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Future research questions for improving COPD diagnosis and care

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Future research questions for improving COPD diagnosis and care

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Editorial: Future research questions for improving COPD diagnosis and care

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Editorial on the Research Topic
Future research questions for improving COPD diagnosis and care

Introduction

The prevalence and burden of chronic obstructive pulmonary disease (COPD) remain on the rise, especially with an increasingly aging population and the relative advancement in healthcare delivery systems. Over the last two decades, our knowledge and understanding of the different aspects of this heterogenous disease have evolved but key challenges in management still exist including earlier diagnosis, reducing exacerbation frequency, and identifying and managing commonly overlooked comorbidities, among others (1). This Research Topic brings together established experts and emerging future leaders to describe future research questions aiming at improving COPD diagnosis and care.

The Research Topic articles

In the past, it was thought that COPD was a disease that mainly affects elderly men given the higher prevalence of smoking compared to women. However, as more women are currently smoking, the prevalence of COPD among women may now surpass that of men. In the current topic, Milne et al. provide a concise review discussing sex differences in COPD from biological mechanisms to therapeutic considerations. Sex differences in the lungs' and the airways' structure are the main mechanisms behind differences in symptoms, resting, and exertional functional measurements.

COPD remains underdiagnosed with symptoms commonly attributed to aging, deconditioning, or concomitant cardiac diseases. This can be especially problematic given the high prevalence of cardiac diseases, in addition to smoking being an important common risk factor for both conditions. Beyer et al. conducted a prospective pilot study of the prevalence of chronic respiratory disease and the relation between the clinical and lung function profiles among non-cardiac symptomatic patients. Those with

abnormal lung function tests (14% of participants) reported dyspnoea that was relatively persistent over a follow-up period of 3 months. This highlights the important role of primary care in early identification and discerning of chronic respiratory disease especially with the aid of simple office spirometry. However, even with good-quality spirometric testing, early disease diagnosis could be missed considering the fact that pathological changes in COPD commonly affect the small airways, the so-called "silent zone" (2). In this regard, Liwsrisakun et al. attempted to explore the role of impulse oscillometry (IOS) and spirometry in COPD, and asthma. They showed higher sensitivity of IOS in assessing small airway dysfunction (SAD) among patients with normal FEV_1/VC while spirometry was found more sensitive in those with reduced FEV_1/VC. In line, integral to COPD management is the delivery of bronchodilator agents capable of deposition in the small airways. However, inhaler type can impact the efficacy of the treatment. Erdelyi et al. conducted a pilot study comparing drug delivery in two low-resistance inhaler devices utilizing numerical modeling in stable and exacerbated patients with severe COPD. Pulmonary deposition was around 10% superior with the use of the soft mist inhaler device compared with the 2 pMDI devices, and notably, no significant difference was observed in pulmonary deposition between stable vs. exacerbated states of COPD. These findings bring to attention the importance of personalizing inhaler prescriptions in COPD.

The ROME proposal has outlined a new approach to define and grade COPD exacerbations (E-COPD) with more focus on objective measures (3). In this Research Topic, a review by Coutu et al. focused on the utility of remote patient monitoring not only for exacerbation detection but also for monitoring diagnostic/treatment-related parameters and aiding delivery of care in stable COPD patients with more efficient proactive management. The prevention of exacerbations is a culprit risk reduction goal in COPD management, given that E-COPD is associated with a rapid progression of disease, decline of functional capacity, and increased risk of mortality. Multiple interventions have proved helpful in reducing E-COPD including vaccinations, inhaled pharmaco-therapies, and long-term Azithromycin (4). In a multicentre prospective study, Cuevas et al. probed into the functional and systemic effects of Azithromycin in frequent COPD exacerbators. They showed notable improvement in gas exchange at rest and with exercise. Also, baseline serum and sputum interleukin-8 elevation were found to be independently predictive of therapeutic response. It is worth noting that long-term azithromycin therapy was associated with a change in the pattern of microorganism isolates to more pathogenic bacteria, a finding that was previously described and worth balancing when considering offering such a treatment option (5). Distinguishing pneumonic and non-pneumonic E-COPD bears important treatment and prognostication implications. In the context of a quite similar presentation and limited sensitivity of the conventional chest x-ray, biomarkers can play an important role (6). In the BioInflame study, a set of plasma biomarkers was investigated for utility in identifying E-COPD and community-acquired pneumonia (CAP) (Jung et al.). Results showed that interleukin-6, neutrophil gelatinase-associated lipocalin and resistin are suitable markers for discrimination between E-COPD and CAP. These findings warrant validation in a larger cohort to deliver more evidence for implementation in clinical settings. In the same context, Amado et al. provided the first evidence of reduced levels of circulating MOTS-c and increased levels of Romo1 in patients with stable COPD; these micropeptides were associated with oxygen desaturation and reduced exercise capacity.

COPD is among the most common causes of hospital and intensive care unit (ICU) admissions, which puts a lot of burden on the patients and healthcare system alike. Cheng et al. shed light on different predictors of prolonged ICU stay among a large cohort of COPD patients. Including a comprehensive set of variables, they have created a normogram that can be applied for prognosticating and helping management guidance in the ICU setting. In this Research Topic, Ling et al. also reported a significant negative correlation between human serum albumin and in-hospital mortality in critically ill patients with COPD.

COPD management not only entails treating the obvious respiratory illness but should also encompass detailed phenotyping of patients as well as identifying and managing the associated comorbidities. Kaenmuang et al. investigated the prevalence, predictors, and progression of osteoporosis - as well as its treatment efficacy over 12 months. They showed an osteoporosis prevalence of 31.5% associated with elevated C-reactive protein levels and lower body mass index. Suffering from an exacerbation in the previous year was associated with almost two times increased odds of osteoporosis. These results shed light on an important commonly "silent" comorbidity that can be associated with a more complicated course of COPD (7). Obstructive sleep apnoea (OSA) is also a common association with COPD. Landete et al. identified overlap syndrome (i.e., OSA plus COPD) in 51% of their sample, which was associated with larger left carotid atherosclerotic plaques, putting patients at higher risk for developing cerebrovascular stroke.

Conclusion

COPD is one of the most common respiratory diseases with significant morbidity and mortality worldwide. Earlier diagnosis will permit the introduction of more cost-effective and relevant therapeutic interventions with improved patient outcomes and less economic burden. This Research Topic describes the cutting-edge understanding of sex differences in COPD, common comorbid conditions associated with COPD, novel diagnostic and prognostic tools, and updates in treatment and preventive pharmacotherapy.

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Circulating levels of mitochondrial oxidative stress-related peptides MOTS-c and Romo1 in stable COPD: A cross-sectional study

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Background: MOTS-c and Romo1 are mitochondrial peptides that are modulated by oxidative stress. No previous studies have explored circulating levels of MOTS-c in patients with chronic obstructive pulmonary disease (COPD).

Methods: We enrolled 142 patients with stable COPD and 47 smokers with normal lung function in an observational cross-sectional study. We assessed serum levels of both MOTS-c and Romo1 and associated these findings with clinical characteristics of COPD.

Results: Compared with smokers with normal lung function, patients with COPD had lower levels of MOTS-c ($p = 0.02$) and higher levels of Romo1 ($p = 0.01$). A multivariate logistic regression analysis revealed that above-median MOTS-c levels were positively associated with Romo1 levels (OR 1.075, 95% CI 1.005–1.150, $p = 0.036$), but no association was found with other COPD characteristics. Below-median levels of circulating MOTS-c were associated with oxygen desaturation (OR 3.25 95% CI 1.456–8.522, $p = 0.005$) and walking <350 meters (OR 3.246 95% CI 1.229–8.577, $p = 0.018$) in six-minute walk test. Above-median levels of Romo1 were positively associated with current smoking (OR 2.756, 95% CI 1.133–6.704, $p = 0.025$) and negatively associated with baseline oxygen saturation (OR 0.776 95% CI 0.641–0.939, $p = 0.009$).

Conclusions: Reduced levels of circulating MOTS-c and increased levels of Romo1 were detected in patients diagnosed with COPD. Low levels of MOTS-c were associated with oxygen desaturation and poorer exercise capacity using 6 min walk test. Romo1 was associated with current smoking and baseline oxygen saturation.

Trial registration: www.clinicaltrials.gov; No.: NCT04449419; URL: www.clinicaltrials.gov. Date of registration: June 26, 2020.

KEYWORDS

COPD, MOTS-c, Romo1, exercise capacity, oxidative stress

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is one of the leading causes of mortality worldwide (1). Oxidative stress (OS) is one of the most important factors contributing to the pathogenesis and severity of COPD (2, 3). COPD is a heterogeneous disease with several potentially treatable traits that have been associated with disease prognosis (4) including muscle weakness (5), reduced exercise capacity (6), and increased oxygen desaturation (OD) during exercise (7). While several biomarkers of OS have been evaluated in COPD (8, 9), none are evaluated on a routine basis.

Mitochondrial open reading frame of the 12S ribosomal RNA type-c (MOTS-c) is a recently discovered micropeptide encoded by the mitochondrial genome. MOTS-c is produced primarily in mitochondria-rich tissues, including skeletal muscle (10). MOTS-c has also been detected in peripheral blood and has thus been tentatively identified as a circulating myomitokine (11). While circulating MOTS-c penetrates target cells rapidly, its mechanism of entry remains unknown (11). Receptors for the hormonal mitokine, humanin, have already been described; by contrast, no receptors have been identified that interact specifically with MOTS-c. *In vitro*, MOTS-c is detected primarily in the mitochondria; production is induced in response to glucose restriction (10) or OS (12). MOTS-c activates sarcoplasmic adenosine monophosphate-activated protein kinase (AMPK) and is then translocated to the nucleus, where it binds to antioxidant response element sequences in the promoter regions of nuclear factor erythroid 2-related factor 2 (NRF2) and other transcription factors, thereby modulating target gene activity (12). Results of recent research reveal that circulating levels of MOTS-c increase with acute intense exercise but decline in association with increasing age as well as obesity, coronary disease, diabetes mellitus, and kidney failure (13).

Reactive oxygen species modulator 1 (Romo1) is a redox-sensitive protein located in the inner mitochondrial membrane that regulates the integrity of mitochondrial cristae and mitochondrial shape under conditions of OS (14). Of note, defective cristae, abnormal branches, and swollen and fragmented organelles are frequently observed in respiratory epithelial cells isolated from COPD patients (3).

To the best of our knowledge, there are no previously published studies that document serum MOTS-c levels in patients diagnosed with COPD or smokers without COPD. On the other hand, the results of one small study documented higher serum Romo1 levels in COPD patients ($n = 49$) compared to healthy volunteers not matched by smoking status ($n = 39$) and a negative correlation between Romo1 levels and forced expiratory volume in the first second (FEV1) (%), but exercise capacity was not evaluated (15). Although MOTS-c and Romo1 are mitochondrial peptides, and are associated with chronic diseases, they have not been measured together before.

We hypothesized that, because of low exercise capacity and high OS characteristic of COPD, serum levels of both MOTS-c and Romo1 would be altered. We also hypothesized that circulating levels might be associated with specific outcomes of this disease, for example, exercise capacity.

Methods

An observational cross-sectional study of patients receiving care at a COPD outpatient clinic in Spain was performed from November 2018 to December 2020. The study was reviewed and approved by the ethics committee of our institution (CEIm of Cantabria; 2018.276). Written informed consent was provided by all patients before entering the study. The study protocol was registered at www.clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT04449419).

Participants

Participants were recruited at a dedicated COPD outpatient clinic during routine visits. Smokers without COPD (control group) were recruited from the smoking cessation clinics held at our institution.

The inclusion criteria were as follows: (i) patients diagnosed with COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (16) who were >40 years of age and (ii) sex, age, and smoking status- matched control patients who had not been diagnosed with COPD.

The exclusion criteria were as follows: (i) patients who experienced a COPD exacerbation within 8 weeks of inclusion in the study; (ii) patients undergoing pulmonary rehabilitation during or up to 6 months before inclusion in the study; (iii) patients previously diagnosed with coronary or peripheral artery disease or cancer; (iv) patients with respiratory diseases different from COPD; (v) patients with serum C-reactive protein levels > 2.5 mg/dL; and (vi) patients with a glomerular filtration rate < 50 ml/min/1.73 m^2; (vii) patients using systemic corticosteroids within 8 weeks of inclusion in the study.

Measurements

Body composition estimates were obtained using a bioelectrical impedance device (OMRON BF511, Omron, Japan). Spirometry and a six-minute walk test (6MWT) were performed according to the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) protocol (17, 18). Maximum hand grip strength was measured with a GRIP-A hand dynamometer (Takei, Niigata, Japan). Disease-associated malnutrition was determined based on the European Society for Clinical Nutrition and Metabolism (ESPEN) consensus guidelines, including body mass index (BMI) <18.5 kg/m^2 or 18.5–22 kg/m^2, combined with a low fat-free mass index (FFMI) at <17 kg/m^2 for men and <15 kg/m^2 for women (19). Participants were categorized as having a high risk of exacerbation (HRE) at the time of entry into the study if they had two or more moderate or one severe

Abbreviations: COPD, chronic obstructive pulmonary disease; MOTS-c, mitochondrial open reading frame of the 12S ribosomal RNA type-c; Romo1, reactive oxygen species modulator 1; 6MWD, six-minute walk distance; 6MWT, six-minute walk test; OD, oxygen desaturation; OS, oxidative stress; SEPAR, Spanish Society of Pneumology and Thoracic Surgery; BMI, body mass index; FFMI, fat-free mass index; HRE, high risk of exacerbation.

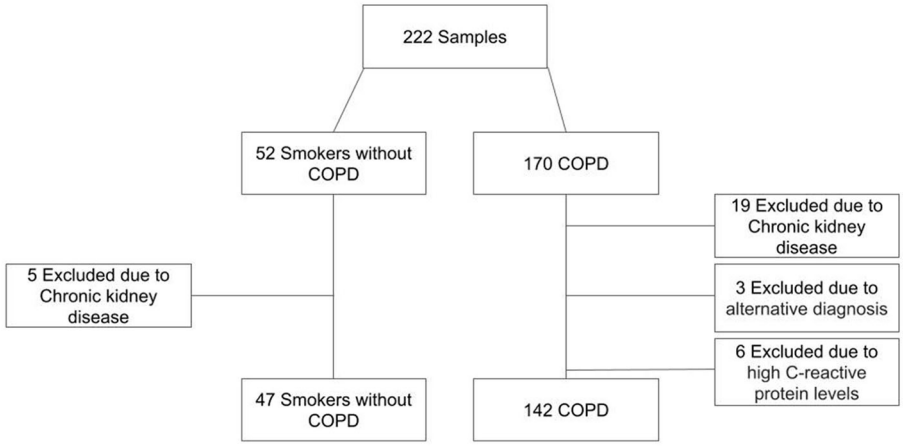

FIGURE 1
Flowchart for patient selection.

COPD exacerbation during the previous year as per GOLD guidelines (17). Oxygen desaturation (OD) was defined as a fall in oxygen saturation (SpO_2) ≥4% or an overall SpO_2 < 90% (20). Serum creatinine, albumin, uric acid, and creatine kinase levels were measured with IDMS-traceable enzymatic assays (Atellica® Analyzer, Siemens, Germany).

Serum levels of MOTS-c were determined using sandwich immunoassay (Mitochondrial Open Reading Frame of the 12S rRNA-c: MOTS-c kit, CEX132Hu, Katy, Cloud-Clone Corp., TX, USA Lot number L210213153). Serum levels of Romo1 were determined using sandwich immunoassay (Reactive oxygen species modulator 1 (Human ROMO1) ELISA Kit, Elabscience®, TX, USA Lot number ET4ZB9UKKQ) as per the manufacturers' protocols.

Blood from each participant was collected early in the morning to avoid any confusion that might result from circadian changes in MOTS-c and ROMO-1 levels. Samples and patient data were preserved by Biobanco Valdecilla (PT17/0015/0019), integrated into the Spanish Biobank Network, and processed according to standard operating procedures with approval from both ethical and scientific committees.

Statistical analysis

Normally distributed data are presented as means ± standard deviations (SDs). Non-parametric data are presented as medians with interquartile ranges. We calculated the sample size in *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC) based on an α risk of 0.05 and a β risk of 0.2. Differences between groups were evaluated with unpaired *t*-tests (for parametric data) or Mann-Whitney tests (for non-parametric data). Normal distribution was determined using the Kolmogorov–Smirnov test. The creation of a dichotomized variable from MOTS-c and Romo1 levels with a cut-off at the median value resulted in the highest discriminative power for the outcomes under study as it resulted in the lowest Akaike information criterion value, similar to that observed in other studies (21, 22). We determined cross-sectional associations by univariate and multivariate logistic regression based on high (i.e., above the median) vs. low (i.e., below the median) values of baseline circulating MOTS-c and Romo1 with baseline characteristics of the patients. Using a similar model, we evaluated the primary outcomes of the study: baseline oxygen saturation, and two outcomes of the 6MWT [6 min walking distance (6MWD) and oxygen desaturation (OD)] using SPSS Software version 25.00 for PC. All *p*-values resulted from two-tailed tests with $p < 0.05$ as statistically significant.

Results

Characteristics of patients and controls

One hundred and forty-two COPD patients and forty-seven sex and age-matched controls (i.e., smokers who were not diagnosed with COPD) were enrolled in our study (Figure 1). Table 1 includes demographic, clinical, and biochemical data. The patient population was 66.2% men with a mean age of 67.5 ± 7.7 years. The COPD patient cohort included a substantial percentage of current smokers (30.6%); most had moderate to severe airway obstruction. The participants included in the control group had normal lung function, lower scores on COPD assessment tests (CATs), and were capable of longer six-minute walk distances (6MWD) than the COPD patients. As shown in Table 1 the percentage of current smokers was similar in COPD and control groups. The prevalence of type 2 diabetes mellitus (T2DM) which is a well-established cause of reductions in serum MOTS-c levels was similar in both groups ($p = 0.842$). Among our findings, MOTS-c levels were lower in the COPD group [median 622 ng/mL; interquartile range (IQR) 482–848 ng/mL] compared to controls (median 764 ng/mL; IQR

TABLE 1 Demographic, clinical, and biochemical characteristics of control (smokers without COPD) and COPD patients.

Variable	COPD $n = 142$	Smokers without COPD $n = 47$	p
Age (years)	67.5 ± 7.7	65.6 ± 6.8	0.113
Sex Male *n* (%)	94 (66.2%)	31 (62.0%)	0.592
FVC (mL)	**2,723 ± 814**	**3,429 ± 861**	**<0.001**
FVC (%)	**83 ± 20**	**102 ± 18**	**<0.001**
FEV_1 (mL)	**1,285 (900–1820)**	**2,635 (2072–3002)**	**<0.001**
FEV_1 (%)	**52 (37–68)**	**98 (86–111)**	**<0.001**
FEV_1/FVC	**49 (39–60)**	**75 (72–79)**	**<0.001**
Weight (Kg)	74.7 ± 16.2	74.3 ± 14.8	0.830
BMI (Kg/m2)	27 (24.1–31.6)	27.3 (25.1–29.8)	0.810
6MWD (m)	**445 (355–495)**	**525 (448–578)**	**<0.001**
Maximum hand grip strength (Kg)	31 (24–40)	33 (23–40)	0.667
FFMI (Kg/m^2)	18.9 ± 2.7	19.2 ± 2.4	0.166
CAT score	**12 (7–18)**	**3 (1–5)**	**<0.001**
Charlson	1 (1–2)	1 (0–2)	0.092
mMRC score 0/I/II/III/IV	**39 (27.5)/43 (30.3)/38 (26.8)/22 (15.5)**	**38 (80.8)/8 (17.0)/1 (2.1)/0 (0) /0 (0)**	**<0.001**
Current smokers *n* (%)	43 (30.6)	22 (46.8)	0.059
Pack-years	41 (21–56)	40 (20–45)	0.098
Patients with malnutri-tion *n* (%)	**36 (25.4)**	**4 (8.5)**	**0.018**
GOLD 1/2/3/4 *n* (%)	19 (13.4)/59 (41.5)/47 (33.1)/17 (12.0)	–	–
GOLD A/B/C/D *n* (%)	49 (34.5)/39 (27.5)/13 (9.2)/41 (28.9)	–	–
High risk of exacerba–tion *n* (%)	56 (39.4)	–	–
ICS treatment *n* (%)	71 (50.0)	–	
Diabetes Mellitus *n* (%)	26 (18.3%)	8 (17.0%)	0.842
MOTS–c (ng/mL)	**622 (482–848)**	**764 (604–906)**	**0.022**
Romo−1 (ng/mL)	**5.42 (2.84–8.72)**	**3.72 (1.64–7.59)**	**0.038**
Albumin (g/dL)	4.80 ± 0.31	4.83 ± 0.28	0.681
Creatinine (mg/dL)	0.82 (0.70–0.96)	0.87 (0.71–0.98)	0.528
Uric acid (mg/dL)	6.19 ± 1.73	5.98 ± 1.38	0.464
CK (UI/L)	65 (45–95)	64 (41–113)	0.785

FVC, Forced Vital Capacity; FEV1, Forced expiratory Volume in the first second; mMRC, modified Medical Research Council Dyspnea score; CAT, COPD Assessment Test; ICS, Inhaled Corticosteroids; GOLD, Global initiative for Chronic Obstructive Lung Disease; BMI, Body Mass Index; FFMI, Fat Free Mass Index; 6MWD, 6- Minute Walking Distance; Bold font indicates statistical significance.

604–906 ng/mL; $p = 0.022$) (Figure 2). Our findings revealed no significant differences between serum levels of MOTS-c detected in patients with COPD either with (median 681 ng/mL, IQR 452–1150 ng/mL) or without T2DM (median 688 ng/mL, IQR 504–924 ng/mL; $p = 0.853$). Furthermore, serum levels of MOTS-c did not correlate with hemoglobin A1c ($r = 0.165$, $p = 0.649$) in patients with T2DM; thus, all COPD patients were evaluated as a single group.

Serum levels of Romo1 were higher among those in the COPD group (median 5.42 ng/mL, IQR 2.84–8.72 ng/mL) vs. controls (median 3.72 ng/mL, IQR 1.64–7.59 ng/mL, $p = 0.038$) (Figure 2).

Association of circulating levels of MOTS-c and Romo1 with baseline characteristics of COPD

Table 2 highlights the associations of MOTS-c and Romo1 with baseline characteristics of COPD and between both peptides. Multivariate logistic regression analysis showed that high levels of MOTS-c were positively associated with Romo1 levels (OR 1.075, 95% CI 1.005–1.150, $p = 0.036$), but no association was found with other COPD characteristics. On the other hand, multivariate logistic regression analysis confirmed that high levels of Romo1

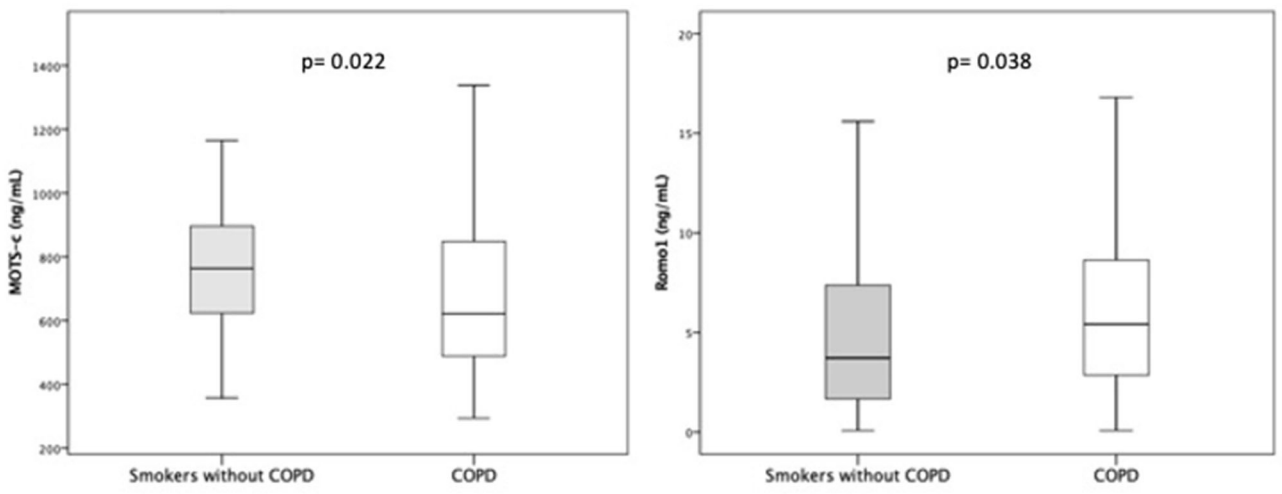

FIGURE 2
MOTS-c and Romo1 distribution in patients with COPD and smokers without COPD.

were independently and positively associated with current smoking (OR 2.756, 95% CI 1.133–6.704, $p = 0.025$) and circulating MOTS-c levels (OR 1.001, 95% CI 1.000–1.003, $p = 0.012$) (Table 2).

Low MOTS-c and high Romo1 levels as predictors of basal oxygen saturation, distance and oxygen desaturation in 6MWT

Forty-eight patients with COPD presented with Oxygen desaturation (OD). Among these, 33 exhibited low MOTS-c levels and 23 patients exhibited high Romo1 levels. Thirty-five patients walked <350 m during the 6MWT; this included 25 patients with low MOTS-c levels and 14 patients with high Romo1 levels. Multivariate logistic regression (Table 3) showed that low MOTS levels were significantly associated with OD (OR 3.25 95% CI 1.456–8.522, $p = 0.005$) and walking <350 meters (OR 3.246 95% CI 1.229–8.577, $p = 0.018$), but not with baseline O_2 levels. On the other hand, high Romo 1 levels were negatively associated with baseline O_2 levels (OR 0.776 95% CI 0.641–0.939, $p = 0.009$), but not with OD or walking < 350 m (Table 4).

Discussion

The results of our study provide the first evidence that circulating levels of MOTS-c are lower in patients with COPD compared with otherwise healthy current smokers; by contrast, circulating levels of Romo1 were higher in patients with COPD. MOTS-c and Romo1 were associated with different COPD characteristics; low circulating MOTS-c levels were associated with worse 6MWD and oxygen desaturation; by contrast, high circulating levels of Romo1 were associated with active smoking and lower baseline levels of oxygen saturation. Interestingly we found a positive association between Romo1 and MOTS-c.

Circulating MOTS-c levels were reduced in COPD patients. Similar responses have been observed in other chronic diseases associated with OS, including T2DM (23), obesity with or without obstructive sleep apnea syndrome (24, 25), endothelial dysfunction/coronary artery disease (26), kidney failure (27), and multiple sclerosis (28). Interestingly, concomitant T2DM resulted in no further reductions in circulating MOTS-c levels compared to patients with COPD alone; these results suggest that the effects of these two diseases on MOTS-c levels are not additive. Low MOTS-c levels, as happens with "low T3 sick euthyroid syndrome", may be a generalized non-specific response to many illnesses (29).

Reductions in circulating MOTS-c levels may result from mitochondrial damage. Alternatively, OS may induce profound sequestration of MOTS-c in the nucleus, thereby blocking its transfer into the peripheral circulation (12). Given that low levels of circulating MOTS-c have been reported in numerous diseases associated with OS, the second explanation may be the more likely of the two.

Lower levels of circulating MOTS-c were associated with shorter distances walked in the 6MWT, specifically with walking < 350 m, a parameter that is associated with the risk of death in COPD (6) and more profound OD. Exercise induces MOTS-c synthesis in healthy individuals (13, 30); MOTS-c in turn activates the synthesis of other enzymes (such as AMP-activated protein kinase) known to be induced by exercise (11, 31). On the other hand, it has been reported recently that MOTS-c promotes muscle differentiation of muscle progenitor cells (32). Thus, it is reasonable to hypothesize that individuals who are unable to induce MOTS-c synthesis will exhibit a comparatively low exercise capacity. One recent study evaluated the relationship between oxidative biomarkers associated with stable COPD and their role in exercise, identifying superoxide dismutase (SOD) as an independent determinant of performance in the 6MWT (33).

Our study shows that patients diagnosed with COPD have higher circulating levels of Romo1. This finding was also suggested

TABLE 2 Univariate and multivariate logistic regression analysis for the associations between baseline chronic obstructive pulmonary disease characteristics and high levels of MOTS-c and Romo1.

		High MOTS–c				High Romo–1			
		Univariate		Multivariate		Univariate		Multivariate	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (years)		0.994 (0.952–1.037)	0.777	0.979 (0.931–1.030)	0.412	0.980 (0.937–1.024)	0.361	0.988 (0.937–1.041)	0.648
Sex									
	Male	1		1		1		1	
	Female	1.660 (0.822–3.353)	0.157	0.436 (0.187–1.020)	0.065	0.880 (0.430–1.799)	0.726	1.553 (0.673–3.588)	0.302
Smoking status									
	Former-smoker	1		1		1		1	
	Current-smoker	1.222 (0.596–2.503)	0.584	1.093 (0.469–2.545)	0.837	**2.411 (1.119–5.195)**	**0.025**	**2.756 (1.133–6.704)**	**0.025**
Exacerbation									
	0	1		1		1		1	
	≥ 1	1.404 (0.725–2.719)	0.314	2.200 (0.932–5.193)	0.072	0.812 (0.408–1.617)	0.554	0.739 (0.315–1.734)	0.487
Charlson									
	1	1		1		1		1	
	2	0.743 (0.273–2.021)	0.561	0.992 (0.317–3.105)	0.989	0.726 (0.252–2.092)	0.554	0.767 (0.242–2.445)	0.656
	>2	1.479 (0.635–3.445)	0.364	2.331 (0.772–7.042)	0.133	0.444 (0.180–1.095)	0.078	0.328 (0.107–1.010)	0.052
FEV1 (%)		1.003 (0.987–1.019)	0.735	0.994 (0.963–1.025)	0.685	1.006 (0.989–1.023)	0.501	0.990 (0.960–1.020)	0.506
FVC (%)		1.007 (0.991–1.024)	0.400	1.017 (0.986–1.048)	0.282	1.008 (0.990–1.025)	0.387	1.022 (0.992–1.052)	0.158
Romo1 /MOTS-c (ng/mL)		1.050 (0.990–1.114)	0.104	**1.075 (1.005–1.150)**	**0.036**	**1.001 (1.000–1.002)**	**0.031**	**1.001 (1.000–1.003)**	**0.012**
Diabetes Mellitus		0.228 (0.353–1.943)	0.665	1.095 (0.377–3.184)	0.867	0.420 (0.167–1.057)	0.066	0.554 (0.184–1.671)	0.294

High MOTS-c levels ≥ 622 ng/mL; High Romo1 levels > 5.42 ng/mL; Exacerbation, Need for antibiotic or systemic corticosteroids; FEV1, Forced expiratory Volume in the first second; FVC, Forced Vital Capacity; Bold font indicates statistical significance.

previously in a cross-sectional study that included a small population of COPD patients (15). The results of our study reveal for the first time an important association between high circulating levels of Romo1 with current smoking and reduced oxygen saturation (i.e., factors intrinsically associated with oxidative stress), although no relationship with exercise capacity. Our data revealed a positive (albeit weak) association between high circulating levels of MOTS-c and Romo1. This relationship that has not been described previously, warrants further research and contrasts with the fact that low MOTS-c is associated with worse outcomes related with exercise capacity but high Romo1 is associated with low oxygen saturation, suggesting that each molecule relates to different characteristics of COPD. In a different model of respiratory disease, Ye et al. (34) have recently reported that serum Romo1 and ROS were increased in patients with obstructive sleep apnea syndrome.

TABLE 3 Multivariate logistic regression analysis showing factors associated with baseline low MOTS-c.

	B	Wald	*p*	OR	95% CI OR	
					Lower	Upper
Baseline $SatO_2$	−0.063	0.694	0.405	0.939	0.810	1.089
Oxygen Desaturation	**1.259**	**7.806**	**0.005**	**3.523**	**1.456**	**8.522**
6MWD < 350 meters	**1.178**	**5.643**	**0.018**	**3.246**	**1.229**	**8.577**

Low MOTS-c levels < 622 ng/mL; All variables adjusted by Age, Sex, Charlson Index, High risk of exacerbation (2 or more exacerbations during previous year or 1 previous admission), FEV1, Forced Expiratory Volume in the first second, smoking status. Oxygen desaturation was defined as ≥ 4% reduction between pretest and posttest arterial oxygen saturation (Δ SpO_2 ≥ 4%) and posttest SpO_2 < 90% measured by pulse oximetry. 6MWD, 6-Minute Walking Distance. Bold font indicates statistical significance.

TABLE 4 Logistic regression analysis showing factors associated with baseline high Romo1.

	B	Wald	*p*	OR	95% CI OR	
					Lower	Upper
Baseline $SatO_2$	**−0.254**	**6.800**	**0.009**	**0.776**	**0.641**	**0.939**
Oxygen desaturation	0.064	0.018	0.892	1.066	0.425	2.673
6MWD < 350 meters	−0.311	0.353	0.552	0.733	0.263	2.043

High Romo1 levels >5.42 ng/mL; All variables adjusted by Age, Sex, Charlson Index, High risk of exacerbation (2 or more exacerbations during previous year or 1 previous admission), FEV1, Forced expiratory Volume in the first second, Smoking status. Oxygen desaturation (OD) was defined as ≥4% reduction between pretest and posttest arterial oxygen saturation (Δ SpO2 ≥ 4%) and posttest SpO2 <90% measured by pulse oximetry. 6MWD, 6-Minute Walking Distance. Bold font indicates statistical significance.

Several of the strengths of this study are worth highlighting. First, this study was designed specifically to evaluate the impact of COPD on circulating levels of MOTS-c and Romo1 in a group of carefully selected and well-characterized patients without comorbidities (other than T2DM and asymptomatic coronary diseases) that might influence the results and a matched for current smoking control group of smokers without COPD (in order to avoid smoking as a potential confounding factor). Second, we considered a variety of factors and clinical characteristics of COPD that might have an impact on circulating levels of MOTS-c and Romo1.

Our study has several limitations. Most importantly, this type of study reveals associations but not causality. Any assessments of causality will require specifically designed *In vitro* and *in vivo* experimental studies. Furthermore, largely because of the complex pathophysiology of mitochondrial dysfunction and oxidative stress, a full understanding of this phenomenon will require consideration of a large collection of markers. Finally, our patient cohort was enrolled from a single center. Thus, these findings will need to be replicated in large multicenter trials with patients from a large range of socio-demographic settings and who exhibit a variety of comorbidities that might influence the results.

Conclusion

Our study provides the first evidence of reductions in circulating levels of MOTS-c levels in patients diagnosed with COPD, lower MOTS-c is associated with lower 6MWD and higher rate of oxygen desaturation. Our study also revealed increases in levels of Romo1 in COPD patients that are associated with current smoking and baseline oxygen saturation but are not associated with 6MWD or oxygen desaturation in 6MWT. Further studies will be needed to confirm our findings which will open new perspectives in the multidimensional management of COPD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ceim of Cantabria. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Guarantor of the paper: CA. Conceptualization: CA and MG-U. Data curation: DF-P, CA, PM-A, and FM. Formal analysis: DF-P and CA. Project administration: CA and PM-A. Methodology: CA, MG-U, DB, AB, and AG. Resources: CA, MG-U, and AB. Visualization: CA and BL. Supervision: MG-U and PM-A. Software: DB. Writing—original draft: CA and CC. Writing—review and editing: CA, PM-A, AB, BL, AG, DB, and CC. All authors contributed to the article and approved the submitted version.

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Conflict of interest

CA has received speaker or consulting fees from Boehringer Ingelheim, Pfizer, AstraZeneca, Novartis, Chiesi, Faes Farma, Esteve, and GSK. CC has received speaker or consulting fees from AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, GSK, Menarini, Novartis, and research grants from GSK, Menarini, and AstraZeneca. DF-P has received speaker or consulting fees from Chiesi and GSK.

