (30.6)	1.26−101.9)
Azithromycin		**0.002**			**0.001**		**< 0.001**			**< 0.001** (6.43,
Yes	5		3 (15)	17 (85)	(8.44, 2.34−30.47)	5		5 (25)	15 (75)	2.2−19.1)
No	3		67 (59.8)	45 (40.2)		2		75 (68.2)	35 (31.8)	

Significant values in bold. GP: general practitioner; OR: odds ratio; CI: confidence interval; med: median values; SD: standard deviation; FEV1: forced expiratory volume in one second. Numbers are n (%) unless otherwise specified.

[1] p value for outcomes as a continuous variable.

[2] p value for outcomes as a binary variable (< 4 or ≥ 4).

Table 3 COPD outcomes in relation to occupational exposure to mould, previous or current.

	GP visits in last 12 months					Antibiotics courses in last 12 months				
	med	P^1	< 4	≥ 4	P^2(OR, 95%CI)	med	P^1	< 4	≥ 4	P^2(OR, 95%CI)
Contact with organic waste		0.124			0.259		0.931			0.846
Yes	4		18 (45)	22 (55)	(1.63, 0.78−3.42)	3		23 (59)	16 (41)	(1.13, 0.53−2.41)
No	3		56 (57.1)	42 (42.9)		3		60 (61.9)	37 (38.1)	
Contact with agricultural		**0.005**			**0.011**		**0.022**			**0.019**
resources			9 (31)	20 (69)	(3.23, 1.35−7.76)			12 (41.4)	17 (58.6)	(2.76, 1.19−6.40)
Yes	5		64 (59.3)	44 (40.7)		4		70 (66)	36 (34)	
No	3					3				
Processing of wood or wood		0.44			0.676		0.891			0.828
products			14 (48.3)	15 (51.7)	(1.27, 0.56−2.88)			16 (57.1)	12 (42.9)	(1.19, 0.51−2.80)
Yes	4		58 (54.2)	49 (45.8)		2.5		65 (61.3)	41 (38.7)	
No	3					3				
Renovation work in old		0.479			0.722		0.442			0.853
buildings			24 (51.1)	23 (48.9)	(1.15, 0.57−2.32)			27 (58.7)	19 (41.3)	(1.14, 0.55−2.35)
Yes	3		49 (54.4)	41 (45.6)		3		55 (61.8)	34 (38.2)	
No	3					3				
Handling of plants		**0.03**			0.113		**0.025**			**0.048**
Yes	5		23 (44.2)	29 (55.8)	(1.84, 0.92−3.69)	3.5		25 (50)	25 (50)	(2.07, 1.01−4.23)
No	3		51 (59.3)	35 (40.7)		2.5		58 (67.4)	28 (32.6)	
Gardening		0.126			0.303		0.717			0.595
Yes	4		27 (48.2)	29 (51.8)	(1.44, 0.73−2.86)	3		32(58.2)	23 (41.8)	(1.22, 0.61−2.46)
No	3		47 (57.3)	35 (42.7)		3		51(63)	30 (37)	
Handling of A/C or cooling		0.314			0.608		0.789			0.439
systems			8 (47.1)	9 (52.9)	(0.73, 0.26−2.01)			9 (52.9)	8 (47.1)	(1.50, 0.54−4.16)
Yes	4		66 (55)	54 (45)		3		74 (62.7)	44 (37.3)	
No	3					3				
Visible mould		0.432			0.480		0.38			0.360
Yes	4		25 (49)	26 (51)	(1.34, 0.67−2.68)	3		27(55.1)	22 (44.9)	(1.47, 0.72−3.01)
No	3		49 (56.3)	38 (43.7)		3		56 (64.4)	31 (36.6)	
Mouldy smell		0.277			0.598		0.52			0.369
Yes	3.5		26 (50)	26 (50)	(0.79, 0.39−1.58)	3		28 (56)	22 (44)	(1.39, 0.69−2.84)
No	3		48 (55.8)	38 (44.2)		3		55 (64)	31 (36)	
Water leakage		0.814			0.854		0.837			0.451
Yes	3		24 (55.8)	19 (44.2)	(0.88, 0.43−1.82)	3		24 (55.8)	19 (44.2)	(1.37, 0.66−2.90)
No	3		50 (52.6)	45 (47.4)		3		59 (63.4)	34 (36.6)	

Significant values in bold. GP: general practitioner; med: median numbers; OR: odds ratio; CI: confidence interval; A/C: air conditioning. Numbers are n (%) unless otherwise specified.

[1] p value for outcomes as a continuous variable.

[2] *p* value for outcomes as a binary variable (< 4 or ≥ 4).

Table 4 COPD outcomes in relation to domestic exposure to mould.

	GP visits in last 12 months					Antibiotics courses in last 12 months				
	med	P^1	< 4	≥ 4	P^2 (OR, 95%CI)	med	P^1	< 4	≥ 4	P^2 (OR, 95%CI)
Visible mould		0.975			0.391		0.509			0.283
Yes	3		32 (58.2)	23 (41.8)	(0.76, 0.37–1.47)	3		37 (67.3)	18 (32.7)	(0.64, 0.31–1.31)
No	3		42 (50.6)	21 (49.4)		3		46 (56.8)	35 (43.2)	
Mouldy smell		0.621			0.828		0.178			0.171
Yes	3		13 (52)	12 (48)	(1.10, 0.46–2.63)	4		12 (48)	13 (52)	(1.97, 0.82–4.74)
No	3		61 (54.5)	51 (45.5)		3		71 (64.5)	39 (35.5)	
Water damage		0.575			0.816		0.98			0.807
Yes	3		11 (52.4)	11 (52.4)	(1.12, 0.44–2.86)	3		14 (66.7)	7 (33.3)	(0.77, 0.29–2.10)
No	3		63 (55.3)	51 (44.7)		3		68 (60.7)	44 (39.3)	
Humidifier use		0.945			0.413		0.866			0.782
Yes	3		10 (66.7)	5 (33.3)	(0.56, 0.18–1.75)	3		10 (66.7)	5 (33.3)	(0.77, 0.25–2.40)
No	3		63 (52.9)	56 (47.1)		3		71 (60.7)	46 (39.3)	
Drying clothes indoors		0.162			**0.033**		0.61			1.000
Yes	3		53 (60.2)	35 (39.8)	(0.46, 0.22–0.93)	3		53 (60.9)	34 (39.1)	(0.98, 0.48–2.01)
No	4		20 (40.8)	29 (59.2)		3		29 (60.4)	19 (39.6)	
Vacuuming		0.463			**0.015**		0.759			**0.024**
Weekly or more often	4		58 (49.6)	59 (50.4)	(4.07, 1.28–12.5)	3		65 (56.5)	50 (43.5)	(4.37, 1.20–16.67)
Less often than weekly	3		16 (80)	4 (20)		2.5		17 (85)	3 (15)	
Ask visitors to take shoes off when entering		**0.094**								
Yes	2		17 (73.9)	6 (26.1)	**0.040**	2	**0.04**	19 (82.6)	4 (17.4)	**0.020**
No	4		57 (49.6)	58 (50.4)	(0.35, 0.13–0.94)	3		64 (56.5)	49 (43.4)	(0.28, 0.09–0.86)
Most rooms have carpets		0.998			1.000		0.166			0.374
Yes	3		36 (53.7)	31 (46.3)	(1.06, 0.54–2.07)	3		38 (57.6)	28 (42.4)	(1.44, 0.72–2.91)
No	3		38 (55.1)	31 (44.9)		2.5		45 (66.2)	23 (33.8)	
Home built		0.719			0.584		0.283			0.570
>40 years ago	3		46 (52.3)	42 (47.3)	(1.30, 0.63–2.67)	3		56 (64.4)	31 (35.6)	(0.76, 0.36–1.58)
<40 years ago	3		27 (58.7)	19 (41.3)		3		26 (57.8)	19 (42.2)	
Owning pets		0.339			0.203		0.861			1.000
Yes	4		46 (49.5)	47 (50.5)	(1.68, 0.81–3.98)	3		55 (60.4)	36 (39.6)	(1.08, 0.52–2.25)
No	3		28 (62.2)	17 (37.8)		3		28 (62.2)	17 (37.2)	
Owning cats		0.541			0.208		0.323			0.462
Yes	4		21 (45.7)	25 (54.3)	(1.62, 0.79–3.30)	3		26 (56.5)	20 (43.5)	(1.33, 0.65–2.7)
No	3		53 (57.6)	39 (42.4)		2		57 (63.3)	33 (36.7)	
Owning dogs		0.824			0.732		0.734			0.723
Yes	3		30 (51.7)	28 (48.3)	(1.41, 0.58–2.25)	3		36 (63.2)	21 (36.8)	(0.86, 0.43–1.73)
No	4		44 (55)	36 (45)		3		47 (59.5)	32 (40.5)	

Significant values in bold. GP: general practitioner; med: median numbers; OR: odds ratio; CI: confidence interval. Numbers are n (%) unless otherwise specified.

[1] p value for outcomes as a continuous variable.

[2] p value for outcomes as a binary variable (< 4 or ≥ 4).

Table 5 COPD outcomes in relation to outdoors exposure to mould.

	GP visits in last 12 months					Antibiotics courses in last 12 months				
	med	P^1	< 4	≥ 4	P^2 (OR, 95%CI)	med	P^1	< 4	≥ 4	P^2 (OR, 95%CI)
Having garden		0.538			1.000		0.685			1.000
Yes	3		63 (53.4)	55 (46.6)	(1.07, 0.41−2.80)	3		71 (61.2)	45 (38.8)	(0.95, 0.36−2.51)
No	3		11 (55)	9 (45)		3		12 (60)	8 (40)	
Gardening		0.846			0.396		0.312			0.287
Yes	3		43 (56.6)	33 (43.4)	(0.74, 0.38−1.46)	3		49 (65.3)	26 (34.7)	(0.65, 0.32−1.30)
No	4		30 (49.2)	31 (50.8)		3		33 (55)	27 (45)	
Using compost when gardening		0.82			0.732		0.607			0.592
Yes	3		32 (55.2)	26 (44.8)	(0.88, 0.44−1.73)			36 (64.3)	20 (35.7)	(0.77, 0.38−1.57)
No	3		41 (51.9)	38 (48.1)		3		46 (58.2)	33 (41.8)	
Composting of garden waste		0.53			1.000	3	0.5			0.834
Yes	3		17 (53.1)	15 (46.9)	(1.01, 0.6−2.23)			19 (63.3)	11 (36.7)	(0.87, 0.38−2.00)
No	3		56 (53.3)	49 (46.7)		2		63 (60)	42 (40)	
Living within 1 mile of farms or agricultural areas		**0.007**			**0.038**	3	**0.027**			0.160
Yes	4		32 (45.1)	39 (54.9)	(2.17, 1.09−4.34)			38 (54.3)	32 (45.7)	(1.68, 0.83−3.40)
No	2.5		41 (64.1)	23 (35.9)				42 (66.7)	21 (33.3)	
Living within 1 mile of industrial composting sites		0.116			0.486	3	**0.008**			**0.008**
Yes	5		10 (45.5)	12 (54.5)	(1.46, 0.58−3.67)			7 (33.3)	14 (66.7)	(3.79, 1.41−10.82)
No	3		61 (55)	50 (45)		5		72 (65.5)	38 (34.5)	
Hobbies or other activities exposing to mould		0.839			1.000	3	0.867			1.000
Yes	3.5		7 (50)	7 (50)	(1.14, 0.38−3.45)			9 (64.3)	5 (35.7)	(0.83, 0.26−2.64)
No	3		65 (53.3)	57 (46.7)		2		72 (60)	48 (40)	
						3				

Significant values in bold. GP: general practitioner; med: median numbers; OR: odds ratio; CI: confidence interval. Numbers are n (%) unless otherwise specified.

[1] *p* value for outcomes as a continuous variable.

[2] *p* value for outcomes as a binary variable (< 4 or ≥ 4).

Table 6 Multivariate analysis of the risk factors for GP attendance and antibiotic prescription.

Four or more visits to GP for chest symptoms in last 12 months	p	Odds Ratio	95% confidence interval
Vacuuming once weekly or more often	0.026	4.01	1.18–13.62
Not asking visitors to remove shoes on entry	0.035	3.33	1.09–10
Occupational contact with agricultural resources	0.017	3.19	1.23–8.30
Living within one mile of farms or agricultural area	0.152	1.73	0.82–3.68
Drying clothes indoors	0.152	0.56	0.25–1.24
Four or more antibiotics courses in last 12 months	*p*	**Odds Ratio**	**95% confidence interval**
Vacuuming once weekly or more often	0.016	5.41	1.37–21.39
Not asking visitors to remove shoes on entry	0.028	4.35	1.18–16.67
Living within one mile of industrial composting sites	0.013	3.74	1.32–10.60
Occupational contact with agricultural resources	0.131	2.13	0.80–5.67
Work handing plants	0.146	1.87	0.81–4.35

and 5 show the association between COPD outcomes and domestic and outdoor exposure to mould, respectively. Table 6 shows the results of the multivariate analysis for the various COPD outcomes. The correlation between another COPD outcome, emergency department visits, and various exposures is included in the Appendix (Table 2A).

Table 7 shows the baseline characteristics of patients with and without CPA. On univariate analysis, reported exposures significantly more common in patients with CPA were: contact with agricultural resources at work (p = 0.058, Odds Ratio [OR] 2.29, 95% Confidence interval [CI] 0.98–5.28), processing wood or wood products at work (p = 0.06, OR 2.26, 95% CI 0.98–5.2), water leakage at work (p = 0.044, OR 2.14, 95% CI 1.03–4.44), not drying clothes indoor (p = 0.020, OR 2.42, 95% CI 1.19- 4.92) and living within one mile of farms or agricultural areas (p = 0.015, OR 2.48, 95% CI 1.23–4.97). On multivariate analysis, only residence within one mile of farms or agricultural areas showed a trend (P = 0.088, OR 2, 95% CI 0.9–4.4) towards being more common in patients with CPA.

Discussion

Activities and exposures related to mould were common in a patient population with COPD seen in secondary care in England and several of these exposures were associated with adverse outcomes such as increased rates of exacerbations and antibiotics courses. In contrast, we did not find an association between these outcomes and eosinophil counts, current smoking, FEV1, or time from COPD diagnosis. In addition, the specific exposures included in this questionnaire did not appear to be a risk factor for CPA in patients

Table 7 Characteristics of patients with COPD with and without chronic pulmonary aspergillosis.

	COPD without CPA	COPD with CPA	p	OR (05% CI)
Gender			**0.002**	3.15 (1.56–6.41)
Male	34 (44.7)	42 (55.3)		
Female	46 (71.8)	18 (28.1)		
Age (mean±SD)	65.5 ± 9.7	68.7 ± 7.9	**0.044**	1.04 (1.001–1.08)
Smoking	20 (25.3)	19 (32.2)	0.45	1.4 (0.67–2.9)
FEV1 (% predicted) (mean±SD)	54.4 ± 27.4	66.7 ± 28.04	0.134	1.02 (0.99–1.04)
Eosinophils (x10^9/L) (mean±SD)	0.25±0.27	0.21±0.16	0.382	0.433 (0.07–2.8)
Azithromycin	14 (18.4)	6 (10.3)	0.23	0.51 (0.18–1.42)
Times saw doctor				1.37 (0.7–2.7)
<4 times in the last year	45(60.8)	29(39.2)	0.392	
≥4 times in the last year	34(53.1)	30(46.9)		
Antibiotics courses				0.97 (0.48–1.96)
<4 times in the last year	48(57.8)	35(42.2)	1.000	
≥4 times in the last year	31(58.5)	22(41.5)		
Bronchiectasis	4 (5.2)	3 (5.2)	1.000	0.99 (0.21–4.6)
Asp-IgG (mg/L)* (mean±SD)	41±37.03	130.2 ± 188.5	**0.001**	1.02(1.004–1.03)
Asp-IgE (IU/mL) (mean±SD)	1.1 ± 2.3	4.1 ± 11.04	**0.06**	1.08 (0.93–1.3)
Total IgE (IU/mL) (mean±SD)	262±345.2	575.8 ± 1723.08	0.423	1.000 (0.99–1.001)

CPA: chronic pulmonary aspergillosis; OR: Odds Ratio; CI: confidence interval. Numbers are n(%) unless otherwise specified.
* ImmunoCAP assay.

with COPD, except for residence in proximity of agricultural areas.

Patients reporting residence in proximity to industrial composting sites or agricultural areas such as farms, suffered from higher frequencies of exacerbations and office visits. An association has been reported previously: a study from the Netherlands reported a higher frequency of wheezing in COPD patients living in areas of higher livestock farm density.[22] However, the rate of COPD and asthma was actually found to be lower in the vicinity of farms in this and another study from the same country.[23] This is likely due to demographic reasons and not a specific effect of agricultural exposure. Rural residence in the US was linked with 70% more exacerbations, but not with worse baseline symptoms.[24]

Certain domestic exposures exhibited a stronger association with adverse COPD outcomes. Participants who reported vacuuming more frequently had more GP visits or antibiotics courses on multivariate analyses. Vacuuming may aerosolise non-biological and biological particles including bacteria and fungi in the environment, either from settled dust or from the cleaner bag.[25,26] Significant diversity was found in vacuum cleaner emission rates from various studies, and it is not clear if the type of home or brand or age of vacuum cleaner may affect these results. The relative contribution of bacteria, fungi, or non-biological aerosols of vacuum cleaner emissions to respiratory symptoms in patients with chronic lung disease such as COPD has not yet been assessed. In addition, colonisation with bacteria and fungi can occur in surfaces such as shoes which therefore may be responsible for introducing a higher burden of allergens or pathogens in the home. Cultural practices differ, but in our survey most participants would not ask visitors to remove their shoes on entry. It may be that this practice, or other associated exposures, may result in a higher fungal burden.

The association between occupational fungal exposure and outcomes was less evident. Most interviewed participants were not actively working; therefore, ongoing mould exposure at work was not an issue. However, participants reporting exposure to agricultural sources at work, or handling of plants as part of their occupation, either current of prior, had increased number of GP visits and antibiotics courses. It cannot be ascertained whether this is related specifically to ongoing fungal exposure in their daily routines following retirement, for example as hobbies.

Fungal exposure has been implicated in hospital-acquired cases of invasive aspergillosis, as well as in allergic bronchopulmonary aspergillosis via occupational exposure.[27] However, CPA has not been linked with a particular mould exposure risk. This study showed an association between presence of CPA and residence in proximity of farms or agricultural areas. This could be due to a real predisposition to CPA or because clinics may have differing catchment areas. In the pathogenesis of CPA, factors other than specific fungal exposure are likely to be at least as important, such as genetic predisposition or unrecognised immune defects.[20]

This study has several limitations. Due to the COVID-19 pandemic, the recruitment method had to change during the study. Participants recruited via online questionnaire could have had milder disease compared to participants recruited in clinic. In addition, laboratory parameters were not available for the group recruited via online questionnaire. A larger proportion of females responded to the online questionnaire compared to those recruited in clinic. The COPD and COPD/CPA populations are dissimilar due to the different recruitment approaches, and therefore not directly comparable. Although the activities included in the questionnaire are perceived to lead to mould exposure, no measurement of domestic fungal load was performed to corroborate this. Therefore, self-reported mould exposure may not be an accurate surrogate for actual exposure. Finally, recall bias may have affected participants with more severe disease or with CPA.

Conclusions

We show that certain self-reported domestic and outdoor exposures thought to be associated with mould were associated with worse outcomes in COPD. Mould exposure, actual or perceived, can be a major source of distress for individuals with chronic disease, and clarifying any association will inform efforts to prevent exacerbations in COPD. A survey of fungal burden in the homes of COPD patients in relation to outcomes will be needed to further investigate this.

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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.2021.05.003.

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ORIGINAL ARTICLE

Sleep apnea in school-age children living at high altitude

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Abstract
Introduction: Among adults, sleep apnea is more common in highlanders than in lowlanders. We evaluated the sleep apnea prevalence in children living at high altitude compared to age-matched low-altitude controls.
Methods: Healthy children, 7-14 y of age, living at 2500-3800m in the Tien Shan mountains, Kyrgyzstan, were prospectively studied in a health post at 3250m. Healthy controls of similar age living at 700-800m were studied in a University Hospital at 760m in Bishkek. Assessments included respiratory sleep studies scored according to pediatric standards, clinical examination, medical history, and the pediatric sleep questionnaire (PSQ, range 0 to 1 with increasing symptoms).
Results: In children living at high altitude (n = 37, 17 girls, median [quartiles] age 10.8y [9.6;13.0]), sleep studies revealed: mean nocturnal pulse oximetry 90% (89;91), oxygen desaturation index (ODI, >3% dips in pulse oximetry) 4.3/h (2.5;6.7), apnea/hypopnea index (AHI) total 1.7/h (1.0;3.6), central 1.6/h (1.0;3.3), PSQ 0.27 (0.18;0.45). In low-altitude controls (n=41, 17 girls, age 11.6y [9.5;13.0], between-groups comparison of age P=0.69) sleep studies revealed: pulse oximetry 97% (96;97), ODI 0.7/h (0.2;1.2), AHI total 0.4/h (0.1;1.0), central 0.3/h (0.1;0.7), PSQ 0.18 (0.14;0.31); P<0.05, all corresponding between-group comparisons.
Conclusions: In school-age children living at high altitude, nocturnal oxygen saturation was lower, and the total and central AHI were higher compared to children living at low altitude. The

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greater score of sleep symptoms in children residing at high altitude suggests a potential clinical relevance of the nocturnal hypoxemia and subtle sleep-related breathing disturbances.

Introduction

World-wide, millions of people permanently reside at high altitudes above 2500 m and even more people travel to high altitudes for professional or leisure activities. Life-long exposure to hypoxia may have adverse health effects and cause chronic altitude illness such as chronic mountain sickness or high altitude pulmonary hypertension (HAPH), both associated with impaired quality of life and survival.[1,2] In Kyrgyz highlanders living at altitudes above 2500 m, we observed a significantly higher prevalence of sleep apnea compared to lowlanders, in particular in those with HAPH.[3] Highlanders with HAPH and sleep apnea performed worse in tests of vigilance and cognitive performance and their quality of life was reduced compared to healthy highlanders and lowlanders.

In children, health consequences of acute and chronic high-altitude exposure have not been extensively studied.[4-8] Children permanently living at high altitude seem to have a reduced rate and pattern of growth[9] but this may be modified by ethnicity.[10] Based on a systematic review of the literature, oxygen saturation in children, 0 to 19 years of age, living at high altitude, decreases with higher altitude but shows a wide inter-individual variability and pronounced differences between sleep and wakefulness states.[11] This variation regresses partially with advancing age from early childhood to adolescence. Both chronic and acute altitude exposure seems to affect cognitive performance among children and adolescents.[12-14] From the scant published data it is not clear whether hypobaric hypoxia per se or other environmental influences, nutrition, socioeconomic conditions, genetics and further unknown factors are responsible for the health consequences in children living at high altitude described here.

In children living at low altitude, the prevalence of sleep disordered breathing (defined by an apnea/hypopnea index, AHI, $\geq$5/h) has been estimated at 1.2%, i.e., seems to be lower than that in adults if the same criteria (AHI $\geq$5/h) are applied.[15] In children affected by obstructive sleep apnea, sleep disordered breathing may cause behavioral disturbances, cognitive impairment, retardation in growth, and, possibly, predispose to cardiovascular disease.[16] Treatment may include adenotonsillectomy, continuous positive airway pressure (CPAP), weight management in obese children, nasal topical corticosteroids, among others.[17-19]

As the type and prevalence and the clinical manifestations of sleep disordered breathing in children living at high altitude have not been exhaustively studied, the purpose of this current investigation is to perform a cross-sectional survey including respiratory sleep studies and clinical evaluations in highlander school-age children in comparison to age-matched lowlander children. Based on our findings in adult highlanders,[3] we hypothesize that children living at high altitude have a higher prevalence of sleep disordered breathing and nocturnal hypoxemia that negatively affects the health status of highland children.

Methods

Design and setting

This is a cross-sectional study performed in children, 7-14 y of age, living in the Tien-Shan mountain range, near the Aksay health post, located at 3250 m, Kyrgyz Republic. Age-matched children living in the Bishkek area at 600-800 m were studied as controls in the National Center of Cardiology and Internal Medicine, Bishkek, at 760 m. The protocol was approved by the Ethics Committee of the National Centre of Cardiology and Internal Medicine. Written informed consent was obtained from children and parents.

Participants

Two groups of healthy, male and female children, 7-14 y of age, were invited to participate in the study by word of mouth among families of presumed Kyrgyz origin known to the study staff and/or living in the area of the study locations: Group 1: Children living in the Aksay region at 2'500-3'800 m (high altitude group [HA-group]); group 2: Children living in the Bishkek area at 700-800 m (low altitude controls [LA-group]).

Exclusion criteria were any chronic or acute disease requiring medical treatment.

Assessments

Clinical examination

A general medical and sleep history was obtained and the pediatric sleep questionnaire (PSQ) was completed (see Supplementary Tables S1 and S2).[20] The PSQ includes 22 items evaluating breathing, sleep, behaviour and some other aspects. The total PSQ score ranges from 0 to 1 with increasing prevalence of symptoms.

Chronic mountain sickness was assessed by the Qinghai score that includes 7 items evaluating breathlessness and/or palpitation, cyanosis, dilated liver veins, paresthesia, headache, tinnitus and sleep disturbance, each rated on a scale of no/mild/moderate/severe with 0-4 points. The chronic mountain sickness score is the sum of all answer scores plus 0-3 points for hemoglobin concentration.[1] In the current study, only the sum of the answer scores (range 0-28) is reported. Acute mountain sickness (AMS) was evaluated by the Lake Louise questionnaire (LLS, 2018 version).[21] It evaluates 4 symptoms (headache, gastrointestinal symptoms, fatigue and/or weakness, dizziness/light-headedness), each rated from 0 (absent) to 3 (severe). The sum of scores is the LLS with a range of 0-12 points.

A physical examination and pulse oximetry were performed. The presence of caries was recorded as the number of affected teeth and rated from 0 (absent) to 3 (3 or more affected teeth). Overbite and overjet (vertical overlap and horizontal distance, respectively, of upper vs. lower front teeth during occlusion) were measured. The Mallampati score of the pharyngeal space (range 1 to 4 with decreasing calibre) and the Brodsky score of tonsillar size (range 0 to 4 with increasing size) were obtained (Supplementary Table S3).[22] Spirometry was performed (Easy One, NDD, Zurich Switzerland) using GLI reference equations.[23]

Respiratory sleep studies

Respiratory sleep studies were performed in a quiet room from 22:00 to 07:00 as described previously.[6] One parent was allowed to stay with the child but instructed to avoid any disturbance. A portable polygraph (Alice PDX, Philips Respironics, Zofingen, Switzerland) recorded pulse oximetry (SpO_2), respiratory inductance plethysmography of rib cage and abdomen, nasal cannula pressure swings, electrocardiogram and body position. Continuous audio-visual recordings were obtained by a low-light infrared camera.

Recordings were analyzed according to the American Academy of Sleep Medicine pediatric rules (see Supplementary Methods) from lights-off to lights-on (=time in bed, TIB).[24,25] An obstructive apnea was defined as a $\geq$90% decrease in nasal pressure amplitude for the duration of $\geq$2 breaths with persistent respiratory effort as evidenced by chest wall excursions; a central apnea was scored in the absence of effort if the event lasted for $\geq$20 s or for $\geq$2 breaths in association with a SpO_2 dip $\geq$3%. An obstructive hypopnea was scored if the nasal pressure swing amplitude dropped by $\geq$30% from pre-event baseline for $\geq$2 breaths in association with a $\geq$3% SpO_2 dip and persistent efforts and/or flattening of the inspiratory nasal pressure contour; a central hypopnea was scored if efforts and signs of inspiratory flow limitation were absent. Individual large breaths, more than twice the baseline amplitude, were scored as sighs[26] and divided into isolated sighs, not associated with any discernable other event, or sighs associated with an oxygen desaturation or an apnea/hypopnea event (Supplementary Fig. S1). The apnea/hypopnea index (AHI), oxygen desaturation index (ODI, $\geq$3% dips) and sigh index were computed as mean number of events per hour of TIB. Behavioural wakefulness and sleep periods were determined by inspection of audio-visual recordings and physiological signals. Estimated behavioural total sleep time (bTST) and sleep efficiency (bTST/TIB) were computed.

Outcomes and sample size estimation

The main outcomes were the AHI and ODI, further outcomes were other variables from sleep studies and clinical characteristics. The study was powered with 80% to detect a minimally important difference in AHI of 1/h, assuming a SD of 1.2/h, two-sided alpha of 0.05.

Data analysis and statistics

Per-protocol analysis was performed on all available data. Descriptive statistics are presented as counts and proportions, and medians (quartiles). Between-group comparisons were performed by Mann-Whitney tests and median differences with 95% confidence intervals (CI). Further analyses included multivariable linear regression models exploring associations among the AHI, sex, age, height and weight. A probability of $<$0.05 or 95% confidence intervals excluding zero were considered to indicate statistical significance.

Results

Participants

Among 60 children screened in Bishkek (LA-group), 41 were included; among 63 children screened in Aksay (HA-group), 47 were included (see participant flow in Supplementary Fig. S3). In the HA-group, 3 sleep studies were not available because of technical failure. Therefore, the per protocol HA-group consisted of 37 children (20 boys, 17 girls), the per-protocol LA-group of 41 children (24 boys, 17 girls). The sex distribution, age, height, weight and pulse rate in the two groups were similar (Table 1). However, the HA-group had a significantly lower median SpO_2 of 92% (quartiles 91;94) and a higher respiratory rate of 23 breaths/min (21;24) than the LA-group (98% [97;99] and 20 breaths/min [19;22]). The assessment of the upper airways and teeth revealed similar, mostly normal findings in both groups. Spirometry showed significantly higher FVC and FEV_1 in highlanders compared to lowlanders, FEV_1/FVC was the same in both populations. The PSQ and the Qinghai chronic mountain sickness scores were significantly higher in the HA-group compared to the LA-group. Various aspects of the sleep history, including the median duration of the nocturnal rest period of 10.0 h (quartiles 9.0;10.5), did not significantly differ between groups although the nocturnal rest period of HA-group started and ended one hour later than those of the LA-group (Supplementary Table S4).