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Publisher's note

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Sleep apnea-COPD overlap syndrome is associated with larger left carotid atherosclerotic plaques

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Background: Little is known about whether the overlap syndrome (OS) combining features of chronic obstructive pulmonary disease (COPD) and sleep apnea-hypopnea syndrome increases the risk of stroke associated with COPD itself.
Methods: We prospectively studied 74 COPD patients and 32 subjects without lung disease. Spirometry and cardiorespiratory polygraphy were used to assess the pulmonary function of the study population and ultrasound measurements of intima media thickness (IMT) as well as the volume of plaques in both carotid arteries were also evaluated.
Results: Polygraphic criteria of OS were met in 51% of COPD patients. We found that 79% of patients with OS and 50% of COPD patients without OS had atherosclerotic plaques in the left carotid artery ($p = 0.0509$). Interestingly, the mean volume of atherosclerotic plaques was significantly higher in the left carotid artery of COPD patients with OS (0.07 ± 0.02 ml) than in those without OS (0.04 ± 0.02 ml, $p = 0.0305$). However, regardless of the presence of OS, no significant differences were observed in both presence and volume of atherosclerotic plaques in the right carotid artery of COPD patients. Adjusted-multivariate linear regression revealed age, current smoking and the apnea/hypopnea index (OR = 4.54, $p = 0.012$) as independent predictors of left carotid atherosclerotic plaques in COPD patients.
Conclusions: This study suggests that the presence of OS in COPD patients is associated with larger left carotid atherosclerotic plaques, indicating that OS might be screened in all COPD patients to identify those with higher risk of stroke.

KEYWORDS

atherosclerosis, chronic obstructive pulmonary disease, carotid atherosclerosis, apnea, sleep obstructive apnea, overlap syndrome

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease with a high global prevalence which is estimated to be currently the third leading cause of death worldwide and the numbers are rising (1, 2). Since COPD is a non-curable disease, smoking cessation is the only effective measure to prevent and slow its progression (3).

The main endpoints in the COPD therapy are: to attenuate disease symptoms, to reduce the frequency and severity of exacerbations, and to improve the prognosis. Noteworthy, a new chronic respiratory disease combining features of COPD and sleep apnea-hypopnea syndrome, named overlap syndrome (OS), has been described. Although little is known nowadays about its clinical and prognostic impact, there is a growing evidence that the clinical outcomes of patients with OS may be more deleterious than those of patients with either COPD or sleep apnea alone (4, 5). The prevalence of OS in the general population has been assessed in distinct epidemiological studies with estimations varying from 10% to 66% (6, 7).

COPD is associated with a high morbidity and mortality largely due to the presence of metabolic and cardiovascular co-morbidities, such as obesity, type 2 diabetes, non-alcoholic fatty liver disease and a wide spectrum of atherosclerosis-related cardiovascular disorders (CVD) (8). Regarding the latter, distinct meta-analysis of observational clinical studies showed that COPD patients have 2-fold higher risk of CVD than subjects without COPD, being ischemic heart disease, ischemic stroke and peripheral artery disease the most frequently observed CVD in COPD patients (9, 10). In fact, several studies have investigated whether CVD are more prevalent in certain phenotypes of COPD patients without conclusive results so far. It has been observed that cardiovascular co-morbidities are not only limited to those with more advanced airflow obstruction, but they are indeed present across the wide spectrum of disease severity (11, 12). Regarding sleep apnea, it has been described distinct inflammatory factors which might cause the progression of atherosclerosis, thus increasing the risk of cardiovascular and cerebrovascular diseases (13). In this context, Trzepizur et al. have recently reported that patients with obstructive sleep apnea and elevated hypoxic burden are at higher risk of a cardiovascular event and all-cause mortality (14). Interestingly, OS has been linked to higher cardiovascular morbidity, poorer quality of life, and higher frequency of COPD exacerbations (15), but these findings need to be confirmed in further clinical studies.

Atherosclerosis is the underlying cause of CVD in most cases (16) and it is considered the first cause of death in CVD as well as a major cause of total deaths (17). Atherosclerosis is a chronic and systemic disease characterized by promoting cholesterol influx in the vascular wall, leading to fatty streaks and fibrotic streaks in early stages, and prompting generation of a necrotic core with thrombogenic capacity in advanced complicated plaques (18). Currently, it is quite unpredictable to know who is going to suffer from atherothrombosis, which depends on the vulnerability of the plaque. Noteworthy, most of the patients are asymptomatic, especially in early stages. For these reasons, the current approaches to improve the diagnosis and prognosis are non-invasive imaging techniques to better characterize vessel morphology as well as biomarkers discovery. Carotid atherosclerosis (CAS) plays a fundamental part in the occurrence of ischaemic stroke, and some morphological characteristics like plaque volume are promising as imaging biomarkers of carotid plaque vulnerability (19). Moreover, mechanisms underlying the pathogenic link between sleep apnea and carotid atherosclerosis may be different for carotid plaque development than for the increase of carotid intima-media thickness (20). On the other hand, despite the growing appreciation of the importance of atherosclerosis in COPD patients, there is still considerable ambiguity about its prevalence and clinical impact. Therefore, in this prospective cross-sectional study we wanted to explore the prevalence of and risk factors for CAS among patients with COPD, either with or without OS, in order to determine whether the coexistence of the OS in COPD patients might impact on the development of CAS.

Patients and methods

Study population

This study was performed in agreement with the Declaration of Helsinki, and with local and national laws. The Institution's Clinical Research Ethics Committee approved the study procedures (report reference, PI16/2,800), and all participants signed an informed written consent before inclusion in the study, providing permission for their medical data to be anonymously used for research.

This prospective cross-sectional study included consecutive patients with clinical, spirometric and polygraphic criteria of COPD, with or without OS, among those who attended to the outpatient clinics of the Respiratory Service at Hospital Universitario de La Princesa (Madrid, Spain) during a 6 months period. In parallel, volunteers who had both spirometry and sleep polygraphy parameters within normality were included in the study and considered as control subjects with normal lung parameters (NLP). Patients and controls were excluded if they drank more than 20 g/day of alcohol, had a diagnosis of asthma or cancer or any concomitant severe clinical disorder. In addition, they were also excluded if had analytical evidence of iron overload, were seropositive for autoantibodies and/or for hepatitis B virus, hepatitis C virus, and human immunodeficiency virus as well as those having actively drugs such as cannabis and cocaine among others.

Demographic, clinical and biochemical assessment

Clinical examination was performed to all participants in this study including a detailed interview with special emphasis on smoking pattern, alcohol and drugs abuse (cannabis and cocaine) and medications use, history of diabetes and arterial hypertension as well as measurements of weight and height. Body mass index (BMI) was calculated and obesity was defined as BMI $\geq$ 30 kg/m2. After overnight fast, venous blood samples of each participant were obtained to test serum levels of different biochemical and metabolic parameters. Insulin resistance was calculated by the homeostasis model assessment method (HOMA-IR) (21). Metabolic syndrome was defined according to the ATP III criteria (22).

Spirometry

To assess the diagnosis and severity of COPD, spirometry was performed to all participants by using a JAEGER^{TM} spirometer (Vyaire Medical, Madrid, Spain) which meets all the specifications required by the Spanish Respiratory Society, the European Respiratory Society and the American Thoracic Society. All patients and control subjects underwent pre- and post-bronchodilator spirometric determinations.

Cardiorespiratory polygraphic study

All polygraphic studies were performed at night in the Sleep Laboratory of the Hospital Universitario de La Princesa by using validated procedures as previously described (23). Sleep studies were performed using a cardiorespiratory polygraphy (SOMNOscreenTM Plus, Randersacker, Germany), previously validated, with DOMINO analysis software (Domino Data Lab, San Francisco, CA). The interpretation of the register was carried out manually, although assisted by a computer, following the consensus recommendations for the diagnosis of apnea, hypopnea with desaturation of 3%, according to the recommendations for diagnosis of sleep apnea-hypopnea syndrome of the Spanish Society of Pneumology and Thoracic Surgery (24). Moreover, episodes of apnea were further characterized as central or obstructive as previously described (23). The presence of an apnea and hypopnea index (AHI) equal to or greater than 5 per hour of sleep was used as diagnostic criterion for certainty of sleep apnea. The severity of apnea-hypopnea was classified according to the value of AHI as mild (AHI, 5–14/h), moderate (AHI, 15–29/h) or severe (AHI $\geq$ 30/h). In addition, other pulmonary parameters were analyzed such as the oxygen desaturation index (ODI) and the percentage of sleep time with oxygen saturation below 90% (Tc90%). Both ODI and Tc90% were considered low when lower than 10 events/hour and 10%, respectively, and were considered high when equal or higher than 10 events/hour and equal or higher than 10%, respectively.

Assessment of vascular damage

Distinct features of vascular damage were determined by using ultrasonography (Applio XG, Canon, Tokyo, Japan) to each patient as follows:

- Intima-media thickness (IMT) was measured in the distal 2 centimeters (cm) of both common carotid arteries. The methodology defined in the Mannheim consensus (ref tesis pedro 193) was used. Each participant had 3 carotid IMT (cIMT) measures by side, which were carried out and scored for quality by 2 experts vascular radiologists (AFR, JMO). We calculated cIMT for each participant as the average value of all measurements that met predefined quality standards.
- Volume of arterial plaques was determined following internationally accepted criteria (25). Arterial plaque was defined when 2 of the following criteria were met: 1- IMT > 1.5 mm. 2- Impression in the vascular lumen. 3- Abnormal wall texture. The plaque burden found in both carotid arteries (2 cm distal common carotid arteries and 1 cm distal internal carotid arteries) was calculated. This plaque load was expressed as the sum of the volumes of all plaques. All ultrasound measurements were performed by 2 experts vascular radiologists (AFR, JMO) using a 7 MHz linear probe (model PLT-704SB, Tokyo, Japan) and a high frequency volumetric linear probe model PLT-1204 MV probe (Canon, Tokyo, Japan) with a 3D/4D volumetric reconstruction software model Toshiba UIMV-A500A (Canon, Tokyo, Japan).

Statistical analysis

The Kolmogorov–Smirnov test was applied to evaluate if variables were adjusted or not to a normal distribution. Qualitative variables are presented as absolute (number, n) and relative (percentage, %) frequencies. Quantitative variables are expressed as measures of central tendency (mean) and dispersion (standard deviation, SD). Qualitative data between groups were compared by Pearson's χ^2 test or Fisher exact test as appropriate. The Student's t test was used to calculate the difference of the means in the variables that followed a normal distribution and the Mann–Whitney U test for the variables with a non-parametric distribution. Logistic regression analysis, adjusted by confounding variables (age, gender BMI, diabetes, arterial hypertension, total cholesterol, current smoking, post-FEV1 and number of exacerbations per year) was performed to identify independent polygraphic variables (AHI, ODI, and Tc90%) associated with the presence of atherosclerotic plaques in either the left or the right carotid artery in the study population. Multiple confounding factors of cardiovascular risk were evaluated, such as creatinine, glomerular filtration rate, albumin, glucose, insulin resistance assessed by HOMA-IR, triglycerides, low and high density lipoproteins, dyslipidemia, alkaline phosphatase and iron metabolism, as well as history of previous cardiovascular disease (atrial fibrillation, chronic heart failure, acute myocardial infarction, cerebrovascular disease and stroke) and medicament use (ACE inhibitors, angiotensin-II receptor antagonists and oral antidiabetics or insulin). Univariate and multivariate regression models were constructed, parameters were selected by likelihood ratio test, and Box-Tidwell procedure was used for testing linearity of logit. The goodness of fit was evaluated using the Hosmer–Lemeshow statistic. Significance was set at a value of $p < 0.05$. Statistical analysis was performed using SPSS software version 26.0 (SPSS Statistics, Armonk, NY: IBM Corp.).

Results

Characteristics of the study population

A total of 74 COPD patients and 32 subjects with NLP were included in the study according to inclusion and exclusion

criteria. Demographic, anthropometric and analytical characteristics of the entire study population are detailed in Table 1. Overall, COPD patients were older and had insulin resistance, arterial hypertension and dyslipidemia more frequently than NLP subjects. Furthermore, COPD patients had significantly higher serum levels of ALT, GGT and ferritin than NLP controls. Regarding pulmonary function parameters, as expected, all spirometry parameters were significantly lower in COPD patients than in NLP subjects as well as basal and minimum oxygen saturation (Supplementary Table S1).

TABLE 1 Characteristics of the study population.

Features	NLP ($n = 32$)	COPD ($n = 74$)	p-value
Age (years)	54.38 ± 8.53	63.38 ± 6.57	<0.001
Gender			0.118
Women, *n* (%)	20 (62.5)	34 (45.9)	
Men, *n* (%)	12 (37.5)	40 (54.1)	
Body mass index (kg/m2)	28.91 ± 5.54	27.63 ± 5.80	0.208
Body mass index ≥30, *n* (%)	10 (31.3)	24 (32.4)	0.905
Glucose (mg/dl)	97.37 ± 13.37	101.84 ± 25.36	0.376
Insulin levels (μU/L)	11.54 ± 7.58	14.50 ± 9.65	0.131
HOMA-IR score	2.93 ± 2.27	3.94 ± 2.98	0.082
HOMA-IR score ≥2.5, *n* (%)	14 (43.8)	50 (67.6)	**0.021**
Glycated Hb (%)	5.63 ± 0.52	5.74 ± 0.58	0.108
Type 2 diabetes mellitus, *n* (%)	2 (6.3)	15 (20.3)	0.088
Hypertension, *n* (%)	9 (28.1)	41 (53.2)	**0.021**
Dyslipidemia, *n* (%)	7 (21.9)	36 (48.6)	**0.011**
Metabolic syndrome, *n* (%)	3 (9.4)	12 (16.2)	0.545
Triglycerides (mg/dl)	106.47 ± 66.57	125.03 ± 69.23	0.116
Total cholesterol	196.81 ± 39.17	198.23 ± 42.32	0.896
HDL-cholesterol (mg/dl)	57.53 ± 12.96	60.58 ± 22.21	0.422
LDL cholesterol (mg/dl)	115.22 ± 30.75	108.99 ± 38.66	0.404
ALT (IU/L)	18.78 ± 7.34	22.77 ± 9.09	0.033
AST (IU/L)	20.28 ± 5.61	23.18 ± 8.18	0.063
GGT (IU/L)	22.19 ± 13.03	36.55 ± 30.07	**0.003**
Iron (μg/dl)	78.47 ± 33.50	89.70 ± 29.33	0.124
Ferritin (ng/ml)	87.41 ± 72.14	134.26 ± 98.40	**0.021**
Transferrin (mg/dl)	244.26 ± 31.58	259.41 ± 39.47	0.051
Alkaline phosphatase (IU/L)	69.62 ± 22.69	71.23 ± 19.55	0.877
Lactate dehydrogenase (U/L)	182.72 ± 36.12	195.59 ± 36.12	0.140
Albumin (g/dl)	4.37 ± 0.27	4.38 ± 0.39	0.941
Platelets (109/L)	0.23 ± 0.07	0.24 ± 0.05	0.392
Total bilirubin (mg/dl)	0.57 ± 0.48	0.55 ± 0.29	0.467
C reactive protein (mg/L)	0.42 ± 0.59	0.42 ± 0.52	0.568

Data are shown as mean ± standard deviation or as number of cases (%). NLP, subjects with normal lung parameters; COPD, subjects with chronic obstructive pulmonary disease; HOMA-IR, homeostatic model assessment-insulin resistance; Hb, hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

Prevalence of carotid atherosclerotic disease in the study population

To this end, left and right carotid artery were assessed by ultrasonography to measure IMT as well as to determine the number and volume of atherosclerotic plaques in the entire study population. We did not found differences in cIMT between COPD and NLP subjects (Figure 1, panels A–D) but atherosclerotic plaques, in both left and right carotids, were significantly more abundant and larger in COPD patients than in NLP subjects ($p < 0.0001$ for all cases) (Figure 1, panels E–H).

Prevalence of overlap syndrome

We carried out cardiorespiratory polygraphic study to all COPD patients included in order to determine the prevalence of OS in our study cohort. According to internationally-accepted diagnostic criteria, COPD patients were stratified by the presence (AHI ≥ 5 events/hour) or absence of OS (AHI < 5 events/hour) and their baseline characteristics are shown in Supplementary Table S2. Overall, 38 out of 74 COPD patients (51%) had polygraphic criteria of OS, being the estimated prevalence of COPD-OS in our study cohort of 51%. These COPD-OS patients were predominantly men and had significantly higher serum GGT levels than those without OS. Pulmonary function parameters of COPD patients according to the absence or presence of OS are summarized in Table 2. To highlight, the majority of COPD patients with OS had a mild or moderate AHI (79%) and an ODI equal or higher than 10 (84.2%).

Increased prevalence of left carotid atherosclerotic plaques in COPD patients with overlap syndrome

No significant differences were observed in COPD patients with or without OS regarding cIMT measurements either in left or right carotid arteries (Figure 2, panels A–D), although there is a trend towards a slight increase in the left carotid artery, as well as in the number of patients with left cIMT above 1 mm, a widely used cut-off point as a surrogate marker of CAS. In the same line, we found that 30 out of 38 patients with OS (79%) and 18 out of 36 patients without OS (50%) had atherosclerotic plaques in the left carotid artery ($p = 0.0509$) (Figure 2, panel E). Interestingly, the mean volume of atherosclerotic plaques was significantly higher in the left carotid artery of patients with OS (0.07 ± 0.02 ml) than in those without OS (0.04 ± 0.02 ml, $p = 0.0305$) (Figure 2, panel F). Conversely, and regardless of the presence of OS, no significant differences were observed in both the presence and volume of atherosclerotic plaques in the right carotid artery of COPD patients with OS (Figure 2, panels G and H).

Risk factors for left carotid atherosclerotic plaques in COPD patients

To further evaluate the impact of OS on the presence of left carotid atherosclerotic plaques in COPD patients, we performed multivariate logistic regression analysis in our study cohort to determine the associated risk factors. We performed univariate analysis of multiple traditional risk factors - detailed in Patients and Methods - for carotid atherosclerosis, COPD and sleep

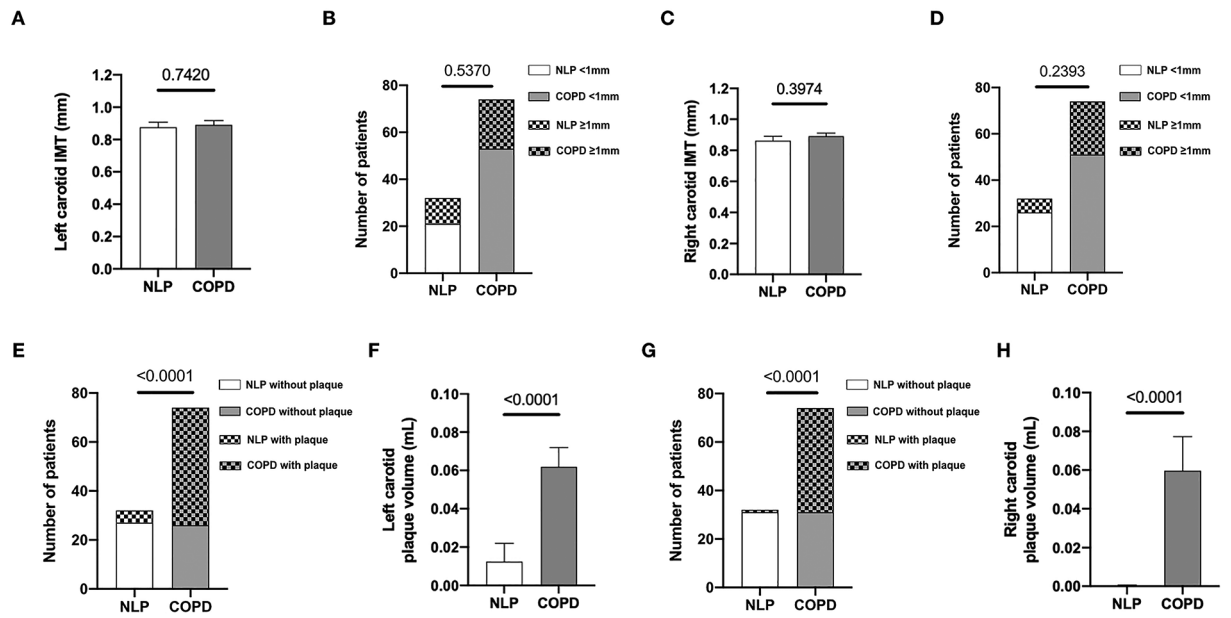

FIGURE 1
Prevalence of carotid atherosclerosis in the study population. Number of COPD patients and NLP subjects with left and right carotid IMT measurements (panels A and C, respectively) and differences between the study groups regarding mean IMT of left and right carotids (panels B and D, respectively). Number of COPD patients and NLP subjects with left and right carotid plaque measurements (panels E and G, respectively) and differences between the study groups regarding mean volume of left and right carotid plaques (panels F and H, respectively). COPD, chronic obstructive pulmonary disease, *n* = 74. NLP, normal lung parameters, *n* = 32.

TABLE 2 Pulmonary function parameter in COPD population according to OS presence.

Features	Non-OS (*n* = 36)	OS (*n* = 38)	p-value
PRE FVC (ml)	2343.89 ± 830.86	2895.55 ± 983.88	**0.013**
PRE FVC (%)	70.48 ± 19.52	74.53 ± 20.19	0.407
PRE FEV (ml)	1200.08 ± 615.17	1634.47 ± 731.00	**0.008**
PRE FEV (%)	47.38 ± 21.18	55.57 ± 18.63	0.087
PRE FEV/FVC	49.95 ± 13.48	55.37 ± 12.35	0.082
POST FVC (ml)	2420.28 ± 831.29	2979.68 ± 1011.79	**0.009**
POST FVC (%)	71.65 ± 16.87	77.46 ± 20.12	0.159
POST FEV (ml)	1261,31 ± 659.57	1733.95 ± 769.66	**0.006**
POST FEV (%)	49.53 ± 22.46	59.42 ± 20.10	0.053
POST FEV/FVC	50.06 ± 13.66	56.60 ± 12.89	0.057
Basal saturation	92.81 ± 5.76	94.29 ± 2.57	0.337
Minimum saturation	78.92 ± 10.83	76.34 ± 8.57	0.067
Mallampati score	1.42 ± 1.00	1.47 ± 0.80	0.869
Dyspnoea grade	1.83 ± 1.03	1.74 ± 1.00	0.697
Physical activity scale	1.08 ± 0.81	1.16 ± 0.72	0.715
Exacerbations/year	0.83 ± 1.08	0.76 ± 1.15	0.718
COPD score (Gold)	1.61 ± 1.10	1.18 ± 1.01	0.087
AHI (events/hour)	1.67 ± 2.26	22.34 ± 17.14	**<0.001**
5–14, *n* (%)	0 (0)	15 (39.5)	
15–29, *n* (%)	0 (0)	15 (39.5)	**<0.001**
≥30, *n* (%)	0 (0)	8 (21.1)	
ODI (events/hour)	2.62 ± 2.65	25.58 ± 20.60	**<0.001**
≥10, *n* (%)	0 (0)	32 (84.2)	**<0.001**
Tc90%	35.19 ± 34.23	40.01 ± 33.63	0.245
≥10, *n* (%)	21 (58.3)	27 (71.1)	0.252

Data are shown as mean ± standard deviation or as number of cases (%). COPD, subjects with chronic obstructive pulmonary disease; OS, subjects with overlap syndrome; FVC, forced vital capacity; FEV, forced expiratory volume; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; Tc90%, percentage of sleep time with oxygen saturation below 90%.

apnea, being the most relevant detailed in **Supplementary Table S3**. Multivariate logistic models were build with variables showing *p*-value <0.10 in univariate analysis, and revealed that only age [OR = 1.19 (95% CI: 1.07–1.32), p = 0.002], current smoking [OR = 10.50 (95% CI: 1.94–56.71), *p* = 0.006] and AHI ≥ 5 [OR = 4.54 (95% CI: 1.39–14.85) p = 0.012] significantly predicted an increased risk for left carotid atherosclerotic plaques in COPD patients (**Supplementary Table S3**).

Discussion

The results of this study provides convincing evidence that COPD patients with concomitant polygraphic criteria of sleep apnea, which are defining the OS, had an increased mean volume of left carotid plaques than those without (0.07 ± 0.02 ml and 0.04 ± 0.02 ml, respectively, p = 0.0305), although the clinical relevance of this finding must be confirmed in further clinical studies. Besides, no differences were detected on right carotid arteries. In patients with OS, frequency of atherosclerotic plaques in the left carotid artery is increased compared to COPD patients without OS (79% and 50%, respectively, p = 0.0509) but the difference in number of patients is rather small and univariate analysis did not achieve statistical significance. For that reason, we investigated the influence of OS on the presence of left carotid plaques in the whole group of COPD patients (with and without OS) besides other traditional factors related to the progression of atherosclerosis, such as age, sex, obesity, diabetes, hypertension, hypercholesterolemia and active smoking. Even after adjustment for these potential confounding factors, the

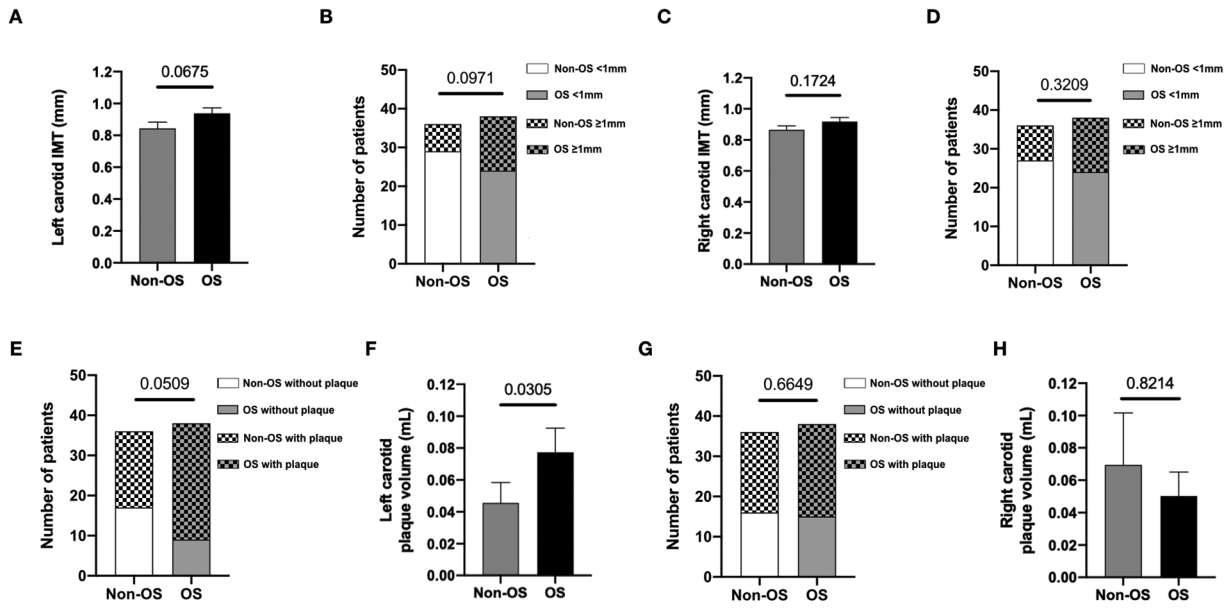

FIGURE 2
Increased prevalence of left carotid atherosclerosis in COPD patients with overlap syndrome. Number of COPD patients, with and without OS, with left and right carotid IMT measurements (panels A and C, respectively) and differences between the study groups regarding mean IMT of left and right carotids (panels B and D, respectively). Number of COPD patients, with and without OS, with left and right carotid plaque measurements (panels E and G, respectively) and differences between the study groups regarding mean volume of left and right carotid plaques (panels F and H, respectively). COPD, chronic obstructive pulmonary disease. Non-OS, non-overlap syndrome, *n* = 36. OS, overlap syndrome, *n* = 38.

presence of OS in COPD patients was still significantly associated with the increased prevalence of left carotid plaques (OR, 4.54, p = 0.012). Among the lung function parameters that we used to assess the severity of OS, the frequency of AHI appeared to be more important that hypoxemia measured by ODI and Tc90%. On one hand, Tc90% was not associated with the increased prevalence of left carotid plaques in COPD patients. On the other hand, since 44.6% of the patients with COPD in our cohort presented both AHI ≥ 5 and ODI ≥ 10, there is an association between ODI and carotid plaque prevalence. However, AHI ≥ 5 included a higher number of patients than ODI ≥ 10, and also provides better fit of the model, suggesting that AHI is an independent predictor of atherosclerotic plaques in the left carotid artery. Nevertheless, longitudinal observational studies in larger cohorts of COPD patients with and without OS are needed to elucidate the precise mechanisms which could play a key role in the cardiovascular outcomes of these patients.

Distinct previous investigations have shown that ischemic cerebrovascular events correlate positively with the increase of cIMT measured by ultrasonography (26–28). More recently, a meta-analysis including 13,428 patients with asymptomatic non-stenotic carotid plaques (NSCP) reported that the presence of NSCP is more closely related to the risk of first-ever o recurrent ischemic stroke than is cIMT (29). One of the most striking finding of the present study is that the potential deleterious effects of OS on the progression of CAS in patients with COPD seem to be largely restricted to left carotid artery. Interestingly, in a population-based cohort study in which carotid MRI scanning was performed to 1,414 stroke-free participants, authors reported that carotid atherosclerotic plaque size and composition are not symmetrically distributed and that high-risk plaque features, such as intraplaque hemorrhage, are predominant in left-sided carotid plaques (30). Based on these previous reports and taken into account that we found COPD patients with OS presented a higher prevalence and larger atherosclerotic plaques in the left carotid artery than those without OS, we consider OS as a potentially-modifiable risk factor of CAS, and suggest that it might have potential implications on ischemic stroke risk, although this should be assessed with additional longitudinal studies designed for that purpose that were not initially in the scope of this research.

It is well known that patients with COPD are at increased risk of ischemic stroke compared to the general population (31, 32), but the mechanisms and molecular mediators underlying the stroke predisposition of COPD patients still remain to be defined. Patients with COPD have also higher risk for increased cIMT than healthy subjects. In this regard, Watanabe et al. (33) have recently demonstrated the association between cIMT and forced expiratory volume (FEV) below 70% and smoking experience. On the other hand, mechanisms underlying subclinical organ damage in the obstructive sleep apnea (OSA) setting are multifactorial, including endothelial dysfunction, hypertension, and vascular remodeling (also comprehending increased cIMT) (34). In the same line, studies by Altin et al. (35) and Wang et al. (36) described an association of cIMT with severe OSA and AHI. Conversely, Myśliński et al. (37) described absence of differences in early lesions between severe OSA patients and healthy controls. However, patients with COPD have increased vascular damage compared to healthy subjects. Thus, according to current evidence and the results of our study, we suggest that OS may impact on plaque development rather than

early atherosclerosis onset. Besides traditional risk factors for ischemic stroke, such as aging, tobacco smoking, diabetes, or hypercholesterolemia and arterial hypertension, there is extensive evidence indicating that chronic low-grade systemic inflammation and oxidative stress, which are key pathophysiological drivers of both pathological wall remodeling in atherosclerosis (16, 38) and COPD (39–41), can also induce cerebrovascular dysfunction and structural alterations of cerebral vessels increasing the risk for ischemic stroke in COPD patients (42, 43). Regarding the impact of OS on cardiovascular morbidity and mortality in COPD patients, distinct large observational studies have yielded conflicting results (44–46). Our results shown herein favor the notion that OS should be considered as a risk factor for atherosclerosis in the left carotid artery, because we observed that COPD patients with an AHI ≥ 5 presented 4.5-fold higher risk for presence of atherosclerotic plaques in the left carotid artery, which were also larger in patients with OS. However, further prospective longitudinal case-control studies in large cohorts of well-characterized COPD patients are warranted in order to determine the real impact of OS on the incidence of major cardiovascular events such as ischemic stroke among others.

The major strength of the present study is the novelty of its design performing ultrasound IMT measurements of both carotid arteries to a large cohort of COPD patients and control subjects assessed by spirometry and cardiorespiratory polygraphy. However, this study design has some limitations because causal interpretations of the impact of OS in the risk of ischemic stroke cannot be drawn from a cross-sectional study and large longitudinal observational studies are needed to accomplish that endpoint. Moreover - although AHI ≥ 5 stays statistically significant as an independent predictor of left carotid plaque presence - our analysis shows very high confidence intervals, suggesting that our study cohort may be too small or heterogeneous and, hence, odds estimations should be interpreted with caution.

In conclusion, the present study provides the first evidence that the presence of OS in COPD patients is positively associated with lager left carotid atherosclerotic plaques, suggesting that ultrasound carotids assessment may be useful to identify those COPD patients at higher-risk for ischemic stroke to whom in-depth cerebrovascular evaluation should be recommended. Nevertheless, in order to prove the efficacy of this screening strategy, in terms of outcomes and cost-effectiveness, further longitudinal clinical studies in larger cohorts of COPD patients are warranted.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Clinical Research Ethics Committe from Hospital Universitario La Princesa, Madrid; report reference, PI16/2,800. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PL, JMM, AF, AG-R and CG-M: conceived and designed the study. PL, JMM, AF and JA: were involved in data acquisition. PL, CEF-G and AG-R: analyzed the data. PL, CEF-G, AG-R and CG-M: wrote the draft. PL, CEF-G, JMM, AF, JA, AG-R and CG-M: wrote the manuscript and discussed it. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1104377/full#supplementary-material.

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Relationship between human serum albumin and in-hospital mortality in critical care patients with chronic obstructive pulmonary disease

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Background: The relationship between human serum albumin levels and the prognosis of critical care patients with chronic obstructive pulmonary disease (COPD) remains controversial.

Objective: To investigate the relationship between serum albumin levels and in-hospital mortality in critical care patients with COPD. METHODS: This study used a retrospective observational cohort from the Medical Information in Intensive Care database (MIMIC-IV) in the United States. Multivariate Cox regression analysis was used to assess the relationship between serum albumin levels and in-hospital mortality. A restricted cubic spline line was also used to explore nonlinear relationship.

Results: A total of 3,398 critical care patients with COPD were included. The overall in-hospital mortality was 12.4%. We found a negative relationship between human serum albumin and in-hospital mortality (HR=0.97, 95% CI 0.96–0.99, p=0.002).

Conclusion: In critical care patients with COPD, there was a negative association between human serum albumin and in-hospital mortality.

KEYWORDS

severe chronic obstructive pulmonary disease, serum albumin, in-hospital mortality, ICU - intensive care unit, relationship

1. Introduction

Chronic obstructive pulmonary disease (COPD) is currently a major public health problem worldwide, with a global prevalence of 11.7% in 2010 (1). COPD is also the third leading cause of death worldwide (2). Patients with acute exacerbation of COPD often require hospitalization, or even need intensive care unit admission (2). Identifying the reversible risk factors during hospitalization is therefore essential to help reduce mortality as well as the burden of disease.

Human serum albumin is a multifunctional plasma protein that accounts for more than 50% of the total plasma protein content. Physiologically, human serum albumin, in addition to its

antioxidant properties (3), is also an acute-phase response protein whose concentration decreases during the acute-phase response (4). Albumin is also a clinical bio-marker of malnutrition. Hypoproteinemia is associated with prolonged hospital stay during acute exacerbations, acute respiratory failure and increased mortality in COPD patients (3, 5, 6). However, other studies reported no correlation between albumin level and prognosis in COPD patients (7).

In this study, we attempted to identify the dose–response relationship between human serum albumin level and hospital mortality in COPD patients using a large data set of critical illnesses (8).

2. Data and methods

2.1. Methods

This study used a retrospective observational cohort of all patients diagnosed with COPD in the Medical Information in Intensive Care database (8) (MIMIC-IV version 1.0). MIMIC-IV is a large, real-world clinical database of critical care patients from 2008 to 2019 in Beth Israel Deaconess Medical Center (9). One of the authors (Shanglin Chen) was granted access to utilize the database (license number: 10756765). This study was written according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (10). All the data accessed complied with relevant data protection and privacy regulations.

2.2. Study population

This study was based on the real-world study concept and included all COPD patients from the MIMIC-IV database. The inclusion criteria: 1. First admission to the intensive care unit. 2. Human serum albumin level measured within 24 h. 3. Age ≥ 18 years.

2.3. Exposure and covariates

This study focused on assessing the relationship between baseline human serum albumin and hospital mortality in patients with severe COPD. Patients were divided into hypoalbuminemia group (<30 g/L) and hyperalbuminemia group (≥30 g/l) according to previous studies (11, 12).Vital signs and laboratory indicators were analyzed using the worst value within 24 h of ICU admission. Covariates were identified based on previous serum albumin-related studies and clinical relevance (10–13). Covariates in this study including age, sex, Glasgow score, mean arterial pressure, respiratory rate, oxygen saturation, serum sodium, serum potassium, blood creatinine, hemoglobin, platelets, myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, renal disease, cancer, diabetes mellitus, co-morbidity index, SAPSII score, SOFA score, and OASIS score.

2.4. Outcome

The outcome was in-hospital mortality.

2.5. Statistical analysis

Data analysis was performed using R.3.3.2, free statistical software version 1.6.1 (13). Categorical variables were expressed as percentages (%) using the $\chi 2$ test; continuous variables with normal distribution were expressed as mean ± standard deviation (x ± s) and t-test were used for comparison between groups. Continuous variables with skewed distribution were expressed as median (quartiles) using Kruskal-Wallis test. Missing data were replaced by dummy variables (14). Multivariable Cox regression analysis was used to analyze the independent association between serum albumin level and in-hospital mortality. A restricted cubic spline function was used to analyze the nonlinear relationship between human serum albumin and hospital mortality, and a log-likelihood ratio test of $p < 0.05$ was used to consider the relationship as nonlinear. Kaplan–Meier survival curves for low and high human serum albumin were plotted and Multivariable Cox regression analysis was performed. $p < 0.05$ (two-sided) was considered a statistically significant difference. Propensity-score matching (PSM) was also used to compare the outcomes between two groups.

2.6. Missing data

There are many variables with missing data in the MIMIC IV database. For PaO_2/FIO_2 ratio, over 20% of the values were missing and were removed from this analysis. In other continuous variables, the missing values were imputed by k-Nearest Neighbors method (15).

3. Results

3.1. Study population

3,398 COPD patients were screened in the MIMIC-IV database who met the inclusion and exclusion criteria of this study.

3.2. Baseline characteristics

Of 3,398 COPD patients, age was 70.3 ± 12.0 years. 1857 (54.6%) were male. The overall in-hospital mortality was 12.4%. 1,062 patients had low human serum albumin (<30 g/L) and 2,336 patients had human serum albumin ≥30 g/L. Glasgow score, mean arterial pressure, respiratory rate, serum potassium, hemoglobin, platelets, PO_2, PCO_2, heart failure, cancer, diabetes mellitus, sepsis, MV, AECOPD, co-morbidity index, and co-morbidity index SAPSII score, SOFA score, and OASIS score were imbalance in two groups (all $p < 0.05$) disease.

3.3. Association between baseline human serum albumin and in-hospital mortality

3.3.1. Univariate and multivariate cox regression analyses

In the extended multivariable Cox models, we observed that the hazard ratios (HRs) of serum albumin were consistently significant in

unadjusted, minimally adjusted (adjusted for age and sex), and fully adjusted (adjusted for all covariates in Tables 1, 2; Supplementary Table S1). The fully adjusted model indicated a negative association between serum albumin level and in-hospital mortality (HR = 0.97, 95% CI 0.96–0.99, $p = 0.002$. Restricted cubic spline analysis (Figure 1) showed nonlinear relationship between human serum albumin and in-hospital mortality (nonlinear test: $p = 0.028$, Table 3). When human serum albumin was <30 g/L, each 1 g/L increase in human serum albumin was associated with a 5% reduction in hospital mortality (HR = 0.95, 95% CI (0.91, 0.98), $p = 0.002$). While human serum albumin was ≥30 g/L, increased serum albumin was not associated with changing in hospital mortality (HR = 1.00, 95% CI 0.96–1.04, $p = 0.775$) (Table 3).

3.3.2. The in-hospital mortality was 21.7% (230/1062) and 8.2% (192/2336) for low and hyperalbuminemia groups, respectively

Kaplan–Meier survival curves (Figure 2) for cumulative hospital survival showed a statistically significant difference between the low and high human serum albumin groups (Log-rank test: $p < 0.001$). Multivariable Cox regression analysis showed that after adjusting for all confounders in Table 1, the in-hospital mortality in high human serum albumin group was 0.25 times lower than in the low human serum albumin group (HR = 0.75, 95% CI: 0.60 to 0.93, $p = 0.008$, Table 2). In Multivariable Cox regression analysis, age, Glasgow score, respiratory rate, oxygen saturation, serum potassium, PCO_2, peripheral vascular disease, renal disease, diabetes mellitus, co-morbidity

TABLE 1 Baseline characteristics of participants.

Covariates	All patients (*n* =3,398)	Albumin<30g/L (*n* =1,062)	Albumin≥30g/L (*n* =2,336)	*p* value
Age(years)	70.3 ± 12.0	70.3 ± 11.6	70.3 ± 12.2	0.474
Sex, n (%)(male)	1857 (54.6)	583 (54.9)	1,274 (54.5)	0.645
Glasgow score	14.0 (12.0, 15.0)	14.0 (11.0, 15.0)	14.0 (13.0, 15.0)	< 0.001
MAP (mmHg)	77.9 ± 10.9	74.6 ± 9.5	79.4 ± 11.2	< 0.001
Respiratory rate (BPM)	29.3 ± 6.6	29.9 ± 6.6	29.1 ± 6.6	< 0.001
Oxygen saturation(%)	96.0 ± 2.7	96.1 ± 3.6	96.0 ± 2.2	0.258
Serum sodium(mmol/L)	136.2 ± 5.8	136.0 ± 6.0	136.4 ± 5.6	0.078
Serum potassium(mmol/L)	4.8 ± 1.0	4.8 ± 1.0	4.9 ± 1.1	0.039
Creatinine (mg/L)	1.3 (0.9, 2.1)	1.3 (0.9, 2.3)	1.2 (0.9, 2.1)	0.208
Hemoglobin (g/L)	9.8 ± 2.3	8.8 ± 2.0	10.2 ± 2.3	< 0.001
Platelets(10^9/L)	182.0 (126.0, 244.0)	165.0 (100.0, 239.0)	189.0 (137.0, 245.8)	< 0.001
PO_2	97.0 (59.8, 176.0)	91.0 (58.0, 165.2)	109.0 (66.8, 198.0)	< 0.001
PCO_2	52.0 (43.0, 65.0)	52.5 (43.0, 66.0)	50.5 (42.0, 61.0)	< 0.001
Myocardial infarction	748 (22.0)	226 (21.3)	522 (22.3)	0.487
Heart failure	1,662 (48.9)	459 (43.2)	1,203 (51.5)	< 0.001
Peripheral vascular disease	570 (16.8)	170 (16)	400 (17.1)	0.420
Cerebrovascular disease	411 (12.1)	120 (11.3)	291 (12.5)	0.337
Renal disease	1,109 (32.6)	324 (30.5)	785 (33.6)	0.074
Cancer	504 (14.8)	224 (21.1)	280 (12)	< 0.001
Diabetes mellitus	1,305 (38.4)	382 (36)	923 (39.5)	0.049
Sepsis	2,151 (63.3)	818 (77)	1,333 (57.1)	< 0.001
MV				< 0.001
Noninvasive-Ventilation	235 (6.9)	53 (5.0)	182 (7.8)	
Invasive-Ventilation	875 (25.8)	377 (35.5)	498 (21.3)	
No-Ventilation	2,288 (67.3)	632 (59.5)	1,656 (70.9)	
Co-morbidity index	7.4 ± 2.7	7.8 ± 2.8	7.3 ± 2.6	< 0.001
SAPSII score	39.0 ± 13.2	43.7 ± 13.8	36.9 ± 12.4	< 0.001
SOFA score	5.8 ± 3.8	7.4 ± 4.2	5.1 ± 3.4	< 0.001
OASIS score	33.5 ± 9.1	36.7 ± 9.4	32.1 ± 8.6	< 0.001
AECOPD	1,268 (37.3)	376 (35.4)	892 (38.2)	0.012

MAP, mean arterial pressure; SAPS II score, Simplified Acute Physiology Score II; SOFA score, Sequential Organ Failure Score; OASIS score, Oxford Acute Severity of Illness Score; PO_2, Partial pressure of oxygen; PCO_2, Partial pressure of carbon dioxide; MV, Mechanical ventilation; COPD, chronic obstructive pulmonary.

TABLE 2 Relationship between serum albumin and in-hospital mortality.

Exposure	Unadjusted model HR(95% CI)	P value	Minimally adjusted model HR(95% CI)	*p* value	Fully adjusted model HR(95% CI)	*p* value
Serum albumin	0.94 (0.93, 0.96)	<0.001	0.94 (0.92, 0.95)	<0.001	0.97 (0.96, 0.99)	0.002
Grouped serum albumin						
<30 g/L	Reference		Reference		Reference	
≥30 g/L	0.51 (0.42, 0.62)	<0.001	0.49 (0.41, 0.60)	<0.001	0.75 (0.60, 0.93)	0.008

Unadjusted model: no adjustment for covariates.
Minimally adjusted model: adjusted for age and gender.
Fully adjusted model: adjusted all covariates in Table 1.

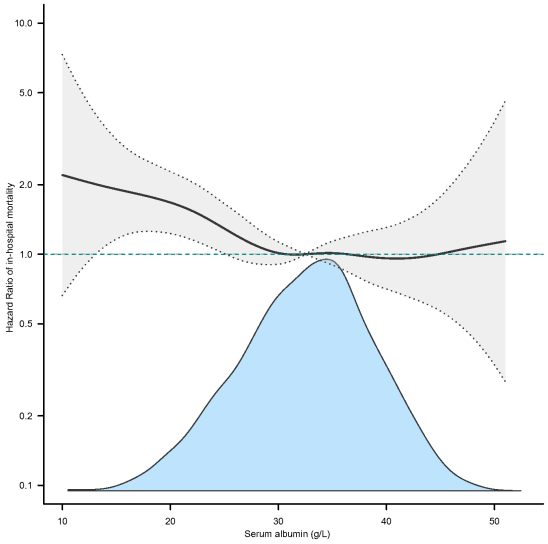

FIGURE 1
Nonlinear relationship between serum albumin and in-hospital mortality (adjusted all covariates in Table 1).

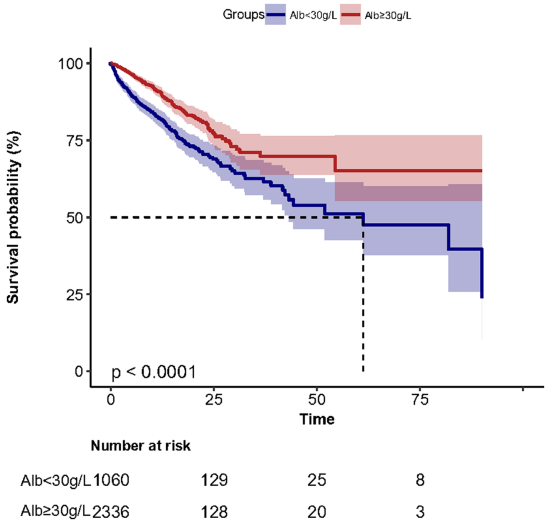

FIGURE 2
Survival curves in the low albumin and high albumin groups.

TABLE 3 Nonlinear relationship between serum albumin and in-hospital mortality.

Serum albumin	HR (95% CI)	*P* value
<30 g/L	0.95 (0.91, 0.98)	0.002
≥30 g/L	1.00 (0.96, 1.04)	0.775
Nonlinear test		0.028

Adjusted all covariates in Table 1.

index，SOFA score were also associated with in-hospital mortality (Supplementary Table S1).

The distribution of albumin levels in those that survived versus those non-survived was 30.0 ± 6.2 and 28.9 ± 7.0 g/L (Supplementary Figure S3). In subgroup analysis (Figure 3), we found the results were stable in different age, sex, MV, sepsis and AECOPD groups. In multivariable Cox regression models, we evaluating the association between serum albumin and 30-day, 90-day and 1-year mortality, the results remained stable.

4. Discussion

The results of this study showed that in ICU, lower human serum albumin is negatively associated with higher in-hospital mortality in patients with COPD. Analysis of dose–response relationship using restricted cubic spline functions indicate a nonlinear relationship between human serum albumin and in-hospital mortality. When human serum albumin was below 30 g/L, there was a negative correlation between human serum albumin and in-hospital mortality. When human serum albumin is above or equal to 30 g/L, the correlation was not significant.

As an important biomarker of nutritional status, lower serum albumin was reportedly associated with worsening clinical status during COPD (16, 17). We also found the same effect in COPD patients with critical illness. Previous studies had also reported that low levels of serum albumin could increase in-hospital mortality in COPD patients. In a retrospective ($n = 574$) cohort study in Spain, serum albumin levels were found to be strongly associated with disease severity and outcome in elderly patients with COPD (6). In another smaller study ($n = 20$), albumin levels were also indicated to be closely related to the prognosis of COPD patients (18). Similar

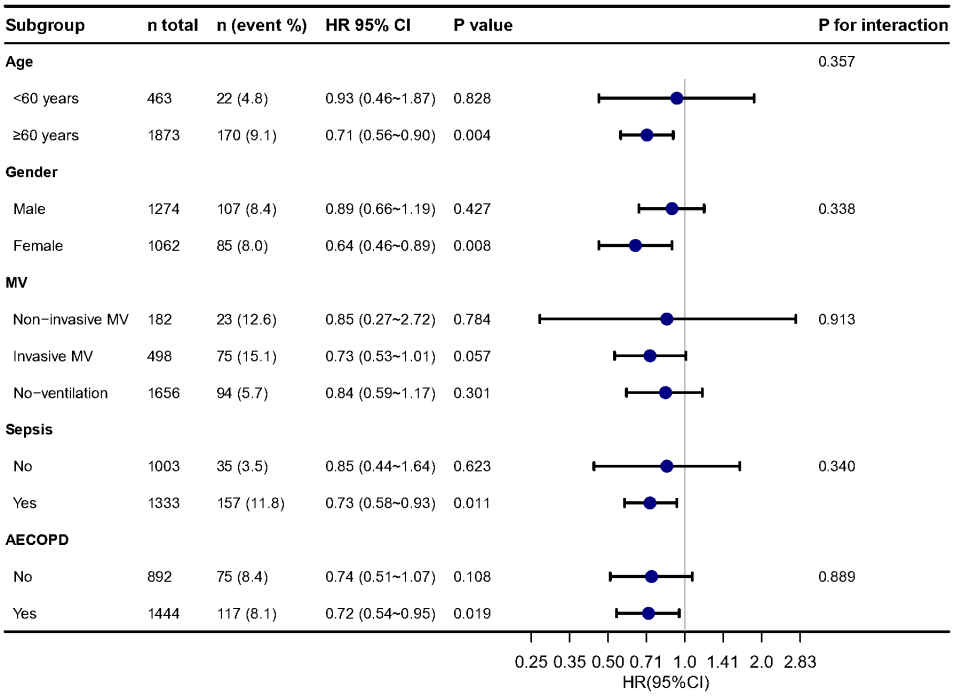

FIGURE 3
Stratified analysis of relationship between serum albumin and in-hospital mortality. Adjusted for all cofounders in Table 1.

findings were found in a larger ($n = 1,647$) cohort (19). However, compared to these studies, the present cohort study had a larger sample size ($n = 3,398$), adjusted for more confounding factors, and had relatively more stable and reliable results.

It has also been shown that there was no relationship between hypoalbuminemia and patient prognosis in a cohort study (7). However, as a result of the small sample size of this study ($n = 431$) and the large difference in the distribution of the number of people in the low and high human serum albumin groups in the cohort (1.5% versus 98.5%), the results were not consisting with our study (HR of low albumin versus normal was 1.67 (0.22, 12.57), $p = 0.604$).

This study also has clinical implications. We found a nonlinear relationship between human serum albumin and hospital mortality in critical care patients with COPD. Our clinical experience also supports this nonlinear relationship. The optimal cut off point for in-hospital mortality was 30 g/L which was similar with previous study (11, 12). Ruiqi Chen et al. found that an albumin level of 30.5 g/l was best to predict the prognosis for in-hospital mortality (11). This cut off point also suggests that clinicians may consider using albumin to increase albumin levels in patients with COPD when human serum albumin is low.

Albumin is a biomarker of malnutrition and frailty in older patients (20). Therefore, we did subgroup analysis based on age groups (>60 years and < 60 years). It seems no different between the two groups. However, for those in the >60 years group higher albumin is associated with lower mortality, while this is not seen in the <60 years group. We looked at the relationship between age and albumin and found that younger patients tended to have higher albumin levels (Supplementary Figure S1A). These patients would fall more on the right side of the curve fit, i.e., after albumin levels above 30 g/L. At this region, the increased serum albumin was not associated with changing in hospital mortality (Supplementary Figure S1B).

Similar to the previous study and our clinical experience, we also found age (21, 22), Glasgow score (23), respiratory rate (24), oxygen saturation (25), serum potassium, PCO_2, peripheral vascular disease, renal disease, diabetes mellitus, comorbidity index (26), SOFA score (27) were also associated with in-hospital mortality.

5. Limitations

There are some limitations of this study. First, this is a retrospective observational single-center study and the effect of uncontrolled confounding factors cannot be excluded, however, the large sample size of this study may reduce bias to some extent. Secondly, this study evaluated the most unwell patients (in the ICU setting) and the findings cannot be applied to hospitalized patients who do not end up needing ICU level care. Third, In the study, data on respiratory-related death could not be found in MIMIC-IV database, further studies need to clarify whether albumin is associated with respiratory-related death in COPD patients.

6. Conclusion

In critical care patients with COPD, there was a negatively association between human serum albumin and in-hospital mortality.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ML and LHu wrote the manuscript. BM and CS conducted the data analysis. LHa modified the manuscript and interpreted the analysis. DZ conducted the literature review. WS reviewed the manuscript. BM and LM designed the study and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1109910/full#supplementary-material

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Modeling of pulmonary deposition of agents of open and fixed dose triple combination therapies through two different low-resistance inhalers in COPD: a pilot study

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Introduction: Inhalation therapy is a cornerstone of treating patients with chronic obstructive pulmonary disease (COPD). Inhaler devices might influence the effectiveness of inhalation therapy. We aimed to model and compare the deposition of acting agents of an open and a fixed dose combination (FDC) triple therapy and examine their repeatability.

Methods: We recruited control subjects (Controls, *n* =17) and patients with stable COPD (S-COPD, *n* =13) and those during an acute exacerbation (AE-COPD, *n* =12). Standard spirometry was followed by through-device inhalation maneuvers using a pressurized metered dose inhaler (pMDI) and a soft mist inhaler (SMI) to calculate deposition of fixed dose and open triple combination therapies by numerical modeling. Through-device inspiratory vital capacity (IVC_d) and peak inspiratory flow (PIF_d), as well as inhalation time (t_{in}) and breath hold time (tbh) were used to calculate pulmonary (PD) and extrathoracic deposition (ETD) values. Deposition was calculated from two different inhalation maneuvers.

Results: There was no difference in forced expiratory volume in 1 s (FEV1) between patients (S-COPD: 42±5% vs. AE-COPD: 35±5% predicted). Spiriva® Respimat® showed significantly higher PD and lower ETD values in all COPD patients and Controls compared with the two pMDIs. For Foster® pMDI and Trimbow® pMDI similar PD were observed in Controls, while ETD between Controls and AE-COPD patients did significantly differ. There was no difference between COPD groups regarding the repeatability of calculated deposition values. Ranking the different inhalers by differences between the two deposition values calculated from separate maneuvers, Respimat® produced the smallest inter-measurement differences for PD.

Discussion: Our study is the first to model and compare PD using pMDIs and an SMI as triple combination in COPD. In conclusion, switching from FDC to open triple therapy in cases when adherence to devices is maintanined may contribute to better therapeutic effectiveness in individual cases using low resistance inhalers.

KEYWORDS

COPD, fixed dose triple therapy, open triple therapy, deposition, repeatability, modeling

1. Introduction

Chronic obstructive pulmonary disease (COPD) affects more than 380 million people worldwide (1). Inhalation therapy is a cornerstone of the treatment of airway diseases, including high burden diseases as COPD and asthma (1, 2). According to international guidelines the inhalation therapy of COPD patients with severe obstructive ventilatory disorder, persistent symptoms and frequent exacerbations (Global Initiative for Chronic Obstructive Lung Disease: GOLD D category in most of our cases) contains long-acting beta2-agonist (LABA) and muscarinic antagonists (LAMA) as bronchodilators and inhaled corticosteroids (ICS) especially in patients with exacerbations and high blood eosinophil count (1). Many commercially available inhalers are a combination of ICS-LABA, LABA-LAMA, or fixed triple combination (ICS-LABA-LAMA; FDC). Despite the availability of triple combinations, many patients use two different devices, mainly combination of ICS-LABA and a mono-LAMA inhaler (3).

The effectivity of inhalation therapy has numerous influencing factors which are connected to the drug, the device or the patient. The largest variety of devices belong to dry powder inhalers (DPI) and many combinations are commercially available including triple FDC. Pressurized metered dose inhaler (pMDI) has a low number of different drug combinations including triple FDC and ICS-LABA, while soft mist inhaler (SMI) is only represented by the device Respimat® and is containing LABA-LAMA or LAMA monotherapy.

Various studies examined the effectiveness of inhalation therapy *in vivo*. Additionally *in vitro* and *in silico* investigations measured the deposition rate of the emitted dose (4, 5). *In vivo* studies mostly apply radioscintigraphy and can be complicated upon repeated measurements as it imposes a burden of radiation on the subjects (6, 7). However, other studies applied pharmacokinetic methods to measure pulmonary deposition of inhaled particles by measuring serum levels and urinary excretion of specific agents (8–10). Nonetheless, pharmacokinetic methods are not able to differentiate between the deposition into different regions of the lung and it is not capable to reveal the amount of drug removed by mucociliary clearance (11). *In vitro* measurements only require the equipment to produce a replica of the airways and is limited by the natural variety of the different subjects' anatomy (5). *In silico* studies such as computational fluid dynamic simulations or numerical simulations (e.g., the Stochastic Lung Model) have the benefit of repeated measurements not requiring personal and material input but they need a validation by *in vivo* models before usage (12–14).

As the device-handling plays a critical role in the success of inhalation therapy, many factors influencing patient conduct can be investigated (15–17). Sufficient peak inspiratory flow (PIF) is crucial using DPI devices, which might be difficult to generate for patients with severe COPD (18). Appropriate handling of pMDI and SMI devices demand the precision from patients regarding the timing of actuation and inspiration, adequate breath-hold time, correct posture and device position, and sufficient inspiratory volumes (16). There are many ways to observe the accuracy of device handling, but limited number of publications focuses on assessing uniformity of inhalation maneuvers through these devices known as repeatability resulting in predictable PD every day.

Our aim was to investigate inhalation maneuvers through commercially available pMDI and SMI devices, and assess deposition repeatability of FDC or open triple therapy in severe GOLD D COPD patients by numerical modeling.

2. Materials and methods

2.1. Subjects

Patients with stable COPD (S-COPD, $n = 13$) were recruited during regular outpatient visits, patients with exacerbated COPD (AE-COPD, $n = 12$) were included <72 h after hospital admission due to an acute severe relapse. Patients had been previously diagnosed with COPD by a respiratory specialist according to 2015 Global Initiative for Chronic Obstructive Lung Disease (GOLD) as post-bronchodilator $FEV_1/FVC < 0.70$ (19). Therapy was decided by the treating physician, but all patients with AE were treated with systemic steroids. Control volunteers (Control, $n = 17$) did not have a chronic respiratory disease and were recruited from employees of the Department of Pulmonology, Semmelweis University, Budapest, Hungary. Individuals in the S-COPD and Control groups with acute respiratory tract infections within 2 weeks and AE-COPD group who suffered from pneumonia or needed non-invasive or invasive ventilation were excluded. Subjects were recruited between April and December 2015.

All procedures were performed in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All subjects were informed about the methods and aims of the measurements and signed the informed consent form. The study was approved by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (SE TUKEB 239/2015).

2.2. Study design

The subjects attended a single visit which was followed by data processing and numerical modeling. All patients performed standard lung function tests, which were followed by the two consecutive inhalation maneuvers per device using two different inhalers after a minimum of a 30-min break. Subjects filled out disease-specific and generic quality of life questionnaires. Subsequently, the deposition calculations were performed by the Stochastic Lung Model (13).

2.3. Lung function measurements

Electronic spirometer and body plethysmography (PDD-301/s, Piston, Budapest, Hungary) were used for lung function measurements performed according to the European Respiratory Society (20, 21). None of the records were post-bronchodilator measurements.

2.4. Inhalation maneuvers through different inhalers

Commercially available pressurized metered-dose inhaler (pMDI inhalation solution placebo for Foster®/Trimbow®) and soft mist inhaler (placebo for Respimat®) were used.

For through-device lung function testing electronic spirometer was used (PDD-301/sh, Piston, Budapest, Hungary), which has built-in ambient temperature, pressure and humidity sensors for the fully automatic BTPS correction, as described in detail in our previous study (22). The spirometer is equipped with a PinkFlow flowmeter (PPF-18, Piston, Budapest, Hungary), which measures flow based on the principle of a symmetric and averaging Pitot tube, and was connected directly to the pMDI or SMI. Subjects were instructed for 5–10 min before the measurements to explain and correct inhalation maneuvers as recommended by the manufacturers of each device. Steps of the inhalation maneuver included: (1) preparation of the device, (2) long exhalation, (3) attachment of the inhaler to the flexible connecting piece, (4) deep inhalation through the inhaler to total lung capacity, with optimal actuation of pMDI and SMI by the examiner and simultaneous recording of the pre-specified parameters, (5) breath-holding for 10 s (when possible) while the inhaler device was detached from the connecting piece; and (6) long exhalation. Through-device inspiratory vital capacity (IVCd) and peak inspiratory flow (PIF_d), inhalation time (t_{in}) and breath-hold time (t_{bh}) were recorded. Measurements for both pMDI and Respimat® were performed and randomly followed after at least 5-min break by the second sequence of maneuvers in all patients and controls.

2.5. Assessment of symptoms and quality of life

Subjects filled out the Modified Medical Research Council (mMRC) and the Hungarian version of the COPD Assessment Test (CAT), and the Visual Analogue Scale (VAS) scaled from 0 to 10, to measure the general health condition of the participants.

2.6. Numerical modeling of pulmonary and extrathoracic deposition

Pulmonary (PD) and extrathoracic (ETD) deposition fraction values were calculated as a percent of the metered dose using the Stochastic Lung Model (SLM). The model was primarily developed by Koblinger and Hofmann and afterwards it has undergone further development. The model has been validated and used to simulate the pulmonary deposition of different aerosols as well as inhaled drug particles (13, 14, 23). In the SLM model the structure of the conducting airways is built up stochastically based on distribution functions of airway lengths, diameters, branching angles and gravity angles Raabe (24). The geometry of the acinar airways is built up based on the description of Haefeli-Bleuer and Weibel (25). The model is calculating deposition fractions in the extrathoracic airways based on empirical deposition formulas. In the pulmonary airways deposition fractions are computed by tracking large numbers of inhaled particles after their inhalation until they deposit in the airways or leave the lungs *via* exhalation. In the model the particles can deposit due to impaction, gravitational settling and Brownian diffusion. As input data the breathing parameters and the size distribution and density of the drug particles need to be provided. The inhalation parameters are the standard spirometry and body plethysmography measurement results, such as residual volume (RV) and through-device spirometry data, such as IVC, T_{in} and T_{bh}, which were provided for both pMDI and Respimat® devices. For the calculation we used the particle size distribution values of Spiriva® Respimat®, Foster® pMDI and Trimbow® pMDI. PD and ETD values were calculated from the first and second inhalation maneuver and their mean was used for further statistical analysis.

2.7. Statistical analysis

Statistical analysis was performed using GraphPad Prism software 8 (GraphPad Software, La Jolla, CA, United States) and SPSS Statistics V22 (International Business Machines Corporation, NY, United States). The results are expressed as the mean ± standard error of the mean (SEM) or median (interquartile range). One-way ANOVA followed by Bonferroni's multiple comparison test or Kruskal-Wallis test with Dunn's multiple comparison test were used as appropriate. Repeatability of deposition values was assessed by the Bland–Altman test (26). Results were considered to be statistically significant when the p value was less than 0.05.

3. Results

3.1. Clinical characteristics of participants

Patient and control volunteer characteristics are summarized in Table 1. COPD patients were significantly older, more often smokers and had higher cumulative smoking impact. All AE-COPD patients fulfilled the criteria of GOLD D category. COPD patients had a high number of comorbidities but there were no significant differences between stable and exacerbated patients in this regard. Patients with exacerbations were more symptomatic using mMRC, CAT and VAS scores. The maintenance inhalation therapy was similar between patient groups, most patients being on triple therapy.

3.2. Lung function results

Lung function parameters revealed similarly severe airflow obstruction and lung hyperinflation in both COPD groups, while normal lung function parameters were noted in the Control group (Table 2).

3.3. Through-device inhalation parameters using different inhalers

IVC_d, PIF_d, t_{in} and t_{bh} were tested for pMDI and SMI devices (Table 3). IVC_d was lower as measured through both devices than during normal spirometry in controls, while only slightly lower in both COPD groups. In the Control and both COPD groups PIF_d was significantly lower as compared to PIF during spirometry for both devices. Inhalation time (t_{in}) was on average between 2–3 s for all groups. Mean t_{bh} was above 10 s in Controls and S-COPD and significantly lower in AE-COPD patients compared to S-COPD patients.

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TABLE 1 Clinical characteristics of controls and patients.

	Control	S-COPD	AE-COPD
Number (*n*)	17	13	12
Female/male	10/7	9/4	9/3
Age (years)	43 ± 4	**65 ± 2***	**61 ± 2***
BMI (kg/m^2)	25.0 ± 0.9	25.6 ± 1.4	27.1 ± 2.0
Smoking habit, *n* (%)**			
Current smoker	8 (47)	4 (31)	7 (58)
Former smoker	1 (6)	9 (69)	5 (42)
Never smoker	8 (47)	0 (0)	0 (0)
Pack years	18 ± 5	**50 ± 5***	**36 ± 3***
GOLD category 2017, *n* (%)			
A	NA	1 (8)	0 (0)
B	NA	1 (8)	0 (0)
C	NA	5 (38)	0 (0)
D	NA	6 (46)	12 (100)
Quality of life			
mMRC	0 (0–0)[a]	**2 (1–2)**[b]	**4 (3–4)***
CAT	2 (0–6)	**11 (7–22)**[b,*]	**27 (18–30)***
VAS	1 (0–3)[c]	**5 (4–5)**[b,*]	**8 (7–10)**[d,*]
Comorbidities, *n* (%)			
Osteoporosis	NA	0 (0)	3 (25)
Diabetes mellitus	NA	1 (8)	3 (25)
Hypertension	NA	4 (31)	2 (17)
Atherosclerosis	NA	4 (31)	4 (33)
Myocardial infarction	NA	0 (0)	2 (17)
Stroke	NA	0 (0)	2 (17)
Maintenance COPD therapy, *n* (%)			
ICS	NA	9 (69)	12 (100)
LABA	NA	12 (92)	12 (100)
LAMA	NA	12 (92)	12 (100)
Theophylline	NA	3 (23)	6 (50)

$p < 0.05$ vs. Control, ** Chi-square test: $p < 0.01$. Significant differences are highlighted in bold. BMI, Body Mass Index; CAT, COPD Assessment Test; AE-COPD: patients with exacerbated COPD; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council; NA, not applicable; S-COPD: patients with stable COPD; VAS, Visual Analogue Scale. Data are shown as mean ± standard error of the mean (SEM) or median (interquartile range).
[a]$n = 16$.
[b]$n = 10$.
[c]$n = 15$.
[d]$n = 11$.

3.4. Pulmonary (PD) and extrathoracic deposition (ETD)

The results of numerical modeling for Foster® pMDI, Trimbow® pMDI and Spiriva® Respimat® are summarized in Figures 1, 2. Both COPD groups and Controls showed significant difference by Spiriva® Respimat® compared to the two pMDIs regarding PD and ETD. Spiriva® Respimat® produced much higher PD than Foster® pMDI and Trimbow® pMDI. For Foster® pMDI and Trimbow® pMDI similar PD were observed in Controls, while ETD between Controls and AE-COPD patients did significantly differ. ETD values were significantly lower in all COPD patients compared to heathy volunteers. Spiriva® Respimat® showed significantly lower ETD values than Foster® pMDI and Trimbow® pMDI.

TABLE 2 Lung function values.

	Control	S-COPD	AE-COPD
Number (*n*)	17	13	12
FVC, % predicted	102 ± 3	**79 ± 6***	**67 ± 7***
FEV_1, % predicted	95 ± 2	**42 ± 5***	**35 ± 5***
FEV_1/FVC, %	79 ± 2	**44 ± 3***	**49 ± 3***
PEF, % predicted	85 ± 8	**41 ± 4***[,a]	**34 ± 3***[,b]
$FEF_{25-75\%}$, % predicted	76 ± 5	**18 ± 3***	**17 ± 2***
PIF, L/s	5 ± 0.4	**2 ± 0.1***	**3 ± 0.3***
IVC, % predicted	99 ± 3	**77 ± 5***	**67 ± 5***
TLC, % predicted	93 ± 2	**103 ± 5***	**113 ± 8***
TGV, % predicted	119 ± 5	**168 ± 11***	**193 ± 15***
RV, % predicted	83 ± 6	**152 ± 15***	**192 ± 19***
RV/TLC	0.28 ± 0.02	**0.56 ± 0.03***	**0.66 ± 0.04***
Raw, % predicted	108 ± 6	**295 ± 25***[a]	**297 ± 31***

*$p < 0.05$ vs. Control, Significant differences are highlighted in bold. AE-COPD: patients with exacerbated COPD; $FEF_{25-75\%}$, forced expiratory flow at 25–75% of the pulmonary volume; FEV_1, forced expiratory volume in the 1st second; FVC, forced vital capacity; IVC, inspiratory vital capacity; PEF, peak expiratory flow; PIF, peak inspiratory flow; Raw, airway resistance; RV, residual volume; S-COPD: patients with stable COPD; TGV, thoracic gas volume; TLC, total lung capacity. Data are shown as mean ± standard error of the mean (SEM).
[a]$n = 12$.
[b]$n = 13$.

3.5. Repeatability of pulmonary (PD) and extrathoracic deposition (ETD) values calculated from repeated measurements

The Bland–Altman analysis was used to define the variability of the PD and ETD values calculated from inhalation maneuver parameters through a given inhaler and the corresponding particle size distribution. Significant individual differences were present in all tested medications regarding PD and ETD (Figures 3, 4). The X-axis represents the mean of the two calculations for deposition values, while the Y-axis shows the difference of the two calculated values from repeated measurements (1st measurement–2nd measurement).

We also calculated the bias (difference between the X-axis and the average mean of the two calculations for all subjects) for PD and ETD in Control, S-COPD and AE-COPD groups for each inhaler. We found that PD was significantly higher by the values calculated from second measurements in Controls using Foster® pMDI and Trimbow® pMDI. There was a tendency in healthy volunteers by Spiriva® Respimat® for the second value to be higher. There was no difference between the two values in either COPD group regarding the two pMDI devices but in S-COPD patients the second value tended to be lower while in AE-COPD patients higher.

TABLE 3 Spirometric and inhalation parameters measured through the different inhalers.

Control group (n =17)		
Spirometry	IVC (L)	4.02 ± 0.26
Spirometry	PIF (L/s)	5.08 ± 0.36
	pMDI	Respimat®
IVC_d (L)	**3.36 ± 0.22***	**3.61 ± 0.21***
PIF_d (L/s)	**2.61 ± 0.22***	**2.19 ± 0.15***
t_{in} (s)	2.23 ± 0.22	2.51 ± 0.23
t_{bh} (s)	9.95 ± 0.12	9.93 ± 0.16
S-COPD group (n = 13)		
Spirometry	IVC (L)	**2.35 ± 0.2****
Spirometry	PIF (L/s)	**2.48 ± 0.15****
	pMDI	Respimat®
IVC_d (L)	**2.23 ± 0.17****	**2.29 ± 0.21****
PIF_d (L/s)	**1.80 ± 0.16*,*****	**1.48 ± 0.14*,*****
t_{in} (s)	2.44 ± 0.26	2.57 ± 0.27
t_{bh} (s)	10.39 ± 0.1	10.57 ± 0.18
AE-COPD group (n = 12)		
Spirometry	IVC (L)	**2.17 ± 0.25****
Spirometry	PIF (L/s)	**2.80 ± 0.32****
	pMDI	Respimat®
IVC_d (L)	**2.06 ± 0.23****	**2.18 ± 0.21****
PIF_d (L/s)	**1.79 ± 0.13*,*****	**1.48 ± 0.12*,*****
t_{in} (s)	2.3 ± 0.28	2.52 ± 0.26
t_{bh} (s)	**9.55 ± 0.16*****	**9.44 ± 0.40*****

IVC, inspiratory vital capacity; PIF, peak inspiratory flow; IVC_d, through-device inspiratory vital capacity; PIF_d, through-device peak inspiratory flow; t_{in}, inhalation time; t_{bh}, breath hold time; *$p < 0.05$ vs. values obtained by standard spirometry; **$p < 0.05$ vs. Control group; ***$p < 0.05$ vs. S-COPD. Significant differences are highlighted in bold. Data are shown as mean ± standard error of the mean (SEM).