Sleep studies

Results from sleep studies are summarized in Table 2 and illustrated in the Figs. 1 and 2. Both groups spent a similar period of approximately 9 h in bed. In the LA-group, the median SpO_2 of 97% (quartiles 96;97), the median ODI of 0.7/h TIB (0.2;1.2) and the total AHI of 0.4/h TIB (0.1;1.0) were normal. In contrast, in the HA-group, the median SpO_2 of 90% (89;91) and other indices of oxygenation were significantly reduced, while the total AHI of 1.7/h (1.0;3.6) and the ODI of 4.3 (2.5;6.7) were significantly elevated due to a higher number of central apneas/hypopneas (Table 2). Periodic breathing (sequences of at least 3 successive apnea/hypopnea cycles), was not observed in any of the groups. The sigh index was similar in both groups but the HA-group had less isolated and more associated sighs (followed by an apnea/hypopnea or desaturation) compared to the LA-group. The HA-group had a significantly higher heart rate than the LA-group (median difference of 8.1/min, 95% CI 4.1 to 21.1). The behavioral sleep efficiency (bTST) was reduced (86% [79;91]) and the sleep latency was prolonged (59 min [40;78]) in the HA-group compared to the LA-group, (92% [83;95] and 39 min [22;71]). Correspondingly, respiratory events referenced to estimated bTST differed slightly to those referenced to TIB but the trends of differences between groups remained unchanged (Supplementary Table S5).

Table 1 Participant characteristics.

Variable	Lowlanders n=41 Medians (quartiles)	Highlanders n=37 Medians (quartiles)	Median Differences (95% CI)	P value
Boys, No. (%)	24 (59)	20 (54)		
Girls, No. (%)	17 (41)	17 (46)		
Age, y	11.6 (9.5;13.0)	10.8 (9.6;13.0)	−0.2 (-1.1 to 0.9)	0.693
Height, cm	148 (133;156)	140 (131;151)	−5 (-11 to 1)	0.115
Weight, kg	35 (30.4;43.9)	34 (28;41.5)	−2 (-6 to 2.2)	0.319
Body mass index, kg/m^2	16.8 (15.1;18.7)	17.0 (16.0;17.9)	0.2 (-0.9 to 1.2)	0.844
Pulse oximetry, %	98 (97;99)	92 (91;94)	−6 (-7 to -5)	<0.001
Pulse rate, /min	93 (82;102)	93 (86;104)	1 (-5 to 7)	0.841
Respiratory rate, /min	20 (19;22)	23 (21;24)	2 (1 to 3)	0.001
Body temperature, C°	36.6 (36.5;36.6)	36.6 (36.2;36.6)	0 (-0.2 to 0)	0.241
Mallampati Score (range 1-4)	1 (1;2)	1 (1;2)	0 (0 to 0)	0.905
Nasal obstruction	0 (0;0)	0 (0;0)	0 (0 to 0)	0.207
Brodsky Score (range 0-4)	2 (1;2)	2 (1;2)	0 (0 to 1)	0.392
Karies, N (range 0-3+)	1 (0;3)	2 (1;3)	0 (0 to 1)	0.080
Teeth missing, N	0 (0;1)	0 (0;2)	0 (0 to 0)	0.282
Overbite, mm	2 (1;3)	1 (1;2)	0 (-1 to 0)	0.380
Overjet, mm	1 (1;2)	1 (1;2)	0 (-1 to 0)	0.387
FVC, %pred	97 (89;105)	105 (98;111)	9 (3 to 14)	0.002
FEV1, %pred	92 (84;105)	102 (94;111)	9.02 (3 to 16)	0.003
FEV1/FVC, %	0.86 (0.82;0.88)	0.87 (0.83;0.92)	0.01 (-0.02 to 0.04)	0.476
Pediatric sleep questionnaire (range 0-1)	0.18 (0.14;0.32)	0.27 (0.18;0.45)	0.09 (0.00 to 0.18)	0.024
Qinghai chronic mountain sickness score (range 0-28)	0 (0;0)	1 (0;4)	1 (0 to 2)	<0.001
Lake Louise Score (range 0-12)	1 (0;1)	1 (0;2)	0 (0 to 0)	0.053

Values are counts (percent) or medians (quartiles). The ranges indicated for several assessments reflects more severe symptoms or more abnormal findings with increasing numbers. For spirometry, data are available for 71 children (LA=36, HA=35) as some were unable to perform the maneuvers. FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second.

Table 2 Sleep studies in children living at high vs. low altitude.

Outcomes	Lowlanders n=41 Medians (quartiles)	Highlanders n=37 Medians (quartiles)	Differences (95% CI)	P value
Time in bed, min	540 (510;540)	538 (522;540)	0 (-6 to 14)	0.754
Mean nocturnal SpO_2, %	97 (96;97)	90 (89;91)	−7 (-7 to-6)	<0.001
Time spent with SpO_2 <90%, %TIB	0 (0;0)	45.6 (23.5;72.2)	45.6 (26.5 to 68.0)	<0.001
ODI, events/h	0.7 (0.2;1.2)	4.3 (2.5;6.7)	3.2 (2.1 to 4.3)	<0.001
AHI total, events/h	0.4 (0.1;1.0)	1.7 (1.0;3.6)	1.3 (0.8 to 2.2)	<0.001
AHI central, events/h with ≥3% SpO_2-dips	0.3 (0.1;0.7)	1.6 (1.0;3.3)	1.2 (0.8 to 1.6)	<0.001
AHI obstructive, events/h	0 (0;0)	0 (0;0)	0 (0 to 0)	0.235
AHI mixed, events/h	0 (0;0)	0 (0;0)	0 (0 to 0)	0.927
Sigh index (total), events/h*	10.0 (8.4;11.6)	9.2 (7.0;10.5)	−1.2 (-2.6 to 0.2)	0.086
Sigh index isolated, events/h	10.0 (7.4;11.4)	7.9 (5.5;9.3)	−2.0 (-3.4 to -0.6)	0.007
Sigh index associated, events/h	0.2 (0.1;0.5)	0.8 (0.4;1.6)	0.4 (0.2 to 0.8)	<0.001
Respiratory rate, 1/min	18 (16;19)	17 (16;18)	−1 (-2 to 0)	0.225
Heart rate, 1/min	70.2 (66.7;77.54)	80.4 (73.7;84.8;)	8.1 (4.1 to 12.1)	<0.001
Behavioral sleep efficiency	0.92 (0.83;0.95)	0.86 (0.79;0.91)	−0.05 (-0.09 to -0.01)	0.008
Behavioral sleep latency, min	38 (22;71)	58 (39;78)	15 (1 to 30)	0.045
Supine body position, %TIB	48 (34;60)	43 (30;56)	−4 (-13 to 5)	0.365

Values are medians (quartiles) and median differences with 95% confidence intervals (CI) during time in bed (TIB). Heart rate is computed during behavioral total sleep time. SpO_2: pulse oximetry; ODI: oxygen desaturation index, ≥3% dips; AHI: apnea/hypopnea index; %TIB: percent of time in bed; * the total sigh index includes the index of sighs without associated event (i.e., isolated sighs) and the index of sighs associated with an apnea/hypopnea or oxygen desaturation (i.e., associated sighs).

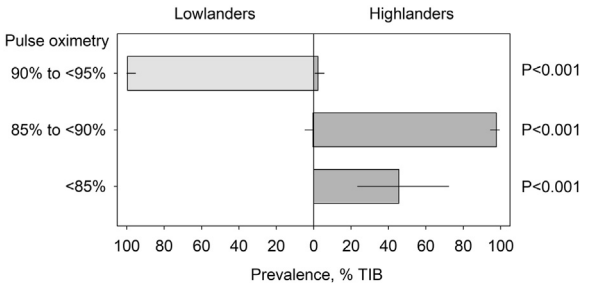

Fig. 1 Nocturnal oxygenation in school-age children living at lowlands and highlands, respectively. The columns with lines represent medians and quartiles of the prevalence of pulse oximetry values in 3 different ranges in lowlanders (to the left) and highlanders (to the right). TIB = time in bed; HL-LL = values in highlanders minus corresponding values in lowlanders.

To assess the effect of altitude on respiratory disturbance after adjusting for potential confounders, multiple regression models were fitted. They confirmed a significant effect of altitude on the total and central AHI even when controlled for age, sex, weight and height (Table 3). In further regression analyses exploring potential effects of altitude and total AHI on height, a negative association was found with altitude but not with the total AHI when controlled for age and sex and explored for the interaction of AHI and altitude (Supplementary Table S6).

Discussion

The current study in school-age children living at high altitude revealed lower indices of nocturnal oxygenation and a higher number of total and central apneas/hypopneas as well as a higher nocturnal heart rate compared to age-matched children living at low altitude. Since highlander children had higher questionnaire scores of sleep disturbance and chronic mountain sickness than their lowland counterparts, hypoxemia, respiratory sleep disturbances and other altitude-related factors may have affected the sleep quality and general well-being of highland children.

Our findings confirm the hypothesis that in children residence at high altitude is associated with hypoxemia and an elevated AHI compared to lowlander controls. The difference in AHI was due to more central events in highlander

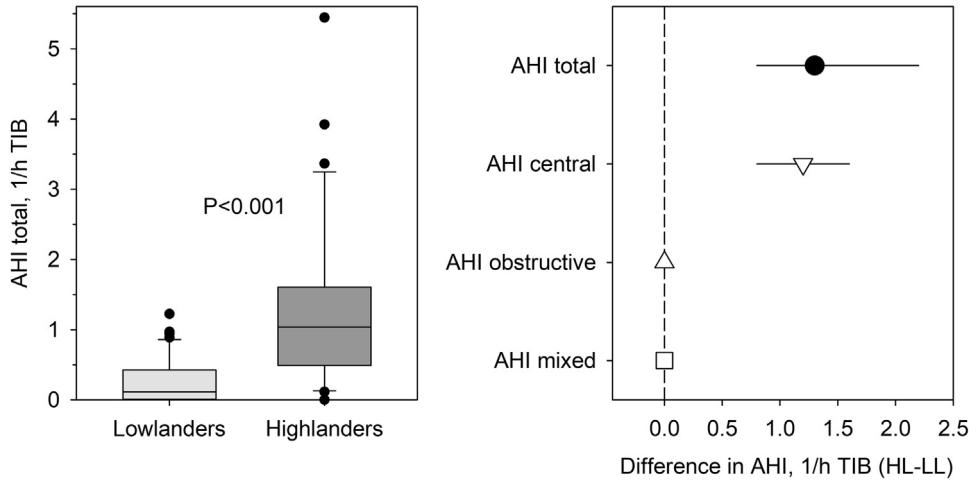

Fig. 2 Apneas/hypopneas in school-age children living at lowlands and highlands, respectively. Left panel: the distribution of the total apnea/hypopnea index (AHI) in lowlanders and highlanders is represented by medians and quartiles (lines and boxes), 10th and 90th percentiles (whiskers) and values outside this range (dots). Right panel: median between-group differences with 95% confidence intervals in total, central, obstructive and mixed AHI.

Table 3 Predictors of the apnea/hypopnea index in multivariable regression analysis.

	Dependent variable total AHI				Dependent variable central AHI			
Predictor	Coefficient	SE	95% CI	P value	Coefficient	SE	95% CI	P value
Location, altitude 3250 m vs. 760 m	1.66	0.31	1.05 to 2.27	<0.001	1.52	0.30	0.93 to 2.12	<0.001
Age, y	−0.07	0.16	−0.39 to 0.25	0.253	−0.03	0.16	−0.34 to 0.28	0.839
Sex, male vs. female	−0.56	0.29	−1.14 to 0.03	0.062	−0.44	0.28	−1.01 to 0.13	0.127
Weight, kg	−0.01	0.03	−0.08 to 0.06	0.717	−0.01	0.03	−0.08 to 0.05	0.713
Height, cm	−0.01	0.03	−0.07 to 0.05	0.712	−0.02	0.03	−0.08 to 0.04	0.483
Constant, events/h	4.32	2.72	−1.11 to 9.75	0.117	5.05	2.64	−0.22 to 10.32	0.060

R^2 of the entire models for the total and central apnea/hypopnea index (AHI) were 0.40, P<0.001, both instances.

children which is consistent with our observations in unacclimatized prepubertal lowlander children travelling to 3450 m,[6] and with studies in children, aged 3-5 years, residing at 1600 m (Denver, Colorado, USA).[27] However, the findings seems to contrast to those of 2 studies performed in South America. Thus, in highlander children, 4-9 years of age, studied at 2560 m, near Bogota, the elevated AHI of 9.2/h was predominantly due to a higher frequency of obstructive events (8.8/h).[28] Similarly, in children, 7-10 y and 13-16 y of age, studied at 3650 m in La Paz the obstructive AHI was higher (2.1/h) than the central AHI (0.7/h).[29] Explanations of the apparent discrepancy in the prevalence of central and obstructive apneas/hypopneas among the current and the 2 South American studies may relate to differences in study procedures, and analysis of respiratory events[28,29] as well as to differences in study populations including age, obesity in some children[28] and, presumably, ethnicity. In accordance with previous studies in lowlander children acutely exposed to high altitude as well as in highlander children,[6,29] sighs were commonly observed in the current study. The physiological significance of sighs is poorly understood, but they may be associated with arousals and interaction with respiratory control.[26,30] Thus, sighs may trigger central apneas/hypopneas by transiently driving the arterial PCO_2 below the apnea threshold, in particular, if the CO_2 reserve is reduced due to an increased respiratory centre drive at altitude or in conditions such as in Down syndrome.[31] In the current study, only a small fraction of sighs was associated with apneas/hypopneas but this type of sigh was more common in highlanders and may have contributed to their elevated central AHI.

Spirometry revealed greater dynamic lung volumes in highlander compared to lowlander children while FEV_1/FVC ratios were similar (Table 1) which was consistent with observations in adult Kyrgyz highlanders vs. lowlanders.[32] Whether the findings indicate greater pulmonary gas stores and, thus, a reduced plant gain of the respiratory control system in highlanders that dampens excessive overshooting of ventilation in response to the enhanced neural respiratory drive at high altitude requires further study.[33]

Highlander children had a higher heart rate than lowlanders suggesting sympathetic activation due to intermittent and sustained hypoxia as observed in healthy adults acutely exposed to high altitude,[35] and in adult Kyrgyz highlanders with high altitude pulmonary hypertension (HAPH) who had also a greater incidence of cardiac arrhythmia and elevated markers of cardiovascular disease and cardiovascular mortality compared to lowlanders.[3,34]

The highlander children reported more sleep apnea-associated symptoms as evaluated by the PSQ, and their scores in the Qinghai chronic mountain sickness questionnaire were higher than those of lowlanders. Therefore, even the slight elevation of the AHI observed in the current study in association with intermittent and sustained hypoxia seems to have affected the perceived well-being of the highlander children during daytime, a novel and clinically important finding.

As observed in adult Kyrgyz highlanders, the body height of highland children tended to be reduced compared to lowlanders.[3] In multivariable regression analysis adjusting for sex and age, the body height was (negatively) associated with altitude but not with the AHI suggesting that hypoxemia and other, unspecified factors, such as nutrition and socioeconomic conditions, rather than sleep disordered breathing may have contributed to the differences in height among highlander and lowlander children. This is of particular interest, as obstructive sleep apnea in children at lowlands is well known to be associated with reduced growth.[18,19]

A potential limitation to the interpretation of our data derives from the fact that factors associated with residence at high vs. low altitude, including socio-economic conditions, nutrition, physical activity, and a recruitment bias of our convenience samples, may have modified the results.

Conclusions

The current study shows that in school-age children living at high altitude, nocturnal oxygen saturation is lower, and the total and central AHI are higher compared to children living at low altitude. Higher symptom scores of sleep disturbance and chronic mountain sickness in children residing at high compared to low altitude emphasize the potential clinical relevance of high altitude exposure and its physiological consequences in terms of hypoxemia and sleep-related breathing disturbances. Further studies in children are needed to scrutinize altitude-related adverse effects on neurocognitive and cardiovascular function and on other aspects of health at long term.

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Conflicts of interest

None.

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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.2023.02.008.

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ORIGINAL ARTICLE

Bronchoalveolar lavage (BAL) amylase and pepsin levels as potential biomarkers of aspiration pneumonia

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KEYWORDS
Aspiration pneumonia;
Microaspiration;
BAL amylase;
BAL pepsin;
Reflux of gastrointestinal contents;
Dripping of oral secretions

Abstract
Background and objective: There are currently no established markers for aspiration pneumonia. We hypothesized that bronchoalveolar lavage (BAL) amylase and pepsin might be candidate biomarkers for aspiration pneumonia.
Methods: This cross-sectional study reviewed consenting adults who underwent clinically-indicated bronchoscopy at Aizu Medical Center. BAL samples were obtained using standardized methods. Amylase levels were measured in our clinical laboratory, and pepsin levels were assessed by ELISA.
Results: Aspiration pneumonia was clinically diagnosed based on the guidelines of the Japanese Respiratory Society in 48 of the 327 participants. Median BAL salivary amylase and pepsin levels in this group were 702.0 U/L and 12.7 ng/ml respectively, which were significantly higher than in non-aspiration pneumonia patients. BAL amylase ≥204 U/L had 77.1% sensitivity and 84.2% specificity as a diagnostic index, and the area under the receiver operating characteristic (ROC) curve was 0.859 (95% confidence interval (CI), 0.803-0.915). Similarly, BAL pepsin levels of ≥7.45 ng/ml had 87.2% sensitivity and 59.9% specificity for identifying aspiration, and the area under the ROC curve was 0.757 (95% CI, 0.688-0.826). Multivariate regression demonstrated that BAL amylase ≥204 U/L and BAL pepsin ≥7.45 ng/ml were associated with significantly higher odds for aspiration pneumonia (odds ratio (OR) 10.0, 95% CI, 4.51-22.2, and OR 8.81 95% CI, 3.32-23.4, respectively). There were no significant associations between risk factors for aspiration pneumonia and BAL amylase and pepsin levels.
Conclusion: BAL amylase and pepsin might be useful biomarkers for suggesting aspiration pneumonia, and could be objective markers without relying on known risk factors for aspiration.

Abbreviations: AP, aspiration pneumonia; BAL, bronchoalveolar lavage; BALF, BAL fluid; CAP, community-acquired pneumonia; CI, confidence interval; FiO_2, fraction of inspired oxygen; GERD, gastroesophageal reflux disease; HAP, hospital-acquired pneumonia; JRS, The Japanese Respiratory Society; NTM, non-tuberculous mycobacteria; OR, odds ratio; PaO_2, pressure of arterial oxygen; P/F, PaO_2/ FiO_2; QR, quartile range; ROC, receiver operating characteristic.

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Introduction

Aspiration pneumonia (AP) occurs at any age, but it is more common in the elderly. Although AP is commonly thought of as hospital-acquired pneumonia (HAP), it is also an important cause of community-acquired pneumonia (CAP). Reportedly, 5 to 15% of cases of CAP are AP.[1] Through multicenter research in Japan, Teramoto et al. reported that more than 60% of hospitalized CAPs in the elderly were AP.[2] Aspiration of small amounts of oropharyngeal secretions during sleep is called "microaspiration", and large volume aspiration is termed "macroaspiration".[3] With a unique technique using indium^{111} chloride pasted on the gums, Kikuchi and his colleague demonstrated that microaspiration plays a pivotal role in the development of CAP in the elderly.[4] In their study, scanning of the thorax demonstrated microaspiration in 71% of CAP patients and only 10% of control subjects.[4]

AP is typically a clinical diagnosis, and there are currently no diagnostic criteria for AP.[3] The Japanese Respiratory Society (JRS) defines AP in the guidelines for management of pneumonia in adults (Figure S1).[5] According to their classification, a case with proven aspiration is a "definite" case. Cases with dysphagia, such as those with central nervous system diseases, dementia due to cerebrovascular disorders or degenerative diseases such as Alzheimer's disease or on antipsychotic medication for delirium management[6] are "probable" cases. While macroaspiration of gastric content can be relatively easily detected, there are also many "suspected" cases of AP in clinical practice. Microaspiration, occult pulmonary aspiration, is pivotal when treating cases "suspected" of AP.

Some researchers suggested the possibility of diagnosis of microaspiration by assessing bronchoalveolar lavage (BAL) pepsin levels.[7] According to these studies, the leading mechanism for microaspiration is gastroesophageal reflux disease (GERD).[8] However, BAL-pepsin only reflects gastrointestinal fluid aspiration.[9]

On the other hand, Weiss et al. demonstrated that BAL-amylase is associated with risk factors for aspiration in mechanically-ventilated patients.[10] Salivary amylase is produced by salivary glands, particularly the parotid.[11] It is rare for amylase to be produced in tracheal or bronchoalveolar cells, except in amylase-producing small cell lung carcinoma cases.[12] Therefore, detection of amylase in the lower respiratory tract suggests dysfunction of the swallowing reflex, which might have diagnostic value in proving aspiration due to dripping of oral secretions. Different studies have shown the utility of tracheal amylase to diagnose microaspiration in mechanically-ventilated patients,[13] and as a marker of chronic pulmonary aspiration in children with chronic respiratory illness.[11]

Here, we investigated the potential of elevated BAL-amylase levels as a diagnostic indicator of AP compared to BAL-pepsin levels. We also evaluated the association between elevated biomarkers and risk factors for AP.

Methods

Patient selection and study design

We conducted a cross-sectional study of adult patients undergoing clinically-indicated bronchoscopy at Aizu Medical Center from June 2014 to May 2020. This study included 327 consenting patients, among whom AP was confirmed in 48 cases (Table 1A) by three experienced pulmonologists and two experienced radiologists based on adult pneumonia guidelines by the JRS.[5]

This study protocol was approved by the Independent Ethics Committee of Fukushima Medical University for conducting this research (Approval No. 29063). All patients provided written informed consent before participation. The study was registered in UMIN Clinical Trials Registry: UMIN 000043587.

Data collection

Clinical data collected included: age, sex, body mass index (BMI), underlying diseases, especially those considered risk factors for aspiration, oral medicines, smoking history, blood tests such as white blood cells, c-reactive protein, salivary amylase, and arterial blood gas analysis, and BAL fluid (BALF).

Bronchoscopy was performed for various clinical indications, including AP, interstitial pneumonia, lung cancer, non-tuberculous mycobacteria (NTM), and sarcoidosis. All procedures were performed under conscious sedation by two pulmonologists with 30 years of clinical experience. BAL was performed in the subsegmental bronchus with the abnormal lesion by instillation of 100-150 ml of buffered saline divided into 2-3 aliquots. BAL-amylase and its isozymes were measured at our clinical laboratory, and BAL-pepsin was analyzed using an ELISA kit for pepsin (Cloud-Clone Corp, TX, USA).[14]

Statistical analysis

Data were expressed as the mean ± standard deviation or the median with 25-75% quartile range (QR). The F test was performed to compare mean values in the two groups. Student's t-test and Welch's t-test were used to compare values with and without homoscedasticity, respectively. One-way ANOVA was used for multiple comparisons. The Mann-Whitney U-test and Wilcoxon signed-rank test were used when comparing the medians of independent and dependent variables, respectively. Kruskal-Wallis test was used for multiple comparisons. Receiver-operating characteristic (ROC) curve analysis was used to evaluate the clinical validity of BAL-amylase and BAL-pepsin, and the Chi-square test was used to examine their association with risk factors for AP. Univariate and multivariate logistic regression analyses were performed to investigate the relationship between BAL-amylase or BAL-pepsin and AP. The

Table 1 **A:** Clinical indications for bronchoscopy in the 327 cases evaluated. **B:** Characteristics of patients with aspiration pneumonia (48 cases). There was overlap in underlying diseases. Data represent mean ± standard deviation. BMI, body mass index; NHCAP, nursing and healthcare associated pneumonia; HAP, hospital acquired pneumonia; CAP, community acquired pneumonia; GERD, gastric esophageal reflux disease; COPD, chronic obstructive pulmonary disease; BA, bronchial asthma; DM, diabetes mellitus; BI, Brinkman index. **C:** Serum and bronchoalveolar lavage (BAL) fluid data in the 48 aspiration pneumonia casesData are presented as mean ± standard deviation and median [interquartile range]. WBC, white blood cell; CRP, C-reactive protein; S-amylase, salivary amylase; P/F, Partial pressure of arterial oxygen (PaO_2) / fraction of inspired oxygen (FiO2) ratio; BALF, bronchoalveolar lavage fluid.

A. Clinical indications for bronchoscopy in the 327 cases evaluated	
Age (years)	69.1 ± 13.3
Female / Male	**134 / 193**
BMI (kg/m^2)	**21.9 ± 3.6**
Clinical indication	
aspiration pneumonia	**48**
collagen disease-related lung disease	**36**
eosinophilic pneumonia	**10**
hypersensitivity pneumonia	**10**
interstitial pneumonia	**43**
lung cancer	**28**
fungal pulmonary infection	**12**
non-tuberculous mycobacteria	**26**
organizing pneumonia	**10**
sarcoidosis	**8**
others	**96**

B. Characteristics of patients with aspiration pneumonia (**48** cases)	
Age (years)	74.5 ± 8.2* (p=0.002)
Female / Male	**15 / 33**
BMI (kg/m^2)	**19.7 ± 3.7* (p<0.0001)**
NHCAP (HAP) / CAP	**3 / 45**
Underlying diseases	**(with overlap)**
cerebrovascular diseases	**3**
dementia	**2**
mental illness	**3**
alcoholic disease	**2**
esophageal surgery & gastrectomy	**9**
GERD	**7**
COPD	**10**
BA	**3**
interstitial pneumonia	**2**
chronic heart failure	**1**
DM	**1**
scleroderma	**2**
Smoking history	
never smoker	**20**
ex-smoker (BI)	**22 (884.1±588.0)**
current smoker (BI)	**6 (1037 ± 356.9)**

C. Serum and BALF data in the 48 aspiration pneumonia cases	
WBC (/ml)	8677 ± 3674.7
neutrophils (%)	71.8 ± 11.0
lymphocytes (%)	19.7 ± 8.7
CRP (mg/dl)	5.0 ± 6.5
S-amylase (U/L)	90.2 ± 31.9
P/F ratio	353.3 ± 67.9
Cell fraction in BALF	
macrophages (%)	15.7 [6.3-41.5]
lymphocytes (%)	8.4 [4.2-17.5]

Table 1 (*Continued*)

C. Serum and BALF data in the 48 aspiration pneumonia cases	
neutrophils (%)	67.0 [29.0-82.4]
eosinophils (%)	0.8 [0.2-3.7]
BAL-amylase (U/L)	702.0 [105.0-2028.0]** ($p<0.0001$)
BAL-pepsin (ng/ml)	12.7 [8.5-23.6]** ($p<0.0001$)

results are expressed as odds ratio (OR)s with 95% confidence interval (CI)s. All analyses were performed using EZR and BellCurve for Excel.

Results

Characteristics of patients with aspiration pneumonia

Forty-eight patients (15 females and 33 males) with aspiration pneumonia were included in the study. HAP was identified in three patients who were not bedridden, and the remaining 45 cases were CAP. Average patient age was 74.5 ± 8.2 years, significantly older than that in the overall cohort, and BMI was 19.7 ± 3.7 kg/m^2, which was significantly lower than in the entire cohort (Table 1B). Medical history and underlying diseases that were risk factors for aspiration were listed, and the number of AP patients with the various risk factors for aspiration is shown in Table 1B. Among them, 18 cases did not have any predisposing risk factors.

Serum and BALF data in aspiration pneumonia patients

Table 1C shows serum and BAL fluid laboratory data in AP patients. Neutrophil-dominated inflammation was detected in serum. The average partial pressure of arterial oxygen (PaO_2) / fraction of inspired oxygen (FiO_2), ratio (P/F) ratio was 348 ± 68, which was not low, and there were no cases of severe hypoxia. The ratio of neutrophils to macrophages and lymphocytes in BAL fluid was higher than normal BAL fractions.[15] The median value of BAL salivary amylase with a probability of 98-100% and BAL-pepsin levels in AP patients were 702.0 U/L and 12.7 ng/ml, respectively, significantly higher than their levels in non-AP cases. Serum amylase levels were not elevated (Fig. 1A, B).

BAL-amylase and BAL-pepsin by disease

Median BAL-amylase levels were significantly higher in AP cases versus other conditions such as interstitial pneumonia, lung cancer, NTM, and sarcoidosis (Figure S2A). Median BAL-pepsin levels also showed a similar tendency (Figure

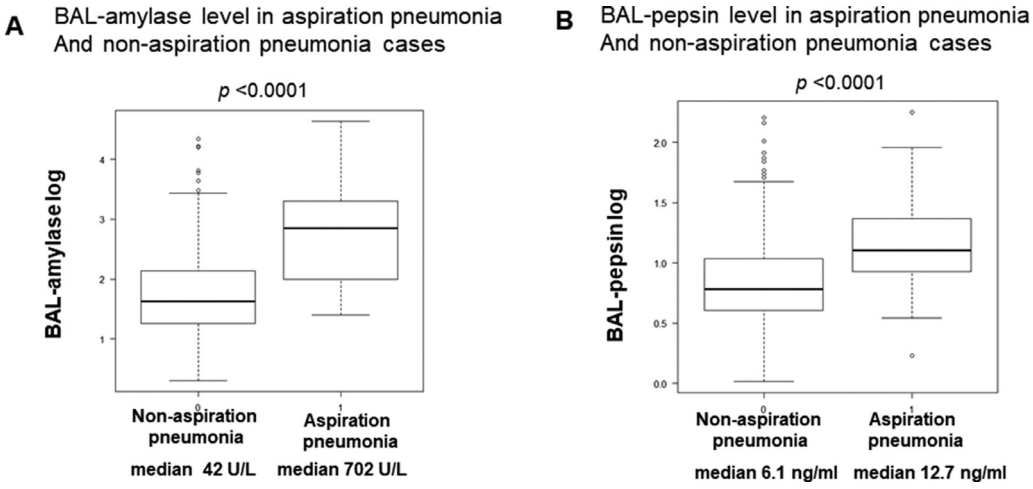
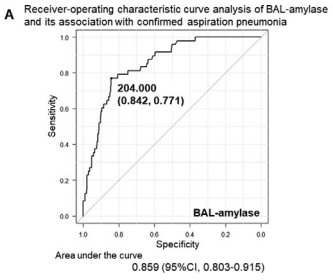
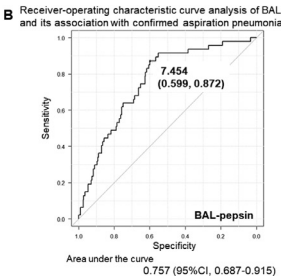


Figure 1 **A:** BAL-amylase levels in aspiration pneumonia and non-aspiration pneumonia cases. Boxplot (median [interquartile range]) of BAL-amylase levels (units/L) in non-aspiration and aspiration pneumonia cases. The vertical axis shows the log scale of BAL-amylase levels. **B:** BAL-pepsin levels in aspiration pneumonia and non-aspiration pneumonia cases. Boxplot (median [interquartile range]) of BAL-pepsin levels (ng/ml) in non-aspiration and aspiration pneumonia cases. The vertical axis shows the log scale of BAL-pepsin levels.