The 95% limits of agreement and the coefficients of repeatability (CR) of PD and ETD through the different inhalers were high and variable in both, controls and patients It is important to highlight that low CR represents better repeatability. Of note, the CR in S-COPD and AE-COPD patients for PD was the largest using Trimbow® pMDI (see Table 4).

3.6. Ranking of inhalers based on the differences between deposition values

Ranking the three inhalers based on the differences between the two values of PD is shown in Figure 5. This highlights the inhalers with the smallest difference (given Rank 1 followed by Rank 2 and Rank 3) in values between the two deposition results. Similarly, to the findings based on the CR values in patients with COPD, Respimat® produced the smallest inter-measurement differences for PD.

4. Discussion

Our study compared commercially available pMDI and SMI devices for PD repeatability of FDC (ICS-LABA-LAMA) and open triple (ICS-LABA pMDI and LAMA SMI) therapy in severe COPD patients. Numerical modeling of PD provided ~25–28% pulmonary drug deposition in our model for pMDI and ~ 36–39% for SMI. Very similar results were shown in gamma scintigraphy studies using the active agents of Trimbow® pMDI in healthy and asthmatic subjects and ~ 37% using Respimat® SMI in untrained COPD patients validating our *in silico* method (7, 27).

According to previous scintigraphy studies, in asthmatic patients with mild airway obstruction there was no difference in pulmonary drug deposition using Trimbow® pMDI as compared to healthy controls (7). In contrast, we examined COPD patients with severe airway obstruction, where no scintigraphy data are available to assess PD using two triple combination regimens. Notwithstanding our

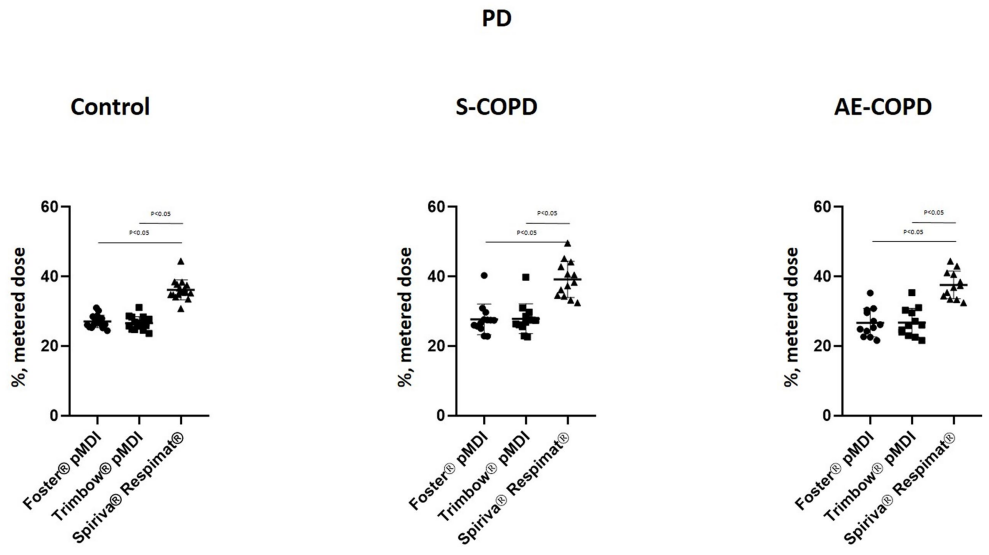

FIGURE 1
Pulmonary deposition (PD). AE-COPD: patients with exacerbated COPD; S-COPD: patients with stable COPD.

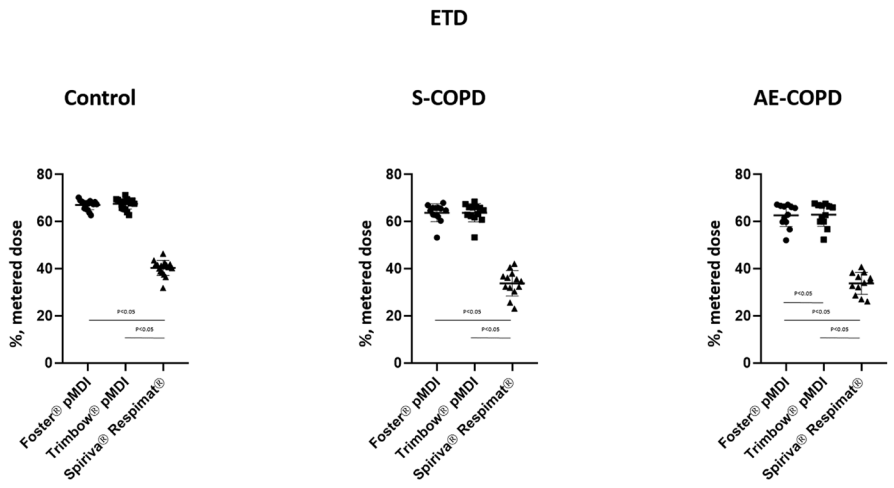

FIGURE 2
Extrathoracic deposition (ETD). AE-COPD: patients with exacerbated COPD; S-COPD: patients with stable COPD.

model cannot separate drug deposition in central and peripheral regions of the lung as gamma scintigraphy, on the other hand it is safe and reproducible. We were able to evaluate deposition values in the lung and extrathoracically and compare drug delivery of FDC and open triple therapies in COPD patients in stable state and during AE. One of the main findings is that there was no difference in PD between S-COPD and AE COPD patients for both low resistance pMDI and SMI devices. Besides the high reproducibility of numerical modeling, we put a lot of emphasis on the repeatability of inhalation maneuvers. Low resistance and repetitive use as per summary of product characteristics (SmPCs) were the reasons why we chose Trimbow® and Foster® pMDIs and Spiriva® Respimat® as patients need two consecutive inhalations twice and once daily, respectively, (28–30).

The availability of triple FDCs is growing, but clinicians are facing new challenges during the therapy of COPD patients. The effectiveness of FDC versus open triple therapy was previously investigated in the TRINITY clinical trial (31). Trimbow® pMDI was non-inferior regarding moderate-to-severe exacerbation rates and pre-dose FEV_1 for week 52 versus the open triple therapy containing Foster® pMDI and a Spiriva® Handihaler® (31). Our study investigated a low resistance SMI as LAMA in open triple therapy and showed that it might produce higher PD in COPD patients independent of stable state or during AE. Consequently, using SMI LAMA might add to more effective therapy especially in patients who might profit from open triple therapy. Our results might suggest that in some cases clinicians can switch to a combination of pMDI and SMI as open triple therapy from triple FDC to increase pulmonary deposition of inhaled drugs in severe COPD patients. GOLD document is also suggesting adjustment of inhaled therapy by switching inhaler device or molecules within the same class. In COPD patients differences in effectivity regarding a given inhaled therapy were previously confirmed for LABA-LAMA combinations underlying the importance and possible benefit of switch (32).

Inhalation performance might be impaired despite the fact that these inhalers are suitable for patients with reduced lung function (33). Critical errors highly impact lung deposition. The higher intra-patient variability with different aerosol devices was described in previous studies often evaluating healthy volunteers or patients with different severity of airway obstruction (34, 35). In our setup patients used the simulation equipment with optimal and controlled technique as described by the manufacturer.

One of the most important disease deteriorating factor during the therapy of COPD is an episode of exacerbation. Exacerbation impairs function, breathing capacity and reduces inspiratory effort so patients are less able to perform sufficient and equal inhalation maneuvers and consequently have instable inhaled drug lung delivery. However, our study revealed that there was no significant difference between stable and exacerbated COPD patients using pMDI or SMI for PD values. Consequently, exacerbation does not considerably influence the effectivity of drug deposition and deposition repeatability for both devices. This can be explained that the use of inhaler techniques is regularly checked at our department patients with both stable and exacerbated COPD.

Several previous studies confirmed the impact of device handling on the effectiveness of inhaled medication. It is well known that the use of different inhalers or more than one device can negatively impact therapy (3, 15, 16). For COPD patients who are not able to generate adequate inspiratory effort, a pMDI or SMI device is recommended (36, 37). However, manufacturers design their device relying on the need to reach a satisfactory inspiratory flow, shortly a new parameter gains greater emphasis, the pressure drop during inhalation (38). It is important to note that our model did not use pressure drop values as input data. Despite that the number of different inhalers can worsen the effectiveness of inhalation therapy, our results suggest that the combination of an SMI and a pMDI can reach higher calculated drug PD compared to a FDC pMDI in individual patients.

COPD patients, especially those with severe disease, need proper education to acquire correct inhaler use. Achieving this goal, appropriate patient education is essential and regular assessment is needed during patient care (39, 40). Severe COPD patients are hospitalized frequently and during acute exacerbation device handling tend to be even more difficult. Our measurements revealed that an SMI performs evenly in patients with acute exacerbations. Repeatability highlights the importance of investigating measurement methods. Besides repeating different measurement on the same

TABLE 4 Repeatability of lung and extrathoracic deposition values calculated from repeated measurements.

	n	Bias	*p*	95% LoA	CR
	C				
Lung					
Foster® pMDI	17	0.80	**0.02***	−1.68 – 3.28	2.87
Trimbow® pMDI	17	0.70	**0.005***	−1.21 – 2.61	2.31
Spiriva® Respimat®	17	1.19	0.13	−4.86 – 7.23	6.31
ET					
Foster® pMDI	17	−0.5	**0.046***	−2.35 – 1.36	2.05
Trimbow® pMDI	17	−0.59	**0.032***	−2.62 – 1.44	2.29
Spiriva® Respimat®	17	−1.35	0.12	−7.93 – 5.22	6.91
	S-COPD				
Lung					
Foster® pMDI	13	−0.89	0.42	−8.45 – 6.67	7.47
Trimbow® pMDI	13	−1.62	0.38	−14.2 – 10.91	12.46
Spiriva® Respimat®	13	0.25	0.83	−7.89 – 8.39	7.84
ET					
Foster® pMDI	13	0.89	0.46	−7.32 – 9.11	8.08
Trimbow® pMDI	13	1.31	0.26	−6.46 – 9.08	7.9
Spiriva® Respimat®	13	−1.17	0.51	−13.28 – 10.94	11.86
	AE-COPD				
Lung					
Foster® pMDI	12	1.91	0.23	−8.24 – 12.06	10.42
Trimbow® pMDI	12	1.8	0.27	−8.78 – 12.38	10.72
Spiriva® Respimat®	12	0.72	0.58	−7.77 – 9.21	8.25
ET					
Foster® pMDI	12	−2.06	0.24	−13.22 – 9.1	11.42
Trimbow® pMDI	12	−2.07	0.25	−13.57 – 9.43	11.74
Spiriva® Respimat®	12	−0.93	0.52	−10.34 – 8.47	9.19

**p*-Value for one-sample *t*-test of the bias.
AE-COPD: patients with exacerbated COPD; CR, coefficients of repeatability; LoA, Bland–Altman 95% limits of agreement; n, number of subjects; S-COPD: patients with stable COPD. Significant differences are highlighted in bold.

subjects by the same examiner, different measurement system can show varying result from same subjects, placing a greater focus on reproducibility (41).

Because many DPI devices cannot be used effectively with severe respiratory function impairment, greater emphasis should be placed on the use of low-resistance inhalers such as pMDI and SMI devices in patients with advanced COPD (42).

5. Conclusion

In summary in severe COPD patients using numerical deposition modeling lung deposition is higher for open triple combination using pMDI plus SMI device as compared to FDC pMDI. As each studied inhaled drug is dosed twice according SmPC for each device repeatability is of high interest. Around 40% of all COPD patients has >3% PD difference between the two inspiratory maneuvers, emphasizing the importance of optimal handling and teaching of devices. Important to note that there was no difference in PD between COPD patients during AE and S conditions. SMI repeatability seemed more robust in our study and might contribute to clinically meaningful difference in patients with persisting symptoms and exacerbation. By the latest recommendations, multiple devices are highly correlated to reduced adherence (43), therefore inhaler usage must be controlled on a regular basis. Further clinical studies and real-world data are needed to confirm the clinical effectiveness in this patient group.

6. Strengths and weaknesses of the study

Our study is the first comparing lung deposition values of a FDC pMDI and open triple therapy containing an SMI and pMDI in COPD patients. Numerical modeling provides us a more reproducible method to evaluate PD values without the burden of radiation. Weakness of our work is the low number of patients and repetitive maneuvers used for data input into the mathematical model.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Semmelweis University Regional and Institutional Committee of Science and Research Ethics. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TE performed the through-device measurements and the calculations using numerical modeling. ZL coordinated the statistical analysis and conducted medical consultations. ÁF and PF ensured the use of the Stochastic Lung Model and provided scientific consultation. AN conducted scientific consultation. VM was responsible for the coordination and professional supervision of the investigation. All authors contributed to the article and approved the submitted version.

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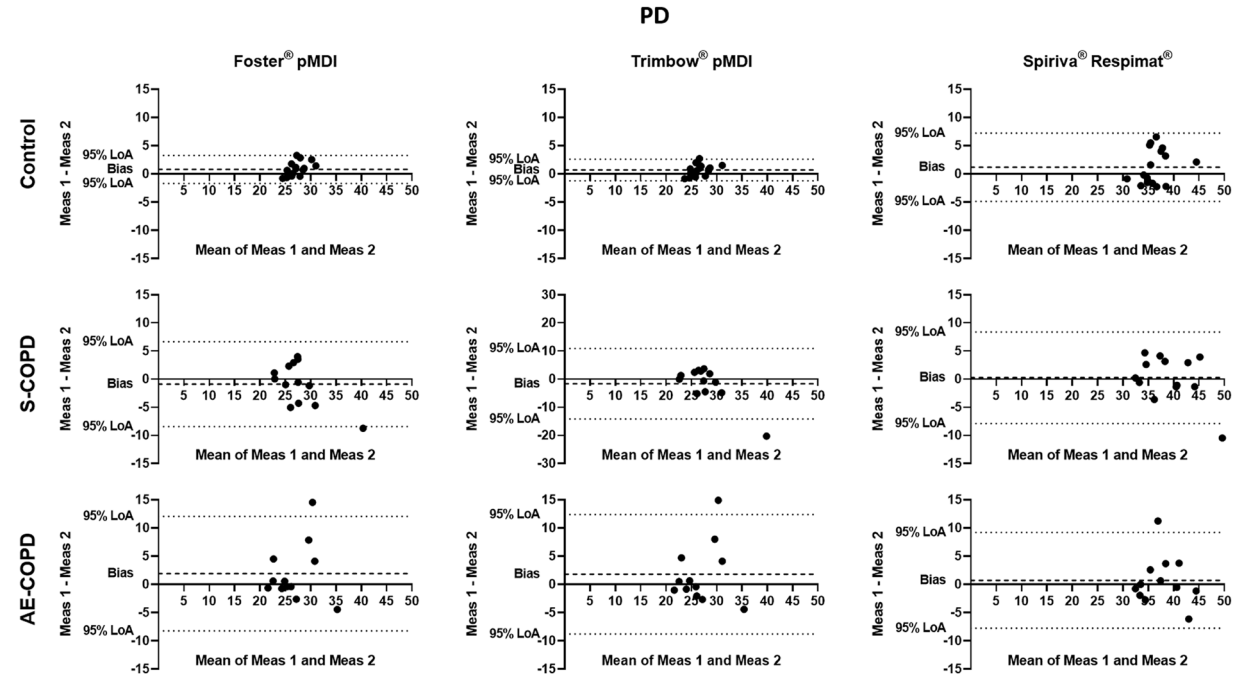

FIGURE 3
Bland–Altman analysis of pulmonary deposition (PD). The X-axis represents the mean of the two measurements for PD, while the Y-axis shows the difference of the repeated measurements (first measurement–second measurement). Each dot represents a person. The dashed line shows the average of the difference for all subjects. AE-COPD: patients with exacerbated COPD; LoA, Bland–Altman 95% limits of agreement; Meas, measurement; S-COPD: patients with stable COPD.

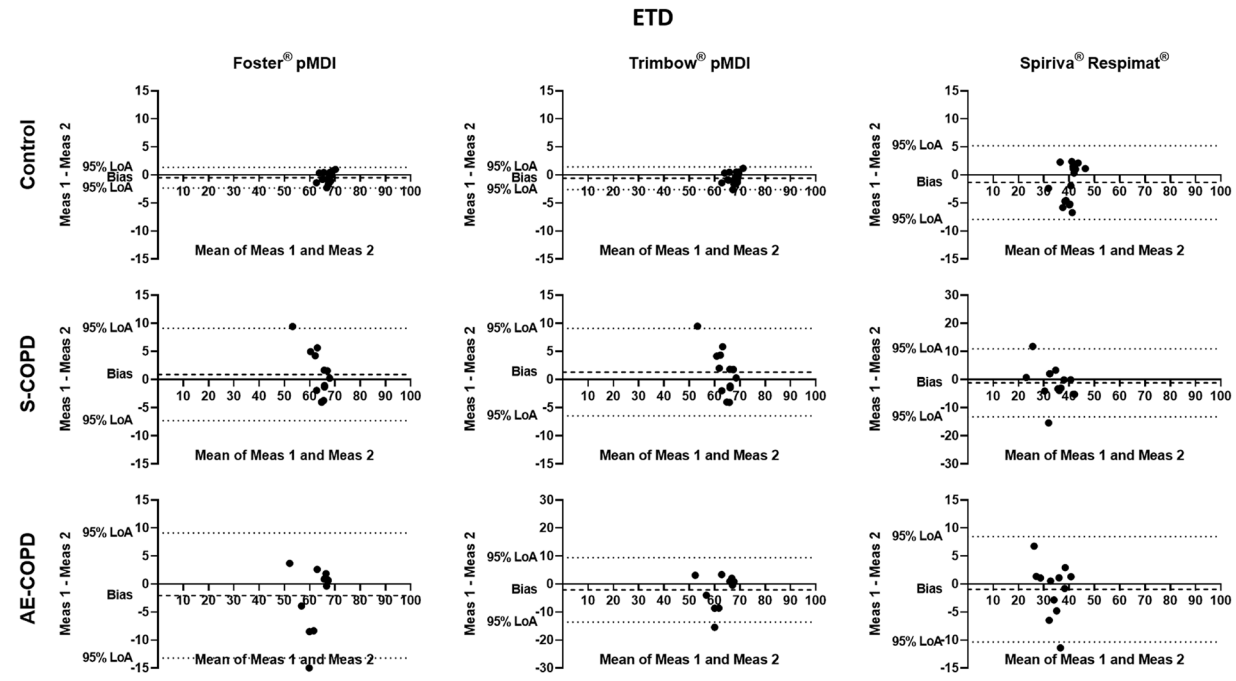

FIGURE 4
Bland–Altman analysis of extrathoracic deposition (ETD). The X-axis represents the mean of the two measurements for ETD, while the Y-axis shows the difference of the repeated measurements (first measurement–second measurement). Each dot represents a person. The dashed line shows the average of the difference for all subjects. AE-COPD: patients with exacerbated COPD; LoA, Bland–Altman 95% limits of agreement; Meas, measurement; S-COPD: patients with stable COPD.

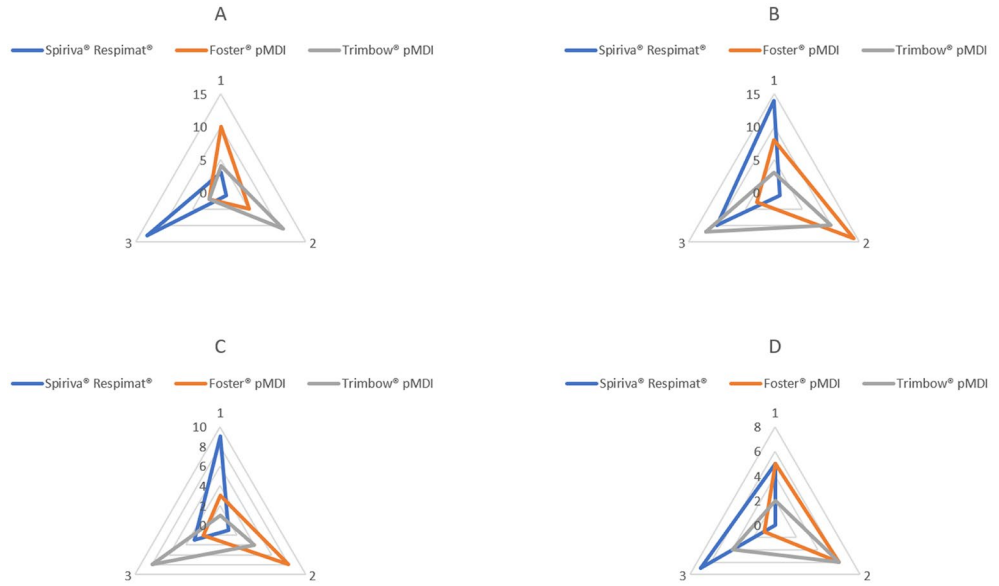

FIGURE 5
Repeatability sequence summary for the three inhalers regarding PD. **(A)** Control: healthy volunteers (*n* =17); **(B)** All-COPD: patients with stable and exacerbated COPD (*n* =25); **(C)** S-COPD: patients with stable COPD (*n* =13); **(D)** AE-COPD: patients with exacerbated COPD (*n* =12). By each control subject and patient, a rank number between 1 and 3 was associated with each inhaler regarding the magnitude of the difference between the two values for PD, respectively. Rank 1 was given to the device with the lowest difference between the two inspiratory measurements followed by Rank 2 and 3. On the figure, rank numbers are shown by three edges of the axes, and the sum of subjects with a certain rank is indicated on the axes. COPD: chronic obstructive pulmonary disease.

Conflict of interest

VM received consultation fees from Astra Zeneca, Boehringer Ingelheim, Chiesi, Berlin Chemie Menarini, Orion Pharma, Novartis, GSK, Teva.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Comparative assessment of small airway dysfunction by impulse oscillometry and spirometry in chronic obstructive pulmonary disease and asthma with and without fixed airflow obstruction

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Background: Small airways play a major role in the pathogenesis and prognosis of chronic obstructive pulmonary disease (COPD) and asthma. More data on small airway dysfunction (SAD) using spirometry and impulse oscillometry (IOS) in these populations are required. The objective of this study was to compare the two methods, spirometry and IOS, for SAD detection and its prevalence defined by spirometry and IOS in subjects with COPD and asthma with and without fixed airflow obstruction (FAO).

Design: This is a cross-sectional study.

Methods: Spirometric and IOS parameters were compared across four groups (COPD, asthma with FAO, asthma without FAO, and healthy subjects). SAD defined by spirometry and IOS criteria were compared.

Results: A total of 262 subjects (67 COPD, 55 asthma with FAO, 101 asthma without FAO, and 39 healthy controls) were included. The prevalence of SAD defined by using IOS and spirometry criteria was significantly higher in patients with COPD (62.7 and 95.5%), asthma with FAO (63.6 and 98.2%), and asthma without FAO (38.6 and 19.8%) in comparison with healthy control (7.7 and 2.6%). IOS is more sensitive than spirometry in the detection of SAD in asthma without FAO (38.6% vs. 19.8%, $p=0.003$) However, in subjects with FAO (COPD and asthma with FAO), spirometry is more sensitive than IOS to detect SAD (95.5% vs. 62.7%, $p<0.001$ and 98.2% vs. 63.6%, $p<0.001$, respectively).

Conclusion: Small airway dysfunction was significantly detected in COPD and asthma with and without FAO. Although IOS shows more sensitivity than spirometry in the detection of SAD in asthma without FAO, spirometry is more sensitive than IOS in patients with FAO including COPD and asthma with FAO.

KEYWORDS

COPD, asthma, fixed airflow obstruction, impulse oscillometry, small airways, spirometry

Introduction

Small airways have a diameter of fewer than 2 mm (1). Small airways contribute a major role in both chronic obstructive pulmonary disease (COPD) and asthma (2, 3) caused by inflammation, hypersecretion of mucus, and airway remodeling (4). Small airway dysfunction (SAD) has been investigated for more than 60 years (5). No gold standard method currently exists for clinically assessing SAD. Spirometry is the most widely used method due to its relatively easy performance and simple measurement device (6).

The mid-maximal expiratory flow rate (MMEF) widely known as the average expired flow over the middle half (25–75%) of the forced vital capacity (FVC) maneuver (FEF25–75%) was proposed as the best parameter to identify SAD by spirometry (7). Its use is based on the hypothesis that the mid-late portion of the FVC reflects the airflow through the small airways, which are prone to expiratory collapse due to their lack of cartilaginous support (8). The American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines do not support using the FEF25–75% to identify SAD but suggest that oscillometry may provide evidence of airflow obstruction (9–11). Moreover, Quanjer et al. also suggested that the FEF25–75% does not contribute usefully to clinical decision-making (12). However, a recent large cohort analysis supports %predicted of FEF25–75% which helps link the anatomic pathology and deranged physiology of COPD independent of the %predicted forced expiratory measurement in the first second (FEV_1) (13).

Impulse oscillometry (IOS) is a simple, non-invasive method, requiring only tidal breathing that allows for the evaluation of airway resistance and airway reactance in the airways and lungs (14). The IOS can be used for the diagnosis of COPD (15). It has been valuable for the evaluation of asthma control (16–18). Moreover, it detects SAD in COPD and asthma (19–22). Additionally, the IOS helped in the differentiation of COPD, asthma, and healthy subjects (15, 21, 23). All of the IOS parameters including resistance at 5 Hz (R5), resistance at 20 Hz (R20), heterogeneity of resistance (R5-R20), reactance at 5 Hz (X5), resonant frequency (Fres), and area under reactance curve between 5 Hz and Fres (AX) were significantly higher in COPD compared to healthy subjects (15, 23). The R20, R5–R20, and Fres were significantly different between COPD and asthma (23). Pornsuriyasak et al. also found significantly different IOS parameters across COPD, asthma with fixed airflow obstruction (FAO), and asthma without FAO (21).

In COPD and asthma, the small airway plays a major role in their pathogenesis (23). Air trapping and small airway wall thickening are associated with the progression of COPD (23). In asthma, inflammation and alterations of the small airways are associated with the severity of asthma and the level of asthma control (18, 24). Many methods have been introduced for measuring SAD including spirometry, plethysmography, IOS, inert gas washout, exhaled nitric oxide, and imaging, e.g., high-resolution computed tomography hyperpolarized magnetic resonance imaging and nuclear medicine (25). Of these, IOS is non-invasive, easy to perform, effort independent, and reproducible (25). By using IOS, more than half of subjects with COPD (60.0–74.0%) had SAD (21, 26–28). Additionally, Crisafulli et al. found the presence of SAD to progressively increase according to severity classifications of COPD (26). In asthma, a systematic review showed that the prevalence of SAD in asthma ranged from 33.0 to 69.9% when using IOS (22). In one study, the prevalence of SAD by using fixed R5–R20 criteria ≥0.075 kPa/L/s in COPD, asthma with FAO, and asthma without FAO were 68, 95, and 77%, respectively (21). By using spirometry, Manoharan et al. found that 54% of asthma had SAD defined using FEF25–75% of <60% predicted (29). The prevalence of SAD in airway diseases utilizing different methods varies. The study of SAD in COPD and asthma prevalence using IOS and spirometry still requires more clarification. Therefore, the objective of this study was to compare the IOS parameters and prevalence of SAD using IOS and spirometry in subjects with COPD, asthma with and without FAO, and healthy controls.

Materials and methods

Study procedures

This is a secondary analysis of cross-sectional studies in patients with COPD and asthma which were previously published (15, 18). The study was conducted at the Lung Health Center, Division of Pulmonary, Critical Care and Allergy, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. All subjects were enrolled between July 2019 and June 2020. All tests were performed by a well-trained technician. Demographic data including age, sex, body mass index (BMI), comorbidities, smoking status, and inhaled medication used were recorded. The study was approved by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University [Institutional Review Board (IRB) approval number: MED-2562-06282, date of approval: 28 June 2019 and filed under Clinical Trials Registry (Study ID: TCTR20190709004, date of approval: 5 July 2019)]. Written informed consent was obtained from all subjects before enrollment.

Subjects

The inclusion criteria were subjects with ages greater than 40 years. The exclusion criteria were the subjects who were unable to perform acceptable spirometry according to the ATS/ERS standard (11) and who were unable to perform the IOS according to the standard recommended by the ERS standard (14). Diagnosis of COPD in this study was based on the post-bronchodilator (post-BD) ratio of FEV_1/FVC below the lower limit of normal (LLN) (9) with a history of smoking ≥10 pack-years, age of onset of symptoms >40 years, and no history of asthma in first-degree family members. Asthma subjects in this study were based on a history of clinically diagnosed asthma based on episodic breathlessness, wheezing, cough, and tightness and/or bronchodilator responsiveness and had a history of non-smoking or ex-smoking of <5 pack-years. Asthma with FAO was defined by the on-treatment ratio of FEV_1/FVC persistently below LLN for at least three measurements during stable visits over a year. Asthma without FAO was characterized by the on-treatment ratio of FEV_1/FVC ≥ LLN measured at the stable visit. Healthy control subjects were classified as subjects with normal spirometry (%FEV_1/FVC value > LLN and FVC > LLN), had no chronic respiratory symptoms, no previous diagnosis of any chronic respiratory diseases, and were non-smokers (30).

Definition

Due to the lack of consensus over which spirometry parameter is the best to identify SAD. FEF25–75% is a more sensitive parameter than FEV_1 for assessing changes in peripheral airway function (7). FEF25–75% has been described as less effort-dependent than FEV_1 and is a measurement of SAD (7, 8). Thus, this study used FEF25–75% from spirometry to identify SAD. However, there is no guideline regarding normal values for FEF25–75%. The most popular arbitrary cutoffs of FEF25-75% were between 60 and 75% (8). The previous study found that the normal 95th percentile for FEF25-75% is actually closer to 56% predicted in subjects with ages over 36 years (31). Therefore, the FEF25–75% < 60% predicted (8) was defined as SAD in our study. For the IOS test, SAD was defined when R5–R20 > ULN [predictive value +1.645 × Root Mean Square Error (RMSE)] (32).

Spirometry

Spirometry was performed using the Vmax 22 spirometer, Care Fusion, Hoechberg, Germany. Pre-BD spirometry was performed according to the standards of ATS/ERS (10). Spirometric parameters were collected including FVC, FEV_1, the ratio of FEV_1/FVC, and FEF25–75%. The predicted values of FVC, FEV_1, and FEF25-75% were calculated using the Global Lung Initiative (GLI) 2012 (Southeast Asian sub-group) reference equations (33). The *z*-scores of FVC, FEV_1, ratio of FEV_1/FVC, and FEF25–75% of each subject were also calculated from the GLI 2012 (Southeast Asian sub-group) reference equations (33).

Impulse oscillometry

Pre-BD IOS was performed in all subjects before spirometry. The respiratory resistance and reactance were measured using IOS (Master Screen IOS, Viasys GmbH, Hoechberg, Germany). Each subject was asked to perform tidal breathing for 30–40 s *via* a mouthpiece that was connected to the IOS machine. A minimum of three tests following the recommendation by ERS standard were required (34). The average values from three IOS measurements were recorded. We collected the following IOS parameters: R5, R20, R5–R20, X5, Fres, and AX. The predicted values of all parameters in IOS were calculated using the Thai predictive value published by Deesomchok et al. (35).

Study size calculation

The size of this study was calculated based on data from the previous study (21) using G*Power Version 3.1.9.2. The proportions of SAD in patients with COPD and asthma with FAO were 68 and 95%, respectively (21). Therefore, at least 140 subjects (35 subjects for each group) needed to be included in this study (power = 0.8 with statistical significance <0.05).

Statistical analysis

Results for continuous data were expressed as mean ± standard deviation (SD) or median, interquartile range (IQR) as appropriate. Results for categorical data were expressed as frequencies and percentages. For baseline characteristics, IOS, and spirometry parameters, one-way analysis of variance (ANOVA) with the Bonferroni adjustment method was used to analyze differences across the four groups for parametric data. Kruskall–Wallis test was used to analyze the differences in baseline characteristics, IOS, and spirometry parameters across the four groups for non-parametric data. The Mann–Whitney *U*-Test was used to compare differences between the two groups for non-parametric data. The chi-square and Fisher's exact test were used to compare the categorical data across the four groups and between groups, respectively. The McNemar test was used to compare the categorical data within the group. The correlations between the IOS parameters and FEF25–75% were determined using Spearman's correlation coefficient analysis. The following cutoff parameters: $0 < |r| < 0.3$ = weak correlation; $0.3 < |r| < 0.7$ = moderate correlation; and $|r| > 0.7$ = strong correlation were used in this study (36). A value of p of <0.05 was considered statistical significance. In multiple comparisons, the adjusted level of significance was estimated by dividing the level of significance by several comparisons of four groups. Therefore, the value of p for multiple comparisons (6 and 3) was set as 0.008 (0.05/6) and 0.017 (0.05/3), respectively. All statistical analyses were performed using STATA version 16 (StataCorp, College Station, TX, United States).

Results

A total of 262 subjects (67 COPD, 55 asthma with FAO, 101 asthma without FAO, and 39 healthy controls) were included in the analysis. The baseline demographic data of all subjects in the four groups are shown in Table 1. There were significant differences in age, proportion of male sex, BMI, smoking status, and cardiovascular comorbidity across the four groups. Inhaled medications used were significantly different between asthma with FAO and asthma without FAO groups. Age and male sex were significantly higher in the COPD group in comparison with the other groups. More data are shown in Table 1.

There were significantly lower %predicted and *z*-score of all parameters of spirometry in the COPD and asthma with FAO groups in contrast to asthma without FAO and healthy control groups. The %predicted and *z*-score of all parameters of spirometry in the COPD group were also significantly lower than asthma with FAO group, except for the *z*-score of FEV_1/FVC and %predicted and *z*-score of FEF25–75%. In asthma without FAO, the *z*-score of FEV_1/FVC and %predicted and *z*-score of FEF25–75% were significantly lower against the healthy controls. More details are shown in Table 2.

Impulse oscillometry parameters of all groups are shown in Table 3. The %predicted and the absolute values of IOS parameters including R5–R20, Fres, and AX were significantly lower in healthy controls in correlation with the other groups. The less negative reactance of X5 was also observed in the healthy control group. In the COPD and asthma with FAO groups, a significant increase in %predicted and the absolute value of IOS parameters, including R5–R20, Fres, and AX, was observed in comparison with asthma without

TABLE 1 Baseline characteristics of all subjects.

Clinical characteristics	Newly diagnosed COPD (*n*=67)	Asthma with FAO (*n*=55)	Asthma without FAO (*n*=101)	Healthy control (*n*=39)	*p*-value
Age (year)	69.1 ± 8.5	62.9 ± 10.9*	60.8 ± 9.9*	60.6 ± 10.4*	<0.001
Male sex *n* (%)	59 (88.1)	23 (41.8)	31 (30.7)	21 (53.8)	<0.001
Body mass index (BMI)[a]	22.7 ± 4.4	24.6 ± 4.6*	26.3 ± 4.4*	23.6 ± 3.0*#	<0.001
Smoking status					<0.001
Non-smoker	0 (0.0)	48 (87.3)	89 (88.1)	39 (100.0)	
Ex-smoker	63 (94.0)	7 (12.7)	11 (10.9)	0 (0.0)	
Current-smoker	4 (6.0)	0 (0.0)	1 (1.0)	0 (0.0)	
Smoking pack-year (median, IQR)	25.0 (16.4, 42.0)	0.0 (0.0, 0.0)*	0.0 (0.0, 0.0)*	0.0 (0.0, 0.0)*	<0.001
Comorbidity *n* (%)					
Cardiovascular disease	40 (59.7)	20 (36.4)	37 (36.6)	5 (12.8)	<0.001
Metabolic disease	13 (19.4)	6 (10.9)	16 (15.8)	0 (0.0)	0.438
Neuromuscular disease	6 (9.0)	2 (3.6)	4 (4.0)	0 (0.0)	0.300
Inhaled medication used[a]					<0.001
ICS	N.A.	0 (0.0)	10 (9.9)	N.A.	
ICS + LABA	N.A.	33 (60.0)	77 (76.2)	N.A.	
ICS + LABA + LAMA	N.A.	22 (40.0)	14 (13.9)	N.A.	