C. Univariate and multivariate analysis of predictors of aspiration pneumonia.

Predictor	Odds ratio (95% confidence interval) for aspiration pneumonia	*p* value
Univariate analysis		
BAL-amylase ≥ 204 U/L	9.56 (4.85-18.9)	<0.0001
BAL-pepsin ≥ 7.45 ng/ml	10.2 (4.19-24.8)	<0.0001
BAL-amylase ≥ 204 U/L and BAL-pepsin ≥ 7.45 ng/ml	19.1 (9.11-40.0)	<0.0001
Multivariate analysis		
Age	1.04 (1.01-1.08)	<0.05
BMI	0.83 (0.745-0.926)	<0.001
BAL-amylase ≥ 204 U/L	10.0 (4.51-22.20)	<0.0001
BAL-pepsin ≥ 7.45 ng/ml	8.81 (3.32-23.40)	<0.0001

Figure 2 **A, B:** Receiver-operating characteristic (ROC) curve analysis of BAL-amylase and BAL-pepsin and their association with confirmed aspiration pneumonia. A: A cut-off value of BAL-amylase of 204 U/L had a specificity and sensitivity of 0.842 and 0.771, respectively, for identifying aspiration pneumonia. The area under the ROC curve was 0.86 (95% confidence interval (CI) 0.80-0.91). B: The cut-off value of BA-pepsin of 7.45 (ng/ml) had a specificity and sensitivity of 0.599 and 0.872, respectively. The area under the ROC curve was 0.76 (95% CI 0.69-0.83). **C:** The table showed univariate and multivariate analyses of predictors of aspiration pneumonia.

S2B). Thus, BAL-amylase and pepsin levels were significantly higher in AP than in other diseases.

Clinical validity of BAL-amylase and BAL-pepsin for diagnosing aspiration pneumonia

ROC analysis demonstrated that BAL-amylase at a cut-off value of 204 U/L differentiates between patients with AP and other conditions with a sensitivity of 77.1% and specificity of 84.2%. The area under the ROC curve was statistically significant, at 0.85 (95% CI 0.80-0.91) (Fig. 2A). On the other hand, ROC analysis of BAL-pepsin at a cut-off value of 7.45 ng/ml had a sensitivity of 87.2% and specificity of 59.9% for differentiating AP, and the area under the ROC curve was also statistically significant, at 0.76 (95% CI 0.69-0.83) (Fig. 2B).

Univariate regression demonstrated that BAL-amylase of 204 U/L and BAL-pepsin of 7.45 ng/ml were associated with significantly higher odds for AP (OR 9.56, 95% CI 4.9-18.9, p=7.57e-11, and OR 10.2, 95% CI 4.2-24.8, p=3.14e-07, respectively). Multivariate regression also demonstrated similar results and indicated that aging and low BMI might also be related to AP. These data suggest the clinical validity of BAL-amylase and BAL-pepsin assessments for the diagnosis of AP (Fig. 2C).

Evaluation of BALF data in aspiration pneumonia patients grouped according to cut-off values of BAL-amylase and BAL-pepsin

Based on the results of Fig. 2, AP patients were grouped according to the cut-off values of BAL-amylase and BAL-pepsin of 204.0 U/L and 7.45 ng/ml, respectively, as: Group 0: BAL-amylase $<$ 204.0 U/L group and BAL-pepsin $<$ 7.45 ng/ml: (n=3), Group 1: BAL-pepsin $\geq$ 7.45 ng/ml (n=13), Group 2: BAL-amylase $\geq$ 204.0 U/L (n=3), and Group 3: BAL-amylase $\geq$ 204.0 U/L and BAL-pepsin $\geq$ 7.45 ng/ml (n=28). Here there was a total of 47 cases excluding one case because it had only BAL amylase data and no BAL pepsin data. BAL-amylase levels in groups 2 and 3 were significantly higher than in the other groups. BAL-pepsin levels were significantly elevated in both groups 1 and 3. Although serum neutrophils were not different among the groups, the median percentage of BAL neutrophils in groups 1 and 3 were 62.7% and 75.5%, respectively, showing a tendency to be higher than in the other groups although the difference was not significant (Table S1).

Risk factors for aspiration and BAL-amylase and BAL-pepsin in aspiration pneumonia cases

GERD, esophageal surgery, and gastrectomy were defined as risk factors for “reflux”, and cerebrovascular diseases, dementia, mental illness with psychopharmaceuticals, and alcoholism, which can cause dysphagia, were defined as “droplet” risk factors. Risk factors for AP were investigated in the four groups mentioned above. Notably, high-BAL pepsin level cases in groups 1 and 3 did not necessarily have risk factors for “reflux”, although nearly half of them showed a tendency for “reflux”. High BAL-amylase level cases in groups 2 and 3 also showed that few cases had risk factors for “droplet” (Table 2). As seen in Table 2, the proportion of cases without any risk factors was higher not only in group 0 but also in group 3. There was no significant association between risk factors for AP and levels of BAL-amylase and pepsin.

Discussion

We investigated BAL-amylase and BAL-pepsin as potential biomarkers for AP. In this study, both BAL-amylase and BAL-pepsin levels were significantly elevated in AP patients. Ours is the first study to investigate the association between BAL-amylase and adult AP. We found that BAL-amylase levels $\geq$ 204 U/L could diagnose AP with a sensitivity of 77.1% and specificity of 84.2%, supporting the results of previous studies, even if the different mechanisms between AP and VAP.[16] Similarly, BAL-pepsin levels $\geq$ 7.45 ng/ml have a sensitivity and specificity of 87.2% and 59.9%, respectively, for diagnosing AP. Additionally, BAL-amylase $\geq$ 204 U/L and BAL pepsin $\geq$ 7.45 ng/ml were associated with significantly higher odds for AP, with ORs of 9.56 and 10.2, respectively, and the presence of both BAL-amylase $\geq$ 204 U/L and BAL-pepsin $\geq$ 7.45 ng/ml had an even higher OR of 19.1. These results suggest the clinical validity of using BAL-amylase and BAL-pepsin levels to diagnose AP, although our study results are limited because this was a cross-sectional study.

Table 2 Relationship between risk factors for aspiration pneumonia and cut-off values in BAL fluid. Patients were grouped as described in Table S1. Risk factors were classified as "Droplet"-related microaspiration due to dripping of oral secretions, "Reflux"-related microaspiration of gastro-intestinal contents, "Both" which included "Droplet" and "Reflux" microaspiration, and "None" with no risk factors for aspiration. Data show the number and percentage of patients in each group. BAL, bronchoalveolar lavage.

Risk factors	Group 0BAL-amylase <204BAL-pepsin <7.45 (n=3)	Group 1BAL-pepsin ≥7.45 (n=13)	Group 2BAL-amylase ≥204 (n=3)	Group 3BAL-amylase ≥204BAL-pepsin ≥7.45 (n=28)
Droplet (%)	0 (0)	1 (7.7)	0 (0)	7 (25.0)
Reflux (%)	1 (33.3)	6 (46.1)	2 (66.7)	7 (25.0)
Both (%)	0 (0)	3 (23.1)	0 (0)	2 (7.1)
None (%)	2 (66.7)	3 (23.1)	1 (33.3)	12 (42.9)

AP is a clinical diagnosis, and in addition to macroaspiration, AP due to microaspiration should be suspected in most cases. The initial expectation was that increases in BAL-amylase and BAL-pepsin levels would occur relatively independently, and AP caused by the dripping of oral secretions and pneumonia caused by reflux of gastrointestinal contents might be diagnosed separately. Contrary to our expectations, however, our study showed that 28 of 48 AP cases had higher levels than the cut-off values of both BAL-pepsin and amylase. Normally, microaspiration is prevented by physiological defense mechanisms, such as the swallowing reflex and cough reflex. Therefore, high BAL-amylase levels, reflecting dripping of oral secretions, and high BAL-pepsin levels, reflecting reflux of gastrointestinal contents, might be considered a requirement for diagnosing AP. Furthermore, BAL-amylase might be considered an initial indicator of the collapse of natural defense mechanisms.

It is essential to determine risk factors for swallowing disturbances. In the present study, 18 cases had no underlying risk factors. As shown in Table 2, although group 3 tended to contain more risk factors than group 2, risk factors for aspiration were not significantly associated with BAL-amylase or pepsin levels. There are several possible reasons for this: (1) medical staff did not obtain their medical history accurately; (2) patients did not divulge or did not remember their history of previous diseases; and (3) they might have had undiagnosed asymptomatic risk factors for microaspiration. Hence, risk factors for AP in our cases could have been underestimated. However, even if medical histories related to microaspiration are thoroughly obtained, there is a limit to understanding all the risk factors in patients. Patients do not always understand their symptoms correctly regarding GERD,[17] and many cases might not have been accurately diagnosed by endoscopy. Basal ganglia strokes are reportedly associated with microaspiration.[18] Asymptomatic undiagnosed cerebral infarction might also lead to dysphagia. Other risk factors, such as low BMI and aging, are reportedly related to microaspiration. As shown in Table 1B, AP cases had significantly lower BMI than other patients, suggesting a decline in muscle mass. Aging-related sarcopenia was previously reported to lead to dysphagia.[19] The results of multivariate analysis in our study also supported this fact. Hence, although it is important to accurately understand the risk factors for AP, the development of objective biomarkers of AP is also urgent.

Our study has several limitations. First, this was a cross-sectional study. A well-designed prospective study is needed to clarify the causal relationship between AP and BAL-pepsin and amylase levels. A prospective study might also prove whether elevation of BAL-amylase is an early indicator of microaspiration leading to AP. Secondly, this study was conducted at a single facility, and the study population was naturally limited. A multi-center clinical trial adopting standardized diagnostic criteria or bronchoscopy procedures for AP is needed in the future. Third, our study showed that BAL-amylase and pepsin levels were not associated with risk factors for AP. As mentioned above, our study might have underestimated the risk factors for AP. Risk factors such as GERD and cerebral infarction should be investigated more actively, and swallowing reflex, as an indicator of microaspiration, should also be evaluated by a simple swallowing provocation test.[20] Finally, bronchoscopy is an invasive approach performed by specialists and cannot be performed everywhere. Additionally, there is the risk of complications due to the procedure, and careful selection of patients must be made to reduce the risk of complications. Hence, bronchoscopy measuring these biomarkers is not always definitively recommended. It should be considered for cases such as recurrent pneumonia with unclear risk factors or pneumonia of unknown cause which AP is a differential diagnosis to consider. Simpler and less-invasive examinations, such as evaluation of exhaled breath condensate pepsin[21] or intratracheal secretions, instead of BAL fluid collection, should be more practical and attempted in the future. As further studies, once BAL-amylase and pepsin are accepted as biomarkers of AP, their association with severity of AP should be proved, and severity index and high-resolution computed tomography image findings should be evaluated in future studies.

Conclusion

Measurement of BAL-amylase and BAL-pepsin levels might contribute to the diagnosis of AP. We found that BAL-amylase $\geq$ 204 U/L and BAL-pepsin $\geq$ 7.45 ng/ml are associated with significantly higher odds of AP. Although a cohort study is needed to prove causality, our study suggests that BAL-amylase and pepsin might be potential biomarkers for substantiating a clinical diagnosis of AP.

Conflict of Interest Statement

The authors have no conflicts of interest 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.2022.04.003.

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ORIGINAL ARTICLE

Reference values for six-minute walk distance and six-minute walk work in Caucasian adults

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KEYWORDS
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6MWORK

Abstract
Rationale: The six-minute walk test (6MWT) is a practical and simple field-based test to assess physical capacity. Several reference equations for six-minute walking distance (6MWD, m) exist, but have a number of limitations that decrease their clinical utility. In addition, no reference equations exist for the 6MWT-derived outcome six-minute walk work (6MWORK, kg.m).
Objectives: To establish new reference equations for 6MWD and 6MWORK on a 20 m course using data from the population-based Canadian Cohort Obstructive Lung Disease study.
Methods and Measurements: A total of 335 participants without obstructive or restrictive pulmonary function, with normal self-reported health status, normal exercise capacity, and $<$30 pack years cigarette smoking history were selected to create a representative sample of Canadian adults aged $\geq$40 years. All participants performed two 6MWTs. Reference equations were derived using multiple regression analyses.
Main Results: On average, 6MWD and 6MWORK were 541$\pm$98 m and 41.3 $\pm$ 11.2 kg.m, respectively. All outcomes were significantly greater in males than females. Sex-specific reference

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equations were derived from the results of 6MWD and 6MWORK with an explained variance of 24 to 35%.
Conclusions: This study established reference equations for 6MWD and 6MWORK on a 20 m course in Caucasian males and females aged ≥40 years with normal pulmonary function, self-reported health status and exercise capacity. These newly derived reference equations add value to the assessment of functional capacity in clinical practice.

Introduction

Physical capacity is often abnormally low in people with non-communicable chronic diseases, such as chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease (ILD), heart failure (HF), or pulmonary arterial hypertension (PAH).[1-12] Because physical capacity cannot be derived accurately from metrics of disease severity (e.g., forced expiratory volume in 1-*sec* (FEV_1) or left ventricular ejection fraction), exercise tests are needed to assess a person's physical capacity.[1-11,13]

The six-minute walk test (6MWT) is a practical and simple field-based exercise test that does not require specialized equipment or advanced training, and is widely used in clinical practice and research to assess physical capacity in patients with chronic diseases.[14,15] During the 6MWT, participants walk as far as possible in six minutes on a pre-determined course.[15] The recommended minimum course length is 30 m,[14] however in many care settings performing the 6MWT in a 30 m hallway is not feasible due to space limitations. Instead, a 20 m course length is often used to perform the 6MWT.[16] The main outcome, the distance walked in six minutes (6MWD, m), is associated with prognosis in various chronic conditions (e.g., COPD, ILD, HF, PAH) and responsive to both pharmacological and non-pharmacological interventions.[9,11,17-20] Additionally, the six-minute walk work (6MWORK, kg.m; defined as the product of 6MWD in metres and body mass in kilograms) can be derived from the 6MWT.[21,22] This 6MWT-derived outcome may be of additional clinical importance in patient groups where overweight-obesity may play a role in exercise limitation, and demonstrate prognostic value in people with COPD.[21]

To enable interpretation of 6MWD, this outcome can be compared with published reference values, which typically consider age, sex, height and/or body mass.[23] This facilitates the assessment of the level of impairment of physical capacity compared to a reference population. Furthermore, using reference equations combined with a lower limit of normal (LLN) can help differentiate between normal variation in outcomes and abnormally low outcome results. Existing studies reporting reference values for 6MWD have several limitations that decrease their clinical utility, namely: (1) the number of participants was small in the majority of studies (median: 109; 67% of studies had a sample size <200 participants[24-29]); (2) there is ambiguity with regard to participant recruitment[24,25,27-29]; (3) very limited information was provided on participant characteristics[24,25,30]; (4) there is considerable variation in the reported reference formulas[24-32] and (5) only a few reference equations for 6MWD on a 20 m course exist.[28] Moreover, reference values for 6MWORK have never been established. Therefore, the current analyses aimed to establish new reference equations for 6MWD and 6MWORK for a 20 m course using unique data from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study,[33] a population-based cohort study in which random sampling was used to recruit participants aged ≥40 years. In addition, we sought to compare our new reference equations for 6MWD to earlier published reference equations.

Methods

Study design and participants

For this study, a subset of data from CanCOLD was used. The 6MWT was performed at the first follow-up assessment (CanCOLD visit 2, ~18 months after the baseline visit) and comprises a subset of 1019 participants. Recruitment for visit 2 was not completed for the entire cohort. CanCOLD is a prospective, random sampled, population-based study conducted across nine sites in Canada (ClinicalTrials.gov Identifier: NCT00920348).[33] Participants were noninstitutionalized males and females aged ≥40 years recruited by random telephone digit dialling. All participants provided written informed consent before completing study assessments. The research ethics board of each participating institution approved the study protocol.

Details on participant selection criteria for the current study are described in Fig. 1. Because of the limited number of non-Caucasian participants only Caucasian participants were selected for these analyses. Furthermore, participants were selected if they performed pulmonary function tests (PFT) (including post-bronchodilator spirometry and plethysmography), two 6MWTs, and had a peak rate of oxygen uptake ($V'O_2peak$) on a symptom limited incremental cardiopulmonary cycle exercise test (CPET) between the 95% upper (ULN) and LLN values.[34] Having an exercise capacity within normal predicted limits indicated that a participant's exercise tolerance was not limited by any ostensible health condition or any health hazards such as exposure to environmental tobacco smoke nor was there an abnormally high cardiorespiratory fitness, for instance resulting from intensive exercise training.

Participants were excluded from the analyses if: 1) their post-bronchodilator spirometry indicated an (reversible) airflow obstruction or abnormal pulmonary function according to Global Lung Function Initiative reference values[35-37] (FEV_1, forced vital capacity (FVC) or forced vital capacity (FVC) less than LLN, or total lung capacity (TLC) less than

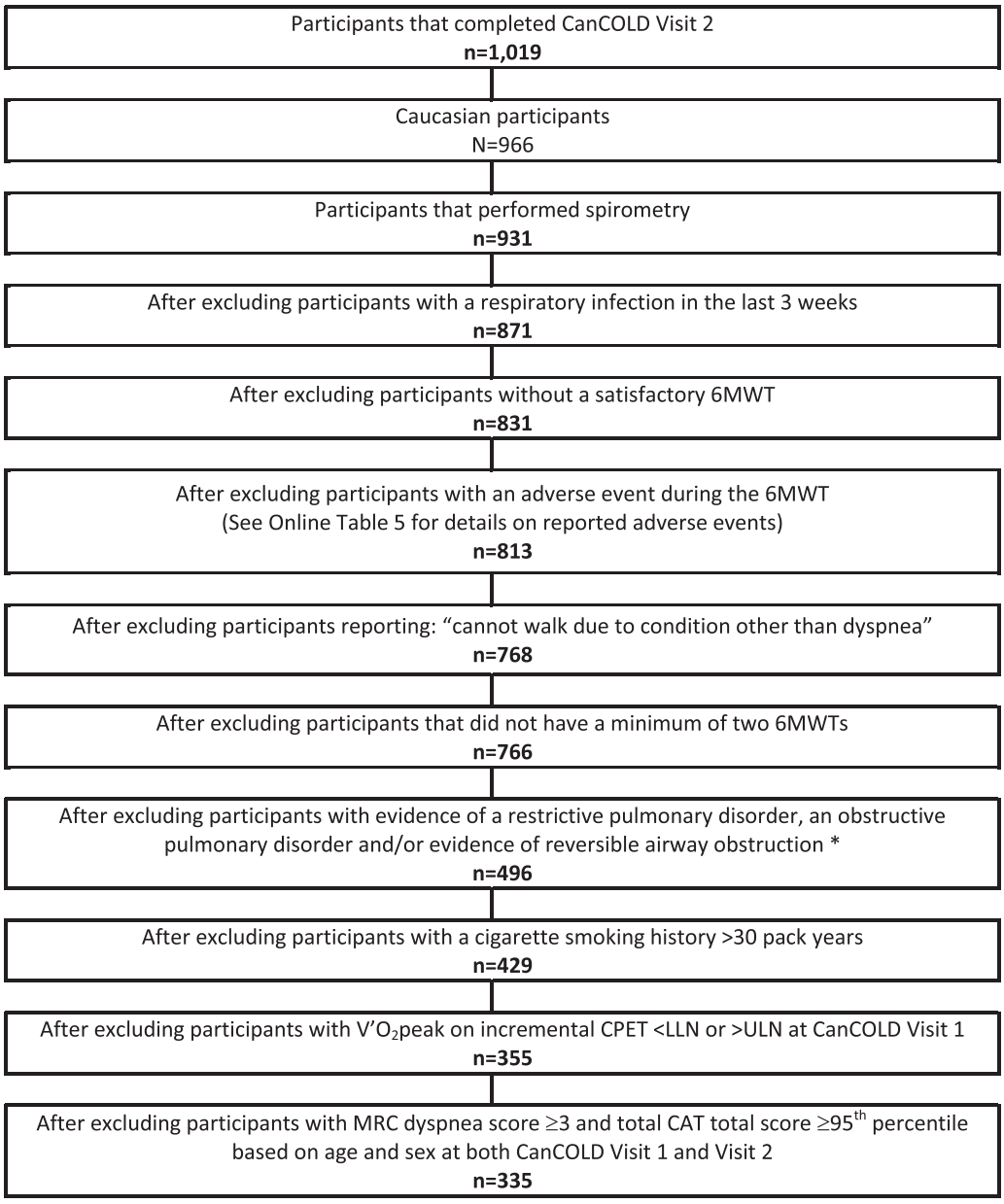

Fig. 1 Flowchart of included participants.

80%-predicted or an increase in FEV_1 or FVC >12% and >200 mL from baseline 10−15 min after bronchodilator administration. A full description of both pre- and post-bronchodilator PFT outcomes are described in Table 1); 2) they had a cigarette smoking history >30 pack years (PY) (based on a univariate regression analyses between different categories of PY, and an additional sensitivity analysis see online Table 3 and online Table 4); and/or 3) they reported clinically significant pulmonary symptoms based on Medical Research Council (MRC) scores (MRC score ≥3) or COPD Assessment Test (CAT) total scores (CAT score ≥95th percentile (ULN) based on age and sex).[38]

Measures

The data used in this study was collected during two time points. Both CPET and PFTs were performed during CanCOLD visit 1. During CanCOLD visit 2, conducted 18 months after visit 1, the 6MWTs were performed. At both visits, pulmonary symptoms were assessed using MRC and CAT. To ensure that no significant changes in pulmonary symptoms occurred in the time between CanCOLD visits 1 and 2, participants needed to report a MRC dyspnoea score <3 and CAT total score <ULN at both visits.

At each visit, general participant characteristics were recorded, as well as previous and current health conditions.

Six-minute walk test (6MWT)

Before the 6MWT, participants were screened for contraindications to exercise. The 6MWT was performed in a corridor, with two cones placed 20 m apart. Instructions were standardized, as per the American Thoracic Society's (ATS) guidelines for the 6MWT.[14] Participants were asked to walk as far as possible in six minutes by walking back and forth

Table 1 Participant characteristics.

	Total	Male	Female	p-value (Male vs. Female)
	n = 335	*n* = 172	*n* = 163	
Age (year)*,~	68.0 ± 9.1	68.0 ± 9.4	68.0 ± 9.4	0.985
Sex, n (%)*				
Male	172 (51.3)	-	-	-
Female	163 (48.7)	-	-	-
Height (cm)*	167.6 ± 9.4	174.3 ± 6.4	160.7 ± 6.4	<0.001
Body mass (kg)*	76.1 ± 14.6	82.4 ± 12.0	69.5 ± 14.2	<0.001
BMI (kg/m^2)*	27.0 ± 4.5	27.1 ± 3.5	26.9 ± 5.3	0.212
BMI <21, n (%)	22 (6.6)	4 (2.3)	18 (11.0)	0.002
BMI 21−24, n (%)	91 (27.2)	44 (25.6)	47 (28.8)	0.503
BMI 25−29, n (%)	154 (46.0)	93 (54.1)	61 (37.4)	0.002
BMI 30−35	46 (13.7)	24 (14.0)	22 (13.5)	0.903
BMI ≥ 36	22 (6.4)	7 (4.1)	15 (9.2)	0.058
Cigarette pack years*	4.7 ± 8.5	4.2 ± 8.1	5.4 ± 8.9	0.190
Cigarette smoking status, n (%)*				
Current smoker	14 (4.2)	4 (2.3)	10 (6.1)	0.103
Ever smoker	106 (31.6)	52 (30.2)	54 (33.1)	0.569
Never smoker	215 (64.2)	116 (67.4)	99 (60.7)	0.201
Self-reported comorbidities, n (%)*	317 (94.6)	161 (93.6)	156 (95.7)	0.394
Lung function				
FEV_1,% predicted*,‡	101.4 ± 14.7	102.1 ± 13.3	100.7 ± 16.0	0.38
FVC,% predicted*,‡	104.9 ± 14.5	106.3 ± 14.0	103.5 ± 15.0	0.082
FEV_1/FVC,%*,‡	74.6 ± 6.1	73.5 ± 6.2	75.8 ± 5.8	<0.001
FEV_1/FVC,% predicted*,‡	96.3 ± 7.4	96.0 ± 7.7	96.5 ± 7.0	0.415
TLC,% predicted†	105.0 ± 14.0	102.9 ± 13.5	107.2 ± 14.1	0.007
IC,% predicted†	105.2 ± 16.6	105.5 ± 15.4	104.8 ± 17.8	0.734
RV/TLC,%†	37.1 ± 7.6	34.2 ± 6.0	40.2 ± 7.9	<0.001
IC/TLC,%†	47.0 ± 8.0	49.1 ± 7.4	44.8 ± 8.1	<0.001
D_LCO,% predicted†	97.5 ± 20.2	100.4 ± 19.2	94.6 ± 20.8	0.009
Cardiopulmonary exercise test				
V'O_2 peak, L/min†	1.7 ± 0.6	2.1 ± 0.5	1.4 ± 0.4	<0.001
V'O_2peak, ml/kg/min†	22.9 ± 6.9	25.7 ± 6.6	20.0 ± 6.1	<0.001
V'O_2 peak,% predicted	94.7 ± 21.1	93.2 ± 19.4	96.3 ± 22.8	0.367
Range (min, max)†	93.6 (49.0, 158.2)	92.9 (49.0, 139.8)	94.0 (53.1,158.2)	0.367
Questionnaire scores				
Visit 1				
MRC dyspnoea grade†	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.5	0.001
median (Q1, Q3)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	0.001
MRC1, n (%)	254 (75.8)	143 (83.1)	111 (68.1)	0.001
MRC2, n (%)	81 (24.2)	29 (16.9)	52 (31.9)	0.001
CAT total score†	5.0 ± 4.2	3.9 ± 3.1	6.0 ± 4.8	<0.001
Visit 2				
MRC dyspnoea grade*	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.5	0.019
median (Q1, Q3)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	0.019
MRC1, n (%)	257 (76.7)	141 (82.0)	116 (71.2)	0.019
MRC2, n (%)	78 (23.3)	31 (18.0)	47 (28.8)	0.019
CAT total score*	4.4 ± 3.9	3.8 ± 3.3	5.1 ± 4.4	0.004
Six-minute walk test results				
Best 6MWD, m	541.5 ± 98.3	571.8 ± 93.4	509.5 ± 93.3	<0.001
Post SpO_2 (%)	96.5 ± 2.3	96.4 ± 2.1	96.5 ± 2.5	0.262
6MWD test 1, m	528.0 ± 94.5	556.9 ± 90.9	497.4 ± 88.8	<0.001
6MWD test 2, m	537.7 ± 100.0	568.8 ± 94.3	504.9 ± 95.4	<0.001
Δ6MWD 1 and 2 (m) (test2-test1)§	9.8 ± 22.2	11.9 ± 21.2	7.5 ± 23.1	0.032
6MWORK, kg.m¶	41,347 ± 11,178	46,977 ± 9790	35,407 ± 9343	<0.001

Data are presented as mean ± SD unless otherwise specified.

* Assessed during CanCOLD visit 2.

† Assessed during CanCOLD visit 1.

‡ Measured during post-bronchodilator spirometry.

~Specifics on age distribution are presented in online table 1a; BMI: Body Mass Index; FEV_1: Forced Expiratory Volume in the 1st second; FVC: Forced Vital Capacity; TLC: Total Lung Capacity; IC: Inspiratory Capacity; RV: Residual Volume; D_LCO: Diffusion Capacity of the lungs for Carbon Monoxide; MRC: Medical Research Council dyspnoea scale; CAT: COPD Assessment Test; CPET: Cardiopulmonary Exercise Test; V`O_2 peak: Peak oxygen consumption; Please see Online Tables 6 and 7 for more details on comorbidities and medication use, and Online Table 2 for more details on the PFT.

§ No significant differences in pre-test SpO2 between test 1 and test 2.

¶ Values based on best 6MWD; SpO_2: transcutaneous oxygen saturation; Results presented per decade of age are presented in Online Table 1b.

from one cone to another. During the test, standard encouragement was given each minute. SpO_2 was measured before, during and after the 6MWT (Masimo Pulse Oximeter, Masimo Corporations, California, USA). A second 6MWT was performed 15 min after the first. 6MWD was recorded after each 6MWT. The best 6MWD was used for analysis. Any adverse events that occurred were recorded (Online supplement Table 6).

6MWORK (kg.m) was calculated as the product of the best 6MWD in metres and body mass in kilograms. Body mass was measured using a digital scale or balance beam after participants emptied their bladder and removed their shoes, hat, coat, and/or heavy items from inside their pockets.

Peak rate of oxygen consumption

Breath-by-breath measurements of $V'O_2$ averaged over the last 30-*sec* of loaded pedalling during the CPET were used to define $V'O_2$peak. A full description of the CPET protocol used in CanCOLD has been previously described.[34]

Statistical analyses

Data distribution was assessed with the Shapiro-Wilke test. Between-group differences were assessed using Chi-square or Fisher-exact tests for categorical variables, and T-tests or Mann Whitney U tests as appropriate for continuous variables.

The cut-off value for PY was determined by a univariate regression analysis between different categories of PY. An additional sensitivity analysis was performed to determine the effect of a lower cut-off value for PY on the results of the univariate regression analyses.

To derive reference equations, univariate regression analyses and multivariate stepwise regression analyses were performed after confirming all assumptions were met. Age, height and body mass (as applicable) were used as predictor variables and 6MWD and 6MWORK as outcome variables. All predictors were included in the final model based on their magnitude (β), significance and physiological impact (r^2) on the outcomes.[15] Separate reference equations were created for males and females.

For each reference equation, the root mean square error (RMSE or standard deviation of the residuals) was calculated and used as an indicator of the data around the regression line. In order to assess the difference between observed and predicted data, the mean absolute error (MAE) was calculated. The lower limit of normal or 5th percentile (LLN), estimated as the predicted value minus 1.645 multiplied by the RMSE, was calculated to determine below which value the outcomes are regarded as being abnormally low. A Pearson correlation coefficient was calculated to assess the association between predicted and measured values. Finally, a comparison between existing[24-31] and our new 6MWD reference equations was made by calculating reference values for all included reference equations using the characteristics from the CanCOLD participants used in our analyses. *A priori*, the level of significance was set at $p<0.05$. Statistical analyses were performed using SAS 9.4 (SAS institute, Cary, NC, USA).

Results

Participant characteristics

1019 participants were screened for eligibility for the current analyses. A total of 335 participants (51% male, age: 68.0 ± 9.1 years) were included. Participants' general characteristics are presented in Table 1 and Online Tables 6 and 7. On average, participants were overweight (body mass index: 27.0 ± 4.5 kg/m^2), and had a $V'O_2$peak (95±21%-predicted) and PFT outcomes within normal predicted limits (FEV_1: 101± 15%-predicted; FVC 105±15%-predicted; FEV_1/FVC: 74±6%; TLC: 105±14%-predicted; and D_LCO: 98±20%-predicted). On average, participants reported 4.7 ± 8.5 PY. Participant were similar to the general Canadian population ≥40 years with regards to body mass and height (Mean body mass: Canadian population: 86.5 kg (men), 73.7 kg (women)[39] vs included participants: 82.4 kg (men), 69.5 kg (women); mean height: Canadian population: 174.4 cm (men), 161.2 cm (women)[39] vs included participants 174.3 cm (men), 160.7 cm (women)). Self-reported health conditions were present in ∼95% of the participants. A full description of the participant's self-reported health conditions and medication use is described in Online Tables 7 and 8.

6MWT outcomes

On average, 6MWD and 6MWORK were 541±98 m and 41.3 ± 11.2 kg.m, respectively. All outcomes were significantly greater in males than females (Table 1).

Reference equations

The univariate regression analysis showed significant associations between age, sex and height versus each of 6MWD and 6MWORK (Online Table 9). The association between body mass and 6MWD was not statistically significant. In the multivariate regression analysis, all predictor variables were significant (Table 2). The derived sex-specific reference equations are listed below: Reference equations for males:

- 6MWD (m) =489.22−4.33*age_{yrs}+3.19*$height_{cm}$-2.18*body mass $_{kg}$
- 6MWORK (kg.m) =−32,501.0−384.40*age_{yrs}+605.84*$height_{cm}$

Reference equations for females:

- 6MWD (m) =498.06−4.80*age_{yrs}+2.64*$height_{cm}$-1.24*body mass $_{kg}$
- 6MWORK (kg.m) =7207.57−460.55*age_{yrs}+370.41*$height_{cm}$

Even though it is recommended to perform two 6MWT's,[14] in clinical practice it may not be possible to perform two 6MWT's and subsequently use the best of the two tests as the final outcome measure. This is why the results of the regression analysis and reference equations based on the first 6MWT are included in the online supplement (Online Table 5).

The online supplement also contains a spreadsheet to calculate predicted values.

Table 2 Multivariate stepwise regression analyses.

	Male (n = 172)			
	Parameters (95% CI)	Cumulative r^2	Partial r^2	p-value
6MWD, m				
Intercept	489.22 (95.57, 882.86)	–	–	0.015
Age, year	−4.33 (−5.76, −2.90)	0.177	0.177	<0.001
Height, cm	3.19 (0.94, 5.45)	0.212	0.035	0.006
Body mass, kg	−2.18 (−3.35, −1.00)	**0.245**	0.033	0.009
	RMSE=81.92 m; MAE=62.38 m; LLN: −134.76 m			
6MWORK, kg.m				
Intercept	−32,501.00 (−70,050.00, 5046.97)	–	–	0.089
Age, year	−384.40 (−523.20, −245.60)	0.116	0.116	<0.001
Height, cm	605.84 (410.56, 801.12)	**0.347**	0.231	<0.001
	RMSE=7959.10 kg.m; MAE=6301.44 kg.m; LLN: −13,092.72 kg.m			
	Female n =163)			
	Parameters (95%CI)	Cumulative r^2	Partial r^2	p-value
6MWD, m				
Intercept	498.06 (138.43, 857.69)	–	–	0.007
Age, year	−4.80 (−6.21, −3.39)	0.229	0.229	<0.001
Height, cm	2.64 (0.59, 4.69)	0.258	0.029	0.012
Body mass, kg	−1.24 (−2.17, −0.32)	**0.280**	0.022	0.034
	RMSE=79.91 m; MAE=61.05 m; LLN: −131.45 m			
6MWORK, kg.m				
Intercept	7207.57 (−27,110.00, 41,525)	–	–	0.679
Age, year	−460.55 (−591.75, −329.36)	0.281	0.281	<0.001
Height, cm	370.41 (178.54, 562.27)	**0.34**	0.06	<0.001
	RMSE=7207.57 kg.m; MAE=5960.95 kg.m; LLN: −11,845.45 kg.m			

6MWD: Six-minute walking distance; 6MWORK: six-minute walk work; RMSE: Root Mean Square Error; MAE: Mean Absolute Error; LLN: Lower Limit of Normal.

The explained variance (cumulative r^2) of the multiple regression model ranged from 0.24 to 0.35. Pearson correlations (r, presented in Fig. 2) between predicted and observed values for 6MWD and 6MWORK varied between 0.495 and 0.589 and were all statistically significant ($p<0.001$). Bland Altman plots of observed and predicted values are presented in Online Fig. 1.

Fig. 3 shows the predicted 6MWD based of the newly derived 6MWD reference equations, both based on the best test and based on the first test, compared to results from other reference equations,[24-32] using data from the CanCOLD dataset (n = 346). The line representing the CanCOLD predicted 6MWDs is within the range of the lines generated from the other prediction equations.[24-31] Compared to Enright et al.[31] and Enright & Sherrill,[30] the newly developed equation's predicted 6MWD values are consistently higher except for the youngest males in the sample. In contrast, the newly developed equation's predicted 6MWD values are consistently lower than those predicted using the equations of Troosters et al.,[29] Hill et al.,[25] Gibbons et al.[28] and Jenkins.[26] The equations of Chetta et al.[27] are mostly below the newly derived predicted 6MWD, but both lines presenting the predicted 6MWDs cross each other in the older participants. The reference values based on Cazzoletti et al.[32] are very close to the CanCOLD reference values for both genders, especially in the men aged 75 years or older and women aged 75 years or younger, while the equations of Beekman et al.[24] show a different pattern for males and females. Whereas the line of the predicted values for females is consistently close to the line of the newly derived predicted values, the predicted 6MWD for males crosses the line of the CanCOLD derived predicted 6MWD around the age of 70 years. Younger participants have higher predicted values and older participants have lower predicted values compared to the CanCOLD reference values.

Discussion

This is the first study to generate prediction equations for 6MWD and 6MWORK on a 20 m course for Caucasian males and females separately, based on 6MWT results from a population-based cohort of people aged ≥40 years with normal pulmonary function and exercise capacity determined by a symptom limited incremental CPET. In addition, we have established the first reference equations for 6MWORK. 6MWORK has shown its value in different patient populations.[21,22,40] For example, in people with COPD, 6MWORK was identified as a predictor of hospitalization[21] and was better correlated to D_LCO than 6MWD. Furthermore, 6MWORK has demonstrated a high relationship to $V'O_2$ and peak O_2 pulse in people with pulmonary vascular disease. The use of prediction equations for 6MWORK may help healthcare providers better interpret the results of an individual's 6MWT and also improve implementation of this outcome variable into clinical practice.

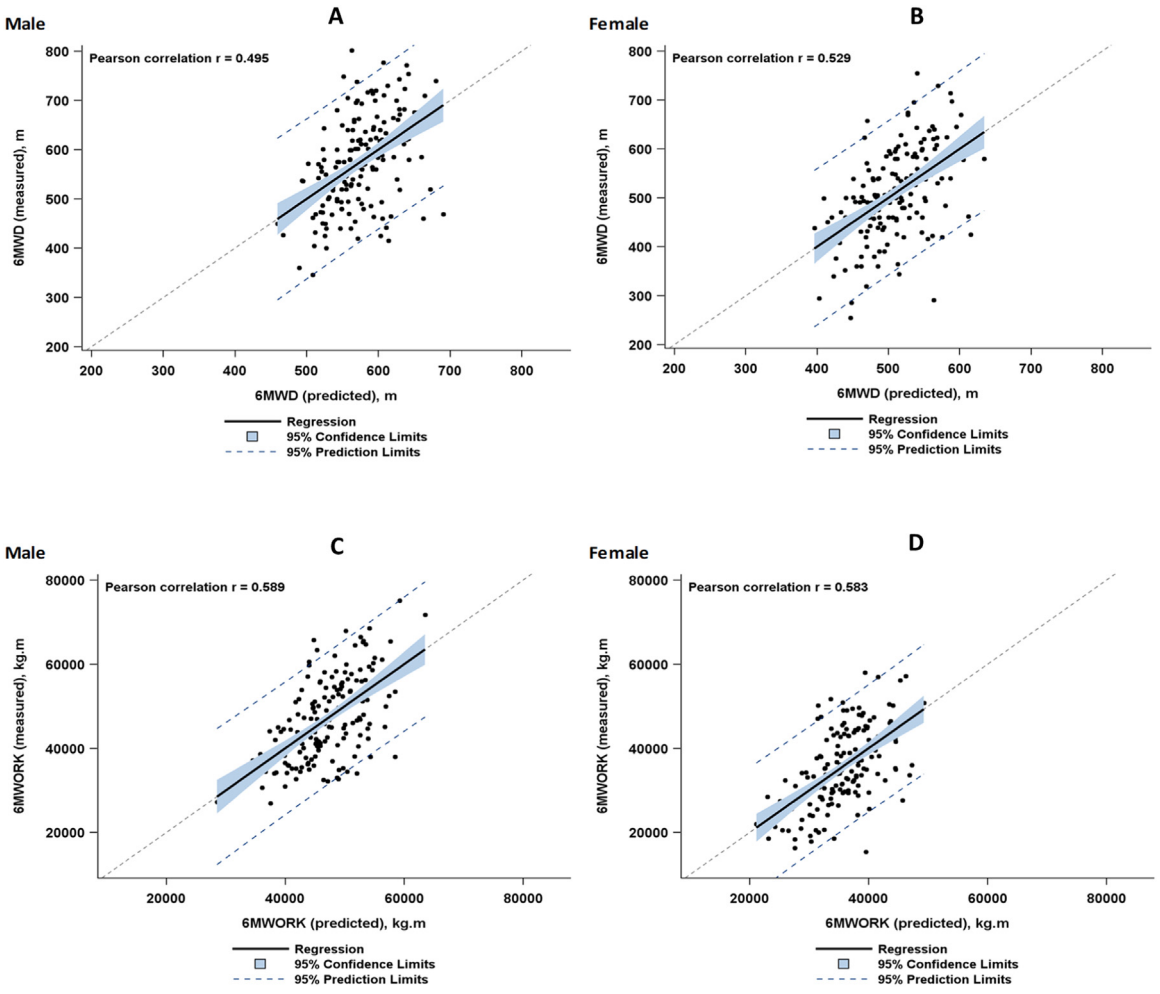

Fig. 2 Correlation between predicted and actual six-minute walk distance (6MWD; Panels A&B) and six-minute walk work (6MWORK; Panels C&D).

Our newly derived references equations were generated using data from a well characterised and relatively large random sample of males and females aged ≥40 years that completed two 6MWTs according to ATS guidelines, with the exception of the recommended course length.[14] The 20 m course length was chosen to standardize the test across all sites, since some study sites were unable to use a 30 m course length due to limited space. Comparing the different available reference equations for 6MWD to our newly derived reference equation is difficult, since a combination of factors could explain the differences (e.g., different course lengths, protocols, populations and sample sizes). However, the predicted 6MWD based on the commonly used reference equation of Enright and Sherrill[30] is below the predicted 6MWD value calculated using the best-test CanCOLD-based reference equations, across all ages. This difference may in part be due to the fact that participants in Enright and Sherrill's[30] study only performed one 6MWT, since it is

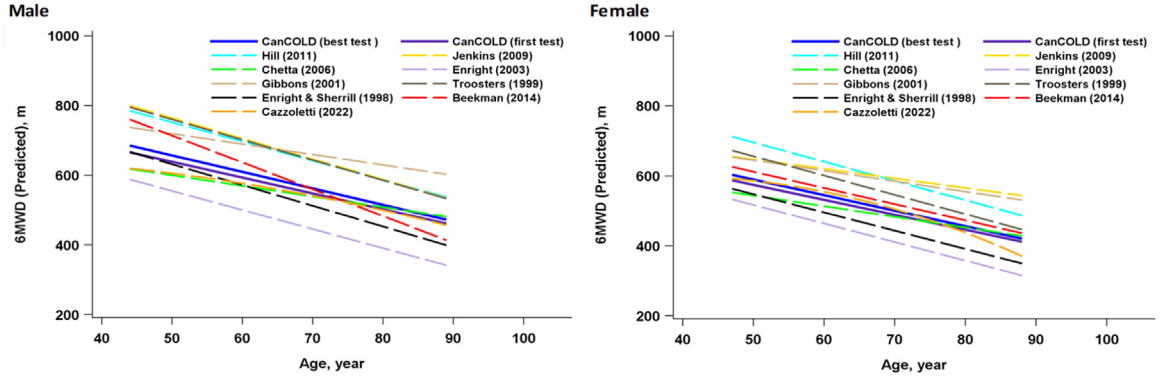

Fig. 3 Comparison of newly derived reference equations for six-minute walk distance (6MWD) to existing reference equations.

well known that a learning effect exists for the 6MWT and therefore multiple tests are recommended to adequately assess an individual's functional exercise performance.[15] This is also demonstrated by the fact that the first-test CanCOLD based reference equations approach and partly overlap Enright and Sherril's values. However, since the size of this learning effect is variable across different studies[41-45] and factors influencing the learning effect are still unclear, more studies are needed to assess the reproducibility of the 6MWT.

A lower predicted 6MWD value leads to a higher percentage of predicted 6MWD when interpreting 6MWT results. Participants with a 6MWD that equals, for example, 70% of the predicted value based on the newly derived reference equations, will have a substantially higher percentage of predicted value based on Enright and Sherrill's equations.[30] Overestimation of physical capacity might lead to a misinterpretation of the influence that a chronic health condition has on an individual's physical capacity.

In contrast, the 6MWD values predicted using the reference equation of Troosters et al.,[29] which is also commonly used, were greater than those predicted using the CanCOLD-derived reference equations across all ages. This may be due to the longer course length of 45 m, smaller sample size (n = 51) and/or influence of selection bias in Troosters and colleagues' study,[29] since no random sampling was used.

The explained variance of the newly derived reference equations ranged from 24 to 35%. These values fall within the previously reported explained variances for 6MWD reference equations (r^2 range: 0.20–0.66)[24-31] (Online Table 10). Even though the explained variance is modest, using reference equations that correct for factors that are known to affect the 6MWT (e.g., sex, height, weight and age) to calculate predicted values provides more valuable insights into the exercise capacity than only using the absolute outcome measures.

The correlation coefficients between the observed and predicted values of 6MWD and 6MWORK (Pearson's r: 0.495 to 0.589) demonstrate that the reference equations are a moderate fit with the observed data. The LLN-values indicate that males or females with a 6MWD $\geq$134 m or $\geq$130 m below the predicted reference value should be identified as having abnormally low exercise capacity, respectively.

Strengths and limitations

A clear strength of this study is the comprehensive assessment performed on CanCOLD participants, which provided us with a unique opportunity to identify a subset of adults with normal pulmonary function, normal self-reported health status, normal breathlessness, and V'O_2peak on symptom limited incremental cycle CPET within normal predicted limits, where CPET is widely considered the gold-standard method of assessing exercise capacity.[46] Next to this, care was taken in determining a valid cut-off value of $\leq$30 PY as inclusion criterion. Next to the univariate regression analysis assessing the effect of different categories of PY (Online Table 3), an additional sensitivity analysis was performed in which the multivariate stepwise regression analysis was repeated with data from participants with $\leq$5 PY. This analysis resulted in similar point estimates, indicating that the seemingly high cut-off value of $>$30 PY is valid (Online Table 4). Using these selection criteria instead of selecting participants based on the complete absence of comorbidities, has led to a unique and representative sample of the Canadian population of adults, aged $\geq$40 years. Since many Canadians suffer from comorbidities,[47] the prediction equations developed in the current study are likely more relevant for use by healthcare providers in clinical practice.

The 6MWD is susceptible to a learning effect, which reaches a plateau after performing two tests within one week.[14] All participants included in our analyses performed two 6MWTs in order to decrease the likelihood of a learning effect and ensure optimal performance.

While interpreting the results, some limitations need to be considered. All 6MWTs were performed on a 20 m course, whereas the ATS guidelines for the 6MWT recommend a 30 m course length.[14] Several studies have investigated the effect of course length on 6MWD and the results are inconclusive. Significantly higher distances in 30 m courses compared to 20 m courses were found in healthy adults,[48] patients with COPD[49,50] and individuals with stroke.[51] In addition, Beekman et al.[52] found a significant effect of a 10 m versus 30 m course length on 6MWD. In contrast, Veloso-Guedes et al.[53] and Sciurba et al.[42] found no significant effect of course length on 6MWD in patients with liver cirrhosis and patients with COPD, respectively. In addition, the European Respiratory Society/ATS technical standard report for field walking tests in people with chronic respiratory disease[15] indicated that for course lengths $>$15 m, differences in 6MWD may be small enough such that 6MWTs performed on courses of different lengths can still be used for risk stratification. However, based on the above-mentioned studies it is recommended to use course length-specific reference equations.

Even though all participants included in our analyses had a V'O_2peak on symptom limited incremental cycle CPET within normal predicted limits, it is nevertheless possible that comorbidities or other factors (e.g., intermittent claudication (reported by one participant), motivation or weather conditions) may have led to a suboptimal performance during the 6MWT despite V'O_2peak being within normal predicted limits.

The CPET and 6MWTs were performed 18 months apart, during which time the health status and functional capacity of our participants might have changed. However, we mitigated the risk of clinically meaningful changes in physical capacity by including only participants with normal self-reported ratings of respiratory health status and activity-related breathlessness at both CanCOLD Visits 1 and 2.

Although the sample is representative of the Canadian population aged $\geq$40 years, the majority of participants was 50–80 years old (86%). Reference values may be less accurate for adults $<$50 and $>$80 years old.[15,30]

Conclusions

This study established new reference values and prediction equations for 6MWD and 6MWORK on a 20 m course in Caucasian males and females aged $\geq$40 years with normal pulmonary function and V'O_2peak within normal predicted limits. These newly derived reference equations have the potential to add value to the assessment of functional capacity in clinical practice. Further research is needed for external

validation in other cohorts and to confirm the utility of these equations in clinical practice.

Author contributions

JMD, DJ, AWV, PZL, JB, WCT, BH, AvH and MAS were responsible for the analysis and interpretation of data for the work. JB and WCT are principal investigators of the CanCOLD study. JMD, DJ, AWV, AvH and MAS drafted the manuscript. All authors take responsibility for the integrity of the data and the accuracy of the analyses and critically reviewed and revised the manuscript. All authors approved the manuscript before publication.

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Data sharing

The Canadian Cohort Obstructive Lung Disease (CanCOLD) study makes de-identified data available for research on respiratory health. Information on how to submit a data access application can be found on the CanCOLD website at: www.cancold.ca

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Conflicts of interest

The CanCOLD study is and/or was funded by the Canadian Respiratory Research Network, the Canadian Institutes of Health Research, AstraZeneca Canada Ltd, Boehringer Ingelheim Canada Ltd, GlaxoSmithKline Canada Ltd, Novartis, the Respiratory Health Network of the Fonds de la recherche en santé du Québec, the Foundation of the McGill University Health Centre, Almirall, Merck, Nycomed, Pfizer Canada Ltd and Theratechnologies and the UBC centre for Heart Lung innovation Vancouver

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Supplementary materials

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REVIEW

COPD treatment — a conceptual review based on critical endpoints

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Abstract
Introduction: Chronic obstructive pulmonary disease (COPD) is one of the main causes of death and disability worldwide. Many treatment options are now available, but criteria for choosing inhaled bronchodilators and inhaled corticosteroids have been under discussion. New trials have highlighted the role of patient`s characteristics, such as eosinophil count and exacerbation history, in selecting the most effective personalised treatment option.
Methods: In this conceptual review, an in-depth rationale is developed with an integrative approach to COPD treatment, gathering data from the main clinical trials performed so far and that may provide support for actual GOLD 2023 recommendations.
Results: According to the patient's characteristics and profile, different treatment options, including mono, dual and triple therapies, are presented in a diagram matrix, comparing their efficacy in terms of reduction of exacerbations and mortality risk.
Discussion and conclusion: Eosinophil counts and past exacerbation profile may play equally relevant roles to predict the individual risk and the potential response to inhaled corticosteroids. Thus, a comprehensive approach considering these two predictors is needed to aid clinicians decide preventative actions and choice of a first-line or step-up treatment.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the main causes of death and disability worldwide, affecting 380 million people according to the World Health Organization (WHO)[1], and its prevalence is predicted to rise, considering the ageing population. Many patients with COPD show poor clinical control, being at risk of exacerbations and death.[2] The main objective of treating these patients is to prevent lung function decline and future exacerbations. Inhaler therapy with bronchodilator drugs is the most widely used treatment, allowing symptom control and reduction of risk of exacerbations and death, but some patients also need combinations with inhaled corticosteroids.[3] However, most patients do not adhere to their regimes, and do not use their inhalers correctly, which contributes to poor outcomes.[4−7]

Many treatment options are now available, involving either inhaled bronchodilator drugs or inhaled corticosteroids, but phenotypic heterogeneity of patients highlights the need for personalised care.[3] In recent years, many important changes have been reflected in clinical guidelines, mainly regarding moderate to severe stages of COPD; this is due to the contribution of major trials such as the IMPACT trial, and more recently, the ETHOS trial.[8,9] These trials yielded new evidence regarding the role of dual therapies (either in a long-acting beta-agonist (LABA) plus long-acting muscarinic antagonist (LAMA) association or as LABA plus inhaled corticosteroids (ICS) combination), as well as the role of LABA/LAMA/ICS triple-therapy in such patients. The IMPACT trial was the first to show a significant reduction of mortality risk as a hard endpoint, which is a key groundbreaking step in COPD research. In addition, with its subsequent results[10,11], criteria for choosing inhaled bronchodilators and inhaled corticosteroids (ICS) have become clearer, basing the decision on the patient`s profile and characteristics, such as eosinophil counts and exacerbation history.[3] Based on these recent trials, the importance of using hard outcomes, such as exacerbations and mortality risk, is growing and deserves further research.

Recently, the Global Initiative for COPD (GOLD) released their 2023 document, which includes two main changes, namely: 1) the initial treatment for GOLD B patients, which is now recommended with LABA/LAMA dual-therapy; 2) a new GOLD E group, resulting from merged GOLD C and D groups, with initial treatment recommended with LABA/LAMA dual-therapy, or LABA/LAMA/ICS triple-therapy for those with eosinophil counts over 300 cells/mm^3.[3] Nevertheless, an in-depth rationale sustaining these new changes is lacking in the GOLD report.

Thus, we developed a comprehensive review, gathering data from the major trials performed so far, namely the ones reporting exacerbation and mortality risk as endpoints, in order to provide an integrative rationale for the COPD treatment recommendations, according to the patient's characteristics and profile.

Methods

We carried out a critical and conceptual review, following the recommendations from Grant et al. published in Health Information and Library Journal.[12]

Searches were conducted in MEDLINE and CENTRAL for papers reporting clinical trials in COPD. A combination of "Pulmonary Disease, Chronic Obstructive" MeSH term with "mortality" or "exacerbation" was used in the queries, covering a period from inception until August 2021. The criteria for study selection were: clinical trial, addressing inhaled drug treatment in COPD patients, either comparing different treatment options or active treatments versus placebo, and reporting hard clinical outcomes such as exacerbation and mortality risk. Studies reporting only lung function, symptoms, or quality of life as the main outcomes were not considered, as they fall out the scope of this review, which aims to address the efficacy of COPD therapies regarding hard outcomes.

Papers were selected according to the established criteria and appraised by two independent reviewers. Data from participants' characteristics, study design features, as well as from outcome effects were collected to perform a critical appraisal between studies. However, considering the conceptual nature of this review, no objective and systematic method was used to analyse the quality of the included studies, nor was any analytical method applied to compare their results.

Results

Sixteen relevant trials published in the last 15 years fell within the scope of this review: IMPACT[8], ETHOS[9], EMAX[13], TRIBUTE[14], SUNSET[15], TRINITY[16], FLAME[17], TRILOGY[18], SPARK[19], INSPIRE[20], TORCH[21], SUMMIT[22], DYNAGITO[23], POET-COPD[24], UPLIFT[25] and the one published by Welte et al.[26] All of these trials were randomised, single or double blinded, comparing different therapies for COPD (mono versus dual vs triple) and reporting exacerbation rates or mortality as outcomes of interest.

Table 1 presents the main characteristics of the most relevant trials reporting COPD drug treatment data. No study has considered environmental and occupational exposures, although they are relevant factors that impact hard outcomes of interest.[27,28]

Analyses of the features and characteristics of these trials identified some aspects which should be highlighted:

- Most studies have included participants of similar age (mean values of 65 years) with adequate follow-up times to provide appropriate outcome estimates (most up to 2−3 years).
- In the majority of studies, asthma patients were excluded or, at least, not likely to be included, except for ETHOS[9] where some asthma patients were included, but exact data were not reported.
- Exacerbation rates, clinical control, quality of life and lung function were the most frequently reported outcomes, although some studies sought to estimate the impact on respiratory and all-cause mortality, but only as secondary outcomes[8,9,20,21], with the exception of TORCH.[21] ETHOS[9] and IMPACT.[8] studies were the most recent ones to address mortality risk and found significant benefit of triple therapies, with reductions of up to 40% in mortality relative risk. The EMAX[13] study addressed a new concept, not frequently used in such

Table 1 Clinical trials reporting the efficacy of COPD treatment on exacerbations and mortality risk and their main characteristics.

Clinical Trial	Participants' characteristics						Intervention		Outcomes
	N°	Mean Age	Eosinophil profile	COPD baseline stage AND history of asthma	Baseline treatment	Exacerbation history	Arms	Follow-up Endpoints	Main results
ETHOS Rabe 2020 (9)	8588	65	60% with ≥ 150 cells/mm^3; 14.7% with ≥ 300 cells/mm^3	GOLD II: 28.5% GOLD III: 60.6% GOLD IV: 10.9% – Mostly GOLD D – Asthma patients included but data not reported	SABA/SAMA: <0.1% LAMA: 0.9% LABA: 0.5% ICS: 0.3% LAMA/LABA: 13.9% ICS/LABA: 31.3% ICS/LAMA: 0.8% ICS/LAMA/LABA: 39.4% None: 0.2%	56.5% with ≥ 2 moderate/severe in the past 12 months	> Budesonide/ glycopyrrolate/ formoterol 320/18/9.6 μg bid > Budesonide/ glycopyrrolate/ formoterol 160/18/9.6 μg bid > Glycopyrrolate/ formoterol 18/ 9.6 μg bid > Budesonide/ formoterol 320/9.6 μg bid	52 weeks Primary: exacerbations annual rate Secondary: time to first exacerbation; use of rescue medication; SGRQ; risk of death from any cause	Triple therapy with: > 24–25% lower exacerbation annual rate compared with LAMA/LABA and 13–14% lower compared with ICS/LABA, regardless of eosinophil count, but less exacerbations in patients with higher counts. > Significant increase of time to first moderate to severe exacerbation. > 46% lower risk of death from any cause compared to LAMA/LABA and 22% lower compared to ICS/LABA (not statistically relevant) > Better quality of life (SGRQ score).
EMAX Maltais 2019 (12)	2431	65	No information	GOLD II: 65% GOLD III: 35% – GOLD B – Asthma not likely to be included	LAMA: 49% LABA: 17%	16% with a moderate in the prior year	> Umeclidinium/ vilanterol 62.5/ 25 μg id > Umeclidinium 62.5 μg id > Vilanterol 50 μg bid	24 weeks Primary: lung function Secondary: TDI; E-RS; SGRQ; CAT; rescue medication use; time to first exacerbation; CID (clinically important deterioration)	LAMA/LABA with: > Higher improvements in patient reported outcomes and lung function (FEV1, FVC, IC) than with monotherapy, except for the E-RS cough and sputum score which was similar to single LAMA. > Lower risk of moderate or severe exacerbation versus LAMA (HR: 0.81) and LABA (HR: 0.64) and fewer CID events. > No differences in LAMA vs LABA, except for a less disease deterioration and higher quality of life with LAMA;
IMPACT Lipson 2018 (8)	10,355	65	57% with ≥ 150 cells/mm^3	GOLD I/II: 36% GOLD III: 48% GOLD IV: 16% – Mostly GOLD B/D – Asthma not likely to be included	None: 10% ICS/LAMA/LABA: 38% ICS/LABA: 29% LAMA/LABA: 8% LAMA: 7% ICS/LABA/ LAMA + Xanthine: 3% ICS: 3% ICS/LABA/Xanthine: 3% LABA: 2% Other: <1%	30% with <2 moderate and no severe; 70% with ≥2 moderate or ≥1 severe	> Fluticasone/ umeclidinium/vilanterol 100/62,5/ 25 μg id > Fluticasone/ vilanterol 100/ 25 μg id > Umeclidinium/ vilanterol 100/ 25 μg id	52 weeks Primary: exacerbations annual rate Secondary: time to first exacerbation; lung function; SGRQ; risk and time to death from any cause; all exacerbations; BDI/ TDI	Triple therapy with: > 16–25% lower rate of exacerbations regardless of eosinophil count, but less exacerbations in patients with higher counts. > Greater improvement in FEV1 compared with ICS/LABA and LAMA/LABA. > Better quality of life (SGRQ score). ICS regiments with: > Lower all-cause mortality. > ICS/LABA was superior to LAMA/LABA in rate of exacerbations.
TRIBUTE Papi 2018 (13)	1532	64	Mean blood eosinophil count: 240 cells/mm^3	GOLD III: 80% GOLD IV: 20% – Mostly GOLD B/D – Asthma excluded	ICS/LABA: 61% ICS/LAMA: 4% LABA/LAMA: 25% LAMA: 10%	81% with a moderate/ severe; 19% with ≥2 moderate/severe	> Indacaterol/ glycopyrronium 85/ 43 μg id > Beclometasone/ formoterol/ glycopyrronium 100/6/ 10 μg 2id	52 weeks Primary: exacerbations annual rate Secondary: time to first exacerbation; lung function; use of rescue medication; E-RS, CAT and SGRQ	Triple therapy with: > 15% lower rate of moderate-to-severe exacerbations, with lower rates in patients with higher eosinophil count, but no difference in the time to first event > Larger change in FEV1, SGRQ and E-RS scores. > Similar adjusted mean changes in pre-dose FVC and mean changes in CAT. > Similar rescue medication use between groups.