Data are mean ± standard deviation (SD) unless otherwise stated; [a]*p*-value from exact test comparing asthma with fixed airflow obstruction and asthma with normal spirometry; *$p < 0.013$ compared with COPD; #$p < 0.013$ compared with asthma with FAO; ##$p < 0.013$ compared with asthma without FAO; value of *p* of difference between the groups was significant with an adjusted level of significance (0.05/4 = 0.013). COPD, chronic obstructive pulmonary disease; IQR, interquartile range; ICS, inhaled corticosteroid; LABA, Long-acting beta2-agonists; LAMA long-acting muscarinic antagonist; NA, not assessment; FAO, fixed airway obstruction.

TABLE 2 Spirometric data of all subjects.

Spirometry data (Pre-bronchodilator)	Newly diagnosed COPD (*n*=67)	Asthma with FAO (*n*=55)	Asthma without FAO (*n*=101)	Healthy control (*n*=39)	*p*-value
%Predicted FVC	82.2 ± 18.8*	91.5 ± 15.5*	98.2 ± 14.3*,#	101.5 ± 11.0*,#	<0.001
z-Score of FVC	−1.1 ± 1.1	−0.6 ± 1.0*	−0.1 ± 0.9*,#	0.1 ± 0.7*,#	<0.001
%Predicted FEV_1	59.9 ± 18.5	70.1 ± 15.1*	92.2 ± 13.8*,#	100.2 ± 11.6*,#	<0.001
z-Score of FEV_1	−2.3 ± 1.0	−1.8 ± 0.9*	−0.5 ± 0.9*,#	0.0 ± 0.7*,#	<0.001
FEV_1/FVC (%)[a]	57.4 ± 9.1	62.1 ± 6.9*	76.9 ± 4.7*,#	80.5 ± 5.2*,#	<0.001
z-Score of FEV_1/FVC	−2.9 ± 1.1	−2.7 ± 0.8	−0.8 ± 0.6*,#	−0.1 ± 0.7*,#,##	<0.001
%Predicted FEF25–75%	31.7 ± 14.1	37.6 ± 11.3	80.0 ± 24.1*,#	106.3 ± 31.7*,#,##	<0.001
z-Score of FEF25–75%	−2.5 ± 0.8	−2.3 ± 0.6	−0.7 ± 0.8*,#	0.1 ± 0.9*,#,##	<0.001

Data are mean ± standard deviation (SD); *$p < 0.017$ compared with COPD. #$p < 0.013$ compared with asthma with FAO; ##$p < 0.013$ compared with asthma without FAO; value of *p* of difference between groups was significant with an adjusted level of significance (0.05/4 = 0.013). FVC, forced vital capacity; FEV_1, forced expiratory volume in the first second; FEF25–75%, forced expiratory flow at 25–75% of FVC; FAO, fixed airway obstruction.

FAO group. A significant decrease in %predicted of X5 was observed in COPD and asthma with FAO when contrasted with asthma without FAO group. The %predicted of AX was significantly higher in the group with COPD when compared with asthma in the FAO group. The %predicted and absolute values of R5-R20 were indifferent between COPD and asthma in the FAO group. More data are shown in Table 3.

Correlations between FEF25–75% and IOS parameters in subjects with chronic respiratory diseases and healthy controls are shown in Table 4. There was only a low-to-moderate correlation between some parameters of IOS and FEF25–75%, in which Fres in asthma with FAO showed the highest correlation. Correlations between FEF25–75% and IOS parameters in subjects with COPD, asthma with FAO, and asthma without FAO and healthy control with preserved FVC are also shown in Table 5. Most of the IOS parameters did not correlate with FEF25–75%. The highest correlation was shown in FEF25–75% and Fres in asthma with FAO, which was only a moderate correlation.

The prevalence of SAD was significantly higher in COPD, asthma with FAO, and asthma without FAO in comparison with healthy control groups both in the whole and subgroups with preserved FVC (Tables 6, 7). In COPD and asthma with FAO groups, the prevalence of SAD was also significantly higher than in asthma without FAO group. But there was no difference in the prevalence of SAD between COPD and asthma with FAO groups (Tables 6, 7). In the case of airway obstruction including COPD and asthma with FAO, the FEF25–75% was more sensitive than R5–R20 for SAD diagnosis. But,

TABLE 3 Impulse oscillometry (IOS) parameters of all subjects.

IOS parameters	Newly diagnosed COPD (n=67)	Asthma with FAO (n=55)	Asthma without FAO (n=101)	Healthy control (n=39)	p-value
R5 ($cmH_2O/L/s$)	4.8 ± 1.6	5.1 ± 2.1	4.6 ± 1.5	3.5 ± 1.2*,#,##	<0.001
% Predicted R5	158.3 ± 59.2	128.1 ± 48.4*	104.9 ± 36.5*,#	97.7 ± 22.6*,#	<0.001
R20 ($cmH_2O/L/s$)	3.1 ± 0.9	3.3 ± 1.2	3.4 ± 0.9	2.9 ± 0.9	0.027
% Predicted R20	121.3 ± 34.8	101.2 ± 39.2*	96.5 ± 34.8*	96.4 ± 18.5*	<0.001
R5-R20 ($cmH_2O/L/s$) (median, IQR)	1.6 (0.9, 2.2)	1.3 (0.8, 2.3)	0.9 (0.4, 1.8)*,#	0.5 (0.3, 0.9)*,#,##	<0.001
% Predicted R5-R20 (median, IQR)	282.1 (171.8, 412.8)	270.2 (153.6, 545.1)	154.7 (87.7, 281.4)*,#	96.7 (51.3, 158.7)*,#,##	<0.001
X5 ($cmH_2O/L/s$) (median, IQR)	−1.9 (−2.7, −1.3)	−1.6 (−2.7, −0.9)	−1.5 (−1.9, −0.9)*	−1.0 (−1.3, −0.5)*,#,##	0.001
% Predicted X5 (median, IQR)	189.9 (141.1, 279.8)	151.7 (87.9, 258.8)*	140.8 (94.2, 177.9)*	95.7 (59.9, 138.4)*,#,##	<0.001
Fres (Hz)	22.9 ± 5.5	21.4 ± 7.4*	17.5 ± 5.1*,#	12.9 ± 3.9*,#,##	<0.001
% Predicted Fres	169.3 ± 47.7	157.3 ± 60.6	121.5 ± 32.7*,#	96.9 ± 25.5*,#,##	<0.001
AX (cmH_2O/L) (median, IQR)	17.2 (8.9, 26.1)	11.0 (6.7, 24.4)	7.1 (3.6, 14.1)*,#	3.3 (1.5, 4.9)*,#,##	<0.001
% Predicted AX (median, IQR)	459.7 (234.9, 779.0)	298.2 (185.5, 567.9)*	166.2 (98.3, 309.5)*,#	91.0 (42.5, 141.3)*,#,##	<0.001

Data are mean ± standard deviation (SD) or otherwise stated; *p < 0.017 compared with COPD; #p < 0.013 compared with asthma with FAO; ##p < 0.013 compared with asthma without FAO; value of p of difference between groups was significant with an adjusted level of significance (0.05/4 = 0.013). R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5-R20; heterogeneity of resistance between R5 and R20; Fres, resonant frequency; X5, reactance at 5 Hz; AX, the area under reactance curve between 5 Hz and resonant frequency; FAO, fixed airway obstruction.

TABLE 4 Spearman correlation coefficients of FEF25–75% and IOS parameters in subjects with chronic respiratory diseases and healthy control.

	R5–R20	%R5–R20	AX	%AX	X5	%X5	Fres	%Fres
Chronic respiratory diseases (n = 223)								
Newly diagnosed COPD (n = 67)	−0.422*	−0.441*	−0.453*	−0.460*	0.426*	−0.340*	−0.472*	−0.508*
Asthma with FAO (n = 55)	−0.213	−0.222	−0.326*	−0.377*	0.205	−0.204	−0.505*	−0.536*
Asthma without FAO (n = 101)	−0.209*	−0.185	−0.222*	−0.241*	0.155	−0.179	−0.271*	−0.246*
Healthy control (n = 39)	−0.354*	−0.292	−0.149	−0.138	−0.059	−0.039	−0.237	−0.275

*p < 0.05. R5-R20, heterogeneity of resistance between R5 and R20; Fres, resonant frequency; X5, reactance at 5 Hz; AX, the area under reactance curve between 5 Hz and resonant frequency; FAO, fixed airway obstruction.

R5–R20 was more sensitive than FEF25–75% for SAD detection in asthma without FAO. Additionally, the overestimation of SAD was observed when using the fixed criteria (R5-R20 ≥ 0.76 cmH_2O) in asthma without FAO and healthy controls. More data are shown in Tables 6, 7.

Discussion

In this study, we found that the prevalence of SAD classified by an increase in small airway resistance (R5–R20 ≥ ULN) was significantly higher in COPD, asthma with FAO, and asthma without FAO compared to healthy controls. The spirometry-derived FEF25–75% was more sensitive than R5–R20 for SAD diagnosis in patients with COPD and asthma with FAO. But, the IOS-derived R5–R20 was more sensitive than FEF25–75% for SAD diagnosis in asthma without FAO. In addition, SAD was overdiagnosed when using the fixed criteria of R5–R20 ≥ 0.76 cmH_2O in asthma without FAO and healthy controls. We also found that the IOS parameters, especially for R5–R20, X5, Fres, and AX, were significantly lower in healthy subjects compared to COPD and asthma with and without FAO.

Respiratory resistance is largely affected by airway caliber (34). The narrower and longer airways have higher airway resistance (34). Our study showed an increase in R5 and R5–R20 in COPD, asthma

TABLE 5 Spearman correlation coefficients of FEF25–75% and IOS parameters in subjects with chronic respiratory diseases and healthy control with FVC≥80% predicted.

	R5-R20	%R5-R20	AX	%AX	X5	%X5	Fres	%Fres
Chronic respiratory diseases ($n=173$)								
Newly diagnosed COPD ($n=40$)	−0.158	−0.171	−0.216	−0.216	0.223	−0.146	−0.058	−0.109
Asthma with FAO ($n=44$)	−0.102	−0.171	−0.224	−0.273	0.134	−0.109	−0.369*	−0.481*
Asthma without FAO ($n=89$)	−0.216*	−0.227*	−0.263*	−0.299*	0.196	−0.206	−0.266*	−0.282*
Healthy control ($n=37$)	−0.305	−0.233	−0.085	−0.086	−0.128	0.008	−0.221	−0.276

*$p<0.05$. R5-R20, heterogeneity of resistance between R5 and R20; Fres, resonant frequency; X5, reactance at 5 Hz; AX, the area under reactance curve between 5 Hz and resonant frequency; FAO, fixed airway obstruction.

TABLE 6 Subjects with small airway dysfunction defined by R5–R20≥upper limit of normal, R5–R20≥0.76 cmH_2O, and %predicted FEF25–75%<60.

Small airway dysfunction	Newly diagnosed COPD ($n=67$)	Asthma with FAO ($n=55$)	Asthma without FAO ($n=101$)	Healthy control ($n=39$)	p-value
R5-R20 ≥ ULN	42 (62.7)	35 (63.6)	39 (38.6)$^{*,\#}$	3 (7.7)$^{*,\#,\#\#}$	<0.001
R5-R20 ≥ 0.76 cmH_2O (0.075 kPa/L/s)	56 (83.6)^{a}	42 (76.4)^{a}	56 (55.4)$^{*,\#,a}$	12 (30.8)$^{*,\#,\#\#,a}$	<0.001
%Predicted FEF25–75% < 60	64 (95.5)^{a}	54 (98.2)^{a,b}	20 (19.8)$^{*,\#,a,b}$	1 (2.6)$^{*,\#,\#\#,b}$	<0.001

Data are n (%); *$p<0.008$ compared with COPD; $^{\#}p<0.008$ compared with asthma with FAO; $^{\#\#}p<0.008$ compared with asthma without FAO; value of p of difference between groups was significant with an adjusted level of significance (0.05/6 = 0.008); ^{a}p < 0.017 compared with R5–R20 ≥ ULN criteria; ^{b}compared with R5–R20 ≥ 0.76 cmH_2O criteria; for ^{a,b}value of p of difference between group was significant with an adjusted level of significance (0.05/3 = 0.017). R5-R20, heterogeneity of resistance between R5 and R20; ULN, upper limit of normal; FAO, fixed airway obstruction.

with FAO, and asthma without FAO compared to healthy controls. Additionally, the R5–R20 was significantly higher in COPD and asthma with FAO compared to asthma without FAO groups. Our results were supported by the previous studies showing that airway resistances were increased in COPD and asthma (with and without FAO) compared to healthy subjects (15, 21, 23). Moreover, our results were comparable to the previous finding indicating that R5–R20 was increased in asthma with FAO compared to asthma without FAO (21).

Respiratory reactance is comprised of both inertance and elastance (34). King et al. suggested that more negative reactance indicated greater elastance or stiffness (34) and this typically occurred in subjects with obstructive airway diseases (34). The previous studies showed a decrease in X5 and an increase in AX in subjects with COPD and asthma compared with healthy controls (15, 23). In asthma with FAO, a decrease in X5 and an increase in AX were also observed in contrast with asthma without FAO (21). Our study also demonstrated that the X5 and AX were significantly decreased and increased, respectively, in COPD, asthma with FAO, and asthma without FAO when compared to healthy subjects.

From the previous studies, the diagnosis of SAD could be made by using IOS parameters, especially the R5–R20 (21, 22, 26, 27, 37). They reported that the ranges of the prevalence of SAD in COPD and asthma varied from 60.0 to 73.8% and 33.0 to 95.0%, respectively. In this study, we used the ULN of R5–R20 value for the diagnosis of SAD. We found the prevalence of SAD in COPD, asthma with FAO, and asthma without FAO to be 62.7, 63.6, and 38.6%, respectively. Our results were comparable with the previous findings (21, 22, 26, 27, 37). However, the prevalence of SAD in asthma with FAO and without FAO in our study was lower than in the previous study published by Pornsuriyasak et al. (21). They found that the prevalence of SAD was 95 and 77% in asthma with FAO and asthma without FAO, respectively. These discrepancies were due to the difference in criteria used for the diagnosis of SAD. The average of ULN of R5–R20 in our study was 1.182 cmH_2O/L/s (0.116 kPa/L/s) (data not shown) which was much higher than the fixed cutoff R5–R20 level of >0.075 kPa/L/s used by the previous study (21). This could lead to overestimating SAD when using the fixed cutoff R5–R20 criteria.

This study found FEF25–75% to be more sensitive than R5–R20 in the case of FAO (COPD and asthma with FAO). R5–R20 was more sensitive than FEF25–75% for SAD detection in groups with normal FEV_1/FVC (asthma without FAO) and in subgroups with preserved FVC. Additionally, the overestimation of SAD was observed when using the fixed criteria (R5-R20 ≥ 0.76 cmH_2O) in asthma without FAO and healthy controls. Our results were supported by a previous study indicating that IOS shows more sensitivity for evaluating SAD than spirometry in patients with normal lung function and spirometry showed more sensitivity than IOS to detect SAD using spirometry in subjects with abnormal lung function (32). The difference in techniques of both tests might explain these discrepant results. The sound waves were applied to measure airway resistance and airway reactance during tidal breathing in IOS, whereas the forced expiratory maneuvers might induce airway collapse which resulted in decreasing of FEF25–75% in spirometry (8, 38). Therefore, the ULN of R5-R20 from IOS is more sensitive than FEF25–75% from spirometry for the

TABLE 7 Subjects with small airway dysfunction defined by R5–R20≥upper limit of normal, R5–R20≥0.76 cmH_2O, and %predicted FEF25-75%<60 in subjects with chronic respiratory diseases and healthy control with preserved FVC (FVC≥80% predicted).

Small airway dysfunction	Newly diagnosed COPD (*n*=40)	Asthma with FAO (*n*=44)	Asthma without FAO (*n*=89)	Healthy control (*n*=37)	*p*-value
R5–R20 ≥ ULN	20 (50.0)	26 (59.1)	34 (38.2)	3 (8.1)*,#,##	<0.001
R5–R20 ≥ 0.76 cmH_2O (0.075 kPa/L/s)	32 (80.0)[a]	32 (72.7)	47 (52.8)*,[a]	11 (29.7)*,#,[a]	<0.001
%Predicted FEF25–75% < 60	37 (92.5)[a]	43 (97.7)[a,b]	18 (20.2)*,#,[a,b]	1 (2.7)*,#,##,[b]	<0.001

Data are *n* (%); *$p < 0.008$ compared with COPD; #$p < 0.008$ compared with asthma with FAO; ##$p < 0.008$ compared with asthma without FAO; value of *p* of difference between groups was significant with an adjusted level of significance; (0.05/6 = 0.008), [a]$p < 0.017$ compared with R5–R20 ≥ ULN criteria; [b]compared with R5–R20 ≥ 0.76 cmH_2O criteria; for [a,b], value of *p* of difference between group was significant with an adjusted level of significance (0.05/3 = 0.017). R5–R20, heterogeneity of resistance between R5 and R20; ULN, upper limit of normal; FAO, fixed airway obstruction.

detection of SAD in subjects with normal FEV_1/FVC and patients with obstructive airway disease with normal FVC.

Impulse oscillometry is currently the most specific and sensitive test for the detection of SAD (37). We found that subjects with chronic respiratory disease including COPD and asthma were in high-risk groups for SAD because small airways play a major role in the pathogenesis and prognosis of both COPD and asthma (18, 23, 24). For example, the SAD classified by value of R5–R20 ≥ 1 cmH_2O/L/s was an accurate tool for the detection of uncontrolled asthma in our previous study (18). SAD diagnosed by IOS in patients with intermittent asthma not treated with controller medications, mostly had normal FEV_1/FVC, was shown to predict the future of more symptoms, more use of rescue medication, poor asthma control, and severe exacerbations (39). In addition, serial R5–R20 measurements were beneficial in predicting the response to treatment (40). These findings confirm that IOS has benefits in both prognosis and management plans in asthma patients. Therefore, the findings of these and our studies suggest that clinicians should regularly perform IOS testing in patients with obstructive airway disease. The results of SAD measured by IOS may be useful for monitoring and treating these patients.

The strength of our study is that the healthy control group was included for comparison with COPD and asthma with and without the FAO group. We also did the subgroup analysis of those with preserved FVC. Moreover, the prediction equations of IOS parameters in the Thai population were used in this study. The %predicted of each IOS parameter was used for analysis. Thus, the diversities of age, sex, height, and weight that had impacts on airway resistance and reactance were minimized (35, 41, 42). We encourage using the ULN criteria of R5-R20 instead of the fixed criteria (R5–R20 ≥ 0.76 cmH_2O) for reducing the over-or underestimation of SAD. However, this study has some limitations. First, only newly diagnosed COPD was included in this study. Thus, the results may not be generalized for treated COPD patients. Second, due to the small sample size of COPD, the prevalence of SAD according to the staging of COPD was not mentioned in this study. Third, due to the lack of consensus over the cutoff value of FEF25–75% for identifying SAD, the threshold of FEF 25–75% < 60% predicted was classified as SAD in the current study. Thus, the results may not be generalized for the other studies which used other cutoff points. Finally, due to the cross-sectional study design, the association between a continuous scale of lung function measurements (FEF25–75% and R5–R20) and clinical symptoms, exacerbations, and comorbidities were not mentioned in this study. Therefore, the effect of SAD on clinical symptoms and exacerbations should be addressed in future prospective studies.

Conclusion

The IOS parameters, especially the R5–R20, can be used to differentiate healthy subjects from chronic airway diseases, including COPD and asthma with or without FAO. The ULN, rather than a fixed cutoff point, of R5–R20 should be used to identify SAD. The prevalence of SAD was significantly higher in COPD, asthma with FAO, and asthma without FAO in comparison with healthy control. Moreover, the prevalence of SAD was significantly higher in COPD and asthma with FAO than in asthma without FAO. IOS is more sensitive than spirometry for the detection of SAD in asthma without AFO; however, for patients with AFO including COPD and asthma with FAO, spirometry is more sensitive.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University [Institutional Review Board (IRB) approval number: MED-2562-06282, date of approval: 28 June 2019 and filed under Clinical Trials Registry (Study ID: TCTR20190709004, date of approval: 5 July 2019)]. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CL, WC, and CP: conceptualization, methodology, validation, investigation, resources, writing–review and editing, and visualization. WC: software, formal analysis, and data curation. CL and WC: writing–original draft preparation. CL and CP: supervision and project administration. WC and CP: funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Novel protein biomarkers for pneumonia and acute exacerbations in COPD: a pilot study

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Introduction: Community-acquired pneumonia (CAP) and acute exacerbations of chronic obstructive pulmonary disease (AECOPD) result in high morbidity, mortality, and socio-economic burden. The usage of easily accessible biomarkers informing on disease entity, severity, prognosis, and pathophysiological endotypes is limited in clinical practice. Here, we have analyzed selected plasma markers for their value in differential diagnosis and severity grading in a clinical cohort.

Methods: A pilot cohort of hospitalized patients suffering from CAP (n=27), AECOPD (n=10), and healthy subjects (n=22) were characterized clinically. Clinical scores (PSI, CURB, CRB65, GOLD I-IV, and GOLD ABCD) were obtained, and interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-2-receptor (IL-2R), lipopolysaccharide-binding protein (LBP), resistin, thrombospondin-1 (TSP-1), lactotransferrin (LTF), neutrophil gelatinase-associated lipocalin (NGAL), neutrophil-elastase-2 (ELA2), hepatocyte growth factor (HGF), soluble Fas (sFas), as well as TNF-related apoptosis-inducing ligand (TRAIL) were measured in plasma.

Results: In CAP patients and healthy volunteers, we found significantly different levels of ELA2, HGF, IL-2R, IL-6, IL-8, LBP, resistin, LTF, and TRAIL. The panel of LBP, sFas, and TRAIL could discriminate between uncomplicated and severe CAP. AECOPD patients showed significantly different levels of LTF and TRAIL compared to healthy subjects. Ensemble feature selection revealed that CAP and AECOPD can be discriminated by IL-6, resistin, together with IL-2R. These factors even allow the differentiation between COPD patients suffering from an exacerbation or pneumonia.

Discussion: Taken together, we identified immune mediators in patient plasma that provide information on differential diagnosis and disease severity and can

therefore serve as biomarkers. Further studies are required for validation in bigger cohorts.

KEYWORDS

pneumonia, COPD, acute exacerbation, severity, biomarker, inflammation

1. Introduction

Community-acquired pneumonia (CAP) constitutes a crucial cause of morbidity and mortality worldwide, predominantly affecting young children and the elderly (1). Representing the most frequent cause of death due to infection in Europe, CAP accounts for 1 million hospitalizations per year, resulting in 230,000 deaths and socio-economical costs of 10.1 billion € (2–4). Due to the abrupt onset of severe illness, the difficulty in identifying the liable pathogen and the challenge of distinguishing CAP from other acute airway infections, there is an urgent need for easily accessible but specific biomarkers allowing rapid and reliable diagnosis and risk stratification. To date, the diagnosis of CAP mostly relies on chest radiographs and analyses of blood and sputum parameters, as well as auscultation of the lungs and measurement of blood pressure, breathing rate, and recent mental confusion (5). For risk stratification, calculation of clinical scores like CRB65, which are based on defined parameters, roughly allows classification into uncomplicated, moderate, or severe CAP. However, specific biomarkers are still missing (6).

Chronic obstructive pulmonary disease (COPD) represents another highly relevant respiratory disease, being the fourth leading cause of death worldwide with an increasing tendency (7, 8). In Europe, COPD affects about 2–10% of the population and accounts for 3% of all deaths (9). Acute exacerbations of COPD (AECOPD), predominantly caused by viral or bacterial infections, contribute considerably to the burden of the disease. In the United States, AECOPD accounted for 726,000 hospitalizations in 2000, resulting in 119,000 deaths (10) and incurring costs of 30 billion $ (8). Diagnosis of AECOPD mostly relies on increasing cough, sputum, and dyspnoea (11), supported by chest radiographs, blood, and microbiological sputum analyses. Depending on symptoms, AECOPD can be subdivided into type I patients suffering from increasing dyspnoea and optionally sputum, and type II patients with purulent sputum (12). The exacerbation history seems to be the most dependable predictor for future exacerbations (13). As in pneumonia, the availability of reliable biomarkers clearly defining either the entity, stage, or severity of the disease or predicting its progression are of utmost importance.

Biomarkers are classically defined as objectively quantifiable molecules specifically indicating a biological state, which can be physiological or pathogenic, or a response to an expose or (therapeutic) intervention (14). Compared to symptom-based clinical findings, biomarkers have the advantage of allowing a better standardization of measurement and a less investigator-dependent interpretation (15). Due to the variety of molecules, the established handling, and the simplicity of collection, blood is a preferred medium for biomarker analyses (16). At present, the level of C-reactive protein (CRP), the blood sedimentation rate, as well as the leucocyte count, constitute clinical parameters classically indicating inflammation. However, whether this inflammation is of infectious etiology cannot be ascertained (15). Procalcitonin (PCT) represents a current biomarker allowing a more specific discrimination between inflammation of bacterial or non-bacterial origin (17). A potential predictor for mortality in COPD patients is the combination of midrange proadrenomedullin (MR-proADM) and ADO (age, dyspnoea, airflow obstruction), BOD (body mass index, airflow obstruction, dyspnoea) or BODE (body mass index, airflow obstruction, dyspnoea, exercise capability) indices (18, 19). Moreover, MR-proADM could be associated with severe AECOPD but not with CAP (20).

Here, we analyzed selected plasma markers that have been shown to indicate their value as biomarkers for the diagnosis and assessment of the severity of CAP and AECOPD.

2. Methods

2.1. Patients and controls

Patients with CAP or AECOPD were recruited within 24 h after hospitalization along with healthy controls. Inclusion criteria for patients with CAP included pulmonary infiltrates on chest radiograph and clinical presentation. The inclusion criteria for patients with AECOPD were patients with a previously confirmed diagnosis of COPD and an acute worsening without pulmonary infiltrates on chest radiograph. Patients receiving specific immunosuppressive therapy were excluded from the study, as were pregnant patients and those with human immunodeficiency virus. The BioInflame study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin (no. EA2/030/09) and the University Medical Center Marburg (no. 55/17). All donors were ≥ 18 years of age and provided written informed consent for the use of their blood samples for scientific purposes. Blood plasma was isolated by centrifugation (3,000× *g*; 10 min at room temperature) of one collected Vacutainer ethylenediaminetetraacetic acid tube. After centrifugation, the plasma phase was transferred and stored at −80°C.

2.2. Biomarker measurements

Biomarker measurements were performed in duplicate on stored frozen plasma samples from the day of study enrollment. Plasma levels of IL-6, LBP, and IL-2R were measured using the IMMULITE immunoassay system (Siemens Medical Solutions Diagnostics, Germany). Additionally, plasma levels of ELA2, HGF, IL-6, IL-8, LTF, NGAL, resistin, sFas, TSP-1, and TRAIL were measured with the MILLIPLEX® MAP Human Circulating Cancer Biomarker Magnetic Bead Panel 1 and the MILLIPLEX® MAP Human Sepsis Magnetic Bead Panel 3 (Merck Millipore, Germany) on a Luminex MAGPIX®

following the manufacturer's instructions (Luminex Multiplexing Instrument, Merck Millipore). Biomarker levels below the lowest standard were extrapolated corresponding to the equation of the standard curve.

2.3. Statistics

Statistical analyses were performed using GraphPad Prism version 9.5 (GraphPad software, Inc., CA, United States). Data were analyzed with non-parametric tests. For comparison of two groups, Mann–Whitney U Test was used. If all three groups were compared, Kruskal-Wallis Test followed by a *post hoc* test (Mann–Whitney U) was used. Receiver Operating Characteristic (ROC) curves were generated to identify biomarkers that clearly distinguish between two groups. To identify a group of parameters that clearly distinguishes between two groups, ensemble feature selection (EFS) was performed.

2.4. Ensemble feature selection

Importance analysis of the plasma biomarkers and their ranking was performed using EFS at the web-interface[1] (21, 22).

2.5. Patients and public involvement

Patients and the public were not involved in this study's design, recruitment and conduct.

3. Results

3.1. Patient characteristics

We included 27 patients hospitalized with CAP on a regular ward, ten patients with an acute exacerbation of COPD, and 22 healthy controls (Table 1). Samples were taken from all the patients within the first 24 h after hospital admission. The healthy control group was significantly younger than the CAP group, but CAP and AECOPD did not differ significantly. It also contained more female subjects, whereas in the CAP group, men were predominant, and the AECOPD group was balanced in terms of gender. In CAP patients, intermediate severity scores were most frequent, but mild or severe cases were also present (Table 2). All patients underwent routine microbiological testing, but did not show bacterial growth in blood culture and no specific causative pathogen in sputum culture. The majority of CAP patients ($n = 17$) were prescribed beta-lactam antibiotics, either alone or in combination with a beta-lactamase inhibitor or macrolide. Additionally, five patients received cephalosporine antibiotics, and four patients were prescribed fluoroquinolone antibiotics. In the AECOPD group, most patients experienced at least one exacerbation per year. They showed higher levels of airflow obstruction and breathlessness (Table 3). For AECOPD patients, systemic corticosteroids (oral or intravenous) were administered as the first-line treatment upon hospital admission, followed by antibiotics (amoxicillin/clavulanic acid). Four out of the ten AECOPD patients were already under systemic corticosteroid treatment prior to hospital admission. As COPD patients are more likely to develop pneumonia and suffer from more severe pneumonia (23), the CAP group was subdivided into patients with underlying COPD ($n = 8$) and without COPD ($n = 19$) (Table 4). All of the patients included here were effectively treated with appropriate medical care, including antibiotics and supportive measures, and were able to overcome the infection and recover; none of them died.

TABLE 1 General characteristics of healthy controls and patients with CAP or AECOPD.

	Healthy controls ($N = 22$)	CAP ($N = 27$)	AECOPD ($N = 10$)
Mean age [years ± SD]	41.0 ± 11.5	64.3 ± 17.7	62.4 ± 9.2
Gender m/f (%)	8/14 (36.4/63.6)	16/11 (59.2/40.8)	5/5 (50/50)

Data are presented as mean ± SD or *n* (%). CAP, community-acquired pneumonia; AECOPD, acute exacerbations of COPD.

3.2. Differential abundance of biomarkers in plasma

We performed multiplex analysis of molecules associated with sepsis and tumor diseases to test their significance in plasma samples as biomarkers for the diagnosis of CAP and AECOPD. The individual statistical analysis showed that eight of the twelve analyzed potential biomarkers were differentially expressed in CAP compared to healthy controls. Plasma levels of ELA2, HGF, IL-2R, IL-6, IL-8, LBP, and resistin as well as leukocyte, monocyte, and neutrophil counts were significantly elevated (Figure 1; Supplementary Figure S1). NGAL showed the same trend ($p = 0.002$). In contrast, levels of LTF and TRAIL were significantly reduced. No significant differences were found for sFas and TSP-1. In AECOPD patients, leukocyte, monocyte, and neutrophil counts were significantly higher compared to healthy controls (Figure 1; Supplementary Figure S1). Levels of LTF and TRAIL were significantly lower. sFas was reduced as well ($p = 0.038$). Comparing CAP with AECOPD, patients with CAP revealed significantly higher levels of ELA-2, IL-6, resistin, NGAL and CRP. To test whether some biomarkers might be expressed simultaneously, we performed Pearson's correlation analysis among all significantly expressed proteins and found the best positive correlations between resistin with NGAL and IL-6 with IL-8 (Supplementary Figure S2).

3.3. Diagnostic value

To augment the diagnostic significance of the analyzed parameters and statistically link each parameter to the prediction of CAP or AECOPD, respectively, we calculated the area under the curve (AUC) of the receiver operating characteristics (ROC) curve for all significantly regulated biomarkers from Figure 1. In CAP patients compared to healthy controls, the AUC values of LBP, IL-8, IL-6, HGF, IL-2R, ELA2, resistin, TRAIL, and LTF had significant *p*-values, but only the top two (LBP and IL-8) are presented in Figure 2. As the

1 http://efs.heiderlab.de/.

TABLE 2 Clinical characteristics of patients suffering from CAP.

CRB65 (%)		CURB (%)		PSI class (%)	
0	4 (15)	0	4 (15)	1	5 (19)
1	15 (56)	1	10 (37)	2	1 (4)
2	6 (22)	2	10 (37)	3	4 (15)
3	2 (7)	3	2 (7)	4	12 (44)
4	0 (0)	4	1 (4)	5	5 (19)
$sO_2 \pm SD$ [%]		94.5 ± 3.1			
Body temperature ± SD [°C]		37.4 ± 1.2			
CRP ± SD [mg/dL]		14.0 ± 11.0			
WBC ± SD [1/nL]		10.4 ± 4.5			

Data are presented as mean ± SD or *n* (%). CRB65, confusion, respiratory rate, blood pressure, 65 years of age, and older; CURB, confusion, urea nitrogen, respiratory rate, and blood pressure; PSI, pneumonia severity index; CRP, C-reactive protein; WBC, white blood cell count.

TABLE 3 Clinical characteristics of patients suffering from AECOPD.

GOLD stage (%)		GOLD group (%)		mMRC (%)	
I	0 (0)	A	0 (0)	I	1 (10)
II	2 (20)	B	0 (0)	II	3 (30)
III	0 (0)	C	2 (20)	III	6 (60)
IV	6 (60)	D	6 (60)	IV	0 (0)
ND	2 (20)	ND	2 (20)		
Exacerbation/year ± SD		1.2 ± 0.7			
Pack years ± SD		62 ± 47			
6MWT ± SD [m]		225 ± 131			
CRP ± SD [mg/dL]		2.4 ± 1.9			
WBC ± SD [1/nL]		10.6 ± 2.4			

Data are presented as mean ± SD or *n* (%). GOLD, global initiative for chronic obstructive lung disease; mMRC, modified British Medical Research Council; 6MWT, six-minutes walking test; CRP, C-reactive protein; WBC, white blood cell count.

diagnostic potential of a composite of potential biomarkers might be higher than single parameters, feature selection was performed. To this end, EFS was chosen, as it combines eight feature selection methods and thereby improves the prediction performance (21). This multivariate analysis returns the importance of each significantly regulated marker, which are normalized quantifications of the predictive capabilities of the given variables (Figure 2C). The selected features are LBP, IL-6, and IL-2R, which we define as a marker panel for CAP diagnosis.

As it is critical in clinical routine to determine which patient has a higher risk to develop a more severe form of pneumonia, we aimed to find plasma markers for this discrimination. We subdivided the CAP patients according to the pneumonia severity index (PSI) risk class (uncomplicated (u) CAP: 1–3; severe (s) CAP: 4–5) and tested whether our collected parameters support this stratification. Smaller group sizes after separation (uCAP: 10; sCAP: 17) precluded robust statistical differentiation between the two groups, but TRAIL emerged as the most appropriate parameter allowing discrimination of uCAP and sCAP with a value of $p < 0.05$ (Supplementary Figure S3A). In ROC analysis, TRAIL had an AUC of 0.7406 (Supplementary Figure S3B). To combine the power of all measured plasma parameters, EFS was performed. The selected features

TABLE 4 Clinical characteristics of CAP patients with and without COPD.

		CAP+COPD (*n*=8)	CAP−COPD (*n*=19)
GOLD (%)	I	0 (0)	
	II	2 (25)	
	III	1 (12.5)	
	IV	1 (12.5)	
	Not classified	4 (50)	
PSI risk class (%)	1	0 (0)	5 (26.3)
	2	0 (0)	1 (5.3)
	3	2 (25)	2 (10.5)
	4	5 (62.5)	7 (36.8)
	5	1 (12.5)	4 (21.1)
Mean age [years ± SD]		72.9 ± 7.5	60.7 ± 19.6
Gender m/f (%)		5/3 (62.5/37.5)	11/8 (57.9/42.1)

Data are presented as mean ± SD or *n* (%). GOLD, global initiative for chronic obstructive lung disease; PSI, pneumonia severity index.

were LBP, sFas, TRAIL, IL-6, and IL-8, of which LBP ranked highest (0.8) according to its normalized ensemble importance (Supplementary Figure S3C).

To elucidate the diagnostic value of the differentially expressed markers in AECOPD plasma compared to healthy controls, ROC analysis was performed for the significantly regulated biomarkers from Figure 1. AUC values of LTF and TRAIL were > 0.89 with significant *p*-values (Supplementary Figure S4).

As CAP and AECOPD often exhibit similar symptoms and can be difficult to distinguish, we performed ROC analyses comparing AECOPD and CAP patients based on all significantly regulated plasma proteins from Figure 1. AUC values of IL-6, resistin, NGAL, and ELA2 showed significant *p*-values, but only the top two (IL-6 and resistin) are presented in Figures 3A,B. Multi-parametric analysis was performed to discriminate CAP from AECOPD. The selected features were IL-6, NGAL, and resistin, of which IL-6 ranked highest (0.78) according to its normalized ensemble importance (Figure 3C).

The selected features to discriminate CAP and AECOPD from the EFS analysis (Figure 3C) were again tested for their reliability when CAP patients with and without pre-existing COPD were compared to AECOPD patients. IL-6 and resistin were still significantly different when the CAP patient had a pre-existing COPD (Figures 4A–C). The ROC analyses for IL-6, NGAL, and resistin, between AECOPD and CAP+COPD revealed AUCs >0.79 with significant *p*-values (Figures 4D–F).

4. Discussion

In this study, we investigated a set of plasma proteins as potential biomarkers for CAP or AECOPD, respectively.

In CAP patients, we found that the plasma levels of ELA2, HGF, IL-2R, IL-6, IL-8, LBP, and resistin were elevated, while LTF and TRAIL were reduced. Among these, LBP, IL-6, and IL-2R are features

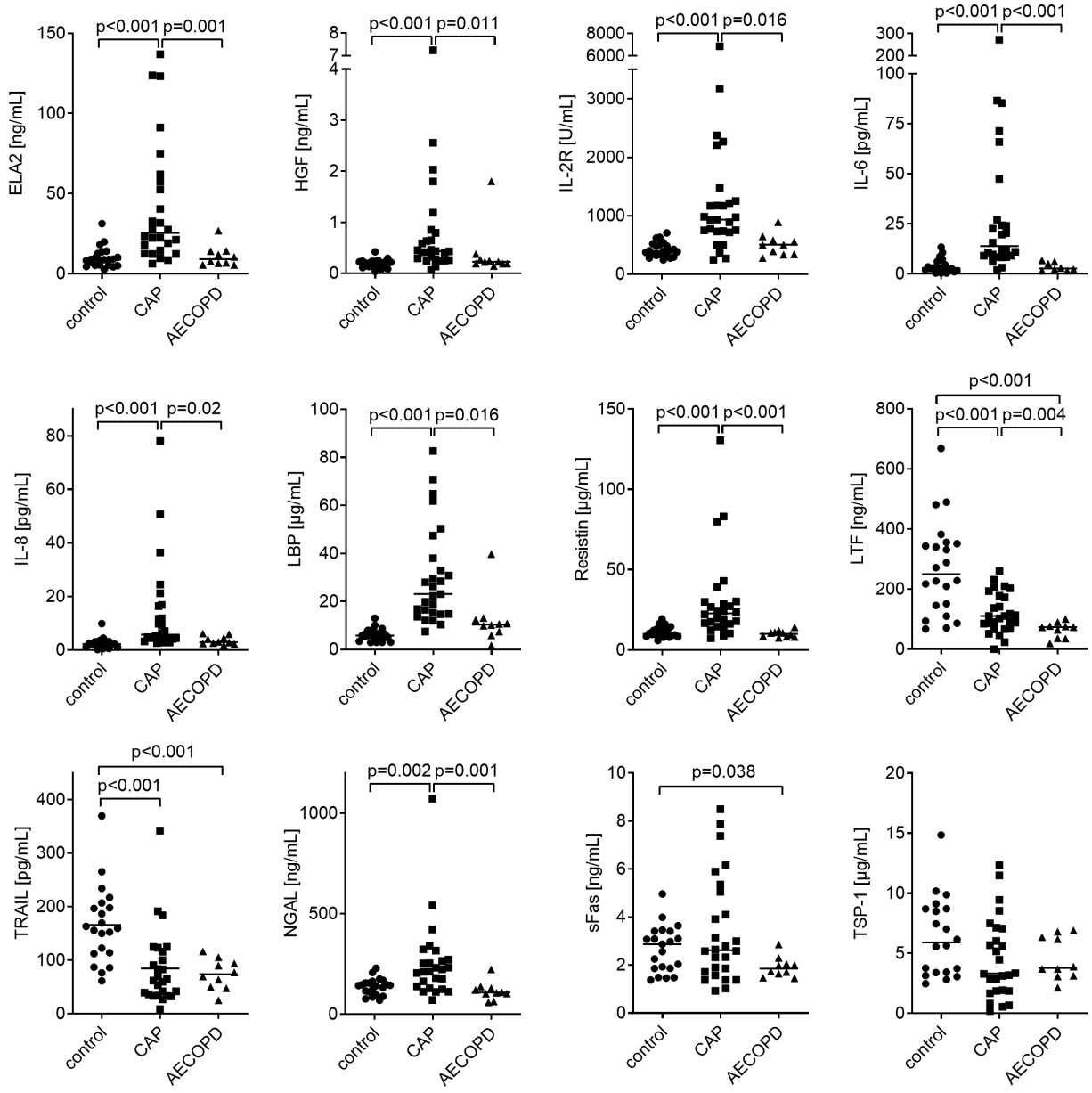

FIGURE 1
Biomarker expression in plasma samples from CAP and AECOPD patients compared to healthy controls. Data are presented as scatter plots with the median shown as a line. Statistics: Kruskal-Wallis test was performed and $p \leq 0.001$ was considered significant.

for CAP diagnosis, and the combination of LBP, sFas, TRAIL, IL-6, and IL-8 allowed discrimination between uncomplicated and severe forms of pneumonia.

LBP is known to be involved in the acute-phase response against gram-negative bacteria by binding the lipid A moiety of soluble LPS and presenting it to CD14 on cellular membranes. It is mainly produced in the liver and its plasma concentration increases exponentially during acute inflammatory response (24), but it is also found in alveolar fluid (25). It was found that the serum level of LBP was significantly higher in patients with sCAP compared to uCAP and correlated with disease severity, which we also observed. Moreover, LBP has a higher predictive power than CRB-65 (26). Tejera et al. found higher serum levels of LBP in hospitalized CAP patients (27). Likewise, the pro-inflammatory cytokine IL-6 has been found to be increased in CAP patients in other studies. The serum levels of IL-6 were significantly higher in high-risk compared to low-risk CAP patients, and its level correlated with disease severity and decreased on day 3 and 5 after hospitalization (28). Bacci et al. and Andrijevic et al. made similar observations, as IL-6 levels correlated with PSI and CURB score and high IL-6 serum levels were associated with higher lethality of hospitalized patients and decreased from the day of admission to day seven of treatment (29, 30). In our study, IL-6 showed a trend of gradual upregulation with pneumonia severity, it was a selected feature for discrimination between uCAP and sCAP and correlated with the plasma levels of IL-8, which has been described to be significantly higher in sCAP patients compared to

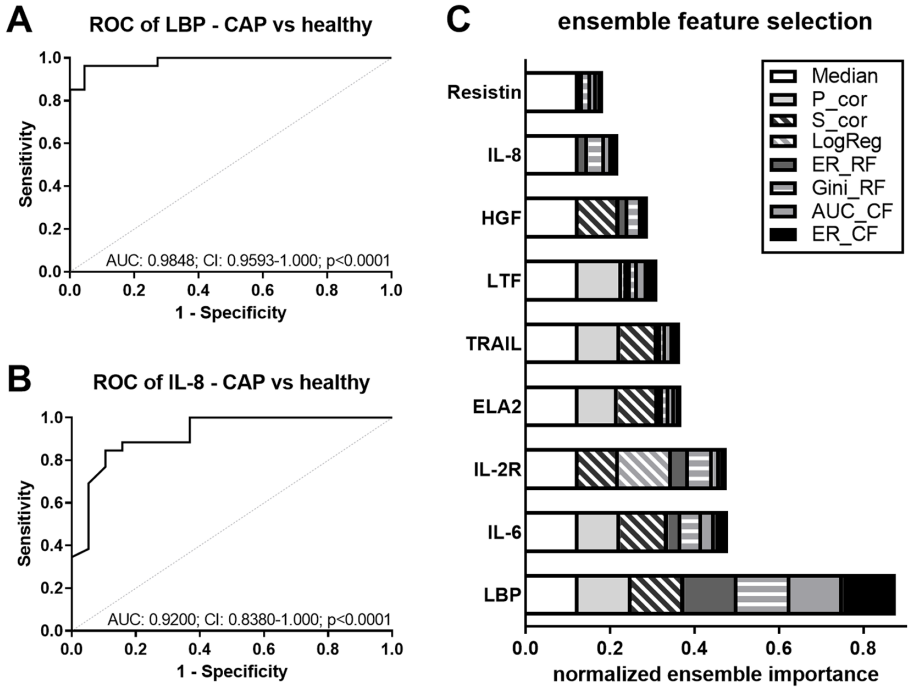

FIGURE 2
Discrimination between CAP and healthy controls. **(A,B)** ROC curves for the discrimination between healthy controls and CAP using LBP **(A)** and IL-8 **(B)**. Dashed line (grey) shows line of identity. AUC, area under the curve; CI, confidence interval, and *p*-values are depicted in the graphs. **(C)** Ensemble feature selection for healthy controls and CAP using all significantly regulated biomarkers. The cumulative barplot shows individual features for all feature selection methods. P_cor, Pearson product moment correlation; S_cor, Spearman's rank correlation; LogReg, logistic regression; ER_RF, error-rate-based variable importance measure embedded in *randomForest*; Gini_RF, Gini-index-based variable importance measure embedded in *randomForest*; AUC_CF, area under the curve embedded in *cforest*; ER_CF, error-rate-based variable importance measure embedded in *cforest*.

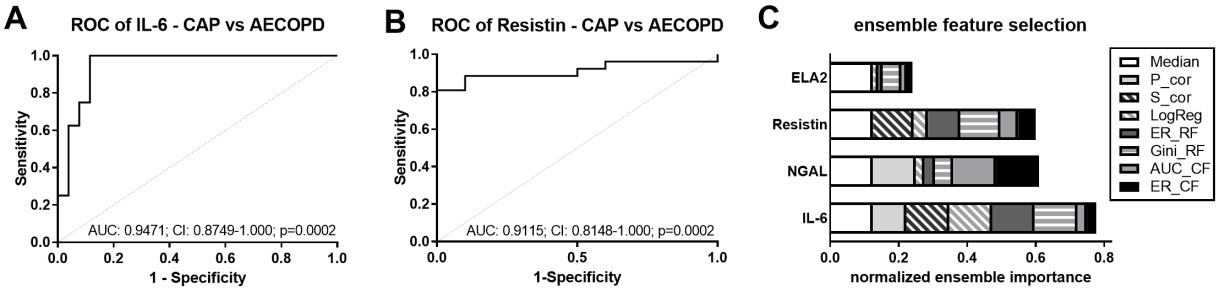

FIGURE 3
Discrimination between CAP and AECOPD. **(A,B)** ROC curves for the discrimination between CAP and AECOPD by IL-6 **(A)** and resistin **(B)**. Dashed line (grey) shows line of identity. AUC, area under the curve; CI, confidence interval and *p*-values are depicted in the graphs. **(C)** EFS for CAP and AECOPD for all significantly regulated biomarkers. The cumulative barplot shows individual features for all feature selection methods. P_cor, Pearson product moment correlation; S_cor, Spearman's rank correlation; LogReg, logistic regression; ER_RF, error-rate-based variable importance measure embedded in *randomForest*; Gini_RF, Gini-index-based variable importance measure embedded in *randomForest*; AUC_CF, area under the curve embedded in *cforest*; ER_CF, error-rate-based variable importance measure embedded in *cforest*.

milder CAP (30). Soluble IL-2R is a marker for T-cell activation (31). sFas, Fas ligand, and their ratio were associated with a high sepsis-related organ failure assessment (SOFA) score in patients with bacteremia (32). We found it to be decreased in CAP compared to healthy controls but higher in sCAP compared to uCAP. TRAIL is a type II transmembrane protein and belongs to the TNF/TNFR superfamily, which is involved in infection control and the regulation of both innate and adaptive immune responses (33). TRAIL level in airway epithelial cells of COPD patients is elevated (34). The serum concentration of TRAIL has been demonstrated to negatively correlate with pulmonary function (35).

In AECOPD patients, LTF, and TRAIL were significantly reduced in plasma samples, and both had AUC values indicating discriminative potential to differentiate between AECOPD and healthy controls. LTF is an iron-binding protein and provides protection against pathogens and their metabolites. Moreover, it has bactericidal properties that lead to the

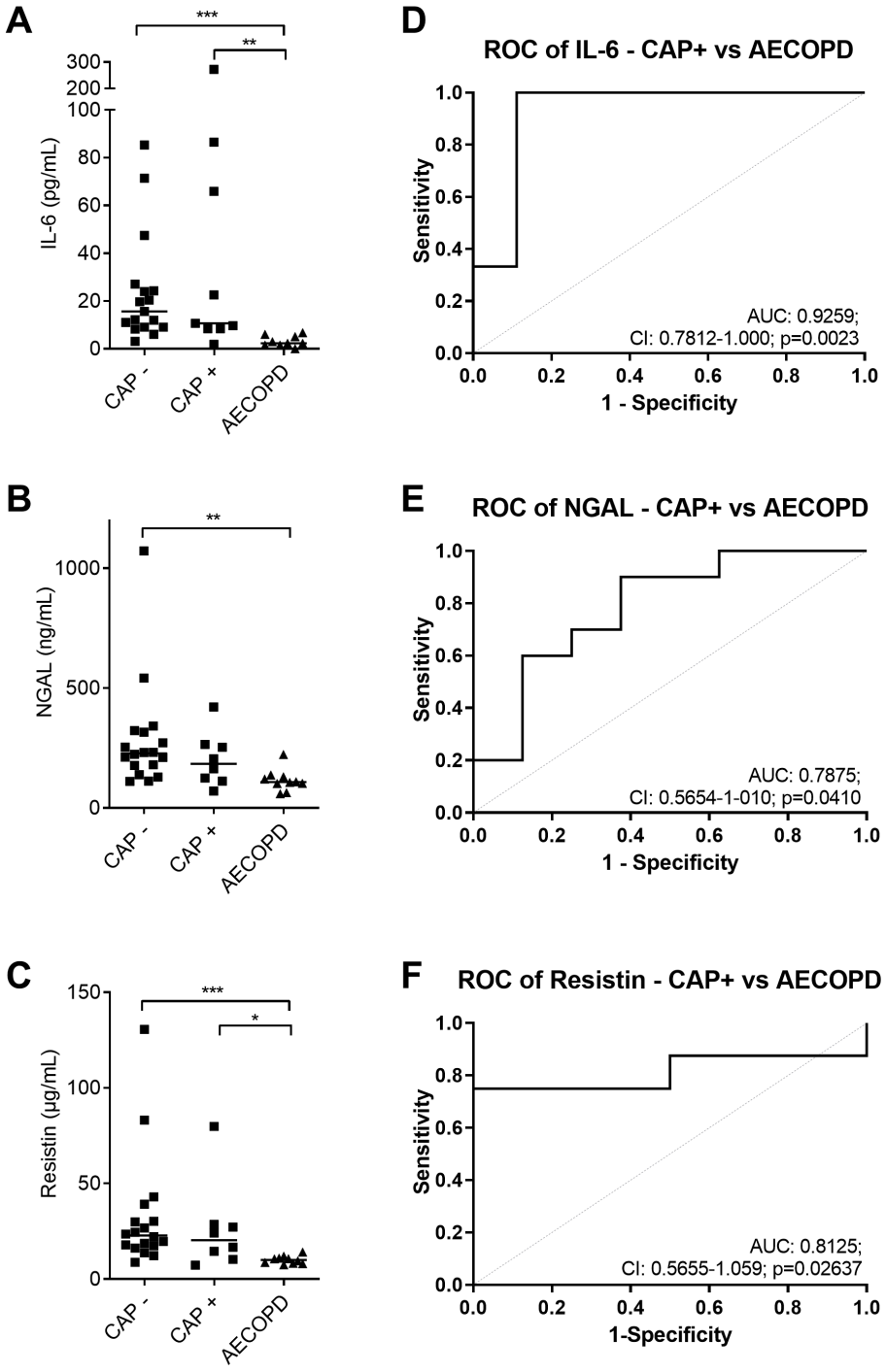

FIGURE 4
Discrimination between AECOPD and CAP with pre-existing COPD. **(A–C)** Amount of IL-6 **(A)**, NGAL **(B)**, and resistin **(C)** in plasma samples from CAP (–/+ COPD) and AECOPD patients. Data are presented as scatter plots and the line shows the median. **(D–F)** ROC curves for the discrimination between CAP+COPD and AECOPD by IL-6 **(D)**, NGAL **(E)**, and resistin **(F)**. Dashed line (grey) shows line of identity. AUC, area under the curve; CI, confidence interval (CI), and *p*-value are depicted in the graph. Statistics: Kruskal-Wallis test was performed and $p<0.05$ was considered significant (*$p<0.05$, **$p<0.01$, ***$p<0.001$).

release of LPS from the outer membrane of gram-negative bacteria (36). It has the capability to enhance phagocytosis of pathogens and cell adherence and controls the release of pro-inflammatory cytokines (37, 38). LTF has been described to be down-regulated in asthmatic patients (39) as observed in our CAP and AECOPD patients.

Since the incidence of pneumonia in COPD patients is almost twice as high as in the general population (40), COPD patients can suffer from both AEs and CAP, which require different clinical treatments and must be differentiated accordingly. This differential diagnosis is traditionally based on radiological findings. It is important

to have biological markers to improve the differential diagnosis, reduce unnecessary use of antibiotics, and lower mortality and expenditures for care. Comparing CAP and AECOPD patients, CAP patients had significantly higher levels of IL-6 and CRP. Huerta et al. also observed higher IL-6 levels in CAP patients compared to AECOPD as well (41). EFS revealed that IL-6, NGAL, and resistin are suitable markers for discrimination between AECOPD and CAP, and the discrimination was still possible with these selected features even when the CAP patient additionally suffers from COPD. Resistin, which correlated with NGAL, is an important pro-inflammatory cytokine produced by monocytes and epithelial cells (42). The levels of resistin were higher in sCAP patients compared to uCAP patients, which is in line with the observation that sepsis patients also have elevated levels of resistin (43, 44). Several studies indicate that resistin and NGAL are increased in sepsis patients and serve as markers for disease severity (45–47). Plasma NGAL concentrations increased with severity and could predict mortality (48), which we did not test. NGAL and IL-6 were significantly higher in patients with lower respiratory tract infections compared to healthy controls, but Liu et al. did not observe differences between CAP and AECOPD in their study (49).

The proposed biomarkers for CAP diagnosis and differential diagnosis between CAP and AECOPD should be validated in larger cohorts in the future. As we had significantly younger healthy controls compared to CAP patients, we wanted to exclude the possibility that the increase in their plasma expression was solely due to the difference in age between the two groups. Therefore, we tested for correlation between age and the suggested markers, but did not observe any correlation (all $R^2 < 0.05$; Supplementary Figure S5).

We identified a plasma biomarker panel that shows potential for CAP and AECOPD diagnosis and stratification even in CAP cases with COPD as an underlying disease. Future studies with larger cohorts and a multicentric design are needed for further evaluation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

BioInflame study was approved by the ethics committee of the Charité–Universitätsmedizin Berlin (no. EA2/030/09) and the University Medical Center Marburg (no. 55/17). The patients/participants provided their written informed consent to participate in this study.

Author contributions

AJ analyzed the data and wrote the manuscript in consultation with WB and BS. KG performed the experiments. CN and DH performed statistical analyses. MH, TG, AK, HP, CV, SH, and NS collected the patient's material. BS supervised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1180746/full#supplementary-material

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Undiagnosed chronic respiratory disorders in symptomatic patients with initially suspected and excluded coronary artery disease: insights from a prospective pilot study

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Background: Chronic respiratory diseases represent the third-leading cause of death on a global scale. Due to mutual symptoms with cardiovascular diseases and potential inappropriate attribution of symptoms, pulmonary diseases often remain undiagnosed. Therefore, we aimed to evaluate the prevalence of chronic respiratory disorders among symptomatic patients in whom suspected coronary artery disease (CAD) was ruled out.

Methods: After CAD was excluded by invasive coronary angiography (ICA), 50 patients with chest pain or dyspnea were prospectively enrolled in this study. All patients underwent lung function testing, including spirometry and diffusion measurements. At baseline and the 3-month follow-up, standardized assessments of symptoms (CCS chest pain, mMRC score, CAT score) were performed.

Results: Chronic respiratory disease was diagnosed in 14% of patients, with a prevalence of 6% for chronic obstructive ventilation disorders. At 3-month follow-up, patients with normal lung function tests revealed a substantial improvement in symptoms (mean mMRC 0.70 to 0.33, p=0.06; median CAT 8 to 2, p=0.01), while those with pulmonary findings showed non-significant alterations or unchanged symptoms (mean mMRC 1.14 to 0.71, p=0.53; median CAT 6 to 6, p=0.52).

Conclusion: A substantial proportion of patients with an initial suspicion of coronary artery disease was diagnosed with underlying chronic respiratory diseases and exhibited persistent symptoms.

KEYWORDS

chronic respiratory disorders, chronic obstructive pulmonary disease, coronary artery disease, dyspnea, chest discomfort

1. Introduction

Chronic respiratory diseases encompass a broad spectrum of various disorders affecting the airways and pulmonary structures. The global prevalence is estimated at 7.1%, with the highest rates in high-income nations (10.6%), where chronic obstructive pulmonary disease (COPD) accounts for more than half of all cases (1). As the third leading cause of death, these conditions pose a substantial global socioeconomic challenge (2).

COPD often remains underdiagnosed in the general population, which prevents patients from receiving effective treatment (3). Even though many chronic respiratory diseases cannot be cured, early diagnosis is of paramount importance to inform patients about risk factors (i.e., cigarette smoking), to allow early treatment, to prevent progression and to preserve a good quality of life. Appropriate therapy also considerably contributes to the prevention of major comorbidities (4). With a 2- to 5-fold higher risk among COPD patients, coronary artery disease (CAD) is one of the most important comorbidities (5, 6).

Moreover, patients with cardiovascular or pulmonary diseases often present with mutual initial symptoms, particularly dyspnea. In clinical practice, once coronary artery disease, the leading cause of death worldwide, as the primary diagnostic focus has been ruled out, further assessment of symptoms often remains neglected. This may impede the identification of underlying pulmonary symptoms in patients and may lead to the potential undetectability of chronic pulmonary diseases (2, 7).

Therefore, the objective of this pilot study was to investigate the prevalence of chronic respiratory diseases in symptomatic patients after CAD had been ruled out by invasive coronary angiography (ICA). As symptomatic individuals without CAD may benefit from downstream pulmonary testing, we additionally conducted a detailed assessment of symptoms in these patients which initially led to ICA and re-evaluated them after a follow-up period of 3 months.

Furthermore, this study aimed to evaluate the feasibility of our study protocol for future multicenter trials as insights from large scale clinical studies will be needed to develop effective strategies to further improve the underdiagnosis of COPD.

2. Materials and methods

2.1. Study design

This prospective pilot study was conducted as a non-randomized, open-label, single-center trial at a tertiary care university hospital.

Prior to its initiation, the local ethics committee evaluated and authorized this study. The investigation was carried out in conformity with the Declaration of Helsinki and the European Data Policy. Written informed consent was obtained from all participating patients.

The primary objective of this study was to evaluate the prevalence of chronic respiratory insufficiency in a sample of symptomatic patients after excluding CAD by ICA. The secondary objective was to examine the potential relationship between abnormal pulmonary function and prior symptom burden and characteristics, including chest discomfort and dyspnea.

Figure 1 depicts the study protocol. To generate conclusive initial findings, a feasible sample size of 50 study participants was defined in this pilot study, with random patient screening based on pre-determined inclusion criteria. Following screening, patients with negative ICA findings were included in the trial after providing informed consent. A physician carried out a thorough standardized symptom evaluation the same day. The following day, spirometry (with bronchodilation in case of obstructive ventilation) and diffusion tests were performed. Every patient had a result-oriented discussion with a pulmonologist. In case of pathologic findings, patients were admitted to outpatient care providers for further tests and therapy. Follow-up was conducted after 3 months via phone to assess symptoms, medication modifications, and any adverse events.

2.2. Study subjects

Individuals who received invasive coronary angiography due to suspected coronary artery disease-related chest pain and/or dyspnea but revealed no evidence of coronary stenoses were recruited for this trial. Patients had to be over 18 years of age and able to provide written informed consent. This study excluded patients with either known or newly diagnosed cardiac conditions, pre-existing lung pathologies, allergies to bronchodilators, and pregnant women.

2.3. Symptom assessment

The standardized assessment of chest discomfort was carried out in accordance with the European Society of Cardiology's 2019 Guidelines on Chronic Coronary Syndromes (8). Therefore, three subcategories were used: typical angina pectoris, atypical angina pectoris, and non-anginal chest pain.

The degree of dyspnea was graded from 0 to 4 using the standardized modified Medical Research Council (mMRC) severity scale (9). In addition, the COPD Assessment Test (CAT) was obtained to detect additional subjective complaints that may indicate pulmonary pathologies (10).

2.4. Statistical analysis

For the statistical analysis, GraphPad Prism for macOS (version 9.5.0; GraphPad Software, LLC, La Jolla, CA, United States) was used. Categorical data are presented as absolute values and percentages. Significant differences between groups were assessed using either the Chi-square test or Fisher's exact test. Where applicable, quantitative values are reported as means ± SD or medians ± first and third quartile. Two-tailed ANOVA testing with post-hoc analyses was used to make comparisons. The Šidák correction was used to adjust for multiple comparisons. The level of significance was set at $p < 0.05$.

3. Results

This prospective pilot study included 50 patients, 24 (48.0%) were women. The patients' demographics are displayed in Table 1.

Seven patients (14.0%) presented with functional respiratory abnormalities, 3 (6.0%) had obstructive and 4 (8.0%) had non-obstructive pulmonary impairments (2 patients with restrictive ventilation disorder, 2 patients with pulmonary diffusion dysfunction).

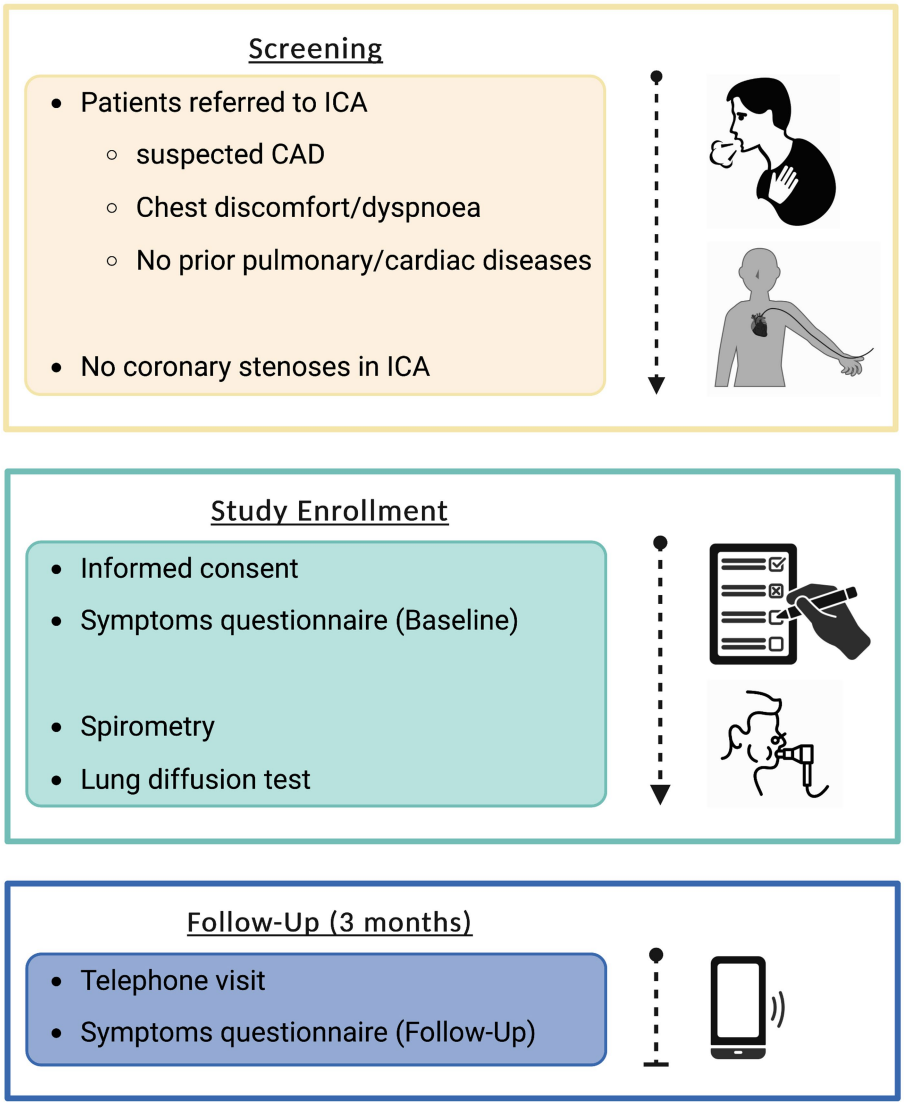

FIGURE 1
Flowchart depicting study protocol. Created with BioRender.com. CAD, coronary artery disease; ICA, invasive coronary angiography.

At the three-months follow-up, the overall number of patients experiencing chest discomfort declined significantly from 40 (80.0%) at baseline to 19 (38.0%) ($p = 0.0001$). This reduction was particularly pronounced in patients who initially had typical angina pectoris, with 17 (34.0%) patients at baseline versus 7 (14.0%) at follow-up ($p = 0.034$). The number of patients with atypical angina pectoris declined from 14 (28.0%) to 8 (16.0%) ($p = 0.23$), while the number of patients with non-specific chest pain decreased from 9 (18.0%) to 4 (8.0%) ($p = 0.07$) (Figure 2). The total number of patients suffering from dyspnea also decreased significantly, from 27 (54.0%) at baseline to 13 (26.0%) at follow-up ($p = 0.007$).

The grouped analysis of initial symptoms leading to ICA revealed that patients with subsequent abnormal respiratory function reported more cases of dyspnea (85.7% vs. 48.9%, $p = 0.11$); in contrast, they reported fewer cases of chest discomfort (57.1% vs. 83.7%, $p = 0.13$) compared to those patients without subsequent pathological pulmonary findings (Table 2). Compared to the initial symptom presentation, patients with pathological pulmonary function revealed a smaller decrease in the mean mMRC score with a decline from 1.14 to 0.71 (−37.7%, $p = 0.53$) compared to patients with normal lung function who experienced a larger decrease from 0.70 to 0.33 (−52.9%, $p = 0.06$) at the follow-up after 3 months (Figure 3A). Similar dynamics were seen regarding the CAT score after 3 months: patients with pathological respiratory findings had unaltered median CAT scores of 6 (±0; $p = 0.52$), whereas patients without pathological respiratory findings had a significant decline in median CAT score from 8 to 2 (−6; $p = 0.01$) (Figure 3B). In a subanalysis of CAT score categories at baseline, no significant difference between the two groups was found. At follow-up, patients with pathological pulmonary tests had a significantly higher mean score in the subcategory "breathlessness" compared to patients without respiratory disorders ($p = 0.003$) (Figure 4).

During the 3-month follow-up period, four patients in the group with normal pulmonary function acquired COVID-19. Symptom

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dynamics did not change when excluding those patients from the statistical analysis.

4. Discussion

This pilot study discovered a significant prevalence of abnormal respiratory function in symptomatic individuals after coronary artery disease had been ruled out by ICA, with a substantial prevalence of chronic obstructive pulmonary disease. Baseline symptom characteristics showed more dyspnea and less chest discomfort among individuals with pulmonary findings. Changes in symptoms were significantly different, with persistent dyspnea in patients with abnormal pulmonary function at follow-up. This is, to the best of our knowledge, the first prospective study to investigate the prevalence of pulmonary diseases in symptomatic patients with suspected CAD, however, in whom CAD was excluded by ICA. The results of our study support the underlying hypothesis that a considerable proportion of patients may be referred for ICA due to underlying pulmonary symptoms.

As the initial point of contact for symptomatic patients, primary care plays a crucial part in the timely diagnosis of chronic respiratory disorders. Lack of spirometry testing in primary care has been shown to be one major reason for missed diagnoses of chronic respiratory disorders (11, 12). According to the US Preventive Services Task Force, however, there are no clear indications that screening asymptomatic individuals for COPD improved their clinical outcome. Therefore, broad diagnostic testing by means of spirometry is not recommended for the general population and should be limited to individuals with risk factors or symptoms (13).

Respiratory symptoms are subjective and may vary in quality and intensity, making symptom-based pulmonary screening difficult and reliant on self-reporting by patients during medical visits (14, 15). Labonté et al. demonstrated that undiagnosed COPD patients utilized health care services to a comparable extent as diagnosed COPD patients due to exacerbation events (16). A real-world retrospective study by Jones et al. revealed that approximately 85% of COPD patients presented with respiratory symptoms to a physician in the 5 years before their diagnosis and 58% within 6 to 10 years prior to diagnosis (17). This may be in line with the results of our pilot study, which indicate that lingering symptoms after a negative ICA result might be strongly indicative of a prior undetected chronic respiratory condition.

Therefore, some studies advocate a questionnaire-based selection of patients for diagnostic spirometry as a cost-effective approach to detect chronic respiratory disease in individuals (18). Our findings support the need for enhanced screening for chronic pulmonary disorders and the feasibility of including persistent symptoms such as dyspnea and chest pain in pre-screening.

TABLE 1 Demographics.

	n=50
Female sex	24 (48%)
Age	64.8 ± 9.0
Body mass index	27.8 ± 4.9
Cholesterol [mg/dl]	162.4 ± 46.0
LDL [mg/dl]	90.9 ± 41.4
Creatinine [mg/dl]	0.95 ± 0.2
GFR > 60 [ml/min/1.73 m^2]	41 (82%)
45–60	9 (18%)
Arterial hypertension	34 (68%)
under treatment	31 (62%)
Dyslipidemia	38 (76%)
under treatment	30 (60%)
Diabetes	12 (24%)
under treatment	6 (12%)
Family history of CAD	20 (40%)
Active smoking	6 (12%)
Former (>1 year)	19 (38%)
Mean packyears (range)	27.9 ± 20.1

Data are represented as *n* (%) or mean ± SD. CAD, coronary artery disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein.

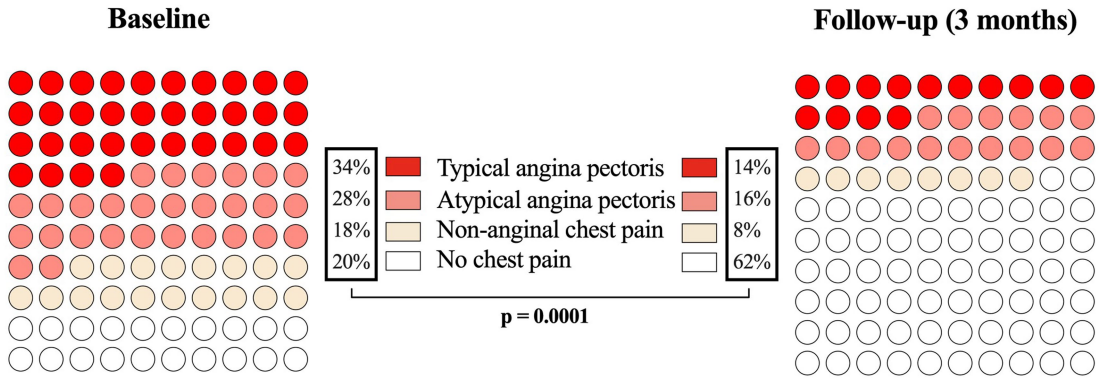

FIGURE 2
Frequencies of the various manifestations of chest discomfort in the study cohort, as classified by ESC guidelines (2019) at two timepoints: Baseline. 3-month follow-up. Data are shown as 10×10 dot plots and percentages.