Table 1 (*Continued*)

Clinical Trial	Participants' characteristics						Intervention		Outcomes
	N°	Mean Age	Eosinophil profile	COPD baseline stage AND history of asthma	Baseline treatment	Exacerbation history	Arms	Follow-up Endpoints	Main results
DYNAGITO Calverley 2018 (22)	7880	66	No information	Mostly GOLD B/D – FEV1=44.5% – Asthma excluded	LAMA/LABA/ICS: 40% LABA/ICS: 26% LABA/LAMA: 12%	44–45% with ≥2 or ≥1 severe exacerbations	> Tiotropium/olodaterol 5/5 μg > Tiotropium 5 μg	52 weeks Primary: moderate and severe exacerbations	LABA/LAMA, compared to LAMA with: > Lower exacerbation rate.
SUNSET Chapman 2018 (14)	1053	65	23.2% with ≥ 300 cells/mm^3	GOLD III: 69.8% GOLD IV: 29.9% – GOLD B/D: 71% GOLD A/C: 29% – Asthma excluded	Triple therapy (LAMA/LABA/ICS) for at least 6 months prior to the study	65.9% with no exacerbations; 34.1% with a moderate/severe	> Indacaterol/ glycopyrronium 110/ 50 μg id > Tiotropium 18 μg id plus salmeterol/ fluticasone 50/ 500 μg bid	26 weeks Primary: change in FEV1 Secondary: exacerbations annual rate and time to event; lung function; TDI; SGRQ; rescue medication use	Triple therapy with: > Improved FEV1 changes, but no differences in FVC, SGRQ, TDI or use of rescue medication. > No differences in exacerbation rates or time to event between groups. Patients with eosinophil blood counts => 300 cells/μl at increased risk of exacerbation after ICS withdrawal
TRINITY Vestbo 2017 (15)	2691	63	Mean blood eosinophil count: 200 cells/mm^3	GOLD III: 79% GOLD IV: 21% – Mostly GOLD B/D – Asthma excluded	ICS/LABA: 73% ICS/LAMA: 3% LABA/LAMA: 13% LAMA: 11%	All with ≥ 1 moderate/severe; Mean exacerbation rate of 1,3 in the prior year	> Beclometasone/ formoterol/ glycopyrronium 100/6/ 5 μg two actuations bid > Tiotropium 18 μg id > Beclometasone/ formoterol 100/6 two actuations bid + tiotropium 18 μg id	52 weeks Primary: exacerbations annual rate Secondary: change from lung function; time to first exacerbation; SGRQ; rescue medication use	Triple therapy, compared with single LAMA, with: > Reduced rates of moderate-to-severe exacerbations and extended time-to-event, with greater effect with higher eosinophil counts. > Significantly improved lung function (FEV1 and IC) despite eosinophil counts. > Greater improvement in mean SGRQ. > Less use of rescue medication. Fixed triple compared with open triple with significant reduction of exacerbation rate
FLAME Wedzicha 2016 (16)	3362	65	No clear information	GOLD II: 33,4% GOLD III: 58,1% GOLD IV: 7,6% – GOLD A: 0,1% GOLD B: 24,4% GOLD C: 0,1% GOLD D: 74,8% – Asthma excluded	ICS: 56,3% LAMA: 60,6% LABA: 67,1%	80,6% with one exacerbation; 19,3% with ≥ 2 exacerbations	> Indacaterol/ glycopyrronium 110/ 50 μg id > Salmeterol/ fluticasone 50/500 μg bid	52 weeks Primary: exacerbations annual rate Secondary: lung function; time to exacerbation; SGRQ; use of rescue medication	LABA/LAMA, compared to LABA/ICS with: > Lower annual rate of exacerbations and longer time-to-event, regardless of eosinophil count. > Greater improvement in trough FEV1, SGRQ and clinically important change in the SGRQ. > Lower use of rescue medication.
TRILOGY Singh 2016 (17)	1368	63	Mean blood eosinophil count: 250 cells/mm^3	GOLD III: 77% GOLD IV: 23% – Mostly GOLD B/D – Asthma excluded	ICS/LABA: 73% ICS/LAMA: 1% LABA/LAMA: 15% LAMA: 11%	Mean exacerbation rate of 1,2 in the prior year	> Beclometasone/ formoterol/ glycopyrronium 100/6/ 12,5 μg two actuations bid > Beclometasone/ formoterol 100/ 6 μg two actuations bid	52 weeks Primary: lung function; TDI Secondary: SGRQ; E-RS; rescue medication use; exacerbations annual rate and time to event	Triple therapy with: > Higher pre-dose and 2 h post-dose FEV1, but similar TDI improvement. > More responders to SGRQ and lower E-RS total score. > Lower use of rescue medication. > 23% less annual rate, and longer time-to-event of moderate-to-severe exacerbations, more relevant in patients with previous exacerbations. > No differences between groups according to eosinophil count.

Table 1 (*Continued*)

Clinical Trial	Participants' characteristics						Intervention		Outcomes
	N°	Mean Age	Eosinophil profile	COPD baseline stage AND history of asthma	Baseline treatment	Exacerbation history	Arms	Follow-up Endpoints	Main results
SUMMIT Vestbo 2016 (21)	16,590	65	No information	No clear information for COPD stage – FEV1 ≈60% mMRC≥2 – Asthma not likely to be included	LABA: 35–36% LAMA: 15–16% ICS: 33–34%	61–62% without exacerbations; 24–25% with one exacerbation; 14–15% with ≥2 exacerbations	> Fluticasone 100 μg > Vilanterol 25 μg > Fluticasone/ Vilanterol 100/25 μg	3 years Primary: mortality Secondary: lung function; cardiovascular events; exacerbations	> Lower risk of mortality in all therapies compared with placebo > No differences between groups on mortality or exacerbation risk. > LABA/ICS with improvement in FEV1.
SPARK Wedzicha 2013 (18)	2224	63	No information	GOLD III: 79% GOLD IV: 21% – GOLD C/D – Asthma not likely to be included	No information	1% without exacerbations; 76% with one exacerbation; 22% with ≥2 exacerbations	> Indacaterol/ glycopyrronium 100/ 50 μg id > Glycopyrronium 50 ug id > Tiotropium 18 μg id	64 weeks Primary: exacerbations annual rate Secondary: pre-dose or lung function; SGRQ; use of rescue medication	LABA/LAMA with: > Significant reduction in the rate of moderate-to-severe exacerbations compared with glycopyrronium, but not compared to tiotropium. > Higher improvement in FEV1 and SGRQ score compared with glycopyrronium and tiotropium. > Reduction in the use of rescue medication compared with glycopyrronium and tiotropium.
POET-COPD Vogelmeier 2011 (23)	7376	63	No information	GOLD II: 48–49% GOLD III: 42–43% GOLD IV: 8–9% – FEV1=49% – Asthma not likely to be included	LAMA: 30% SAMA: 29% LABA: 51% SABA: 52% ICS: 53% ICS/LAMA: 18% ISC/LABA: 43%	All with ≥ 1 moderate/severe	> Tiotropium 18 μg > Salmeterol 50 μg	1 year Primary: exacerbations	LAMA, compared to LABA, with: > Lower exacerbation rate.
Welte 2009 (25)	660	62	No information	No clear information for COPD staging – FEV1=38% – Asthma not likely to be included	ICS: 60–67% LAMA: 51–54% SAMA: 29–34% LABA: 75–77% SABA: 56–60% LABA/ICS: 38–45% LABA/LAMA: 40% Triple: 37–40%	All with ≥ 1 moderate/severe – Mean exacerbations/ previous year: 1.4	> Tiotropium/budesonide/ formoterol 18/320/9 μg/mg > Tiotropium 18 mg	12 weeks Primary: lung function Secondary: health status, severe exacerbations	Triple therapy, compared to LAMA, with: > Improvement in FEV1 and reduced risk of severe exacerbations.
UPLIFT Tashkin 2008 (24)	5993	65	No information	GOLD II: 46% GOLD III: 44% GOLD IV: 9% – FEV1=48% – Asthma excluded	ICS: 62% LAMA: 2% SAMA: 44% LABA: 60% SABA: 68% LABA/ICS:% LABA/LAMA:%	No clear information	> Tiotropium 18 μg id > Placebo	4 years Primary: lung function Secondary: exacerbations; mortality; SGRQ;	LAMA, compared to placebo, with: > No differences in FEV1 decline. > Improvement in quality of life and reduced risks of exacerbations, related hospitalizations, and respiratory failure.
INSPIRE Wedzicha 2008 (19)	1323	65	No information	GOLD III: 81% GOLD IV: 15% – GOLD B/D – Asthma not likely to be included	SABA: 55% LABA: 45% ICS: 50% SAMA: 39% LAMA: 14% Oral corticosteroids: 4% Xanthines: 19%	No clear information	> Salmeterol/ fluticasone 50/500 μg bid > Tiotropium 18 μg id	2 years Primary: exacerbations annual rate Secondary: mortality; SGRQ; lung function	LABA/ICS, compared to LAMA, with: > No significant differences in exacerbation rate. > Improved SGRQ and lower mortality. > More exacerbations requiring antibiotics but less requiring systemic corticosteroids. > No difference in mean post-dose FEV1.

Table 1 (*Continued*)

Clinical Trial	Participants' characteristics						Intervention		Outcomes
	N°	Mean Age	Eosinophil profile	COPD baseline stage AND history of asthma	Baseline treatment	Exacerbation history	Arms	Follow-up Endpoints	Main results
TORCH Calverley 2007 (20)	6112	65	No information	No clear information for COPD staging – FEV1 <60% – Asthma excluded	LABA: 9% ICS: 20% ICS/LABA: 28%	Mean rate requiring antibiotics or corticosteroids: 1.0; Mean rate requiring hospitalization: 0.2	> Salmeterol/ fluticasone 50/500 μg bid > Placebo bid > Salmeterol 50 μg bid > Fluticasone 500 μg bid	3 years Primary: time to death from any cause Secondary: exacerbations annual rate; SGRQ; lung function	> Lower annual rate of exacerbations in all therapies compared with placebo. LABA/ICS with: > No differences in risk of death compared to LABA. > Lower HR for death compared to ICS. > Improved SGRQ and mean baseline FEV1 compared to ICS or LABA.

CAT - COPD Assessment Test; COPD - Chronic Obstructive Lung Disease; E-RS - EXACT-Respiratory Symptoms; FEV1 - forced expiratory volume in the first second; FVC - forced vital capacity; GOLD - Global Initiative for Chronic Obstructive Lung Disease; HR - hazard ratio; IC - inspiratory capacity; ICS - Inhaled Corticosteroids; LABA - Long Acting Beta Agonist; LAMA - Long Acting Muscarinic Antagonist; mMRC - modified Medical Research Council dyspnoea scale; SABA - Short Acting Beta Agonist; SAMA - Short Acting Muscarinic Antagonist; SGRQ - Saint George's Respiratory Questionnaire; TDI - Transition Dyspnoea Index.

trials, which is a global assessment of disease severity, defined by the "clinically important deterioration" (CID) composite endpoint. CID is defined by a deterioration from baseline in individual patients in terms of forced expiratory volume in one second (FEV_1), and/or in any patient-reported outcomes and/or the occurrence of a moderate or severe COPD exacerbation.

- Most studies included COPD patients in GOLD B and D stages (predominantly highly symptomatic patients), except for SPARK[19], which included a relevant proportion of patients in GOLD C stage (less symptomatic but with previous exacerbation history). No clear information was found to categorise patients in the TORCH[21] and SUMMIT[22] studies.
- Some studies included participants with a history of higher number/intensity of previous exacerbations (such as ETHOS[9], IMPACT[8], TRIBUTE[14], DYNAGITO[23], TRINITY[16] and SPARK[19]): for those, the benefit of ICS combination therapies was higher; on the other hand, studies with participants with fewer previous exacerbations (such as SUNSET[15], EMAX[13], FLAME[17] and SUMMIT[22]) showed greater benefit with LABA/LAMA therapies.
- SUNSET[15], IMPACT[8] and ETHOS[9] trials allowed a clear discrimination of participant's blood eosinophil levels. We can assume that the presented mean blood eosinophil counts in the TRIBUTE (240 cells/mm^3)[14], TRINITY (200 cells/mm^3)[16] and TRILOGY (250 cells/mm^3)[18] trials also represent a majority of patients with elevated blood eosinophil counts (>150 cells/ mm^3), compared with the remaining ones. However, SUNSET[15] had a shorter follow-up period and included participants with low exacerbation profile, while IMPACT[8] and ETHOS[9] included participants with higher exacerbation history.
- FLAME[17] revealed no differences in exacerbation rates, regarding ICS response to different levels of blood eosinophils count, but most of the included participants had a low profile of previous exacerbations.

Considering such aspects, we elaborated an original conceptual diagram comparing the potential benefit of different options of inhaled treatment for COPD in reducing the risk of exacerbation and mortality (Fig. 1). The diagram positions the main trials conducted so far according to their reported results and the most relevant patients' characteristics. Apart from such features, critical judgement may also include a third dimension, i.e. symptom intensity, which might influence the choice of different drug combinations with similar potential benefits.

Thus, when considering the risk of exacerbation and mortality, there may be greater benefit of dual bronchodilator therapy (LABA plus LAMA) over single therapy (LABA or LAMA) in patients at GOLD stages A and B (mainly in patients with persistent mild or moderate symptoms, but with lower blood eosinophil counts and without previous exacerbations). Alternatively, when considering a single bronchodilator therapy, LAMA should be preferred over LABA, as it may have greater benefits in terms of preservation of lung function.

Regarding patients with higher blood eosinophil counts and a relevant history of past exacerbations, either in frequency or in intensity, triple therapy (LABA plus LAMA plus ICS) should be considered over any dual therapies, as it is

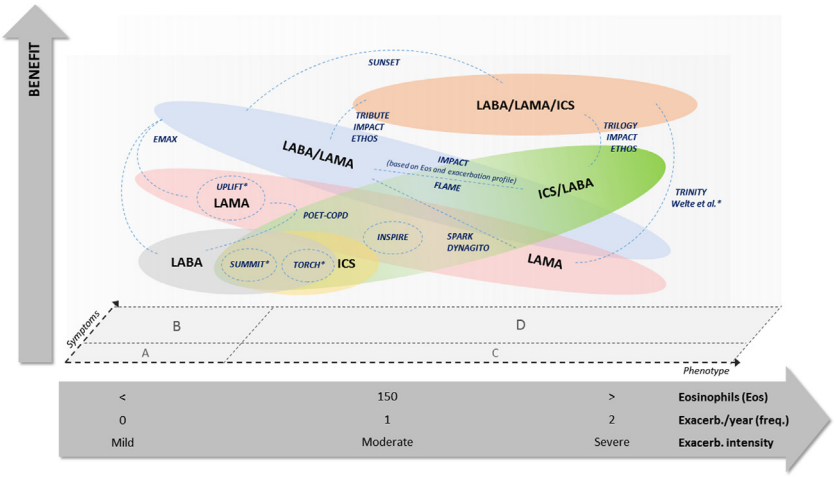

Fig. 1 Comparison of potential benefit of COPD treatment options on exacerbation and mortality risk reduction, according to clinical trials results and patients' characteristics. Notes: X-axis shows a concept of integrative clinical judgement on patients' phenotypic features, but positioning of such different aspects is not truncated and may suffer overlapping adjustments. Studies are located according to their participants' features in order to estimate their potential comparisons. Most studies are situated in GOLD B and D symptoms regions, while SPARK study is situated in GOLD C and D symptoms regions. *Studies with unclear participants' profile, either regarding eosinophil count or COPD symptoms group.
This figure is original, produced by authors according to their conceptual rationale, and reproduced with permission to journal policies.

more beneficial in preventing exacerbations and mortality; this includes mostly patients at (*previous*) GOLD stages C and D. As an alternative, whenever triple therapy is not a feasible choice or unavailable, dual therapy with LABA/ICS should be an option to consider, particularly in patients with higher blood eosinophils count that will respond better to the ICS.

Discussion

The role of COPD patients' phenotypes has been under discussion over the last few years in light of new evidence that major trials have revealed. GOLD reports have been changing significantly, including new insights into the role of blood eosinophil counts and exacerbation profile in clinical decision making[3], mostly in high-risk patients and concerning the choice of drug combinations, including or not the ICS. Indeed, it is important to note that an observational study in different Italian areas, in which 176 general practitioners (GPs) enroled their patients with a COPD diagnosis (n = 526), found a higher prescriptive appropriateness when using the 2011 GOLD classification, with respect to the previous GOLD classifications.[29] This might be because the 2011 GOLD classification, unlike the old ones, included common anamnestic features considered by GPs in their clinical practice.

Some studies have highlighted the importance of blood eosinophil counts as an independent predictor for individual risk regarding exacerbations and mortality.[11,30] However, looking at patients' profiles in the studies, we can figure out that blood eosinophil counts and past exacerbation profile may be equally relevant to trace individual risk and potential response to ICS. For instance, SUNSET[15], IMPACT[8] and ETHOS[9] studies had many participants with high blood eosinophil counts. Nevertheless, SUNSET[15] participants had a lower exacerbation profile, probably related to triple-therapy effects prior to the study (and thus, ICS therapies), which allowed the discontinuation of ICS during the study, thereby precluding major differences compared with ICS-free therapeutic schemes. On the other hand, IMPACT[8] and ETHOS[9] included participants with higher exacerbation profiles, and therefore the benefit of triple-therapy was higher. Thus, the frequency and intensity of past exacerbations may, to some extent, overcome the role of eosinophil counts in predicting ICS response. This may explain the results found in the FLAME study[17], where patients had a lower exacerbation profile, and no differences in the outcome were found along the spectrum of eosinophil levels. These results may provide a solid rationale to position the potential benefit for triple therapy on those patients.

Triple-therapy has come under the spotlight over the last few years, mostly due to the IMPACT[8] results, that, for the first time in COPD drug therapy research, found a statistically significant reduction of mortality risk. The higher the individual risk patients presented the more pronounced were the results, mainly regarding eosinophil levels or the frequency and severity of previous exacerbations. Such findings were reinforced by the ETHOS[9] trial and by real-world studies.[31] The benefits of triple-therapy may extend to quality of life and lung function itself as reported by most of these trials[32–34], although this has not been proven in real life practice in the long term, thus far. However, it should be highlighted that mortality was assessed as a secondary outcome in most trials, and their sample size was not powered to adequately allow this analysis. Thus, future trials should be designed with mortality as the main outcome. Furthermore, this overall mortality reduction seems to occur despite a slight but statistically relevant increase in pneumonia and other ICS related adverse effects. Nevertheless, the potential benefit regarding exacerbation should be balanced with the risk of pneumonia.[35]

The EMAX study[13], on the other hand, brought new evidence regarding the superiority of dual bronchodilator therapy versus single therapy in mild stages of COPD. However, there were insufficient data regarding eosinophil counts, which limits the possibility of assuming its potential benefit when comparing these two treatment options. Moreover, most patients were selected from a GOLD B symptoms spectrum, and no study has yet addressed GOLD A (less symptomatic) patients, which hampers the ability to conclude about the superiority of dual therapy over single therapy in such patients.

Most of the trials included in our analysis involved patients in GOLD B and (*previous*) D stages, except for SPARK[19], which had a significant proportion of GOLD (*previous*) C patients. The latter present fewer symptoms but have a higher exacerbation profile. SPARK revealed a less robust benefit of dual therapy, but the true magnitude of the ICS benefit in the previous GOLD C group patients is still unclear and deserves further research.

Patients with higher eosinophil counts and/or a history of previous moderate-severe exacerbations seem to benefit more from ICS containing therapies. Nevertheless, the true determining magnitude of each predictor, and whether one plays a more important role than the other, is still unclear. Based on these findings, new approaches are now recommended by GOLD guidelines[3], namely:

- Dual therapy with LABA/LAMA as the first-line treatment for GOLD B patients, without previous exacerbations and despite the intensity of symptoms. Those patients most likely have low eosinophil levels and therefore get a less clear benefit with LABA/ICS combination.
- Update on patients with previous exacerbations, with the development of a new GOLD E group, resulting from the merged (*previous*) groups C and D. Those patients should be initiated with LABA/LAMA dual-therapy, as was previously stated. However, those with higher eosinophil counts will benefit the most from inclusion of the ICS to prevent future exacerbations, and as an add-on to bronchodilator therapy to preserve lung function. As an alternative, dual therapy with LABA/ICS should be an option to consider in those patients, whenever triple therapy is not a feasible choice or is unavailable.
- A step-up treatment, for patients starting on single-bronchodilator therapy, directly to triple-therapy, particularly in the presence of high eosinophil counts and frequent moderate or severe exacerbations. Those patients will benefit the most with the presence of the ICS to prevent future exacerbations. Moreover, considering that they are frequent (or intense) "exacerbators", they have a higher risk of lung function decline; therefore the choice of giving them a combination of LABA and LAMA is potentially better than each one isolated, to preserve lung function.

It seems reasonable to consider that all patients diagnosed with COPD benefit most from an initial combined therapy, either a LABA/LAMA for patients without previous exacerbations but with persistent symptoms (mostly GOLD B, but possibly some at higher risk in GOLD A), a LABA/LAMA for patients with previous exacerbations, and maybe a LABA/LAMA/ICS for those with higher blood eosinophil counts (GOLD E). Moreover, a step-up therapy approach should lead to triple therapy in the presence of frequent or severe exacerbations or higher blood eosinophil counts. This approach will probably optimise the potential benefit to patients in terms of preventing lung function decline, exacerbations, and mortality risk. However, it may not be reasonable and feasible in all settings, especially in low and middle-income countries, where access to combined therapies may be limited due to lack of supply or economic constraints. Moreover, other aspects such as patient preference for different types of inhalers, treatment adherence, a patient's ability to acquire and perform proper inhalation manoeuvres, or even doctors' adaptability to different inhaler treatment features, may all play a role in the final treatment choice. For that reason, alternative approaches may prevail in certain circumstances, such as a single bronchodilator initial therapy for GOLD A and B patients (mainly at a lower individual risk, such as non-smokers, healthy and physically active, etc.), or even dual therapy with LABA/ICS for patients in GOLD E group.

This review focuses on the main patient characteristics reported in clinical trials, such as clinical staging, exacerbation history and blood eosinophil counts. However, *grey areas* remain about which is the best drug combination for each specific patient, considering the multidimensional matrix of such features. This limitation, however, is the reason why the present paper puts forward a conceptual exercise, positioning different drug options and combinations, regarding their potential benefit in the risk of exacerbations and mortality as a misbalancing factor in clinical decision. Another aspect that may hamper the objectiveness of this review concerns the differences amongst specific drugs, even within each class, which we did not directly address, and which has been reported for instance in the bronchodilator effect of LAMA and the pharmacodynamics of ICS.[36,37]

A relevant topic in bronchodilation in COPD involves the side effects of the different molecules, which we did not specifically take into account in the formulation of the clinical decision conceptual diagram. This question has been studied, especially regarding ICS containing inhalers and the increased risk of pneumonia.[38] Some of the most recent reviews consider that the all-cause mortality risk reduction outweighs the risk of pneumonia with ICS.[39] Since we developed this rationale over the existing GOLD framework, which takes into consideration the risk-benefit of inhaled bronchodilators, and that recent evidence favours the benefits of most of the referred bronchodilators over the risks, we do not consider this limitation as a drawback to the conclusions that led us to the conceptual diagram.

Nevertheless, we should highlight that this is a critical and conceptual review, as no systematic methods were used to address our research question/hypothesis or to search and select the included studies.[12] In addition, the lack of an objective and systematic method to analyse the results and the quality of the included studies may be regarded as a limitation. However, we wish to point out that our critical review may contribute to the discussion initiated in the respiratory community after the release of the new GOLD 2023 document. We envisage new systematic reviews conducted with analytical methods to compare clinical trials results, and to further enrich these results with observational data. That might help to establish quantitatively if

eosinophil counts and past exacerbation profile play equally relevant roles to predict ICS response.

Future trials should focus on mortality as the primary endpoint, but also try to clarify the role of patients' phenotypic features, such as exacerbation history, eosinophil levels, and many others, at all COPD stages and across disease progression spectra.

Particular attention should be paid to the ubiquitous environmental exposures, which, according to the World Health Organization (WHO) are responsible for 13 million anticipated deaths per year worldwide, including more than seven million people who are killed each year from exposure to air pollution.[40] Indeed, all clinicians dealing with chronic respiratory patients should know the importance of air pollution also for the hard outcomes of interest[27] and manage the issue both at the level of doctor-patient relationship and at the community level as clean air advocates.[41–43]

Of particular interest, we suggest that a new COPD research agenda regarding inhaled therapy should focus on the long-term outcomes of therapy naïve patients initiating dual or triple therapy inhalers, considering exacerbations, COPD mortality and all-cause mortality, but also lung function preservation and clinically important deterioration. Studies should also focus on the comparison of single to triple therapies step-ups in terms of exacerbations and mortality risk reduction, using the time-to-event endpoints. Finally, a debate is ongoing on the definition and severity classification of exacerbations, as well as their predictive potential for other future exacerbations. Thus, studies are needed to also address those aspects, as they may ultimately change the phenotype classification and treatment of COPD patients.[44,45]

Conclusion

The role of patients' phenotypic features has been changing in the last few years. New trials have shown the importance of eosinophil counts and past exacerbation profile to predict the individual risk and the potential benefit of ICS containing therapies. The conceptual review here presented offers a comprehensive approach that considers patients' main phenotypic features and the potential benefit of different COPD drug treatment options. Moreover, this may, to some extent, provide a possible rationale for the choice of the first-line option and of the step-up treatment with dual therapies containing or not ICS, or even a step-up directly from monotherapy to triple therapy.

Statement of ethics

This review was developed under the ethical principles. No human participation was necessary, and no personal data was used, therefore no ethical committee appraisal was conducted.

Author contributions

All authors contributed to all stages of the manuscript development, namely: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Conflicts of interest

There is no conflict of interests to declare, and no funding sources.

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LETTER TO THE EDITOR

The lung-protective effect of prior mRNA vaccination on breakthrough COVID-19 patients receiving high flow nasal oxygen for hypoxemic acute respiratory failure

It is a widely held view that messenger RNA (mRNA) COVID-19 vaccines, including mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech), effectively reduce the risk of SARS-CoV-2 infection and COVID-19-related hospitalization. Unexpectedly however, despite the protective effects of those vaccines, as many as 25% of the individuals currently being admitted to Intensive Care Units (ICUs) are fully vaccinated against COVID-19.[1,2] It is hypothesized that as vaccine coverage increases, breakthrough cases will rise proportionately.

Chest X-ray scoring systems quantifying the severity and monitoring the progression of the disease were developed during COVID-19 outbreak. Retrospective studies investigating their prognostic accuracy have demonstrated that these systems help predict mortality in patients with COVID-19.[3,4] Notably, the COVID-19 chest radiography (CARE) score, a chest radiography rating system which assesses the extension of the ground-glass opacities (GGs) and consolidations (Cos) in three distinct radiograph zones (upper, middle, and lower lung), has been validated and has predicted in-hospital mortality.[5]

While recent evidence suggests that mRNA vaccinations may attenuate disease severity in breakthrough COVID-19 patients requiring hospitalization,[7,6] its impact on critically ill patients receiving non-invasive respiratory support (i.e., high-flow nasal oxygen, or continuous positive airway pressure, or noninvasive ventilation) remains unclear. The current study set out to retrospectively investigate the effect of mRNA vaccination on the extent of lung involvement as assessed by the CARE score in breakthrough COVID-19 patients receiving high-flow nasal oxygen (HFNO) because of severe hypoxemic acute respiratory failure (hARF) that was unresponsive to conventional O_2—therapy. The patients studied were admitted to an Intermediate Respiratory Care Unit (IRCU).

The chest X-rays (CXRs) of 32 consecutive, fully vaccinated patients (the vaccinated group) and of 41 unvaccinated patients (the unvaccinated group), all critically ill and affected with COVID-19, admitted to the SARS-CoV-2 IRCU of the University-City Hospital in Padua between 1 September 2021 and 31 December 2021 were retrospectively reviewed. The criteria for admission to the IRCU was the inability of conventional O_2-therapy to maintain $SaO_2 \geq 92\%$. All the patients meeting these criteria were contacted and asked to sign informed consent forms releasing their medical records for review. The need for ethical approval was waived by the local Ethics Committee given the study's retrospective design and the fact that the unit's standard treatment protocol was consistently followed for all the patients involved.

All of the CXRs taken during the patients' RICU stay were reviewed. The severity of lung involvement was evaluated using the CARE score. A radiologist with 12 years of experience in thoracic imaging and blind to the patients' information examined the CXRs and scored them using the CARE system. The patients' scores at the time of their admission, their highest score during their IRCU stay, and their highest GG and Co sub-scores were reviewed and compared.

The patients' baseline demographic and clinical features, clinical symptoms and laboratory test results at the time of their IRCU admission and their clinical outcomes were likewise reviewed and compared.