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TABLE 2 Patient characteristics and symptoms at baseline.

	Respiratory+(*n*=7)	Respiratory−(*n*=43)	value of *p*
Age	66.1 ± 10.0	64.5 ± 8.9	0.664
Female gender	3 (42.9%)	21 (48.9%)	1.000
Body mass index	29.9 ± 5.8	27.4 ± 4.7	0.205
Smoker	1 (14.3%)	5 (11.6%)	1.000
Chest pain	4 (57.1%)	36 (83.7%)	0.133
Dyspnea (mMRC ≥1)	6 (85.7%)	21 (48.9%)	0.107
CAT ≥10	3 (42.9%)	11 (25.6%)	0.384

Data are represented as *n* (%) or mean ± SD. CAT, COPD assessment test; mMRC, modified Medical Research Council; Respiratory+, patients with pathological results; Respiratory−, patients with normal results.

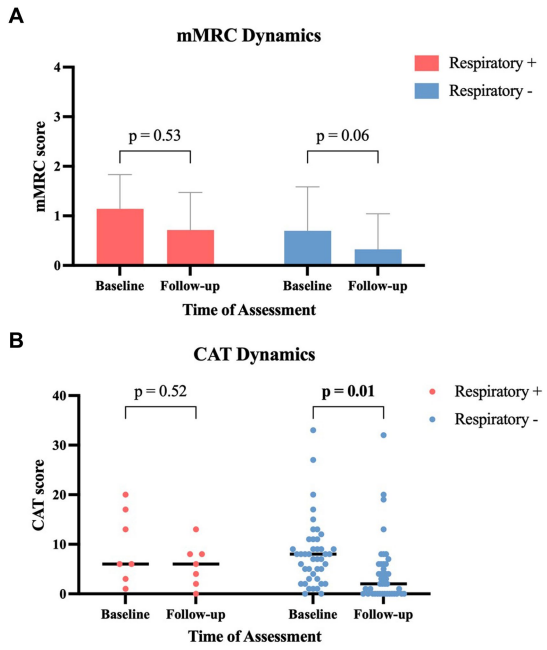

FIGURE 3
Symptom-score changes between baseline and 3-month follow-up in patients with and without abnormal respiratory tests: **(A)** modified Medical Research Council (mMRC) score (data provided as mean±standard deviation). **(B)** COPD assessment test (CAT) score (data provided as scatter dot plot and median). CAT, COPD assessment test; mMRC, modified Medical Research Council; Respiratory+, patients with pathological respiratory tests; Respiratory−, patients with normal respiratory tests.

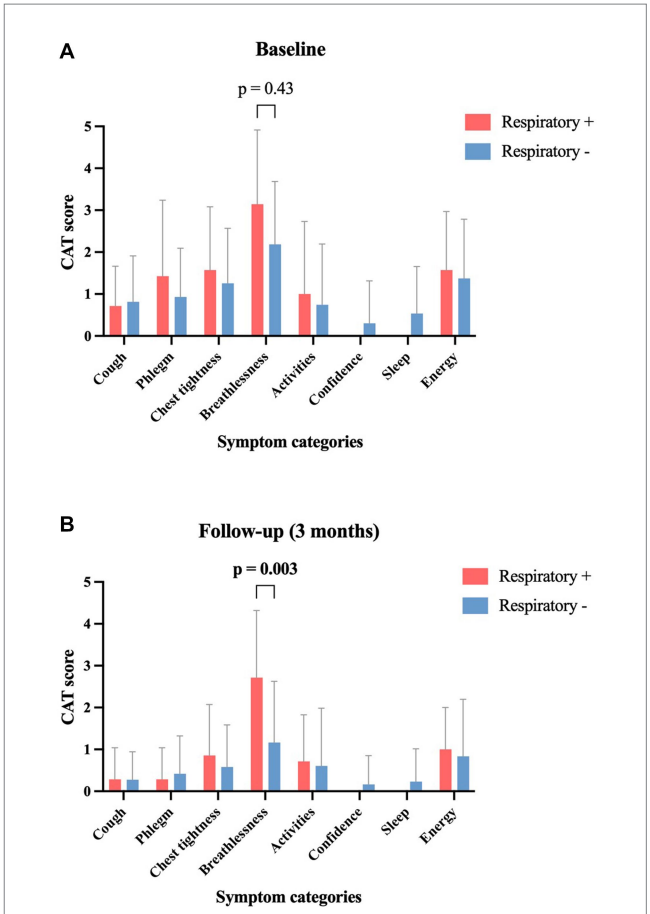

FIGURE 4
Symptom-score changes in patients with and without abnormal lung tests between baseline and 3-month follow-up, according to the 8 CAT symptom classes. Data provided as mean±standard deviation. CAT, COPD assessment test; Respiratory+, Patients with pathological respiratory tests; Respiratory−, Patients with normal respiratory tests.

However, the reliability of questionnaire-based findings is subject to large variations among individuals, and like the quality of physician-patient dialogues, it heavily depends on the active participation of patients (19). On this basis some research suggests that handheld flow meters may be more effective than questionnaires in pre-selecting individuals for diagnostic spirometry (20).

Even if patients accurately report symptoms, general practitioners may misinterpret them, which also could substantially delay the diagnosis of lung diseases. Physicians may incorrectly attribute symptoms such as chest tightness or dyspnea to cardiovascular diseases as opposed to bronchoconstriction in asthma or COPD (21–23). Particularly physicians without pulmonary focus are prone to substantially underdiagnose COPD, while representing the first point of contact for most patients with undiagnosed pulmonary conditions (12, 24). According to a survey, most pulmonologists suggest that a lack of awareness of chronic respiratory diseases appears to be the leading cause of insufficient early diagnoses (25). However, modest educational training has been proven to significantly increase physicians' expertise in COPD diagnosis (26). This demonstrates the yet-untapped potential of education and training in the early identification of respiratory diseases to further campaign undiagnosed chronic respiratory disorders.

While our pilot study is limited by a small sample size, our objective was to explore the prevalence of clinically confirmed chronic respiratory disorders in a highly homogeneous population. The absence of pre-existing pulmonary or cardiac conditions (i.e., heart failure, valvular heart disease) in this study population prevented potential distortion in the analysis of symptoms. The

diagnostic approach of our study protocol was designed to be practical and readily accessible, hence, we restricted pulmonary function testing to spirometry and diffusion measurement. However, this approach limited the classification of potential restrictive pulmonary dysfunction to data derived from spirometry, as body plethysmography was not incorporated. The purpose of this pilot study was to assess the feasibility of the present study protocol for multicenter trials with large patient populations. Such large-scale investigations will be needed to develop effective ways to counteract pulmonary underdiagnosis in people with chest symptoms but no cardiovascular diseases.

In conclusion, following the exclusion of coronary artery disease through ICA, a relevant portion of symptomatic individuals were found to have respiratory dysfunction, with a substantial prevalence of obstructive ventilation abnormalities. Downstream pulmonary testing may be reasonable in individuals with persistent symptoms after CAD exclusion.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics committee of the Medical University of Innsbruck Approval number: 1296/2019. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CB, AnB, AP, AxB, GW, JL-R, GFr, and FP conceived and designed the study. CB, AnB, and FP collected the data. CB, AnB, AP, PG, GFe, AxB, GW, JL-R, GFr, and FP analyzed and interpreted the data, revised and approved the manuscript, and agreed to be accountable for all aspects of the work. CB and FP drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A risk nomogram for predicting prolonged intensive care unit stays in patients with chronic obstructive pulmonary disease

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Background: Providing intensive care is increasingly expensive, and the aim of this study was to construct a risk column line graph (nomograms)for prolonged length of stay (LOS) in the intensive care unit (ICU) for patients with chronic obstructive pulmonary disease (COPD).

Methods: This study included 4,940 patients, and the data set was randomly divided into training (n=3,458) and validation (n=1,482) sets at a 7:3 ratio. First, least absolute shrinkage and selection operator (LASSO) regression analysis was used to optimize variable selection by running a tenfold k-cyclic coordinate descent. Second, a prediction model was constructed using multifactorial logistic regression analysis. Third, the model was validated using receiver operating characteristic (ROC) curves, Hosmer-Lemeshow tests, calibration plots, and decision-curve analysis (DCA), and was further internally validated.

Results: This study selected 11 predictors: sepsis, renal replacement therapy, cerebrovascular disease, respiratory failure, ventilator associated pneumonia, norepinephrine, bronchodilators, invasive mechanical ventilation, electrolytes disorders, Glasgow Coma Scale score and body temperature. The models constructed using these 11 predictors indicated good predictive power, with the areas under the ROC curves being 0.826 (95%CI, 0.809–0.842) and 0.827 (95%CI, 0.802–0.853) in the training and validation sets, respectively. The Hosmer-Lemeshow test indicated a strong agreement between the predicted and observed probabilities in the training (χ^2=8.21, p=0.413) and validation (χ^2=0.64, p=0.999) sets. In addition, decision-curve analysis suggested that the model had good clinical validity.

Conclusion: This study has constructed and validated original and dynamic nomograms for prolonged ICU stay in patients with COPD using 11 easily collected parameters. These nomograms can provide useful guidance to medical and nursing practitioners in ICUs and help reduce the disease and economic burdens on patients.

KEYWORDS

chronic obstructive pulmonary disease, intensive care unit, length of stay, nomograms, prolonged intensive care unit stays

Introduction

Chronic obstructive pulmonary disease (COPD) is a common progressive disease with persistent respiratory symptoms and airflow limitation caused by the combination of chronic bronchitis and emphysema (1). It is one of the most common chronic diseases worldwide that can lead to prolonged cough, dyspnea, and fatigue, and accounts for a large proportion of intensive care unit (ICU) admissions (2, 3). In the year 2019, a staggering number of 212.3 million cases of COPD were reported worldwide, leading to 3.3 million fatalities and 74.4 million years of disability adjusted life (4). Furthermore, in the same year, COPD ranked as the third most prevalent cause of death (5). Due to its high prevalence, morbidity, and mortality, COPD is a significant area of concern for both medical care and public health (6). Furthermore, research has shown that COPD imposes a considerable economic and social burden on patients and healthcare systems (7, 8). Efforts to prevent and manage COPD are crucial not only for improving patient outcomes but also for reducing the economic and societal impact of the disease.

An ICU is a place where medical professionals apply modern medical theories and high-technology modern medical equipment to provide specialized centralized monitoring, treatment, and care for critically ill patients, and is an integral part of the healthcare system (9, 10). ICUs provide complex and expensive care (11), and account for a significant portion of the financial expense of healthcare in many countries worldwide (12), for example, in the United States, ICU medical costs account for approximately 13% of hospital costs and 4% of national health expenditure (13). Despite the enormous investment in critical care medicine in many countries, ICUs are often underresourced to meet the needs of critically ill patients, especially in less-developed countries (14). Length of stay (LOS) in the ICU is a key indicator of healthcare efficiency and an important indicator of the quality of critical care provided by a hospital (15, 16). Prolonged ICU stays often result in large resource utilization and thus markedly increased healthcare costs (17). A multistate, multihospital analysis found that ICU utilization rates varied widely among patients hospitalized with COPD. It is therefore particularly important to determine the factors that prolong LOS in the ICU for patients with COPD in order to help accelerate ICU bed turnover, reduce patient care and financial burden, and prevent poor prognoses.

The literature (18–22) has suggested that LOS in hospitalized patients with COPD may be influenced by various factors, such as age, smoking history, Charlson Comorbidity Index, comorbidities, malnutrition, mobility, and mechanical ventilation. Some vital-sign parameters such as higher respiratory rate on admission, systolic blood pressure > 140 mmHg, and diastolic blood pressure > 90 mmHg have also been considered as risk factors for LOS (23, 24). However, the factors that influence the length of ICU stay for patients with COPD are not well defined.

Previous nomograms (25) often suffered from small sample sizes, which could limit the generalizability of their results and hinder their applicability in diverse populations of critically ill patients. Moreover, these models relied on predictors that were difficult or time-consuming to collect, making them less practical for real-world clinical application. Additionally, the representation of the entire spectrum of severity among critically ill patients was not always achieved in previous models, potentially affecting their predictive accuracy and clinical usefulness. In this study, we aimed to address these limitations by constructing a novel nomogram for predicting prolonged ICU stays in patients with COPD. We utilized the large and reliable MIMIC-IV (Medical Information Mart for Intensive Care IV) database, which contains comprehensive, deidentified, and well-maintained clinical data on ICU patients, providing an excellent foundation for the development of our predictive model. This study therefore aimed to identify predictors of prolonged LOS in the ICU and attempted to construct a valid predictive model. This could help clinicians and nurses identify patients who require extended ICU stays and develop appropriate interventions to speed up ICU bed turnover and reduce healthcare costs.

Materials and methods

Data source and ethics statement

The MIMIC-IV database is available primarily for researchers from the Massachusetts Institute of Technology Computational Physiology Laboratory and Collaborative Research Group (26). This database includes demographic information, vital signs, laboratory indicators, medications, and medical-care information. The database has a large sample, comprehensive information, and long-term patient follow-ups, while being free to use and providing a rich resource for critical-care research (27).

This study adhered to the provisions of the Declaration of Helsinki, and ethics approval was provided by the Ethics Committee and Institutional Review Board of the First Affiliated Hospital of Jinan University. Besides, our authors received permission after completing the "Protecting Human Research Participants" web-based training program from the National Institutes of Health (record ID: 45369280). The requirement for obtaining individual patient consent was waived in the present study since it did not have any direct implications on clinical care, and all confidential health data was anonymized to safeguard patient privacy.

Study population

The number of 69,211 patients admitted to ICU in MIMIC-IV database from 2008–2019. This study used the Ninth Revisions of the International Classification of Diseases (49,120, 49,121, 49,122, 496) and the Tenth Revisions of the International Classification of Diseases (J44, J440, J441, J449) codes to extract 9,980 patients admitted to the ICU with a COPD diagnosis (including acute exacerbated COPD) from the MIMIC-IV database. The following populations were excluded in this study: (1) patients under the age of 18, (2) patients who had multiple admissions other than the first hospital/ICU admission, (3) patients with ICU stays of less than 1 day, including those who died upon ICU admission, and (4) patients with a hospital stay shorter than their ICU stay. The final population for our study was 4,940 patients. Figure 1 illustrates the detailed patient selection process.

Data extraction

The following data were extracted from the MIMIC-IV database using structured query language (28): (1) general patient data and

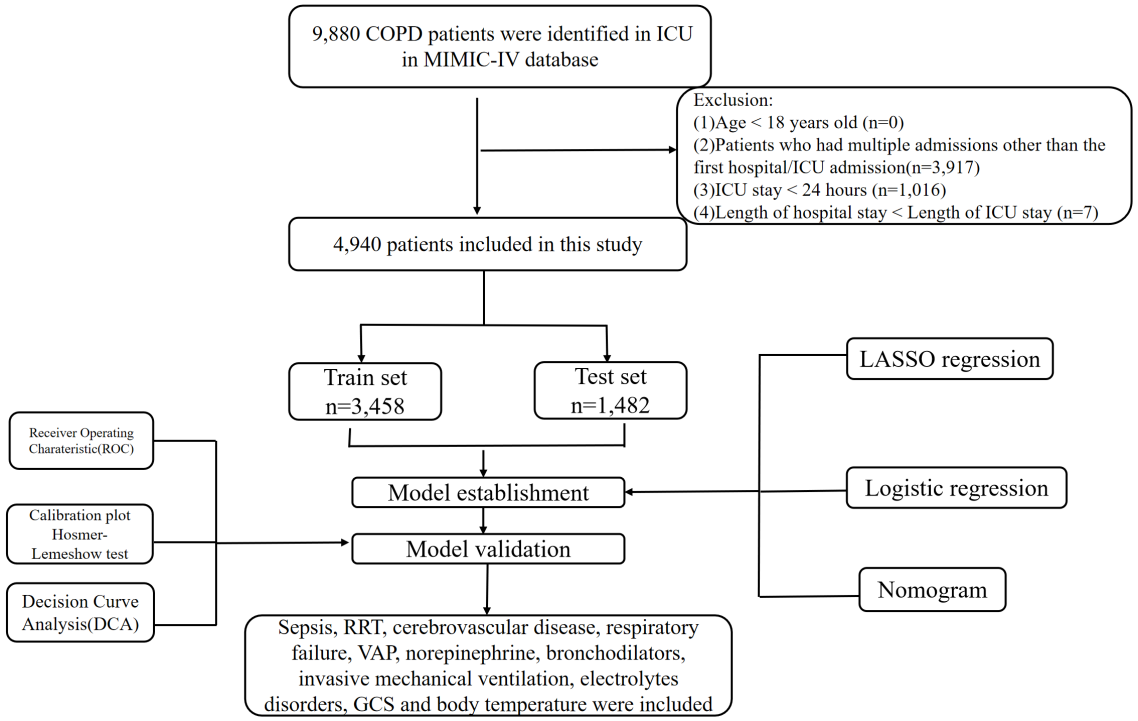

FIGURE 1
Inclusion and exclusion flowchart of the study.

demographic characteristics: sex, age, weight, height, race, smoking history, marital status, and length of ICU stay; (2) vital signs: body temperature, heart rate, respiratory rate, mean blood pressure, and pulse oximetry-derived oxygen saturation; (3) laboratory test results: pH, glucose, hematocrit, hemoglobin, platelets, white blood cell count, anion gap, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, sodium, potassium, internal normalized ratio, prothrombin time, partial thromboplastin time(s), PaO_2, Lactate, total CO_2, $PaCO_2$, lymphocytes, basophils, eosinophils, monocytes, neutrophils and urine output; (4) comorbidities: sepsis, myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, rheumatic disease, peptic ulcer disease, mild liver disease, uncomplicated diabetes, paraplegia, renal disease, malignant cancer, severe liver disease, metastatic solid tumor, acquired immunodeficiency syndrome, respiratory failure, ventilation associated pneumonia (VAP), hypertension, pneumonia, septic shock, electrolytes disorder and asthma; (5) scores on assessment scales: Charlson comorbidity index, Acute Physiology score III (APSIII), Oxford Acute Severity of Illness score (OASIS), Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Scale (GCS) score and Braden Scale score; and (6) treatment and medications: renal replacement therapy (RRT), antibiotic, norepinephrine, invasive mechanical ventilation, bronchodilators and glucocorticoids. For vital signs and laboratory test results, we extracted the mean values on the first day of ICU admission. The multiple interpolation (29) was used to process missing data. However, features with a missing rate higher than 20% (height) were removed since we aimed to build a prediction model that can be generalized in the real clinic which should contain accessible data. The missing rate of all extracted variables was shown in Supplementary Figure 1.

Nomograms construction and validation

After applying the inclusion and exclusion criteria, the final population analyzed comprised 4,940 patients. Given the largeness of the sample, we used the Type 2a scheme TRIPOD (30) (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) for prediction-model building and validation. The data set was first randomly divided into training ($n = 3,458$) and validation ($n = 1,482$) sets at a 7:3 ratio. The predictor variables included in the column line graph (nomogram) were selected in two steps. First, we analyzed the data in the training set using least absolute shrinkage and selection operator (LASSO) regression (31, 32) to select the best risk factors for prolonged ICU stay. LASSO analysis (33, 34) is performed by generating a penalty function that is a compression of the coefficients of the variables in the regression model to prevent overfitting and solve the problem of severe covariance. Second, the most important features selected by the LASSO regression from the training set were used in a multifactorial logistic regression analysis. Variables with $p < 0.05$ were included in the nomogram, and multifactorial analysis was used to predict the respective probabilities of prolonged ICU stay in patients with COPD.

The validation of the prediction model consisted of three main processes: discrimination, calibration, and clinical validity. In this study, the areas under the receiver operating characteristic (ROC) curves (area under curve, AUC) were used to determine the discrimination of the model, the Hosmer-Lemeshow test and calibration plots were used to evaluate its calibration, and decision-curve analysis (DCA) was used to assess its clinical validity.

Study outcomes

The primary outcome was prolonged ICU length of stay. Detailed ICU admission time and discharge time were recorded for all patients in MIMIC-IV. Length of ICU stay was calculated as the difference between ICU discharge time (icu_outtime) and ICU admission time (icu_intime). Currently, there is no universally accepted definition of prolonged ICU length of stay (35). ICU length of stay >5 days was defined prolonged LOS in the ICU in this study (36) (based on the 75th percentile of ICU LOS in our sample).

Statistical analysis

We performed a descriptive analysis of the above variables. The baseline data of all patients were grouped by prolonged ICU stay (yes or no). Continuous variables were expressed as medians (25th–75th percentiles); categorical variables were expressed as counts and percentages. The Wilcoxon rank sum test was used to compare group differences for continuous variables, and Chi-squared tests were used to compare categorical variables. For covariance between continuous variables in the logistic regression, we used the variance inflation factor (VIF), with VIF < 4 indicated no multicollinearity among predictors (37).

All data were analyzed and processed using R software (version 4.2.1, https://www.r-project.org/) for statistical analysis and processing (38). Multiple interpolation was performed using the "mice" package, descriptive analysis and comparisons of differences between groups were performed using "tableone" package, LASSO regression analysis was performed using "glmnet" package, multifactor logistic regression analysis was performed using "rms" package, ROC curves were plotted using "pROC" package, and DCA was performed using "rmda" package. A probability value of $p < 0.05$ was considered statistically significant, and all statistical tests were two-sided.

Results

Characteristics of included patients

The number of 4,940 patients were included in this study, and 1,255 (25.4%) prolonged ICU stay (length of stay more than 5 days). The baseline characteristics of all patients were lied in Table 1. The median age of all patients was approximately 72 years old, and 2,660 (53.8%) men were included in the study. Compared with the non-prolonged ICU stay patients, prolonged ICU stay patients generally had more comorbidities, medication, treatment, and tended to have more severe illness severity scores (Table 1). The demographics and clinical characteristics of the patients in the training and validation sets are listed in Supplementary Table 1. There was good comparability between the two groups of patients.

Variable filtering of the training set

Among the 72 relevant feature variables extracted, 13 potential predictor variables were selected based on the data from the training set (Figures 2A,B) that had nonzero coefficients in the LASSO regression model. Features fitted to construct prediction models were selected by the largest λ at which the mean square error (MSE) is within one standard error of the minimal MSE (Supplementary Table 2). These predictors were sepsis, renal replacement therapy cerebrovascular disease, respiratory failure, ventilator associated pneumonia norepinephrine, bronchodilators, invasive mechanical ventilation, electrolytes disorders, Glasgow Coma Scale score acute physiology score III oxford acute severity of illness score and body temperature. However, in the multivariate logistic regression, two variables (APSIII and OASIS) were excluded because they were not statistically effects (Supplementary Table 3). Finally, we included 11 variables to construct the model.

Construction of predictive models

The results of the multifactorial logistic regression analysis for sepsis, renal replacement therapy (RRT), cerebrovascular disease, respiratory failure, ventilator associated pneumonia (VAP), norepinephrine, bronchodilators, invasive mechanical ventilation, electrolytes disorders, Glasgow Coma Scale score (GCS) and body temperature were listed in Table 2. All of these predictor variables had significant effects, and hence they were used to construct a nomogram of the risk of prolonged LOS in the ICU for patients with COPD, which is presented in Figure 3A. Each predictor variable indicator corresponds to a set of values on the scale with the score scale on the top (points), the scores of all the indicators were summed to obtain the total score, and the position of the total score on the bottom total points scale (total points) corresponds to the probability of having a prolonged LOS in the ICU for patients with COPD. This study also applied the "shiny app" package of R software,[1] which is mostly used to help physicians and nurses working in clinical settings to predict risks and individualize patient assessments. As an example to help the reader better understand the nomogram, if a COPD patient with sepsis, respiratory failure, and ventilate associated pneumonia has been treated with bronchodilators, invasive mechanical ventilation, norepinephrine, a Glasgow Coma Score of 9, and a temperature of 38°C during ICU stay. Then the probability of prolonged LOS in his/her ICU was about 90.1% (95%CI, 0.835–0.943; Figure 3B).

Validation of predictive models

To validate the predictive models, we first performed a VIF test with all variables scoring less than 4. There was no covariance and the model fit was good. The AUC values (equal to C-index) were 0.826 (95%CI, 0.809–0.842) and 0.827 (95%CI, 0.802–0.853) in the training and validation sets, respectively (Figure 4), which indicates good performance. The results of a Hosmer-Lemeshow test indicated strong agreement between the predicted and observed probabilities in the training ($\chi^2 = 8.21$, $p = 0.413$) and validation ($\chi^2 = 8.21$, $p = 0.413$) sets. The calibration curves of the nomograms used to predict the risk of prolonged LOS in the ICU for patients with COPD also indicated

1 https://cht19991225.shinyapps.io/Dynamic_nomogram/

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TABLE 1 Comparison of baseline data between non-ICU p-LOS and ICU p-LOS cohort

Variables	Total (*n*=4940)	Non-ICU p-LOS Group(*n*=3685)	ICU p-LOS Group(*n*=1255)	*p*-value
General characteristics				
Age (years old)	72.00 (64.00, 80.00)	72.00 (64.00, 80.00)	71.00 (63.50, 79.00)	0.005
Sex, male (%)	2660 (53.8)	1970 (53.5)	690 (55.0)	0.368
Weight (kg)	78.80 (65.00, 95.00)	78.40 (64.45, 94.20)	80.00 (65.94, 97.28)	0.007
Race, White (%)	3590 (72.7)	2735 (74.2)	855 (68.1)	<0.001
Smoke (%)	1503 (30.4)	1161 (31.5)	342 (27.3)	0.005
Vital signs				
Temperature (°C)	36.80 (36.60, 37.00)	36.80 (36.60, 37.00)	36.90 (36.60, 37.20)	<0.001
Heart rate (beats/minute)	84.00 (75.00, 96.00)	83.00 (74.00, 94.00)	87.00 (75.00, 99.00)	<0.001
Respiratory rate (beats/minute)	19.00 (17.00, 22.00)	19.00 (17.00, 22.00)	20.00 (18.00, 23.00)	<0.001
MBP (mmHg)	76.00 (70.00, 83.00)	76.00 (70.00, 83.00)	75.00 (69.00, 82.00)	0.004
SpO_2 (%)	96.00 (95.00, 98.00)	96.00 (95.00, 98.00)	96.00 (95.00, 98.00)	0.167
Laboratory tests				
pH (units)	7.37 (7.30, 7.42)	7.37 (7.31, 7.42)	7.36 (7.28, 7.42)	<0.001
Glucose (mg/dL)	132.00 (113.00, 161.25)	131.00 (113.00, 159.00)	136.00 (114.00, 167.00)	0.008
Hematocrit (%)	32.50 (28.60, 37.20)	32.50 (28.70, 37.00)	32.40 (28.45, 37.60)	0.743
Hemoglobin (g/dL)	10.60 (9.30, 12.20)	10.60 (9.30, 12.10)	10.50 (9.20, 12.20)	0.604
Platelets (10^9/L)	196.00 (146.00, 260.00)	196.00 (148.00, 261.00)	195.00 (138.00, 259.00)	0.162
WBC (10^9/L)	11.40 (8.50, 15.30)	11.10 (8.30, 14.90)	12.10 (8.80, 15.90)	<0.001
Anion gap (mEq/L)	14.00 (12.00, 17.00)	14.00 (12.00, 16.00)	14.00 (12.00, 17.00)	0.011
Bicarbonate (mEq/L)	24.00 (21.50, 27.00)	24.00 (22.00, 27.00)	23.50 (20.50, 27.00)	<0.001
BUN (mg/dL)	22.00 (15.00, 35.00)	21.00 (15.00, 33.00)	25.00 (17.00, 40.00)	<0.001
Calcium (mg/dL)	8.4 (8.00, 8.80)	8.4 (8.00, 8.80)	8.30 (7.80, 8.80)	<0.001
Chloride (mEq/L)	103.00 (99.00, 107.00)	103.00 (99.00, 107.00)	103.00 (99.00, 107.00)	0.436
Creatinine (mg/dL)	1.00 (0.80, 1.50)	1.00 (0.80, 1.50)	1.10 (0.80, 1.80)	<0.001
Sodium (mEq/L)	139.00 (136.00, 141.00)	139.00 (136.00, 141.00)	139.00 (136.00, 142.00)	0.009
Potassium (mEq/L)	4.30 (3.90, 4.70)	4.30 (3.90, 4.70)	4.30 (3.90, 4.80)	0.051
INR	1.30 (1.10, 1.50)	1.30 (1.10, 1.50)	1.30 (1.10, 1.60)	<0.001
PT (s)	13.80 (12.30, 16.30)	13.70 (12.20, 16.10)	14.20 (12.50, 17.40)	<0.001
PTT (s)	31.70 (27.60, 41.20)	31.20 (27.40, 40.10)	33.30 (28.25, 44.45)	<0.001
PaO_2 (mmHg)	88.00 (60.00, 100.00)	88.00 (60.00, 100.00)	88.00 (60.50, 100.00)	0.764
Lactate (mmol/L)	1.60 (1.10, 2.40)	1.60 (1.10, 2.40)	1.60 (1.10, 2.36)	0.745
Total CO_2 (mEq/L)	27.00 (23.00, 30.00)	27.00 (24.00, 30.00)	26.00 (23.00, 31.00)	0.049
$PaCO_2$ (mmHg)	44.50 (38.00, 53.00)	44.00 (38.00, 53.00)	45.00 (38.00, 55.00)	0.021
Lymphocytes (%)	10.70 (5.80, 17.70)	11.50 (6.10, 18.80)	8.70 (4.80, 14.20)	<0.001
Basophils (%))	0.30 (0.10, 0.50)	0.30 (0.10, 0.50)	0.20 (0.10, 0.40)	<0.001
Eosinophils (%)	0.60 (0.10, 1.70)	0.70 (0.10, 1.90)	0.30 (0.00, 1.20)	<0.001
Monocytes (%)	5.10 (3.20, 7.50)	5.10 (3.30, 7.50)	5.00 (3.00, 7.40)	0.046
Neutrophils (%)	80.40 (71.40, 87.40)	79.70 (70.50, 87.00)	82.80 (74.30, 88.70)	<0.001
Urine output (ml)	1480.00 (950.00, 2260.00)	1530.00 (990.00, 2304.00)	1335.00 (844.50, 2119.50)	<0.001
Comorbidities				
Sepsis (%)	2813 (56.9)	1756 (47.7)	1057 (84.2)	<0.001
Myocardial infarct (%)	1150 (23.3)	842 (22.8)	308 (24.5)	0.235

(Continued)

TABLE 1 (Continued)

Variables	Total (*n*=4940)	Non-ICU p-LOS Group(*n*=3685)	ICU p-LOS Group(*n*=1255)	*p*-value
Congestive heart failure (%)	2154 (43.6)	1559 (42.3)	595 (47.4)	0.002
Peripheral vascular disease (%)	959 (19.4)	718 (19.5)	241 (19.2)	0.86
Cerebrovascular disease (%)	745 (15.1)	513 (13.9)	232 (18.5)	<0.001
Dementia (%)	194 (3.9)	152 (4.1)	42 (3.3)	0.254
Rheumatic disease (%)	243 (4.9)	185 (5.0)	58 (4.6)	0.625
Peptic ulcer disease (%)	141 (2.9)	106 (2.9)	35 (2.8)	0.95
Mild liver disease (%)	497 (10.1)	325 (8.8)	172 (13.7)	<0.001
Uncomplicated diabetes (%)	1295 (26.2)	969 (26.3)	326 (26.0)	0.853
Paraplegia (%)	186 (3.8)	118 (3.2)	68 (5.4)	0.001
Renal disease (%)	1229 (24.9)	896 (24.3)	333 (26.5)	0.125
Malignant cancer (%)	763 (15.4)	599 (16.3)	164 (13.1)	0.008
Severe liver disease (%)	164 (3.3)	94 (2.6)	70 (5.6)	<0.001
Metastatic solid tumor (%)	362 (7.3)	287 (7.8)	75 (6.0)	0.039
AIDS (%)	21 (0.4)	15 (0.4)	6 (0.5)	0.934
Respiratory failure (%)	1998 (40.4)	1148 (31.2)	850 (67.7)	<0.001
VAP (%)	180 (3.6)	28 (0.8)	152 (12.1)	<0.001
Hypertension (%)	2165 (43.8)	1638 (44.5)	527 (42.0)	0.138
Pneumonia (%)	935 (18.9)	630 (17.1)	305 (24.3)	<0.001
Septic shock (%)	616 (12.5)	331 (9.0)	285 (22.7)	<0.001
Electrolytes disorders (%)	2210 (44.7)	1417 (38.5)	793 (63.2)	<0.001
Asthma (%)	165 (3.3)	125 (3.4)	40 (3.2)	0.796
Scores on assessment scales				
APSIII	45.00 (34.00, 62.00)	42.00 (32.00, 54.00)	62.00 (46.00, 83.00)	<0.001
GCS	14.00 (11.00, 15.00)	14.00 (13.00, 15.00)	11.00 (7.00, 14.00)	<0.001
SOFA	5.00 (3.00, 8.00)	4.00 (2.00, 6.00)	7.00 (5.00, 10.00)	<0.001
Charlson comorbidity index	7.00 (6.00, 9.00)	7.00 (5.00, 9.00)	7.00 (6.00, 9.00)	0.044
Braden score	15.00 (13.00, 16.00)	15.00 (13.00, 17.00)	14.00 (12.00, 16.00)	<0.001
OASIS	33.00 (27.00, 40.00)	31.00 (26.00, 37.00)	39.00 (32.00, 46.00)	<0.001
Treatment and medications				
RRT (%)	336 (6.8)	152 (4.1)	184 (14.7)	<0.001
Antibiotic (%)	3684 (74.6)	2534 (68.8)	1150 (91.6)	<0.001
Norepinephrine (%)	1199 (24.3)	608 (16.5)	591 (47.1)	<0.001
Invasive mechanical ventilation (%)	1930 (39.1)	1168 (31.7)	762 (60.7)	<0.001
Bronchodilators (%)	4008 (81.1)	2913 (79.1)	1095 (87.3)	<0.001
Glucocorticoids (%)	2280 (46.2)	1595 (43.3)	685 (54.6)	<0.001

Medians and interquartile ranges (25th and 75th percentiles) were computed for continuous variables, and frequencies and percentages for categorical variables. The Wilcoxon rank-sum test was used to compare group differences for continuous variables, and Chi-square tests for categorical variables. ICU: Intensive Care Units; p-LOS, Prolonged length of stay; RRT, renal replacement therapy; AIDS, Acquired Immune Deficiency Syndrome; VAP, ventilation associated pneumonia; MBP, mean blood pressure; APSIII, acute physiology score III; GCS, Glasgow Coma Score; SOFA, sequential organ failure assessment; OASIS, oxford acute severity of illness score; SpO_2, pulse oximetry-derived oxygen saturation; PaO_2: arterial partial pressure of oxygen ; $PaCO_2$: partial pressure of carbon dioxide; WBC, white blood cell count; BUN: blood urea nitrogen; PT: prothrombin time; PTT: partial thromboplastin time; INR: internal normalized ratio.

good consistency (Figures 5A,B). Together these validation results indicate that the nomograms of the model had good predictive effects.