All of the patients in the vaccinated group had successfully completed the COVID-19 mRNA vaccination course, meaning two standard doses of the Pfizer-BioNTech COVID-19 vaccine; none of them had received a booster dose. The mean time interval between the last vaccine dose and admission to the IRCU was 5.86 (0.9-8.8) months. Genomic sequence analysis, performed only in the vaccinated patients, identified, without exemption, the SARS-CoV-2 delta variant. With the exception of age, the baseline characteristics and clinical and laboratory data of the patients at the time of admission to the IRCU were not significantly different in the two groups. The patients in the vaccinated group were, in fact, significantly older [74 (36-90) vs 58 (40-90) yrs; p=0.0018]. The CARE score at the time of IRCU admission, the highest score during their IRCU stay, as well as the highest GG and Co sub-scores were significantly worse in the unvaccinated group. The clinical outcomes of the patients in the two groups were not significantly different (Table 1). The stratified log-rank test indicated that the vaccinated patients had slightly longer survival times in relation to their unvaccinated counterparts [mean survival time: 95.53 (95%CI, 80.76 to 110.30) vs 83.22 (95%CI, 75.82 to 90.61) days; p= 0.2261]; their hazard ratio of death was 0.5174 (95% CI, 0.1780 to 1.5039).

An analysis of the study's data suggests that mRNA vaccination conferred a protective effect on the extent of lung involvement in the breakthrough COVID-19 patients with

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Table 1 Patients' baseline demographic and clinical characteristics, clinical, laboratory and blood gas data at RICU admission, CARE values and clinical outcomes.

	Vaccinated patients (N=32)	Unvaccinated patients (N=41)	p-value
Baseline demographic and clinical data			
Gender, M/F	24/8	23/18	0.1393
Age, yrs	74 (36-90)	58 (40-90)	0.0018
BMI, kg/m^2	32 (30.12-33.26)	30 (26.67-43)	0.6973
Smokers, n°	6	6	0.7538
Patients with co-morbidities, n°	31	34	0.0717
Metabolic disorder (diabetes, obesity)	14	14	0.4708
Respiratory disease (asthma, COPD)	3	1	0.3129
Hemato-oncology disease	3	0	0.0797
Other active oncology disease	3	0	0.0797
Cardiac disease (cardiac arrhythmia, previous MI, angina pectoris, and/or CHF)	23	21	0.0939
Chronic renal failure	5	2	0.2283
Clinical, laboratory and blood gas data at RICU admission			
PaO_2 (O_2 suppl), mmHg	82.95 (48.8-207.8)	77.80 (48.00-296.1)	0.1515
$PaCO_2$, mmHg	33.4 (25.4-48.2)	34.4 (27.0-44.4)	0.6247
PaO_2/F_IO_2, mmHg	225.76 (48.80-479.23)	225.43 (59.05-519.47)	0.9225
Arterial pH	7.48 (7,34-7,56)	7,48 (7,39-7,57)	0.5033
Heart rate, b/min	80 (47-135)	86 (62-120)	0.3084
Respiratory rate, b/min	19 (12-30)	21.5 (12-35)	0.2753
Total WBC count (x10^9/L)	8.615 (2.62-18.80)	8.32 (4.01-20.65)	0.9734
Serum CRP, μg/mL	70 (2.90-210)	60 (6.10-450)	0.2778
CARE values			
Global CARE at RICU admission, pts	9 (1-28)	20 (5-32)	$<$0.001
Highest global CARE, pts	18 (0-35)	26 (6-36)	$<$0.001
Highest GG subscore, pts	7.5 (0-14)	12 (2-16)	$<$0.001
Highest CO subscore, pts	9 (0-26)	16 (4-28)	0.012
Clinical outcomes			
Hospital stay, days	18.5 (1-80)	15.5 (3-124)	0.1845
RICU stay, days	4 (1-33)	3 (1-44)	0.8840
Pts who required intubation, n	3	5	1.000
Pts died during RICU stay, n	5	4	0.4927

Values are expressed as median (interquartile range). P-values refer to differences between vaccinated and unvaccinated groups. (BMI= Body Mass Index; CARE= COVID-19 chest radiography score; CO= consolidation; CRP= C-Reactive Protein; GG= Ground Glass; MI= myocardial infarction; RICU= Respiratory Intensive Care Unit; WBC= White Blood Cell).

severe hARF requiring HFNO treatment. The study's results are in line with those described by Lee et al. who, on the basis of the clinical and imaging characteristics of 412 hospitalized COVID-19 patients, concluded that those with COVID-19 breakthrough infections had a significantly higher proportion of CT scans *without* pneumonia with respect to their unvaccinated counterparts.[8]

While the CARE scores of the vaccinated patients were significantly lower, the PaO_2/F_IO_2 ratio, a widely used indicator of hypoxemia reflecting the extent of acute lung damage, was not significantly different in the two groups. The result could be explained by the fact that although hypoxemia caused by the SARS-CoV-2 infection is primarily due to the ventilation/perfusion (V/Q) mismatch in non-aerated lung regions (something which can be assessed by the CARE score), in 3 out of the 32 vaccinated patients it was associated to submassive pulmonary embolism, a disorder that cannot be accurately assessed by the scoring system.

Since the individuals in the vaccinated group were significantly older, it is possible that the vaccination's protective effect on mortality risk may have been offset by the age difference between the vaccinated and unvaccinated groups. A recent analysis by Italian investigators confirmed, in fact, that old age was by far the most significant risk factor for COVID-19 mortality in hospitalized patients.[9]

While it is true that the limited number of patients analyzed here and the study's retrospective nature may have caused a bias, its findings demonstrate that mRNA vaccination may exert a protective effect on pulmonary involvement in the breakthrough COVID-19 patients undergoing HFNO for severe hARF and confirm the importance of a judicious, mass vaccination strategy.

Conflicts of interest

The author has no conflicts of interest to declare.

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LETTER TO THE EDITOR

Diaphragm thickening fraction and inspiratory effort in patients with SARS-COV II pneumonia receiving different non-invasive respiratory supports

The assessment of inspiratory effort in the patient with acute hypoxaemic respiratory failure (AHRF) can be performed invasively by measuring the oesophageal pressure swing (ΔPes) during the inspiratory act.[1] The reduction in ΔPes after two hours of non-invasive ventilation (NIV) in patients with AHRF is a predictor of NIV success.[2]

The study of diaphragm thickening fraction (TFdi) is a predictor of NIV failure in patients hospitalised for COPD exacerbation with respiratory acidosis.[3]

A correlation between TFdi and ΔPes has been demonstrated in patients undergoing different levels of support during invasive (IMV)[4] and NIV.[5] So far, the validity of TFdi vs. ΔPes in recording the patient's effort during Continuous airways pressure (CPAP) and High Flow Nasal Cannula (HFNC), where any form of inspiratory support is lacking, has not yet been assessed.

De Vita et al. demonstrated that the values of PaO2, SpO2, respiratory rate, recorded during Venturi mask oxygen therapy and during CPAP are associated with CPAP failure.[6] However, finding predictors of failure of non-invasive respiratory supports (NRS) has always been a challenge. For this reason, between February and May 2021, we conducted a randomized short-term physiological study within the first 24 h of hospital admission to compare the effects of standard oxygen therapy, HFNC, CPAP and NIV on breathing pattern, gas exchange, inspiratory effort, and dynamic transpulmonary pressure (PLDyn) in patients with moderate-to-severe AHRF due to COVID-19 pneumonia.[7]

This research letter is a new analysis of our previous investigation in which we compare the inspiratory effort during standard oxygen therapy (SOT) and 3 forms of NRS, using both the Oesophageal pressure swing (ΔPes) and the diaphragm ultrasound.

The local Ethic Committee approved the study (691/2020/Sper/AOUBo) and written informed consent was obtained from all the patients. The study was registered at the Clinical Trial Registry (NCT04741659).

We considered eligible any adult patient (≥ 18 years old) with AHRF and a PaO2/FiO2 ratio < 200 mmHg evaluated during spontaneous unassisted breathing trial (FiO2 of at least 0.40), due to pneumonia and a confirmed molecular diagnosis of COVID-19. Exclusion criteria were: previous clinical, radiological and histological diagnosis of pneumopathy, body mass index > 30 kg/m2; known diagnosis of sleep-disorders, restrictive pulmonary/chest wall disease, cardiac arrest, severe haemodynamic instability (> 1 vasoactive amine for at least 24 h), acute coronary syndrome (unstable angina/IMA), severe arrhythmias, inability to protect the airway, respiratory arrest and need for intubation, pregnancy or suspected, use of sedative drugs, long-term home oxygen therapy.

Patients underwent trials of 30 min each where they were randomly alternated with CPAP, HFNC and NIV; between each trial, there was a 30-min wash-out period where SOT was administered, as described in ref.[6] TFdi was measured using a linear probe at functional residual capacity and after each tidal inspiratory act. TFdi was calculated as follows:

$$TFdi = (end - inspiratory\ thickness - end - expiratory\ thickness)/end - expiratory\ thickness * 100$$

After excluding the presence of right or left chronic elevated hemidiaphragm and/or paralysis by ultrasound, at each protocol step, two investigators performed bedside ultrasound evaluation of the right hemidiaphragm on the zone of apposition between the anterior and medial axillary lines,[8] with the patient in semi recumbent position. Each investigator performed and recorded three sets of measurements independently, which were then averaged.

Measurements of oesophageal pressure (Pes) were obtained by placing a nasogastric tube equipped with an oesophageal balloon in the lower 1/3 of the oesophagus. Oesophageal pressure swing was calculated as the maximum decrease or increase in Pes from the end-expiratory level. The study of patient's tidal volume and minute ventilation (Vt and Ve) was obtained by respiratory inductance plethysmography. Measurements were obtained during each trial and during SOT.

Relationships between variables TFdi, ΔPes and Ve were studied using the Spearman correlation. Differences in TFdi values between groups were analyzed by one-way analysis of variance (ANOVA). P values lower than 0,05 were considered statistically significant. The IBM SPSS Statistics software (version 21) was used for data analysis.

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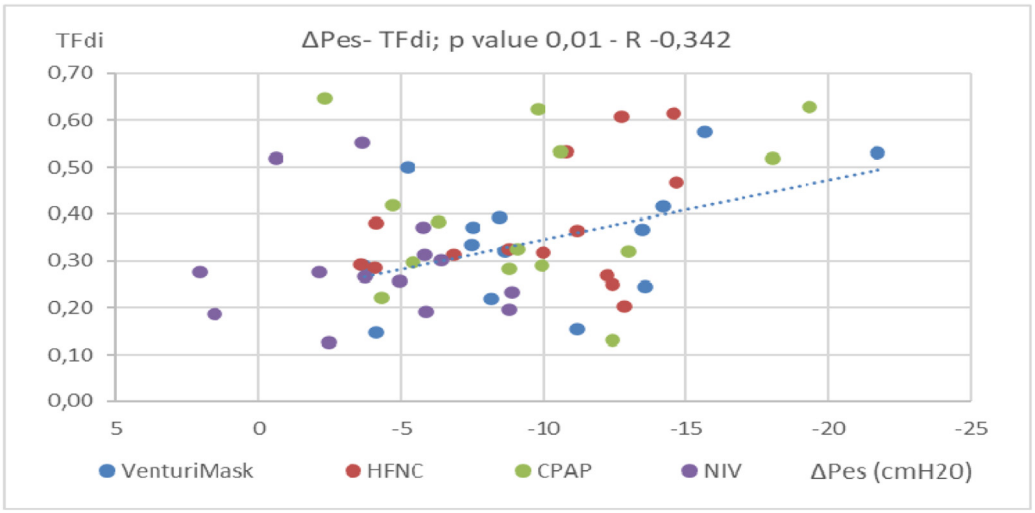

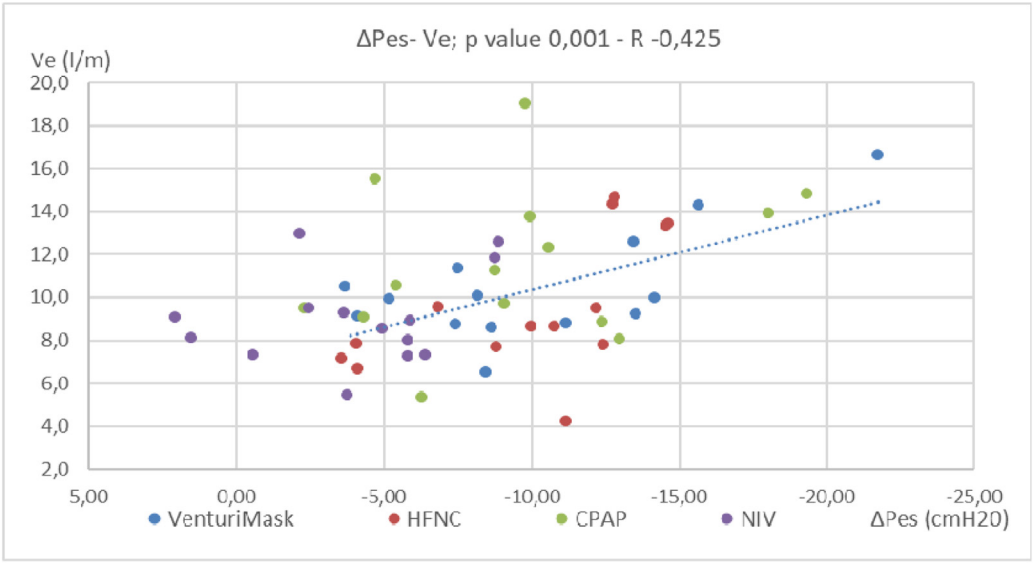

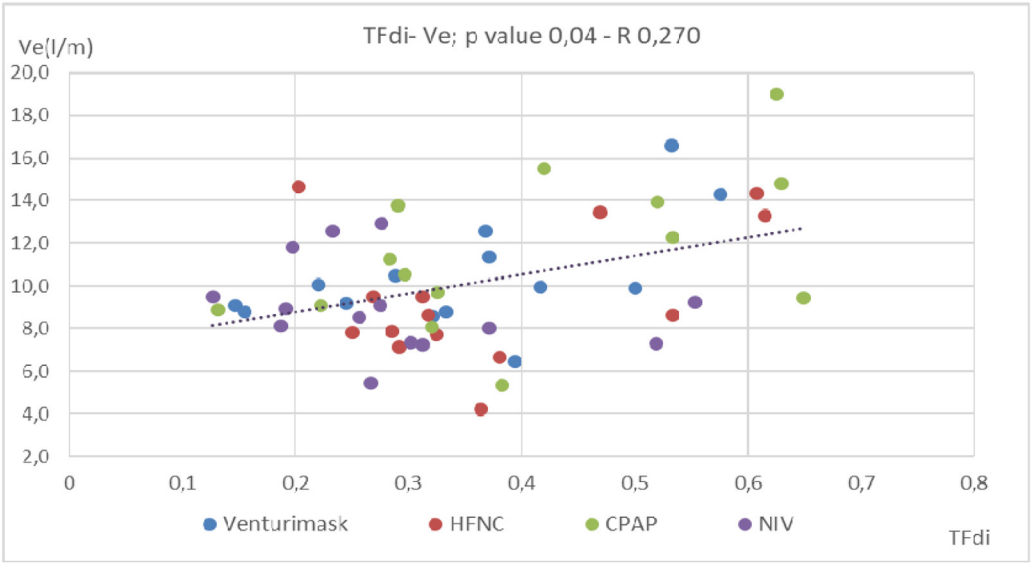

Fig. 1 **Upper part:** Spearman Correlation analysis between TFdi and ΔPes (p value 0,01): inspiratory effort measured by oesophageal manometry was directly correlated to TFdi, regardless of the type of NRS applied. Each dot corresponds to the mean value of 6 measurements of ΔPes and their linear correlation with TFdi, for each patient during each different NIRS trial (colors).

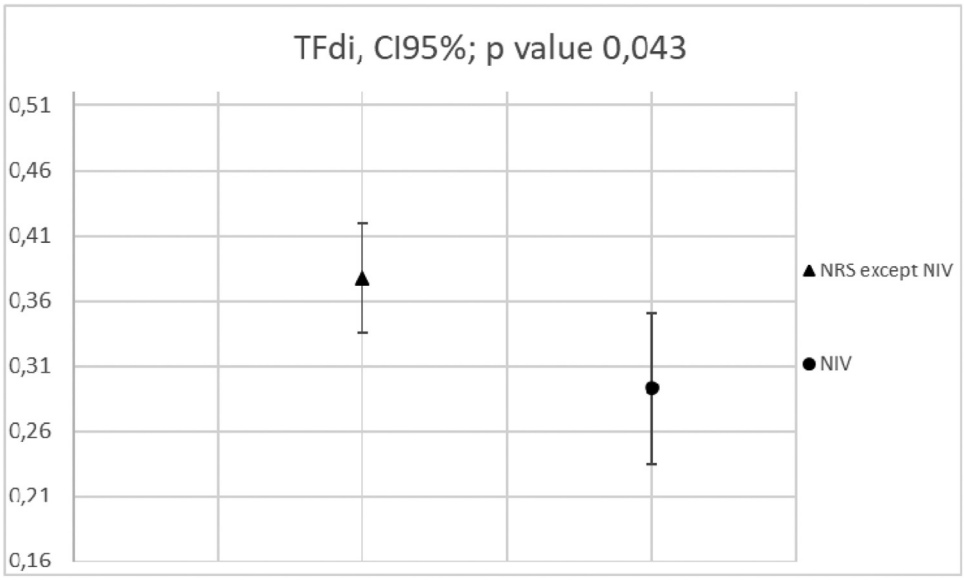

Fig. 2 Effects of Pressure support application on TFdi (one-way ANOVA). NIV was the only NRS to significantly reduce TFdi compared to VenturiMask, HFNC, or CPAP (p value 0,043). *TFdi: diaphragm thickening fraction; NIV; non-invasive ventilation; NRS: non invasive respiratory support. HFNC= high flow nasal cannula; CPAP= continuous positive airway pressure.*

Fifteen patients were enrolled. Patient's mean age was 63 ±9 years old, mean SAPS II and APACHE scores at admission were 22±6 and 8,7±2, respectively. Mean PaO2/Fio2 ratio was 126±34 and mean respiratory rate was 24.6±5.4 breaths per minute.[7] There was a direct correlation between ΔPes and TFdi detected by ultrasound, regardless of the type of NRS used (Fig. 1 upper part; *p* value 0,01 R = -0,342). The Ve was found to be directly correlated to the patient's TFdi (*p* value 0,04 R = 0,270) and ΔPes (*p* value 0,001 R = -0,425) (Fig. 1, middle and lower part). The use of NIV resulted in a significant reduction in TFdi developed by each patient compared to all other NRS used (respectively mean TFdi = 0,292±0,12 versus 0,377 ±0,142 p value 0,043, Fig. 2).

To the best of our knowledge, this is the first study comparing the extent of inspiratory effort assessed by ΔPes and TFdi of the diaphragm during the 3 major forms of NRS.

In patients with AHRF receiving NIV, the evaluation of patients' inspiratory effort is desirable to predict NIV failure and to avoid a delay in endotracheal intubation.[2] Nonetheless, assessing ΔPes is not always feasible since it is not widely used in clinical practice. Alternatively, ultrasound study of TFdi is a simple, reproducible method,[9] which can be performed at the patient's bedside. The correlation analysis in our first study[7] revealed that VE was directly correlated with the patient's inspiratory effort (p value 0,001): patients with higher ΔPes experienced an increase in VE. In line with these findings, here an increase in VE was directly proportional to the TFdi.

Our results showed that there was a moderate correlation between ΔPes and TFdi. This can be explained by the fact that the change in ΔPes is influenced not only by diaphragmatic contraction, but also by the contraction of all the inspiratory muscles. The measurement of transdiaphragmatic pressure (Pdi) may have a better correlation with TFdi. Recent studies, however, show controversy even when comparing these two variables.[10,11] For instance, Puolard et al. found that the Pdi was weakly related to diaphragm thickening fraction.[10] Furthermore, even when diaphragmatic contractility is equal, oesophageal pressure changes may be influenced by a different ratio of chest wall and lung elastance.

In the absence of an esophageal balloon to monitor ΔPes, this modest correlation between ΔPes and TFdi would allow us to determine relative changes in the patient's inspiratory effort over time and following the application of different types of NRS: NIV was the only support that significantly reduced ΔPes.[7] Similarly, the use of a pressure support (NIV)

Middle part: Spearman correlation analysis between Ve and ΔPes (p value 0,001). Each dot corresponds to the mean value of 6 measurements of ΔPes and their linear correlation with VE, for each patient during each different NIRS trial (colors).
Lower Part: Spearman correlation analysis between VE and TFdi (p value 0,04). Each mark corresponds to the mean value of 6 measurements of TFdi and their linear correlation with VE, for each patient during each different NIRS trial (colors).
ΔPes: oesophageal pressure swing; TFdi: diaphragm thickening fraction; VE: minute ventilation; HFNC; High flow nasal cannula, CPAP; continuous positive airway pressure, NIV; non-invasive ventilation.
Lower part: correlation analysis between Ve and ΔPes (p value 0.001) and TFdi (p value 0,04).
Each mark corresponds to the mean value of 6 measurements of ΔPes and TFdi (triangles and dots, respectively) and their linear correlation with Ve, for each patient during each different NIRS trial (colors).
ΔPes: oesophageal pressure swing; TFdi: diaphragm thickening fraction; Ve: minute ventilation; HFNC; High flow nasal cannula, CPAP; continuous positive airway pressure, NIV; non-invasive ventilation.

resulted in a reduction of the TFdi, when compared to any other NRS.

This research has limitations. First, it represents a physiological study with a small sample size. Second, diaphragm sonographic assessment could be influenced by the operator. However, to overcome this limitation, ultrasound assessment was performed independently by two operators, and, consistent with previous studies,[12] the interclass correlation was found to be high, reducing the risk of bias. Third, as we mention before, we have not correlated TFdi with the Pdi, since we did not measure it.

In absence of diaphragm dysfunction,[13] TFdi can be used to estimate a change in patients' inspiratory effort during NRS, similar to what Umbrello demonstrated in patients undergoing IMV.[4] Further studies are needed to assess the correlation between the TFdi and the patients' clinical outcomes.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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LETTER TO THE EDITOR

Blood pressure and sleep during a 12-month stay at Concordia Station (3233 m), Antarctica

Crewmembers overwintering at Concordia Station in Antarctica are exposed to daylight alterations, hypobaric hypoxia, confinement and cold. Previous studies reported persistent sleep disturbances, sleep-disordered breathing and reduced daytime performance over a period of 12 months but consequences on the cardiovascular function remain unknown.[1,2] Concordia is located at 3233 m of altitude and non-Antarctic altitude studies have shown acute altitude-induced increases in systemic blood pressure (BP) up to several weeks.[3,4] Revealing persistent cardiovascular stress, e.g. elevated incidence of day-to-night BP non-dipping,[5] in Concordia crewmembers over a period of 12 months would call for immediate actions to identify risk factors and investigate prophylactic measures that can prevent adverse cardiovascular events in future expeditions.

Therefore, the main purpose of this study was to prospectively investigate cardiovascular function in the presence of sleep disturbances in crewmembers staying for 12 months at Concordia. Secondary, to distinguish the effect of altitude from other Antarctic conditions (e.g., daylight alterations), observations in Concordia were compared to a low-altitude control group stationed for 12 months at Dumont d'Urville (DdU), located on the Antarctica coast.

This study was approved by a French ethical committee (CPP Nord-Ouest 1, no.19.02.28.36850). Healthy crewmembers without any chronic disease or intake of regular medication, living ≤1200 m and who gave their written consent performed baseline sea-level measurements in France 5–6 weeks before embarking on their 12-month mission at Concordia (3233 m, barometric pressure 645 hPa, corresponding to ∼3800 m at the latitude of 45° in the Northern hemisphere) or at DdU (20 m, 985 hPa). No pre-acclimatization to high altitude was performed. During baseline measurements and in the 1st and 12th month in Antarctica, participants underwent 24-hour ambulatory blood pressure (BP) monitoring (24h-ABPM, Novacor Diasys 3+, France) according to international standards[5] and sleep stage assessments for 2 consecutive nights using a DREEM headband (Dreem 1, France). 24h-ABPM was analysed by linear mixed regression analyses incorporating all valid BP measurements (n = 4181) obtained during the three 24h-ABPM sessions (measurements were performed in 15 and 30 min intervals during day and night, respectively). Night periods were adjusted to individual habits and were detected by the position sensor of the BP device when a participant was in supine position for at least two consecutive measurements. To detect clinically relevant nocturnal (abnormal) non-dippers, non-dipping was defined by a <10% decrease from day-to-night BP.[5] Sleep outcomes with a confidence quality score of >50% were automatically scored by the DREEM algorithm.[6] A $P < 0.05$ was considered as statistically significant.

Overall, 12 healthy crewmembers (17% women, mean±SD age 30.6 ± 11.7 yrs) at DdU and 11 (36% women, age 36.2 ± 10.0 yrs) at Concordia (P = 0.129 between groups) participated in the study. All tolerated the stay in Antarctica and no regular medication was used against altitude illnesses or to facilitate sleep. At both Stations, indoor temperature was around 22 °C. Crewmembers at Concordia were hypoxemic but showed improved sleep onset latency and sleep efficiency during the 1st and 12th month compared to baseline. However, they spent a higher proportion of total sleep time (TST) in superficial sleep stage 2 and a lower proportion in deep sleep stage 3 compared to baseline (Table). More micro-arousals were observed during the 1st and 12th month at Concordia compared to baseline and DdU. No changes in sleep stages and micro-arousals were observed at DdU. At Concordia, crewmembers showed elevated night BP values in the 1st month compared to baseline and DdU (Table, Figure Panel A to D), whereas nocturnal diastolic and mean BP elevations persisted at 12 months. Additionally, the proportion of non-dippers in Concordia increased from 0% at baseline to 64% and 45% in the 1st and 12th month, respectively (P<0.05 vs. baseline, McNemar Tests) (Figure, Panel E and F). Corresponding proportions of non-dippers in DdU were 17%, 25% and 42% (P>0.05, all comparisons).

This prospective cohort study confirms sleep disturbances and reveals elevated night BP in Antarctic overwintering crewmembers staying for 12 months at Concordia when compared to baseline and to a low-altitude control group. These alterations indicate persistent and uncompensated cardiovascular stress at Concordia for 1 year. The observed findings are probably driven by the difference in altitude and hypobaric hypoxia[7] since confinement (e.g. psychological distress), climatic conditions (e.g. cold during outdoor activities) and altered daylight between Concordia and DdU were comparable, although this was not quantitatively assessed in this study. Our findings extend previous reports

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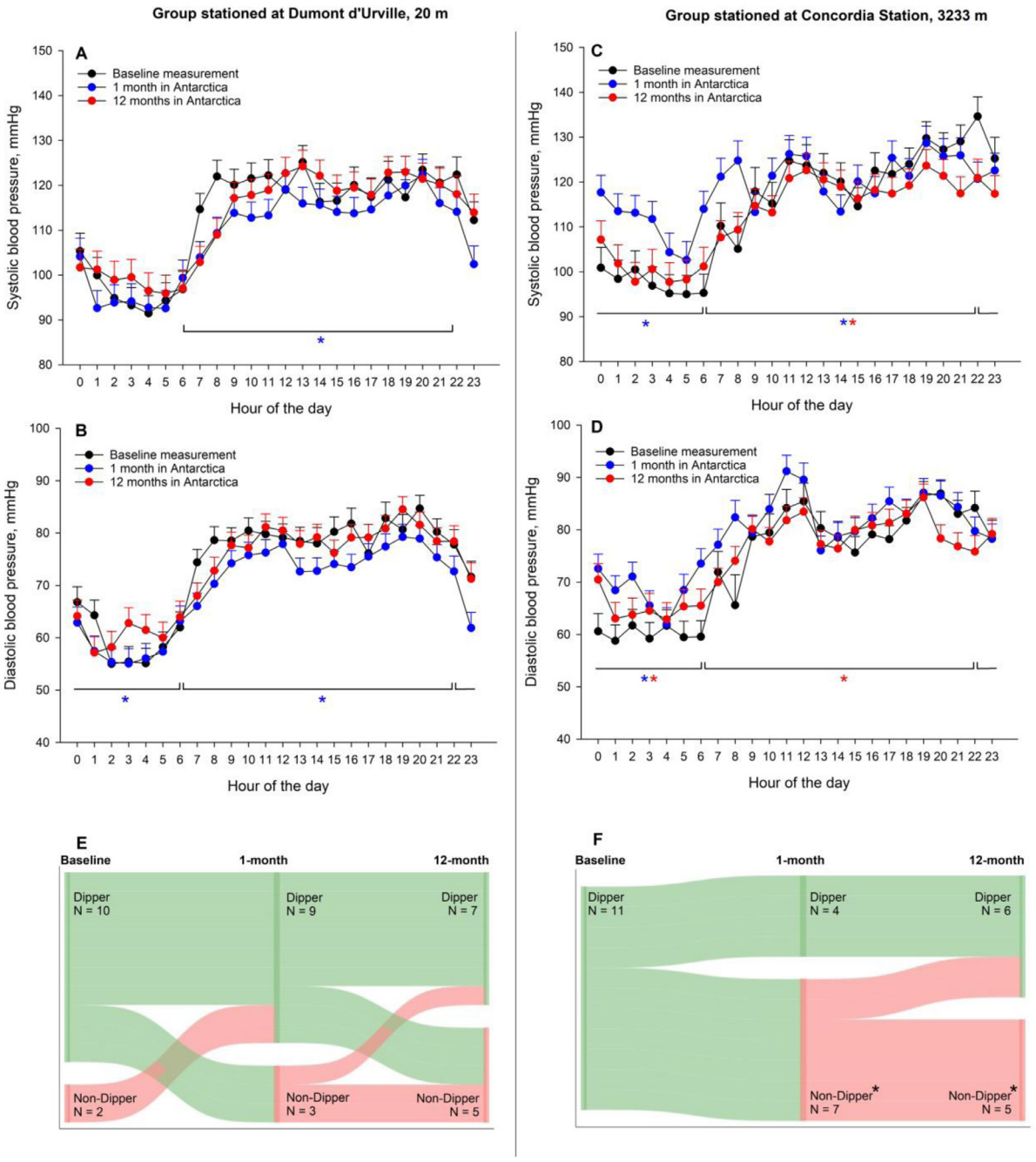

Fig. 1 24-hour ambulatory blood pressure monitoring at baseline, during the 1st and during the 12th month at Dumont d'Urville (20 m, Panel A & B) or Concordia Station (3233 m, Panel C & D), respectively. Dots represent mean values of all measurements within the same hour of the day, separated for the time point. Whiskers represent the standard error of the mean of the corresponding hour of the day. Mean and SE values were calculated by linear mixed regression models using all valid, single blood pressure measurements available (4181 single measurements). *$P<0.05$ between diurnal/nocturnal blood pressure measurements obtained during the 1- (*) or 12- (*) month in Antarctica compared to baseline measurements. **Panel E (DdU) and F (Concordia)** represent the proportions of participants having normal (Dippers) or abnormal (Non-Dippers) day-to-night blood pressure reductions at the corresponding time points. *$P<0.05$ in the proportion of Dippers to Non-Dippers within the same group when staying in Antarctica compared to baseline (assessed by McNemar Tests of paired proportions).

on altered cardiovascular function during acute (days) and prolonged (weeks) exposure to high altitude.[4] Especially, nocturnal and not daytime BP remained elevated during 12 months, which is in accordance with the presence of more superficial sleep, hypoxia-related arousals and high-altitude periodic breathing.[2,8] Moreover, a large proportion of crew-members at Concordia showed insufficient day-to-night BP reductions, an important clinical marker for cardiovascular outcomes.[5] These cardiovascular findings based on 4181 valid BP measurements are novel and of clinical importance

Table 1 Sleep- and ambulatory blood pressure-related outcomes.

	Dumont D'Urville Station (20 m)			Concordia Station (3233 m)			Mean difference in change between groups (95% CI)	
Exposure time, months	Baseline	1	12	Baseline	1	12	1 month vs. baseline	12 month vs. baseline
Daytime SpO_2,%	97.6±0.5	97.6±0.5	98.0±0.5	96.6±0.5	89.7±0.5*	90.6±0.5*	−7.0 (−8.2 to −5.7)‡	−6.5 (−7.7 to −5.2)‡
Sleep-related outcomes								
Time in bed, min	400±23	436±17	387±18	434±21	438±15	458±15	−32 (−109 to 45)	37 (−22 to 95)
TST, min	357±24	391±19	344±20	358±20	384±17	408±16	−8 (−88 to 72)	64 (−5 to 133)
Sleep onset latency, min	15±5	15±4	15±4	32±4	19±4*	17±4*	13 (−27 to 1)	15 (−30 to 1)
N1, %TST	5.3±0.8	5.0±0.6	5.8±0.7	5.9±0.7	6.5±0.6	6.7±0.6	0.9 (−1.5 to 3.3)	0.3 (−2.2 to 2.8)
N2, %TST	38.4±3.0	36.7±2.5	40.0±2.5	43.0±2.7	49.6±2.4‡,*	50.6±2.2*	8.3 (0.2 to 16.4)‡	6.0 (−3.7 to 15.8)
N3, %TST	33.2±2.7	28.0±2.3	33.6±2.4	24.4±2.5	17.6±2.1*	18.0±2.0*,‡	−1.5 (−10.3 to 7.3)	−6.7 (−13.4 to −0.1)‡
REM, %TST	22.5±2.4	29.7±1.9*	21.5±1.9	26.1±2.2	25.6±1.9	23.3±1.6	−7.7 (−16.3 to 0.9)	−1.7 (−10.4 to 6.9)
NREM, min	276±17	272±14	269±14	262±16	284±13	310±12*	26 (−37 to 89)	56 (0 to 112)
Wake, min	44±9	38±8	42±8	69±8	56±7	49±7*	−7 (−34 to 21)	−18 (−50 to 14)
Awakenings, number	22±3	17±2*	19±2	21±2	23±2‡	22±2	7 (1 to 14)‡	5 (−4 to 13)
Sleep Efficiency, %	89±2	91±2	90±2	84±2	86±2	89±2*	1 (−6 to 7)	5 (−3 to 13)
WASO, min	27±5	19±4	17±4	33±5	24±4	24±3	−1 (−24 to 22)	1 (−22 to 25)
Micro-Arousal Index, 1/h	8.0±1.4	6.9±1.1	7.1±1.2	7.1±1.2	10.1±1.0‡,*	11.5±1.0‡,*	4.1 (1.9 to 6.4)‡	5.4 (1.7 to 9.1)‡
24-hour ambulatory blood pressure								
24 h BP								
Systolic BP, mmHg	114±3	111±3*	115±3	117±3	119±3*,‡	115±3	6 (3 to 8)‡	−2 (−5 to 0)
Diastolic BP, mmHg	74±2	71±2*	75±2	76±2	79±2*,‡	77±2	7 (4 to 9)‡	1 (−1 to 3)
Mean BP, mmHg	88±2	84±2*	88±2	89±2	92±2*,‡	90±2	6 (4 to 8)‡	0 (−2 to 2)
Systolic-SD, mmHg	13±1	12±1	13±1	13±1	13±1	13±1	1 (−2 to 3)	−1 (−3 to 2)
Diastolic-SD, mmHg	12±1	10±1	11±1	11±1	11±1	11±1	1 (−1 to 3)	0 (−2 to 2)
Heart rate, bpm	72±2	70±2*	74±2*	74±2	79±2*,‡	78±2*,‡	8 (6 to 10)‡	3 (1 to 5)‡
Day period[1]								
Systolic BP, mmHg	120±3	115±3*	119±3	124±3	122±3*,‡	118±3*,‡	3 (1 to 6)‡	−4 (−7 to −2)‡
Diastolic BP, mmHg	79±2	75±2*	78±2	82±2	83±2‡	79±2*	6 (4 to 8)‡	−1 (−3 to 1)
Mean BP, mmHg	93±2	88±2*	92±2	96±2	96±2‡	92±2*,‡	5 (3 to 7)‡	−2 (−4 to 0)‡
Systolic-SD, mmHg	12±1	12±1	15±1*	12±1	13±1	14±1	2 (−2 to 5)	−1 (−4 to 3)
Diastolic-SD, mmHg	11±1	10±1	12±1	11±1	12±1	11±1	2 (−1 to 5)	−1 (−4 to 2)
Heart rate, bpm	74±2	72±2*	78±2*	77±2	85±2*,‡	81±2*	9 (7 to 12)‡	1 (−2 to 3)
Night period[1]								
Systolic BP, mmHg	100±3	98±3	102±3	102±3	114±3*,‡,#	104±3#	14 (10 to 18)‡	1 (−4 to 5)
Diastolic BP, mmHg	62±2	60±2*	64±2	63±2	71±2*,‡,#	68±2*,#	11 (7 to 14)‡	3 (0 to 7)
Mean BP, mmHg	75±2	72±2*	77±2	76±2	85±2*,‡,#	80±2*,#	12 (9 to 15)‡	3 (−1 to 6)
Systolic-SD, mmHg	13±1	12±1	12±1	14±1	13±1	13±1	0 (−4 to 3)	0 (−4 to 3)
Diastolic-SD, mmHg	12±1	10±1*	10±1*	12±1	11±1	11±1	1 (−2 to 4)	1 (−2 to 4)
Heart rate, bpm	67±2	62±2*	63±2*	66±2	68±2‡	68±2*,‡,#	7 (4 to 11)‡	7 (3 to 11)‡

Values are presented as means ± SE and were obtained from multivariable regression analyses. All valid, single measurements obtained during the three 24-hours ambulatory blood pressure sessions were included in the regression analyses (a total of 4181 valid blood pressure measurements in 23 participants).

# $P<0.05$ for difference in night-day change between groups. N1 to N3, sleep stage 1 to 3; TST, total sleep time; REM, rapid eye movement; NREM, non-rapid eye movement; WASO, wake after sleep onset; BP, blood pressure; SD, standard deviation.

[1] Day- and night period was defined by the individual habit of each participant and was detected by the position sensor of the blood pressure device. Therefore, the night period started when a participant was in supine position for at least 2 consecutive blood pressure measurements. In the morning, the daytime period started when a participant was in standing or sitting position for at least 2 consecutive blood pressure measurements.

* $P<0.05$ vs. baseline.

‡ $P<0.05$ for difference in change to baseline between groups.

since evacuation or treatment according to international guidelines in case of cardiovascular events is impossible at Concordia and in many Antarctic stations, but also in other remote high-altitude environments.

The limitations of this study are to provide no additional measurements during acute (days) Antarctic exposure; no gold-standard polysomnographies to assess sleep stages[9] and additional cardiovascular risk factors, such as nocturnal arterial oxygenation or sleep-disordered breathing. However, the DREEM headband and algorithm have been validated against polysomnography[6] and showed good reproducibility between the two consecutive nights in this study, with mean differences (95%CI) in sleep stages 2 and 3 (%TST) of −0.2%TST(−3.4 to 3.0) and 0.9%TST(−1.9 to 3.6). Due to the small sample size, it was not feasible to investigate explanatory factors behind the observed findings. However, a strength of this study was to prospectively follow for 12 months the Antarctic coastal DdU crewmembers. This control group accounts for many confounding factors in Antarctica and allows underlining the effect of chronic hypoxic exposure in Concordia.

Overall, our data emphasize persistent cardiovascular stress in the presence of impaired sleep and of hypoxia over a 12-month duration. Based on our findings, randomized clinical trials investigating long-term preventive measures, e.g. oxygen or acetazolamide therapy,[10] against cardiovascular risk factors are warranted during long-term stays at Concordia.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2023.02.012.

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LETTER TO THE EDITOR

Ultrasound-guided needle aspiration biopsy of isolated anterior mediastinal masses

Dear Editor:

Isolated masses of the anterior mediastinum are most commonly expression of primary tumors such as lymphomas, thymomas, germ cell neoplasms, neurogenic tumors, and thyroid lesions.[1] Due to the histological complexity of the above disorders, they have been traditionally diagnosed with CT-guided biopsy performed by interventional radiologists or with surgical procedures.[2] However, when feasible, ultrasound-guided needle aspiration biopsy (US-NAB) offers several potential advantages among which real-time guidance, availability of oblique needle paths, possibility of carrying out the procedure at the bedside of critically ill patients who cannot tolerate the supine position, and reduced costs, deserve mention.[2] We aimed to assess the feasibility, diagnostic success, and safety of US-NAB of isolated anterior mediastinal masses (AMM) in the hands of pulmonologists.

We reviewed the US-NABs performed by pulmonologists for the diagnosis of isolated AMM during a 2-year period (2020-2021) at the Interventional Pulmonology Division of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS. The Institutional Review Board approved the research (ID 5037), and patients signed a written informed consent. Patients were eligible if they were 18 old and had indications for a tissue diagnosis of an isolated anterior mediastinal mass. Exclusion criteria were: i) unwillingness to consent; ii) platelet count $<$50.000 per μL; and iii) inability to stop anticoagulant or antiplatelet therapy before the procedure (except acetylsalicylic acid 100 mg/day). Demographic, clinical, imaging and pathological data were retrieved for each case. US-NABs were performed using a parasternal approach without any biopsy guide system ("free hand technique").[3] B-mode and color-doppler ultrasound study of the chest aimed at localizing the lesion and identifying a safe path for needle placement were always performed with both linear and convex probes before sampling. A 16G or 18G cutting needle needles (Biomol biopsy set, Hospital Service SPA, Rome, Italy) was used (Supplemental videos 1 and 2). After the procedure, all patients underwent an ultrasound examination to rule out pneumothorax and were observed for 2 hours prior to discharge. The primary endpoint was the diagnostic yield, whereas the secondary endpoints were feasibility of lesion sampling, and safety. Clinical and pathologic results are presented as standard descriptive statistics. Continuous variables are reported as mean $\pm$ standard deviation (SD), whereas categorical variables are given as percentages.

During the study period, 11 patients were evaluated and in 10 a US-NAB was attempted (91% feasibility); in the remaining patient the US evaluation did not show a safe path to the mass due to the interposition of the mammary vessels. Table 1 shows the main characteristics of patients and lesions. Patients were predominantly male (6/10) and middle-aged (mean $\pm$ SD= 47.7 $\pm$ 18). The lesion size was large both in short (median (IQR) mm = 61 (46.3-108.8)) and in long axis (median (IQR) mm = 108.5 (92-135.3)). A definitive diagnosis was obtained in 8/10 patients (80% diagnostic yield) in which US-NAB was attempted, lymphoma being the most common etiology by far (6/10, 60%). Of the 2 patients with a non-diagnostic procedure, one had a thymic carcinoma diagnosed with a surgical biopsy. In the other patient, US-NAB was used to diagnose an undifferentiated epithelial malignancy (Fig. 1G-I); the patient then underwent an anterior mediastinotomy, but even on the surgical specimen, which contained a vast necrotic component, a more specific diagnosis could not be obtained despite a very large immunohistochemistry panel. No patient in the present cohort developed complications after the US-NAB.

This study suggests that US-NAB of isolated AMMs can be performed safely and successfully by pulmonologists. In a literature review, we found only a handful of studies in which pulmonologists carried out US-NABs of AMMs, and in none was the inclusion limited to patients with isolated AMMs. In the landmark study, Saito et al. were able to obtain a definitive diagnosis in 69% of the patients, of whom 60% had a benign AMM.[4] Koegelenberg et al. achieved an excellent 93% diagnostic yield in a study cohort in which 62% of the patients had an anterior mediastinal metastasis from lung cancer.[5] A few more recent studies in which pulmonologists were likely to have been involved in the US-NAB procedure tend to confirm both feasibility and satisfactory success rate in the setting of AMMs of different etiology.[6,7]

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Table 1 Characteristics of patients and lesions.

No.	Sex	Age	Smoking	Lesion size short axis (mm)	Lesion size long axis (mm)	Needle size (gauge)	Final diagnosis
#1	M	46	Never	63	95	16	Diffuse large B-cell lymphoma
#2	F	31	Never	120	140	16	Diffuse large B-cell lymphoma
#3	M	19	Current	59	109	16	Diffuse large B-cell lymphoma
#4	M	40	Never	59	108	16	Diffuse large B-cell lymphoma
#5	M	38	Former	120	121	18	Epithelial malignancy NOS
#6	F	44	Never	42	56	16	Diffuse large B-cell lymphoma
#7	F	59	Current	115	350	18	Pulmonary adenocarcinoma
#8	M	79	Never	41	47	18	Small lymphocytic lymphoma
#9	M	71	Current	10	91	16	Thymic neuroendocrine tumor
#10	F	50	Former	90	150	16	Clear cell thymic carcinoma

The diagnosis of primary tumors of the anterior mediastinum with US-NAB pose challenges both from a technical and a pathological standpoint. From a technical perspective, the acoustic window between sternum and adjacent ribs needed to safely sample the mass is often minimal compared with the overall lesion size, and is partly occupied by the mammary vessels (Fig. 1). From a pathological standpoint, these tumors are histologically complex, often contain a massive

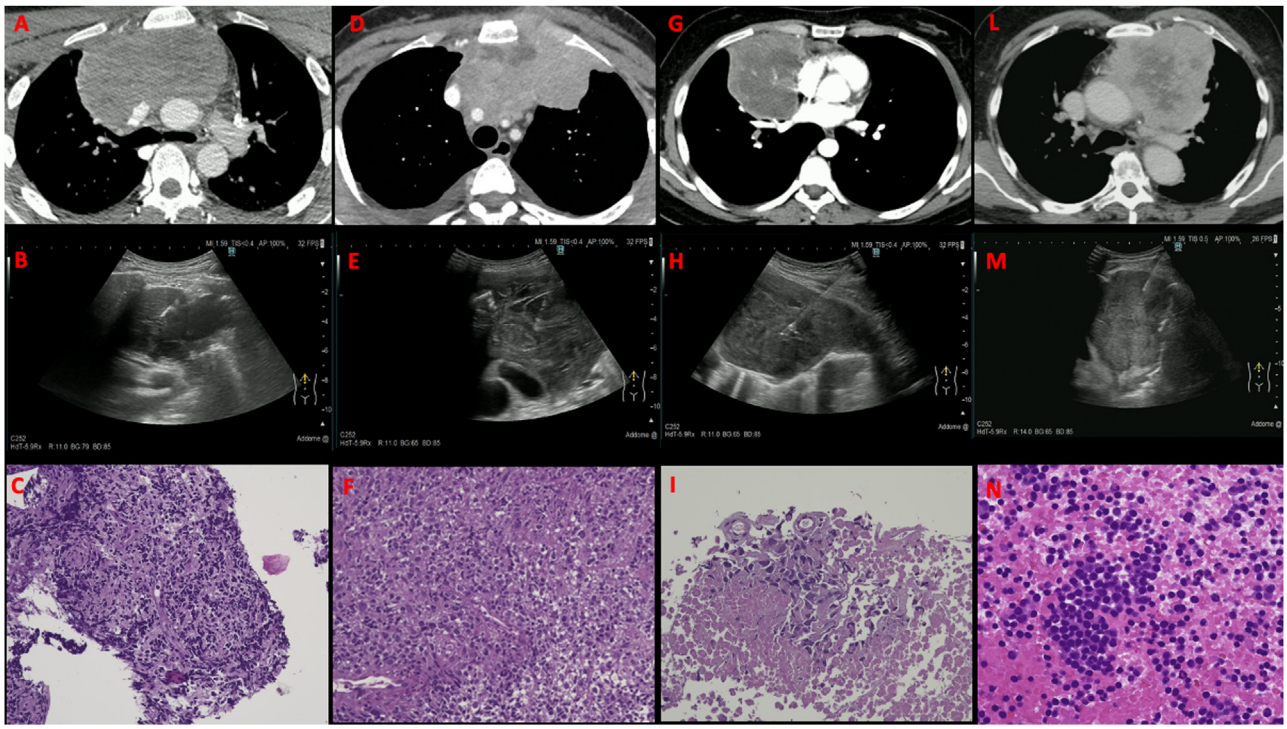

Fig. 1 Computed tomography, ultrasound image and corresponding histology of 4 cases of US-NAB of anterior mediastinal masses expression of diffuse large B-cell lymphoma (panels A-C and D-F), undifferentiated epithelial malignancy with massive necrotic component (panels G-I) and primary thymic neuroendocrine tumor (panels L-N).

necrotic component (Fig. 1G and 1L) and are more reliably diagnosed and subtyped -especially lymphomas and thymomas- when large biopsy samples are available. As a consequence, large cutting biopsy needles need to be used to achieve a satisfactory diagnostic success. A few of these lesions (Fig. 1A and 1D) might have been theoretically reached with a convex EBUS procedure, but the tissue cores obtained with EBUS-TBNA are often insufficient for the diagnosis of primary tumors of the anterior mediastinum. As for lymphomas, in particular, only 24% of subjects with *de novo* lymphoma were able to be appropriately subtyped using endosonographic specimens in one of the largest studies available in the literature.[8] Taking into account the technical and pathological challenges, we started our diagnostic invasive ultrasound-guided biopsy program for AMMs after an extensive experience with less complex US-NABs, such as those of pulmonary masses and "superficial" metastases.[9] In the last decade, different scientific societies have made recommendations about which topics to include in a structured thoracic ultrasound training curriculum.[10] Several theoretical and practical training courses exist, but they rarely involve ultrasound-guided interventions and present major challenges to education such as variable caseload, limited availability of expert supervision and different learning paces among trainees.[10] It is therefore unsurprising that studies have clearly demonstrated a lack of uniform, competency-based training programs and assessment tools in this setting.[11]

In conclusion, our pilot experience suggests that properly trained pulmonologists can safely and successfully diagnose isolated AMMs with US-NAB despite the technical challenges of the procedure and the pathological complexity of these lesions, that are usually expression of primary tumors. This would offer, whenever possible and safe, a less invasive and costly diagnostic alternative to procedures (anterior mediastinoscopy and CT-guided biopsy) currently used in this setting.

Conflicts of interest

None of the Authors has conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pulmoe.2022.10.007.

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LETTER TO THE EDITOR

Chronic thromboembolic pulmonary hypertension — the challenging approach of a young patient with distal disease

Dear editor,

Chronic thrombo-embolic pulmonary hypertension (CTEPH) is the consequence of fibrotic organization of unresolved pulmonary emboli and secondary microvascular remodeling, that can ultimately lead to right heart overload, failure and death.[1—4] It is associated with a high burden of disease with 5-year survival being reported as low as 10% for untreated patients.[5] Depending on the nature and location of the disease, surgical pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA) and pulmonary vasodilator therapy (PVT) should be considered for proximal, distal and microcirculation lesions, respectively.[1]

The authors report a successful case of BPA and PVT combined treatment in a young patient with predominantly distal CTEPH. A 35-year-old Caucasian male, with hypertension, former smoking history and recurrent deep vein thrombosis, was referred to our pulmonary hypertension (PH) dedicated center because of low-effort fatigue (WHO class III) and signs of right heart failure. He had no history of syncope. At the time of admission, he was under long-term oxygen therapy (LTOT) (8 h/day) and warfarin (which he was only compliant with only 8 years after the first DVT episode).

Initial evaluation was compatible with severe right chambers pressure overload and a high probability of pH (Fig. 1). Impaired functional capacity was also documented, with a 6 min walking test distance of 270 m (37% of the predicted value), additional oxygen desaturation (92% to 88%) and blood pressure fall (BP 96/55 mmHg to 77/50 mmHg). Due to high probability of pH, the patient was submitted to a right heart catheterization (RHC) that confirmed pre-capillary PH with multiple high-risk criteria (Table 1). CTEPH was diagnosed after the etiologic workup revealed multiple and bilateral perfusion defects in ventilation/perfusion scan; blood tests (including liver and thyroid function, serologies and autoimmunity) and pulmonary function test were normal. Screening for acquired or genetic thrombophilia was also negative. Computed tomography pulmonary angiography was highly compatible with CTEPH and revealed multiple bilateral segmental and mostly subsegmental pulmonary artery filling defects (Fig. 1).

Due to very distal disease (mostly affecting the subsegmental branches and microvasculature), the patient was considered inoperable by an expert and high-volume surgical center and medical therapy alone was proposed. Combined PVT was started with oral Bosentan and intravenous Epoprostenol delivered by a Hickman line. Switch to subcutaneous Treprostinil was motivated by a total thrombosis of the internal jugular vein (despite adjusted oral anticoagulation by the I.N.R.). Gradual switch to oral Selexipag was needed due to refractory pain in the injection site.

After 3 months under optimized PVT (Riociguat 2.5 mg t.i.d., Bosentan 125 mg b.i.d. and Selexipag 1600 μg b.i.d.) the patient retained several increased-risk criteria. Therefore, he integrated a BPA program of seven sessions (a total of 11 segments, 31 vessels). Follow-up performed at 6 months showed significant clinical improvement (WHO class I and suspension of LTOT), as well as right heart dimension and function on echocardiogram and only residual pH on RHC (Table 1).

CTEPH treatment is very complex and requires management by a multidisciplinary team.[1] PEA is the treatment of choice as it may cure the disease and effectively improve symptoms and survival (reported as >75% at 3 years).[1—3] However, since its feasibility depends on the nature and location of the lesions, it is only possible for fewer than 60% of cases[1,4,6] either because patients are technically inoperable (distal lesions not accessible by surgery) or because comorbidities impose a high surgical risk.[1] Furthermore, approximately 50% of operated patients maintain residual PH or have recurrent disease.[4] For inoperable patients, for those with residual or recurrent CTEPH after surgery and also for very distal disease, PVT is recommended to change the microvascular remodeling in response to obstruction, allowing symptom reduction and improvement in functional capacity.[1,2,4—6] Although targeting endogenous nitric oxide, prostacyclin and endothelin pathways may help improve symptoms

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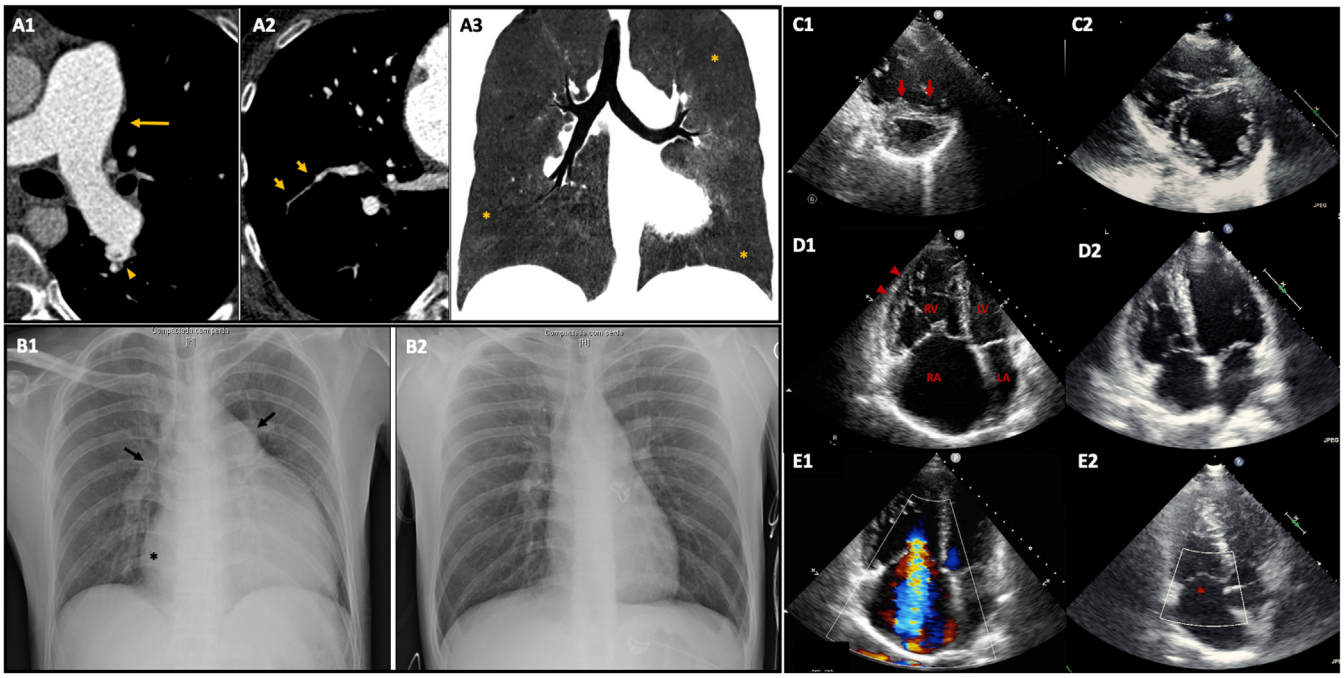

Fig. 1 Imaging findings before and after combined treatment with pulmonary vasodilator therapy and balloon pulmonary angioplasty.
Capture A: Vascular and pulmonary findings of chronic thromboembolism on CT pulmonary angiography. (A1) and (A2) Axial plane images reveal main pulmonary artery dilation (arrow), linear filling defects within pulmonary arterial vessels – webs (arrowhead), caused by residual thrombotic material, and bronchial arteries dilation followed by abrupt transition of size, irregularity and stenosis of multiple peripheral arteries (short arrows). (A3) Mosaic perfusion pattern (MinIP reconstruction image, coronal plane) defined by variable lung attenuation and due to heterogeneity of lung parenchyma, in which hypoperfused peripheral regions have low attenuation (*) compared to those of normal lung perfusion.
Capture B: Comparison of chest X-ray before and after treatment (B1 and B2, respectively). (B1) Severe cardiomegaly, dilation of the right atrium (*), dilation of the main pulmonary artery and right pulmonary enlargement (arrows). (B2) Almost normal chest x-ray after treatment.
Captures C to E: Comparison of transthoracic echocardiogram images before and after treatment (C1-E1 and C2-E2, respectively). (C1) End-diastolic short-axis view showing severe right ventricle (RV) dilation and interventricular septum deviation to the left caused by RV pressure overload (interventricular septal D-shape – short arrows), significantly impairing left ventricle diastolic filling. (D1) and E1) Apical four-chamber end-diastolic view (D) and Doppler mid-systolic image (E) showing initial dilated and hypertrophied RV (arrowheads), severely dilated right atrium (RA), associated with severe tricuspid regurgitation with an estimated PSAP of 88 mmHg. After treatment there was a significant decrease in right chambers' size with only mild tricuspid regurgitation and improvement of LV diastolic filling.

and haemodynamics in CTEPH patients, medical therapy alone does not cure the disease and these patients still have high mortality rates when compared to surgery.[5,6] Hence, percutaneous reperfusion of segmental and subsegmental lesions with BPA emerged as an option for patients unsuitable to surgery or with residual/recurrent disease after PEA.[1,2,5,6] Besides there is increasing evidence supporting its efficacy in improving symptoms, right heart function and haemodynamics,[1,2,5–7] increasing experience and refinement of the technique significantly reduced rates of severe complications related to BPA (such as reperfusion pulmonary edema, bleeding or wire injuries),[1] making its effectiveness comparable to surgery (2-year survival rate of 94.5% in a Japanese multicentric registry).[7] These results are reflected in the most recent European guidelines on pH, that increased BPA class of recommendation from IIb to I.[1]

A careful consideration of the patient age and functional status as well as lesion location and response to medical therapy seems particularly relevant as this disease is associated with a high morbidity, mortality and health related costs. This case is intended to reflect how a multimodality approach was essential to improve this young patient's quality of life and prognosis.

Table 1 Clinical, imaging and haemodynamic parameters before treatment initiation, 4 months after pulmonary vasodilators introduction, after 7 sessions of BPA (under triple PVD) and 6 months of follow-up (under triple PVD).

	Before treatment (April 2020)	4 months PVD (August 2020)	After BPA (7sessions) (June 2021)	6 months follow-up (under triple PVD) (October 2021)
WHO-FC	III			I
NTproBNP (pg/mL)	4087			135
6MWT (meters)	270	410	490	–
TT Echocardiogram				
TAPSE (mm)	11	14	20	–
FAC (%)	27,5	22,7	38,5	–
RA volume (mL)	171	191	53	–
cMRI				
RVEF (%)	17			
SVI (mL/m^2)	29,7			
RVESVI (mL/m^2)	203			
Right heart catheterization				
mRAP (mmHg)	12	12	3	7
mPAP (mmHg)	48	45	29	31
PAP/SAP ratio	0,56	0,40	0,23	0,32
PCWP (mmHg)	7	7	5	5
PA saturation (%)	40	63	70	77
PVR* (UWood)	21,84	10,11	5,59	3,91
PVR index (UWood/m^2)	13,24	6,36	3,39	2,20
SVR*(UWood)	39,43	26,88	28,4	13,85
PVR/SVR ratio	0,55	0,38	0,20	0,28
CO* (mL/min)	1,88	3,76	4,30	6,64
CI* (L/min/m^2)	1,14	2,37	2,61	3,73

CI – cardiac index; cMRI – cardiac magnetic resonance imaging; CO – cardiac output; FAC – fractional area change; mPAP – mean pulmonary artery pressure; mRAP – mean right atrial pressure; NTproBNP – N-terminal-pro-brain natriuretic peptide; PA – pulmonary artery; PCWP – post-capillary wedge pressure; PVR – pulmonary vascular resistance; RA – right atrium; RVEF – right ventricular ejection fraction; RVESVI – right ventricular end-systolic volume index; SAP – systolic arterial pressure; SVI – stroke volume index; SVR – systemic vascular resistance; TAPSE – tricuspid annular plane systolic excursion; TT – transthoracic; WHO-FC – world health organization functional class; 6MWT – 6 min walking test.

* Measurements performed by the Fick method.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.pulmoe.2023.03.001.

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LETTER TO THE EDITOR

Mepolizumab in severe asthma exacerbation in a respiratory ICU—a successful off-label use

Severe eosinophilic asthma is a clinical phenotype of asthma; the underlying mechanism is an eosinophilic inflammatory pattern in the airway, characterized by recurrent exacerbations and poor disease control. Both in atopic and non-atopic subphenotypes, IL-5 plays a major role across the pathway of eosinophilic inflammation.[1]

Pharmacological agents targeting IL-5 have shown to significantly reduce severe exacerbations and oral corticosteroids (OCS) use in severe eosinophilic asthma patients, particularly in those with higher eosinophilic count and a history of frequent exacerbations.[2,3] Mepolizumab is an anti-IL5 monoclonal antibody, approved as an add-on therapy in both allergic and non-allergic patients with severe eosinophilic asthma, and recommended on step 5 of the 2022 GINA guidelines.[4]

Despite the continuous decrease in asthma mortality, severe asthma exacerbations still represent the highest contribution for all-cause mortality during the first month following the event.[5]

Therefore, this report addresses a potential additional role of anti-IL5 in treating acute refractory severe asthma exacerbations and reduce its mortality. We report an off-label use of mepolizumab in a patient without previous maintenance treatment, during a life-threatening asthma attack.

A 25-year-old female presented to the emergency department complaining of severe dyspnea, wheezing and cough, with progressive worsening in the previous 4 weeks. The patient had history of allergic asthma without any maintenance therapy, having abandoned anti-asthmatic treatment during childhood. The patient did not mention any comorbidities, medication, or smoking habits, nor any asthma related exacerbations.

On admission the patient was restless, showing signs of respiratory distress, and decreased pulmonary sounds. Chest x-ray showed parenchymal hyperinflation with no signs of infiltrates. Blood gas assessment showed severe hypoxemia, normocapnia and no other alterations. Given the persistent signs of tachypnea, paradoxical breathing, and high oxygen requirements, the patient was promptly admitted to a respiratory ICU, and initiated on invasive mechanical ventilation. In the following hours the patient evolved with refractory bronchospasm and severe blood gas deterioration with pH 6.85 and carbon dioxide partial pressure ($PaCO_2$) 145 mmHg, under pressure-regulated volume control-mode (settings: tidal volume 380 mL; respiratory frequency 22 cycles per minute; positive end-expiratory pressure, PEEP 0 mmHg, inspiratory to expiratory ratio 1:4). Blood tests at admission and prior to corticosteroid administration revealed blood eosinophils of 11% (2680/μL) and no other alterations. In the subsequent days, and despite adjusted ventilatory settings, deep sedation, analgesia, muscle paralysis and anti-asthmatic and bronchodilator therapy [inhaled salbutamol (200 mcg q4h), ipratropium (80 mcg q4h) and beclomethasone (500 mcg q8h), IV methylprednisolone (125 mg q6h — withdrawal after 6 days), IV aminophylline (240 mg q12h), IV magnesium sulphate (2 g q12h), IV salbutamol (5—10 mcg/min intermittently during 3 days), IV ketamine (0.5—1.25 mg/kg/h intermittently during 5 days)], mechanical ventilation remained a challenge, considering dynamic hyperinflation, high auto-PEEP values (maximum 12 cmH2O), and high peak inspiratory pressures. No CT scan or bronchoscopy was performed in the acute phase due to the hemodynamic instability and the absence of infiltrates in the chest x-ray. Eosinophilic granulomatosis with polyangiitis (EGPA) was not fully ruled out; however, no symptoms of ear, nose, and throat involvement nor systemic vasculitis manifestations were present, and serum cANCA were negative.

On the 4th day of ventilatory support,100 mg mepolizumab was administered subcutaneously, as an off-label last-resort attempt to recover from the critical ventilatory state. After 48 h of mepolizumab injection, we observed a clinical improvement, normalization of $PaCO_2$, peak pressures, and residual auto-PEEP. Then, the patient started IV corticosteroids tapering, and was weaned from mechanical ventilation and extubated on the 11th day of ventilation. No minor or serious adverse effects were registered. The timeline of the patient's clinical evolution is shown in Fig. 1.

The patient was discharged from the ICU after 19 days. At 1-month follow-up, systematic assessment revealed variable airflow limitation with a FEV_1 of 72% (2410 mL) and FVC of 89% (3420 mL), a positive post-bronchodilation test, with FEV_1 reaching 82% (2760 mL), high serum total IgE levels 650 IU/mL, high fraction of exhaled nitric oxide (FeNO) 56 ppb, and sensitization to house dust mites. Eosinophilic count was depleted (1% — 100/μL), and thoracic and sinus CT were normal. Clinical improvement was documented through validated quality-of-life questionnaires related to rhinitis — Self Assessment of Allergic Rhinitis and Asthma (SACRA) and asthma — Asthma Quality of Life Questionnaire (AQLQ). The Asthma Control Test at 1-month follow-up

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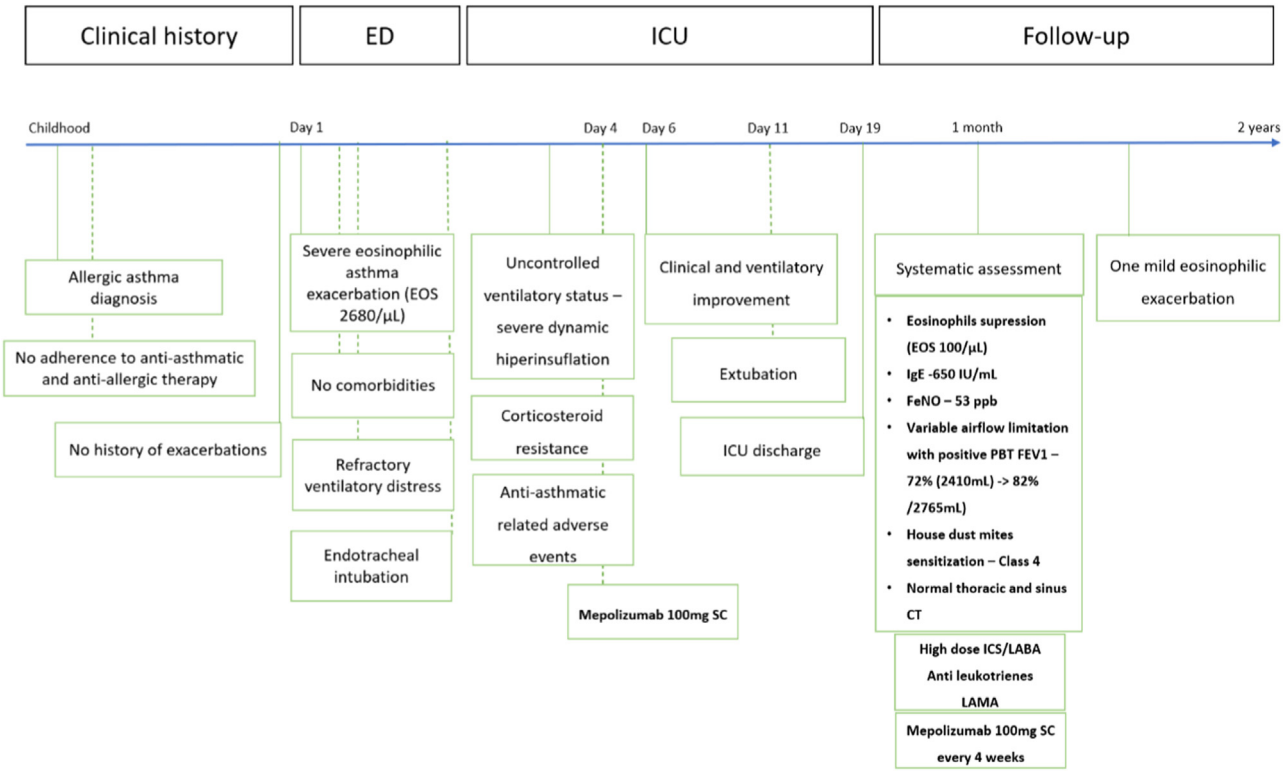

Fig. 1 Case report timeline following the CARE guidelines.
Abbreviations: EOS — eosinophils; CT — computerized tomography; ED — emergency department; ICU — intensive care unit; FeNO — fraction of exhaled nitric oxide; FEV1 — forced expiratory volume in first second; PBT — post bronchodilation test; SC — subcutaneous; ICS — inhaled corticosteroid; LABA — long-acting beta-agonist; LAMA — long-acting muscharinic antagonist.

documented symptomatic improvement (ACT-19). The patient maintained follow-up at the severe asthma outpatient clinic, and has been under inhaled treatment with high dose ICS/LABA, LAMA, anti-leukotrienes and mepolizumab for two years, with present adequate asthma control (ACT-22) and only one documented mild eosinophilic exacerbation.

Although its outcomes have been studied for medium/long term, pharmacokinetic studies with mepolizumab identified pronounced and maximal reductions in eosinophil count 3—4 days after infusion and estimated at ~85% relative to baseline, with a single administration.[6,7] This short-term benefit, together with a vast local and multicenter experience regarding its safety and effectiveness as a corticosteroid-sparing agent, guided its choice over other anti-IL5 agents.[3]

Other studies have previously reported the use of mepolizumab, reslizumab and omalizumab in severe asthma exacerbations, also with similar degrees of success.[8—10] Benralizumab, a monoclonal antibody against IL5—Rα, has also proven to induce a rapid response to treatment during exacerbations of severe asthma, with peak flow improvements after four days of administration,[11] eosinophil count suppression, and 19% increase in FEV_1 after 48 h.[12] We posit that, in this case, the observed objective improvement in the ventilatory mechanic pressures 48 h after mepolizumab can be interpreted as an equivalent outcome.

Starting mepolizumab during an exacerbation and continuing it after follow-up assessment represented a unique approach, with short and long-term benefits. The early response to mepolizumab proved to be crucial in limiting the eosinophilic inflammatory pathway, allowing for a faster corticosteroid withdrawal, and being of paramount importance in reversing a critical ventilatory state, refractory to high dose corticosteroids and bronchodilators. Its off-label use has also revealed a good safety profile.

The main limitation of our case is the deficient phenotype assessment of the previous asthma diagnosis. We also could not fully rule out other diagnoses of eosinophilic also disorders such as EGPA; however, mepolizumab 100 mg every 4 weeks has also been shown to be effective in controlling respiratory manifestation of EGPA.[13]

This case supports the hypothesis of a novel role for mepolizumab in acute settings in refractory severe exacerbations of eosinophilic asthma.

Ethical considerations

Written permission for off-label use was obtained from the legal representative of the patient.

This study was retrospectively approved by the Institutional Ethic Committee.

Informed consent

Appropriate written informed consent was obtained from the patient for the publication of this case report.

Conflicts of interest

The authors declare to have no conflict of interest directly or indirectly related to the manuscript contents.

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LETTER TO THE EDITOR

Effect of elexacaftor–tezacaftor–ivacaftor modulator on lung structure in cystic fibrosis

Cystic fibrosis (CF) is a genetic disease caused by mutations in the CFTR (CF transmembrane conductance regulator) gene[1] and characterized by morbidity and mortality primarily related to progressive lung disease.

Over the last decade, modulators correcting CFTR protein folding, processing and trafficking to the cell membrane were developed to improve CFTR function.[2]

Recently, the triple combination of two CFTR correctors (tezacaftor and elexacaftor) and a CFTR potentiator (ivacaftor) showed exceptional effectiveness in people with CF homozygous for the Phe508del mutation.[3,4] A large multicentre phase 3 trial demonstrated clinically significant improvements in lung function within 4 weeks of beginning of elexacaftor–tezacaftor–ivacaftor (ELX/TEZ/IVA) combination and significant improvement in body mass index (BMI), CF quality of life scores and sweat chloride (SwCl) concentration.[4]

Between February and April 2021, three Phe508del homozygous patients with CF were started on ELX/TEZ/IVA following the approval by European Medicines Agency (EMA). All three were previously on CFTR modulator therapy with lumacaftor–ivacaftor (LUM/IVA), the first combination of a CFTR corrector (lumacaftor) and potentiator (ivacaftor) approved for Phe508del homozygous patients in 2015. The impact of ELX/TEZ/IVA on lung morphology was assessed by chest magnetic resonance imaging (MRI) before and 21–22 weeks after initiation of therapy. MRI T2-weighted sequences and T1-weighted sequences were acquired using a clinical 1.5T MRI scanner (Philips Ingenia; Philips Healthcare, Best, Netherlands) and images were assessed for abnormalities in lung morphology using a dedicated morphology MRI score.[5] Data on lung function (i.e. spirometry), nutritional status (BMI), SwCl concentrations and exacerbations before and 24 weeks after the initiation of ELX/TEZ/IVA were also collected from clinical records. In particular, the median forced expiratory volume in the first second (FEV_1) and BMI and the mean number of pulmonary exacerbations requiring antibiotics or hospitalization were calculated from the values recorded over the 24 weeks before and after the treatment.

Median age of patients was 17.8 years (range 16.4–35 years), all patients were males and pancreatic insufficient. Median FEV_1 was 31.6% predicted (range 68.1–30.6% predicted) and median BMI 20.2 $kg{\cdot}m^{-2}$ (range 13.8–21.4 $kg{\cdot}m^{-2}$). Baseline mean SwCl concentration was 58.9 ± 14.7 $mmol{\cdot}L^{-1}$. Due to pulmonary exacerbations, patients had a mean of 4.6 ± 2 antibiotic courses and a median of 2 hospitalizations (1-4) in the previous 24 weeks before starting ELX/TEZ/IVA.

At baseline, MRI showed morphological abnormalities such as bronchiectasis, bronchial wall thickening, mucus plugging and pleural effusion (Fig. 1), resulting in a mean MRI morphology score of 14.7 ± 5.5.

Twenty-four weeks after treatment with ELX/TEX/IVA, median improvement of FEV_1 was 15.1% percentage points (range 7.7–36.8%) (median FEV_1 post treatment: 67.4% predicted, range 46.7–75.8%). BMI also improved with a mean increase of 1.93 ± 0.95 $kg{\cdot}m^{-2}$ (median BMI post treatment 21.8 $kg{\cdot}m^{-2}$, range 16.8–22.6 $kg{\cdot}m^{-2}$). Mean SwCl was 44.3 ± 21.2 $mmol{\cdot}L^{-1}$. Infective exacerbations reduced in frequency with only one exacerbation in one patient requiring a 15-days course of oral antibiotics. ELX/TEX/IVA treatment was generally well tolerated.

After 21–22 weeks of treatment with ELX/TEX/IVA the MRI morphology score was reduced to 4 ± 1 with drastic decrease of lung consolidations and reduction of bronchial wall thickening. Complete resolution of tree-in-bud nodules and pleural effusion was observed in one patient (patient C). In all three cases, bronchiectasis were unchanged in extent and size.

After initiation of ELX/TEX/IVA, Phe508del homozygous patients with CF showed an overall clinical improvement as demonstrated by FEV_1, BMI, exacerbation rate and SwCl concentration, and MRI detected an evident favourable evolution in lung structure and morphology.

Interestingly, all patients had been on CFTR modulator therapy with LUM/IVA for a mean of 44 ± 8.5 months. This modulator has been associated with positive effects in terms of lung function, BMI and number of exacerbations[6] and with significant changes in lung perfusion and morphology in terms of reduction in pleural reactions[7]. The further clinical benefits and the improvement in consolidations and airway wall thickening observed in these three patients with the triple combination of ELX/TEZ/IVA highlight the clinical meaning of this novel disease-modifying therapy in patients homozygous for Phe508del.

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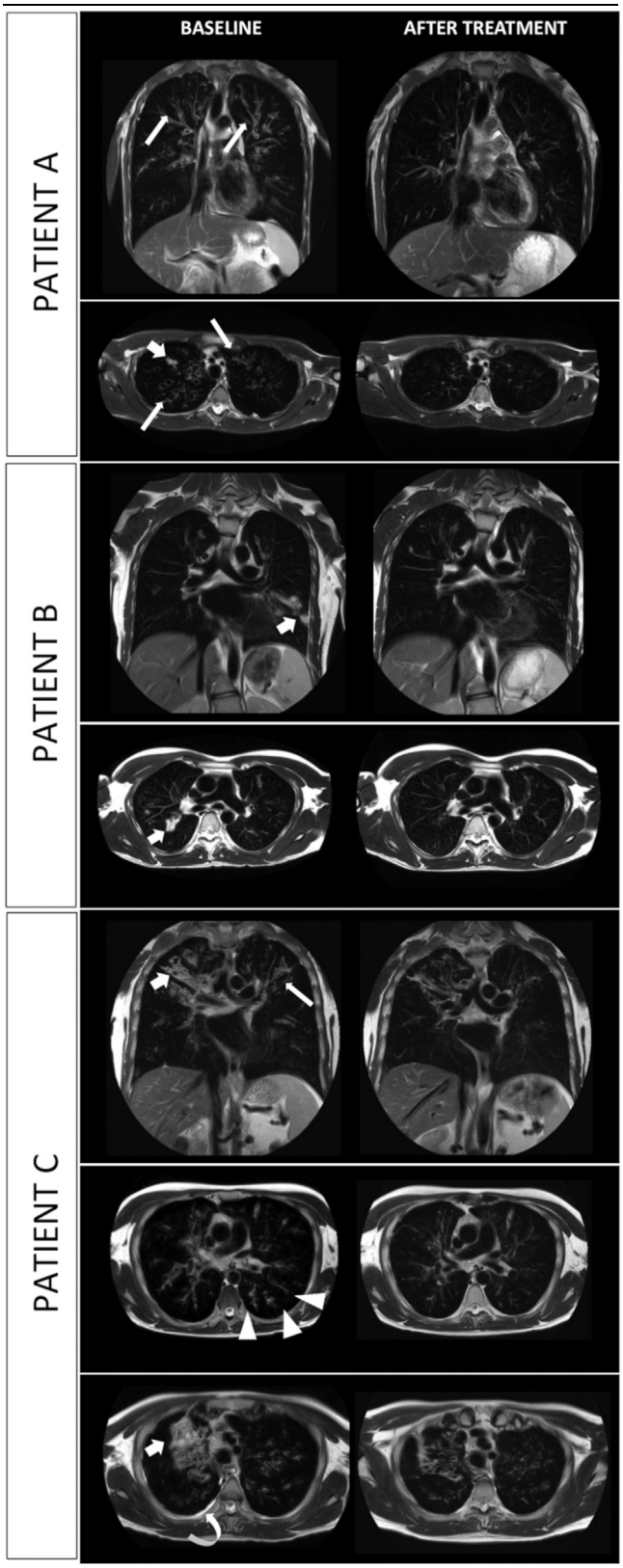

Fig. 1 MRI scans of three consecutive patients (A. 18-y-o boy; B. 17-y-o boy; C. 35 y-o man); T2-weighted images on coronal and axial plane are shown. Evolution of most common lung alterations before (left column) and after (right column) initiation of treatment with elexacaftor-tezacaftor-ivacaftor. In every scenario lung consolidation either drastically decreased in extension or completely resolved. Bronchial wall thickening is widely reduced. Tree-in-bud nodules and pleural effusion disappeared (shown in patient C). Bronchiectasis are unchanged in extent and size. *Fat arrow*: parenchymal consolidation; *thin arrow*: bronchial wall thickening; *arrow-head*: tree-in-bud appearance; *curved arrow*: pleural effusion.

However, not all people with CF are current candidates for CFTR modulators due to young age or CFTR mutation. Early use of modulators, possibly at time of diagnosis, but also close monitoring and optimal CF care of those waiting for the eligibility are essential to prevent irreversible lung abnormalities.

MRI is a radiation-free imaging technique and a viable alternative to computed tomography. Over the last decade there is increasing evidence that this method can detect subtle changes in lung structure in CF disease. An increasing number of people with CF are now treated with the highly effective therapy of modulators and in these patients MRI may be a sensitive measure to assess early response to treatment and follow-up CF progression.[7,8]

Ethics Statement

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Ethic Committee Az. Ospedaliera-Universitaria di Parma (407/2022/OSS/AOUPR). All adult participants provided written informed consent to participate in this study.

Declaration of Competing Interest

Authors have no conflict of interest.

CRediT authorship contribution statement

V. Fainardi: Conceptualization, Writing – original draft, Data curation, Writing – review & editing, Validation. **K. Skenderaj:** Formal analysis, Data curation, Investigation, Writing – review & editing, Validation. **A. Ciuni:** Data curation, Investigation, Formal analysis, Visualization, Writing – review & editing, Validation. **S. Esposito:** Supervision, Writing – review & editing, Validation.
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LETTER TO THE EDITOR

Correspondence: "The One Health concept applied to dirofilariasis—a zoonotic disease"

To the Editor,

We have read with interest the paper by Silva et al.[1] "human pulmonary dirofilariasis: a pitfall in solitary pulmonary nodule".

After careful analyses, we would like to comment on certain statements from the article.

In this paper authors report the case of a 38-year-old man who presented to the emergency department with face edema, eosinophilia (2000/uL) and a chest X-ray showing a small peripheral solitary lung nodule on the right lung. Postoperative histopathological diagnosis was consistent with a central zone of necrosis surrounded by granulomatous inflammation and a fibrous wall. Besides that, a filarial worm was found in the lumen of an artery within the area of necrosis containing remnants of *Dirofilaria immitis*.

The zoonotic implication of *Dirofilaria* spp. infections is important since shortly after the inoculation of stage 1 larvae (L1) by vector mosquitoes, there is the possibility of larval migration along human tissues.[2] This can provoke ocular, skin and pulmonary nodular lesions, which are frequently and erroneously diagnosed as pulmonary carcinomas.[2] Moreover, the diagnosis of malignant neoplasm requires invasive procedures before reaching the correct diagnosis.[2]

The paper by Silva et al.[1] caught our attention as, upon biopsy, the morphological identification of dirofilariae parasites can be difficult to obtain, due to a loss of parasite integrity after tissue excision with consequent underdiagnosis, and a diagnosis based solely on the histological features only allows the determination of the genus *Dirofilaria*.[3] In addition, there are confirmed *Dirofilaria* spp. circulating in Portugal, namely *Dirofilaria repens*,[4] which has been reported to cause human pulmonary dirofilariasis with nodules that can be mistakenly diagnosed as malignant.[5] Noteworthy, Ferrari et al.[5] have reached definite diagnosis by multiplex-PCR targeting mitochondrial cytochrome oxidase subunit I gene (mtDNA cox1).

Determining *Dirofilaria* spp. based solely on histological diagnosis is yet to be confirmed and, when the parasite's DNA extraction is possible, the methods of molecular diagnosis based on sequencing can play a fundamental role in the identification of the etiological agent involved.[2] Hence, we would like to highlight the diagnostic accuracy of PCR followed by dideoxy chain termination sequencing as a valuable and affordable method to confirm worm species.

Dirofilariasis/dirofilariosis is not difficult to treat when diagnosed with accuracy; however, it remains an underdiagnosed infection and disease because of the complexity in identifying the parasites involved. The use of molecular biology techniques to detect and identify them is likely to overcome the complexity associated to the diagnosis.[3]

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PHOTO

Mediastinal cavernous hemangioma with concurrent primary lung adenocarcinoma

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Cavernous hemangiomas of the mediastinum (CHM) are widely recognized as a rare congenital vascular-related tumor and are pathologically formed from variable-sized masses by dilated cavernous sinuses.[1] They have an incidence rate of less than 0.5 % of all diagnosed mediastinal neoplasms.[2] There are no previous reports of a CHM case with a concurrent primary lung carcinoma.

Here, we reported an unusual CHM with an associated primary lung carcinoma and a unilateral pleural effusion. A 59-year-old female, presented to our outpatient clinic with complaints of progressive cough. Chest-enhanced computed tomography (CT) showed a ground-glass nodule in the right upper lobe, as well as a heterogeneous high-density mass in the posterior mediastinum and a small right pleural effusion. One month later, the patient was admitted with mild wheezing. Chest magnetic resonance imaging (MRI) revealed a posterior mediastinal mass with low signal on T1WI, high signal on T2WI, and significantly high diffusion-weighted magnetic resonance imaging (DWI) signal. The previously identified right-sided pleural effusion increased at the time of admission. The patient underwent a right upper lobectomy and resection of the posterior mediastinal mass. Postoperative pathology diagnosed lung adenocarcinoma in the apical segment of the right lung (Fig. 1. D-F), while the size of posterior mediastinal mass was 3 cm × 2.2 cm × 1.5 cm, with a grey-brown surface and an encapsulated spongy dark red solid component (Fig. 1. A). Light microscopic examination of the posterior mediastinal mass demonstrated numerous ectatic vascular sinusoids filled with red blood cells and lined with endothelium. These vascular sinusoids were heterogeneously distributed throughout the spongy tissue. In addition, peripheral lymphoid hyperplasia was observed (Fig. 1. B-C). Immunohistochemistry revealed CD34 (+), CD31 (+), S100 (-), SMA (+), and Ki67 (+ > 1%). A final diagnosis of CHM with concurrent lung adenocarcinoma T1cN0M0, stage IA, was made. The patient was discharged seven days postoperatively, with no evidence of recurrence at a 22-month follow-up visit.

In conclusion, CHM should be taken into consideration if a patient presents with a mediastinal lesion which shows angioma-like enhancement on contrast-enhanced CT scan, or high signal on T2WI and DWI. CHMs may complicate with unilateral pleural effusions. The presence of coexisting intrapulmonary lesions, particularly lung cancers, needs to be investigated in these patients.

Ethics approval

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice. The study was approved by Tianjin Chest Hospital Ethics Committee.

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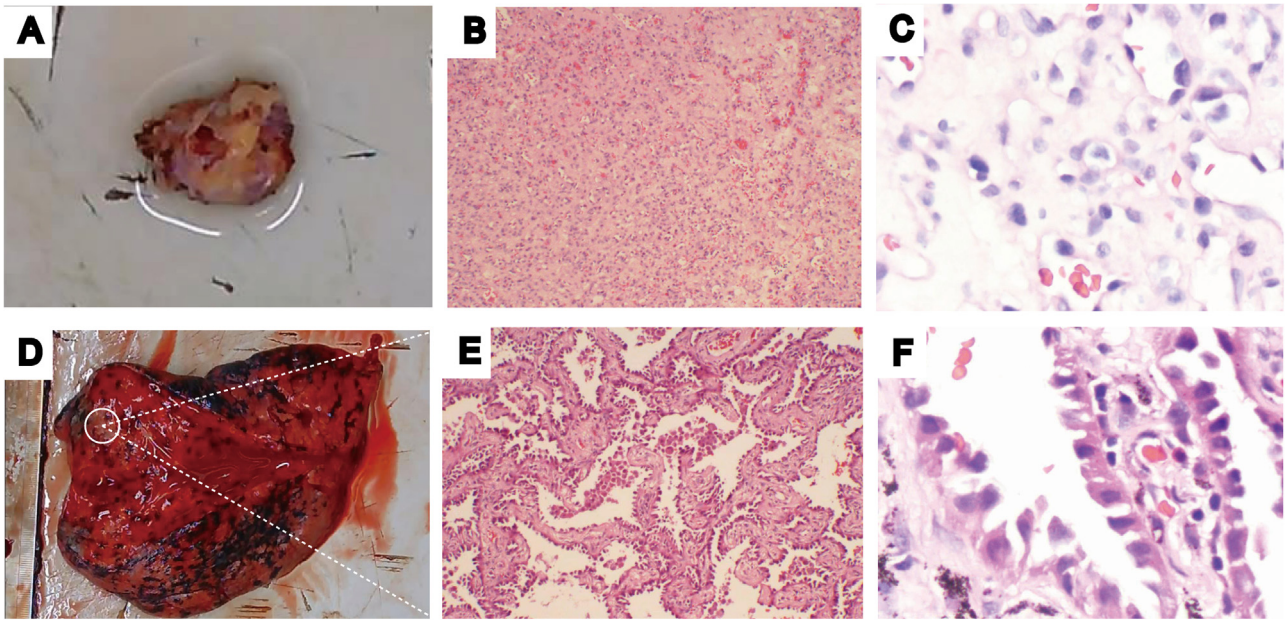

Fig. 1 Macroscopic photograph demonstrating (A) a soft irregular mass consisting of a grey-brown surface and an encapsulated spongy solid with an abundance of blood vessels (D), and a white nodule in the apical segment of the right lung; (B) Medium-powered microscopic view revealing a tumor composed of ectatic vascular sinusoids and lymphoid aggregates. Blood clots can also be seen in dilated vascular lumens (Hematoxylin and eosin stain, 100 x); (C) High-powered microscopic view revealing endothelial cells lining red blood cell-containing vascular lumens. The blood vessels are rich and the lumens are variable in size (Hematoxylin and Eosin stain, 400 x); (E) Medium-powered microscopic view showing a large population of heterogeneous tumor cells arranged in nested/papillary patterns, consistent with an invasive adenocarcinoma (Hematoxylin and Eosin stain, 100 x); (F) High-powered microscopic view revealing mostly adherent adenocarcinoma tumor cells (Hematoxylin and eosin stain, 400 x).

Ethical considerations

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

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during the study are included in the published article.

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Authors' contributions

L.Y., J.L., and J.W. participated in the design of the study. J. L., and J.W. analyzed imaging data. L.Y. wrote the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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