The blue line in the DCA graph in Figure 6 indicates the scenarios in which this model predicts the occurrence of prolonged LOS in ICUs for patients with COPD. For comparison purposes, the horizontal and diagonal lines represent the two extreme cases: the former represents all samples being negative, while the latter represents all samples being positive. The DCA results indicated that patients with COPD would obtain higher net clinical benefits when using nomograms to predict prolonged ICU stay in both the training

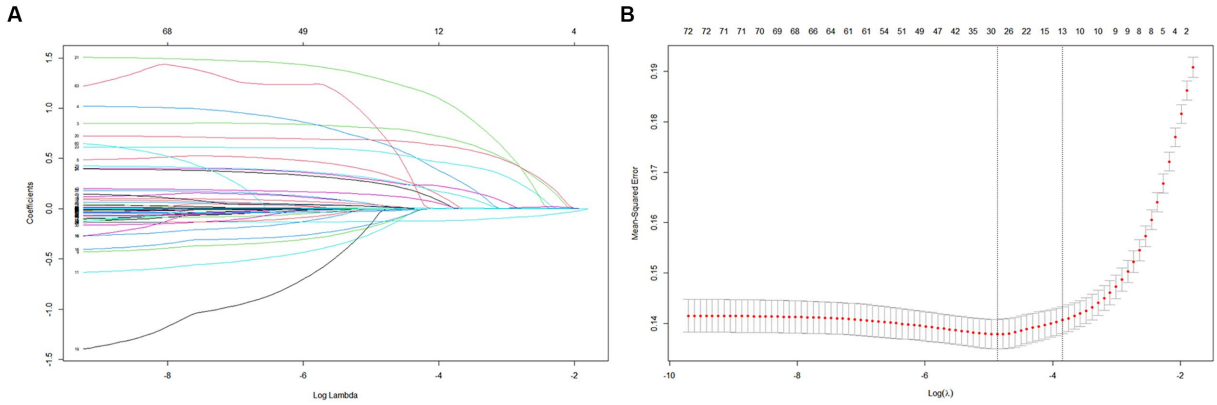

FIGURE 2
Variable selection by LASSO binary logistic regression model. (A) Each curve with different colors represents the change trajectory of each independent variable coefficient, the y-axis is the coefficient value; the upper x-axis is the number of non-zero coefficients in the LASSO model; (B) Represented the cross-validation result with different λ value, the left dot line represented lambda.min which was the lowest λ of minimum mean cross-validated error, the right dot line represented the lambda.1se which was the largest value of λ such that error is within 1 standard error of the cross-validated errors for lambda.min.

TABLE 2 Multivariate logistic regression analysis of the selected significant clinical characteristics in the training set.

Variables	OR[a]	95%CI[b]	*p*-value
GCS	0.86	0.84–0.89	<0.001*
Temperature	1.29	1.09–1.53	0.003*
Sepsis			
Yes	2.46	1.97–3.08	<0.001*
No	Reference		
RRT			
Yes	2.11	1.51–2.96	<0.001*
No	Reference		
Cerebrovascular disease			
Yes	1.67	1.30–2.14	<0.001*
No	Reference		
Respiratory failure			
Yes	2.06	1.69–2.51	<0.001*
No	Reference		
VAP			
Yes	4.78	2.86–8.37	<0.001*
No	Reference		
Norepinephrine			
Yes	1.79	1.46–2.21	<0.001*
No	Reference		
Bronchodilators			
Yes	1.58	1.21–2.06	<0.001*
No	Reference		
Invasive mechanical ventilation			
Yes	1.45	1.19–1.75	0.004*
No	Reference		
Electrolytes disorder			
Yes	1.36	1.12–1.65	0.001*
No	Reference		

*$p < 0.05$; [a]OR odd ratio; [b]CI confidence interval; GCS, Glasgow Coma Score; RRT, renal replacement therapy; VAP, ventilation associated pneumonia.

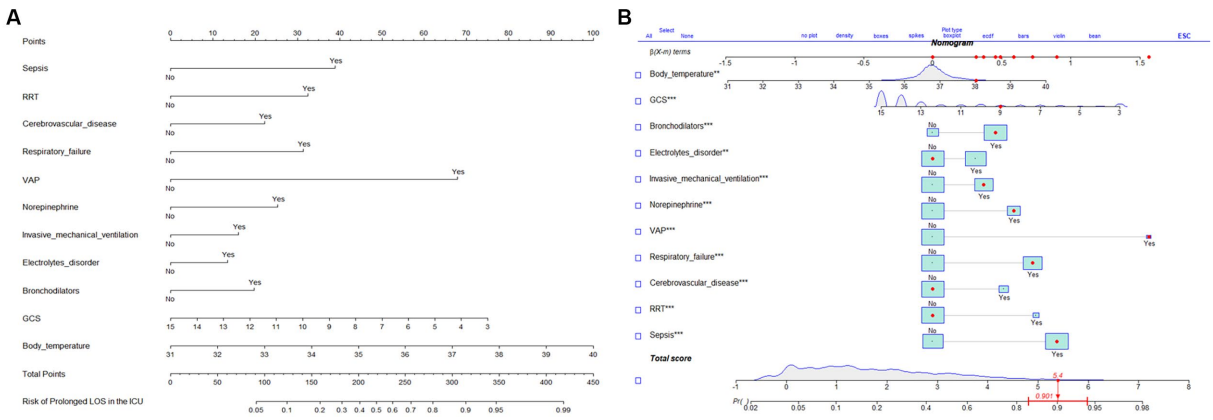

FIGURE 3
Developed risk nomograms for prolonged ICU length of stay with COPD patients. (A) Normal nomograms. (B) Dynamic nomograms. p-LOS, prolonged length of stay; RRT, renal replacement therapy; VAP, ventilation associated pneumonia; GCS, Glasgow Coma Score.

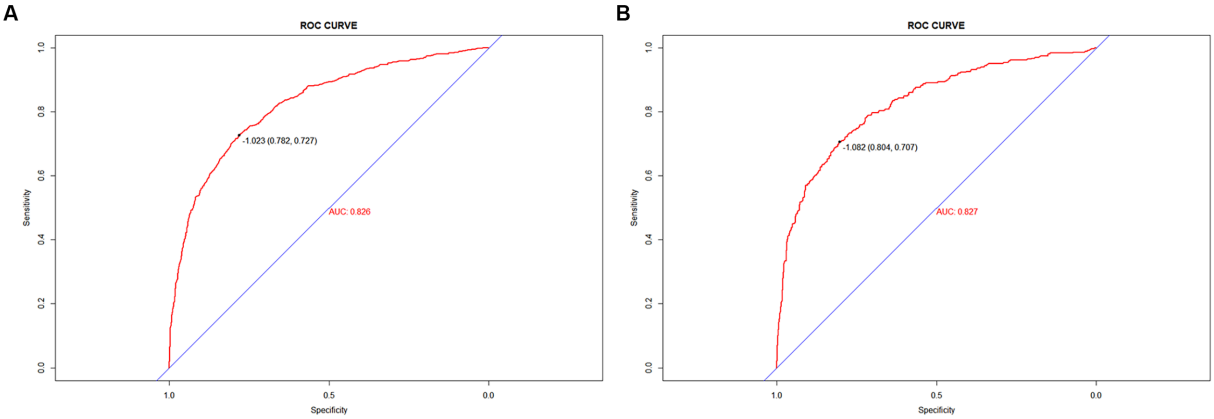

FIGURE 4
The receiver operating characteristic curve for the train and validation cohort. (A) The receiver operating characteristic curve for the train cohort. (B) The receiver operating characteristic curve for the validation cohort.

and validation sets (Figures 6A,B). For example, in the validation set, assuming a timely intervention for patients with COPD with a 40% risk of developing an prolonged ICU stay, 9 people would benefit for every 100 interventions.

Discussion

Column line graphs (nomograms) are simple, reliable, and practical forecasting tools (39). They have been widely used in clinical settings to help predictions and decision-making by identify several relevant predictors (40). We have constructed the first risk prediction model for a prolonged ICU stay in patients with COPD that has good predictive effects, with an AUC of 0.827 (95%CI, 0.802–0.853) in the validation set. The prediction model established in this study was also strongly calibrated and had good clinical validity. Sepsis, RRT cerebrovascular disease, respiratory failure, VAP norepinephrine, bronchodilators, invasive mechanical ventilation, electrolytes disorders, GCS and body temperature of patients with COPD can be used as predictors. We can therefore clinically predict the probability of prolonged ICU stays of patients with COPD by obtaining healthy history information, performing physical examinations, drugs and treatment measures. This prediction model can provide guidance for the development of strategies to prevent prolonged ICU length of stay.

Sepsis is a clinical syndrome that poses a life-threatening risk to patients due to the dysregulation of their response to infections, which leads to organ dysfunction (41). Similar to previous studies, sepsis could result in prolonged ICU stays for patients (42, 43). The treatment of sepsis would take a long time and consume a lot of medical resources, which led to a longer stay in the ICU (44). Renal replacement therapy is a therapeutic approach that utilizes blood purification technology to clear solutes, in order to replace the impaired renal function as well as play a protective and supportive role on organ function (45). The use of RRT will prolong ICU stay in our study. Contrary to our conclusion, a meta-analysis showed that early renal replacement therapy was associated with significantly shorter ICU length of stay (46). This disparity may be explained due to

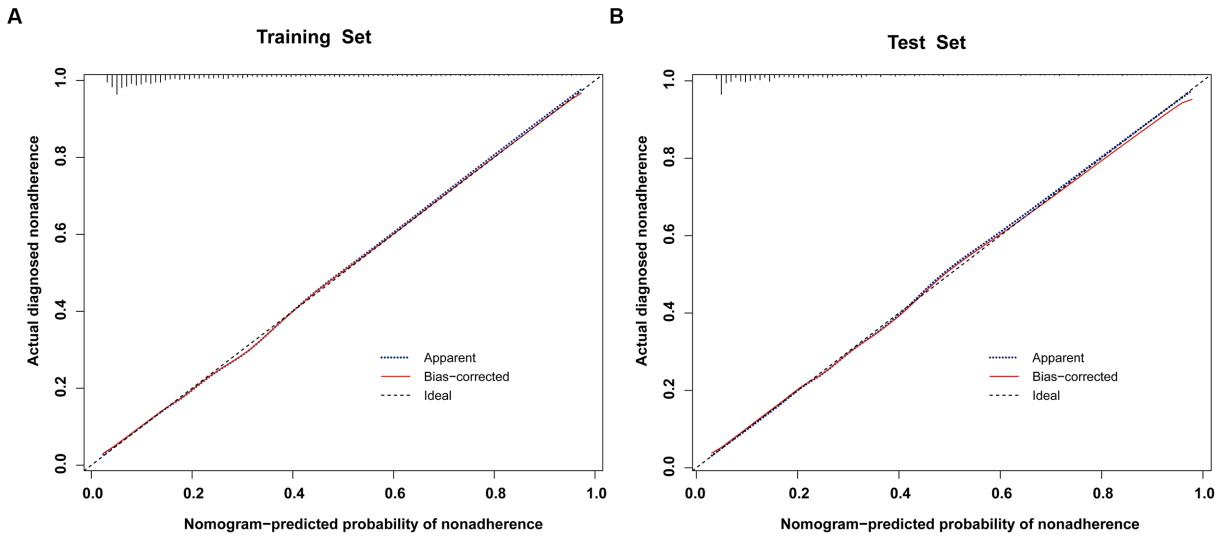

FIGURE 5
The calibration curve for the train and validation cohort. (A) The calibration curve for the train cohort. (B) The calibration curve for the validation cohort.

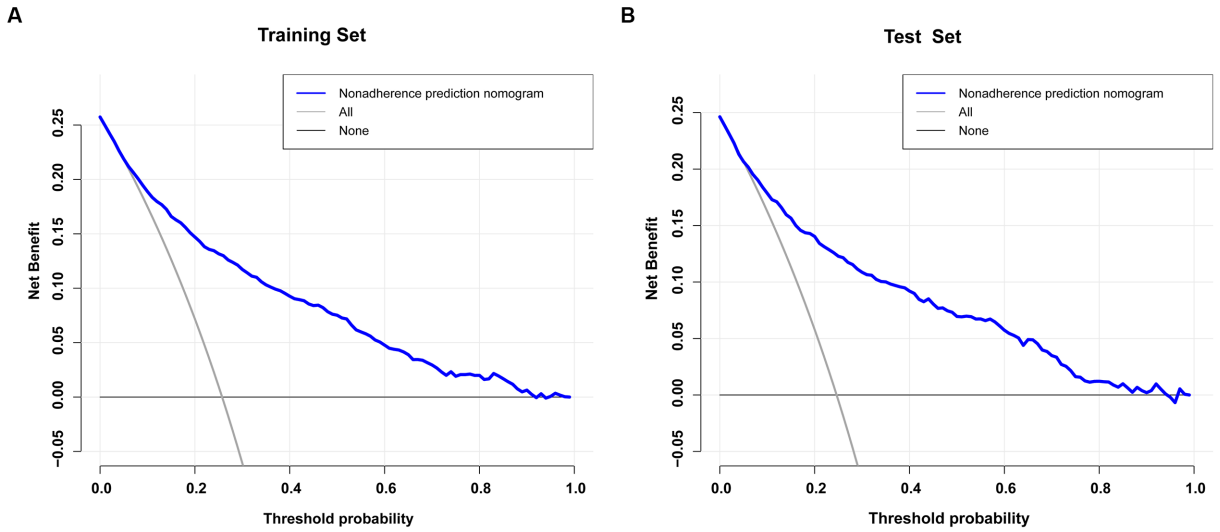

FIGURE 6
The decision analysis curve for the train and validation cohort. (A) The decision analysis curve for the train cohort. (B) The decision analysis curve for the validation cohort. The horizontal line means that all samples are negative, and the oblique line means that all samples are positive. The blue line represents the risk nomograms.

differences in data collection. This study was concerned only with the use of RRT with COPD patients instead of the timing of RRT use.

The GCS is composed of the eye-opening response, verbal response, and body movement (47). It is not surprising that the GCS score is a protective factor for longer LOS in patients with COPD (OR = 0.86, 95% CI = 0.84–0.89, $p < 0.001$), which is consistent with results in clinical practice (48). This is because a lower GCS score is indicative of a more-severe case of impaired consciousness and therefore a longer ICU stay.

Bronchodilators, which include β_2-adrenergic agonists, anticholinergics, and theophyllines, are the main measures to control symptoms in patients with COPD (49). Bronchodilators were associated with prolonged ICU stay in this study. Because patients with COPD who are treated with bronchodilators usually experience acute exacerbations, they will have increased dyspnea symptoms and declined respiration function and will require ICU observation for a longer duration than nonusers, resulting in a longer ICU stay. Similarly, cerebrovascular disease, one of the major health problems worldwide (50), is accompanied by multiple forms of neurological dysfunction and altered vascular statuses, including stroke. This undoubtedly increases the risk of patient care and prolonged patient stays. In additional, electrolyte disorders are common in the ICU and can seriously affect the blood supply and metabolism (51). This led to longer ICU stays for patients (52).

Previous studies (53–55) have found that the body temperature of a patient on admission affects their LOS in the ICU. Although those

studies were performed on other populations, body temperature was still a predictor for the model in this study. Changes in body temperature is one of the important indicators of condition monitoring, and can affect subsequent treatment and prognosis. Geffroy et al. (56) found that patients with early fever were more likely to have a poor prognosis and hence a prolonged ICU stay.

Similar to the results of previous studies (57–61), invasive mechanical ventilation, respiratory failure and ventilator associated pneumonia increased the LOS in the ICU for patients with COPD. This is due to these patients usually had a more-severe gas exchange impairment, require respiratory support, and have a longer ICU stay. However, unlike previous studies (53), norepinephrine was associated with prolonged LOS in the ICU, and was therefore a risk factor. Possible reasons for this are that patients using norepinephrine have unstable circulatory function and greater variability in their condition and LOS, thus requiring more attention and monitoring by nurses and doctors (48).

Our study aimed to construct a nomogram for predicting prolonged LOS among patients with COPD hospitalized in the ICU. This study differs from the previous study in that our outcome of interest is prolonged LOS, while the other study focused on 30-day mortality prediction (62). Furthermore, we utilized a distinct set of variables to identify predictors specifically relevant to extended LOS among COPD patients in the ICU. Our study contributes to the literature by providing healthcare professionals with a practical tool to stratify patients, optimize resource allocation, and improve patient care. By developing a nomogram that can predict prolonged LOS, we offer clinicians an additional means to identify patients at high risk for prolonged ICU LOS, allowing for more informed decision-making and targeted interventions. Overall, our study represents a significant advancement in understanding and managing COPD patients in the ICU, and has important clinical implications for improving patient outcomes and resource utilization.

Identifying patients at risk of prolonged length of stay may help ICU management and avoid ICU a shortage of ICU beds (53). Considering the specificity and complexity of patients with COPD in the intensive care unit, this study selected 4,940 patients with severe COPD from a large intensive care medicine database for a retrospective population-based study. The predictors selected for this study (e.g., temperature, GCS, RRT, and use of invasive mechanical ventilation) are simpler and more accessible to critical care physicians and nurses than respiratory specialty indicators, and help clinicians in their decision making.

Limitations

This study was based on a large and diverse population of the MIMIC-IV database, but in practice it was subject to several limitations. First, this study had a retrospective single-center design and the sample may be underrepresented. External validation of the line plots was not performed (only internal validation), which may lead to overfitting of the new model, requiring the use of data from other sources to validate the findings. Second, some potentially important factors were not included in our study, making it less comprehensive, including, body mass index (BMI), certain psychosocial factors such as anxiety, depression, and social support. Third, limited by our current capabilities and the extent to which the database was available, we still found that antibiotic and vasopressin use prolonged ICU stays in patients with COPD, which was only expressed simply using categorical variables, which makes the effect of specific dosages on the LOS of patients unclear. Fourth, the included study population meant that important variables such as body temperature ranged from 31°C to 40°C in our nomograms, and there was no way to make good predictions for patients with body temperatures outside this range; this needs to be addressed in future studies. Finally, our research did not specifically examine the repercussions of malnutrition on the intensive care unit length of stay for patients with chronic obstructive pulmonary disease. Malnutrition, a crucial element, has been proven to affect clinical outcomes in individuals with this condition. Regrettably, owing to the absence of exhaustive nutritional data in our patient sample, we could not explore the correlation between malnutrition and length of stay (63). This constraint might have hindered our comprehensive understanding of the intricate factors influencing disease prognosis, potentially leading to an underestimation of nutritional status significance in our conclusions. Consequently, we propose that forthcoming investigations incorporate malnutrition evaluation tools, such as the Mini Nutritional Assessment, Subjective Global Assessment, and Nutritional Risk Screening, to appraise the nutritional condition of patients with chronic obstructive pulmonary disease (64). This approach would yield invaluable insights into malnutrition's impact on disease progression and outcomes, ultimately aiding in the creation of more focused and efficacious interventions to address this critical aspect of disease management. Moving forward, we intend to encompass as many predictor variables as feasible and validate the model using an external cohort to achieve heightened accuracy in our findings.

Conclusion

Based on the MIMIC-IV database, we have constructed and validated original predictive and dynamic nomograms for prolonged ICU stays in patients with COPD using 11 easily collected parameters The nomograms (available at https://cht19991225.shinyapps.io/Dynamic_nomogram/) will help medical doctors and nursing practitioners to accurately assess the probability of a prolonged ICU stay in specific COPD patients and to distinguish high-risk patients who may require aggressive medical/nursing measures.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: the data were available on the MIMIC-IV website at https://mimic.physionet.org/.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee and Institutional Review Board of the First Affiliated Hospital of Jinan University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HC, JLi, and FW created the study protocol, performed the statistical analyses, and wrote the first manuscript draft. JLy and FZ conceived the study, critically revised the manuscript, contributed to data interpretation and manuscript revision. SY and XY assisted with the study design and performed data collection. XH assisted with data collection and manuscript editing. SY confirmed the data and assisted with the statistical analyses. HC maintained the localized database and worked on SQL coding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1177786/full#supplementary-material

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Glossary

APSIII	Acute physiology score III
AUC	Area under curve
BMI	Body mass index
BUN	Blood urea nitrogen
COPD	Chronic obstructive pulmonary disease
DBP	Diastolic blood pressure
DCA	Decision curve analysis
GCS	Glasgow coma scale
ICU	Intensive care units
INR	Internal normalized ratio
LASSO	Least absolute shrinkage and selection operator
LOS	Length of stay
MAP	Mean arterial pressure
MIMIC-IV	Medical information mart for intensive care-IV
MSE	Mean square error
OASIS	Oxford acute severity of illness score
PaCO2	Partial pressure of carbon dioxide
PaO2	Arterial partial pressure of oxygen
p-LOS	Prolonged length of stay
PT	Prothrombin time
PTT	Partial thromboplastin time
ROC	Receiver operating characteristic curve
RRT	Renal replacement treatment
SBP	Systolic blood pressure
SOFA	Sequential organ failure assessment
SpO2	Pulse oximetry-derived oxygen saturation
TRIPOD	Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis
VAP	Ventilation associated pneumonia
WBC	White blood cell

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Systemic and functional effects of continuous azithromycin treatment in patients with severe chronic obstructive pulmonary disease and frequent exacerbations

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Background: Continuous treatment with azithromycin may lead to fewer acute exacerbations of chronic obstructive pulmonary disease (AECOPD), but little is known of its impact on systemic and functional outcomes in real-life settings.

Methods: This was a multicenter prospective observational study of patients with severe COPD who started treatment with azithromycin. Tests were compared at baseline and after 3 and 12 months of treatment. These included lung function tests, a 6-min walking test (6MWT), and enzyme-linked immunosorbent assays of serum and sputum markers, such as interleukins (IL-6, IL-8, IL-13, IL-5), tumor necrosis factor receptor 2 (TNFR2), and inflammatory markers. Incidence rate ratios (IRR) and their 95% confidence intervals (95% CI) are reported.

Results: Of the 478 eligible patients, the 42 who started azithromycin experienced reductions in AECOPDs (IRR, 0.34; 95% CI, 0.26–0.45) and hospitalizations (IRR, 0.39; 95% CI, 0.28–0.49). Treatment was also associated with significant improvement in the partial arterial pressure of oxygen (9.2 mmHg, 95% CI 1.4–16.9) at 12 months. While TNFR2 was reduced significantly in both serum and sputum samples, IL-13 and IL-6 were only significantly reduced in serum samples. Moreover, an elevated serum and sputum IL-8 level significantly predicted good clinical response to treatment.

Conclusion: Continuous azithromycin treatment in a cohort of patients with severe COPD and frequent exacerbations can significantly reduce the number and severity of exacerbations and improve gas exchange. Treatment changes the pattern of microorganism isolates and decreases the inflammatory response. Of note, IL-8 may have utility as a predictor of clinical response to azithromycin treatment.

KEYWORDS

inflammatory markers, interleukins, exacerbations, COPD, azithromycin, microorganisms

1. Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory and systemic disease that affects the airways. Acute exacerbations of COPD (AECOPD) affect not only the natural history of the disease but also quality of life, the number of hospitalizations, and mortality rates (1). Exacerbations, which are frequently caused by respiratory viral or bacterial infections, are events characterized by increases in respiratory symptoms that worsen in <14 days, may be accompanied by tachypnea and/or tachycardia, and are often associated with increased local and systemic inflammation (2). Various interventions have been shown to prevent AECOPDs, including both non-pharmacological measures (e.g., quitting smoking, respiratory rehabilitation, and vaccines) and pharmacological measures (e.g., bronchodilator and corticosteroid inhalers) (3). Nevertheless, 25–30% of patients still experience AECOPD, indicating that these measures do not prevent all cases (4).

Randomized controlled trials have demonstrated the efficacy of prophylactic azithromycin in reducing AECOPDs, and as such, current clinical guidelines recommend its use in patients with frequent exacerbations despite optimal inhaled therapy (5–7). However, there is limited evidence on the most appropriate time of administration or the most effective dose needed to control exacerbations and minimize side effects. Albert et al. compared the use of 250 mg of azithromycin per day for 1 year irrespective of COPD severity or frequency of AECOPD. They showed both an increased time lag between exacerbations and a decrease in the frequency of exacerbations compared to placebo (5). The COLUMBUS trial also showed that 500 mg of azithromycin three times a week for 1 year significantly reduced (42%) the exacerbation rate compared with placebo in patients with three or more AECOPDs annually (6). Finally, a more recent study found that doses of 250 mg and 500 mg three times a week had comparable effectiveness at preventing exacerbations in patients with severe COPD and frequent exacerbations, and that this could minimize the potential side effects of a long-term antibiotic therapy (7).

Antibiotic prophylaxis in AECOPDs may increase the risk of selection for resistant bacteria, facilitating the spread of antimicrobial resistance. Even though azithromycin is usually well-tolerated drug, undesirable side effects can still result from polypharmacy, advanced age, and comorbidities in real-world settings. Moreover, the therapeutic response can vary depending on the characteristics and baseline statuses of patients. Investigating what factors predict a favorable response, both in the number of exacerbations and their functional effects, is of particular clinical interest.

This study aimed to analyze the systemic and pulmonary functional changes associated with severe COPD in patients with frequent exacerbations after continuous azithromycin treatment, their effect on microbiological isolates in residual exacerbations, and the potential involvement of inflammatory and immunomodulatory mechanisms.

2. Methods

2.1. Study design

This was a multicenter, observational, and prospective study of patients with severe COPD and frequent exacerbations who regularly attended comprehensive care programs in the respiratory day hospitals of three university hospitals in Barcelona. The participating hospitals were Hospital Universitari de Bellvitge (HUB), Hospital Parc Taulí (HPT), and Hospital Germans Trias i Pujol (HGTiP). All patients who started treatment with azithromycin according to clinical guideline recommendations and practice (8) were included consecutively between January and December, 2017.

2.2. Patient selection

COPD was defined according to the GOLD recommendations: a history of smoking (>10 pack-years) and an FEV1 (forced exhalation volume in 1 second) to FVC (forced vital capacity) ratio < 70% (8). By clinical consensus, and with the objective of homogenizing the selection between the different centers, we included patients at the maximum therapeutic step in the 6 months prior to inclusion if they had frequent exacerbations, defined as ≥4 moderate AECOPDs in the last year (≥3 if two were severe), and had sputum cultures negative for mycobacteria. Patients with contraindications to macrolide therapy (allergy, long QT syndrome), different respiratory pathologies, lack of suitability for macrolide treatment, according to the clinician's criteria (severe cardiovascular disease, hearing loss, use of co-therapies that prolong the QT interval or drug interactions) and prior use of azithromycin or inhaled colimycin (not concomitant initiation) were excluded.

All patients signed an informed consent form in accordance with the principles outlined in the Declaration of Helsinki, and the local ethics committee approved the study (CEIC, ref. SSP-AZI-2016-01).

2.3. Visits and follow-up

All included patients started treatment with azithromycin 250 mg three times per week for 1 year. Sociodemographic data, anthropometrics, COPD history, and symptom evaluations were

Abbreviations: 6MWT, 6-min walking test; AECOPD, acute exacerbation of COPD; AMI, Acute myocardial infarction; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; ELISA, Enzyme-linked immunosorbent assay; HGTiP, Hospital Germans Trias I Pujol; HPT, Hospital Parc Taulí; HUB, Hospital Universitari de Bellvitge; ICS, inhaled corticosteroids; JNK, c-Jun N-terminal kinase; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MMP9, Matrix metalloproteinase 9; MUC5AC, Mucin 5 AC; URT, Upper respiratory tract.

collected in all patients. Symptom tests included the COPD Assessment Test (CAT), London Chest Activity of Daily Living Scale (LCADL) (9), and the modified Medical Research Council (mMRC) Dyspnea Scale. In addition, participants underwent a 6-min walking test (6MWT), respiratory functional test, and arterial blood gas analyzes at baseline and after 3 and 12 months of follow-up. Blood and sputum samples were collected at all visits for laboratory determinations. All moderate and severe exacerbations were recorded and treated according to appropriate criteria and guidelines. Exacerbations from the year before starting treatment were also registered. An exacerbation was defined as any event that caused a worsening of respiratory symptoms and that required modification of the patient's usual treatment.

2.4. Quantification of inflammatory parameters in blood and sputum

Serum samples were obtained from venous blood. After allowing the sample to stand at room temperature for 2 h, it was centrifuged for 15 min at 1000 × *g*, and the supernatant was taken for analysis.

Sputum was separated from contaminating saliva by macroscopic examination, before being weighed and homogenized with 4 volumes of dithiothritol (Sputasol, Oxoid Ltd., Hants, United Kingdom). After 15 min at room temperature, the same volume of phosphate-buffered saline was added and the whole mixture was filtered and centrifuged at 600 × *g* for 15 min. The supernatant was stored at −80°C for determinations.

Analysis was performed by enzyme-linked immunosorbent assay (ELISA). Cytokine concentrations (IL-5, IL-6, IL-8, IL-13) were measured in serum samples and supernatant sputum samples using a multiplex immune-bead assay (Milliplex MAP High Sensitivity Human T cell panel Kit; Merck Millipore). TNR2 was analyzed with a Human soluble TNF Receptor 2 ELISA Kit (sTNFRII; RAB0490). All procedures were performed according to the manufacturer's instructions, centralized in one of the centers.

2.5. Sputum collection and bacterial load detection

Sputum samples were obtained spontaneously at visits and during AECOPD episodes before starting any antimicrobial treatment. Only good quality sputum samples were considered (i.e., 25 leukocytes per low-power field) following the microbiological routine (10). Briefly, samples were homogenized with dithiothreitol (Sputasol, Oxoid Ltd., Hants, United Kingdom), and plated onto blood agar, chocolate agar, and MacConkey agar before overnight incubation at 37°C in a 5% CO_2 atmosphere (blood and chocolate agar) or ambient air atmosphere (MacConkey agar). Bacterial colonies were sub-cultured for identification by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonik GmbH, Bremen, Germany).

2.6. Statistical analyzes

Data are expressed as means ± standard deviation (SD) or medians [25th–75th percentile] for continuous data and as frequencies (percentage) for categorical data. Multiple comparisons were evaluated by chi-squared (categorical), student *t* (parametric), or Mann–Whitney (nonparametric) tests, applying the Bonferroni method if the Kruskal–Wallis test found significant differences. A negative binomial regression model was used to study the number of exacerbations after treatment, reporting the incidence rate ratio (IRR) and 95% confidence interval (95%CI). Different predictive statistical models were fitted for each analytical or clinical variable of interest, adjusted by age and Charlson index. A value of p of 0.05 was considered statistically significant. IBM SPSS version 22 (IBM Corp., Armonk, NY, United States) was used for all analyzes.

3. Results

3.1. Study subjects

Of the 478 eligible patients with severe COPD in three respiratory day hospitals, we included 42 (8.8%) who started azithromycin (Figure 1; mean age 72.2 ± 7.09 years). Fifty-eight patients were already under treatment with long-term azithromycin therapy and were excluded; therefore, 21% of patients in this cohort were treated. At the time of inclusion, all patients were receiving combined inhaled bronchodilator therapy, long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), 39 (93%) inhaled corticosteroids (ICS) and nine (21%) long-term oxygen therapy. Participants corresponded to group E of the current GOLD classification (8), having severe airflow obstruction (mean FEV_1 44.5% ± 13.8%), an average mMRC dyspnea symptom score of 2, and a median of 5 (4–6) exacerbations during the previous year (Table 1). Patient characteristics were comparable among the three participating hospitals. Only 37 patients finished the study, with patients withdrawn due to cardiac pathology ($n = 3$; 1 acute myocardial infarction, 2 QT prolongations), diarrhea ($n = 1$), and personal preference ($n = 1$).

3.2. Clinical and functional effects after continuous azithromycin treatment

A significant improvement in the partial arterial pressure of oxygen (PaO_2) was observed after treatment with azithromycin at 3 and 12 months compared with the baseline visit (9.21 mmHg increase at 12 months; 95%CI, 1.45–16.97). This was also associated with a significant improvement in oxygen saturation both at rest and during exercise. However, symptoms (except for a slight improvement in CAT and LCADL scores), the 6MWT distance, and lung function did not differ significantly after 12 months (Table 2).

3.3. Inflammatory changes in serum and sputum

Most serum and sputum inflammatory parameters improved after treatment with azithromycin (Table 3). Of note, treatment significantly lowered serum IL-13, IL-6, and TNFR2 levels, but only lowered sputum TNFR2 levels, with no significant correlation found between serum and sputum levels (data not shown). The decreased

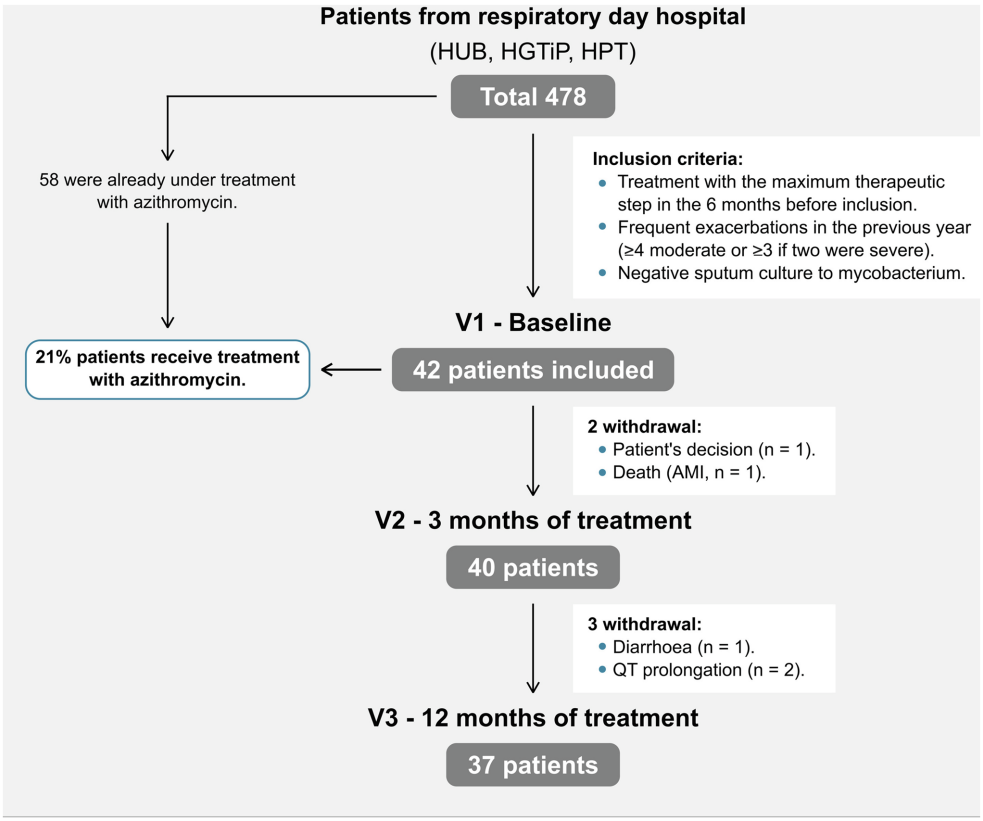

FIGURE 1
Patient flowchart. AMI, acute myocardial infarction; HUB, Hospital Universitari de Bellvitge; HGTiP, Hospital Germans Trias I Pujol; HPT, Hospital Parc Taulí.

inflammatory response was more consistent in serial serum determinations.

3.4. Predictors of clinical response in study participants

After analyzing all serum markers and functional variables, an increase in baseline IL-8 predicted a positive response to azithromycin treatment and a reduction in exacerbations (Supplementary Table S1). Among the sputum markers, a high IL-8 level was also independently associated with good clinical response (Supplementary Table S2).

3.5. Effect of treatment with azithromycin on COPD exacerbations

The 37 participants had 188 exacerbations (5.1 ± 1.6 AECOPD/patient) in the year before starting azithromycin compared with only 65 during treatment (1.8 ± 1.4 AECOPD/patient; $p < 0.0001$; Figure 2). The IRR of AECOPD after treatment was 0.34 (95%CI, 0.26–0.45), indicating that patients had an approximate 66% reduction in acute exacerbations after treatment. Before treatment, 162 (86%) exacerbations were moderate and 26 (14%) were severe and required hospitalization (mean, 184 days in hospital). During treatment, 55 (84.6%) exacerbations were moderate and 10 (15%) were severe and required hospitalization (mean, 74 days; Table 4). Therefore, hospitalizations fell by 61.5% at 12 months (IRR, 0.39; 95%CI, 0.28–0.49). Although fewer patients required hospital admission, their mean hospital stays tended to be longer (7.7 ± 3.7 vs. 12.3 ± 14.7 days).

3.6. Microbiological effect of continuous azithromycin treatment

A total of 95 microorganisms were obtained during the 188 AECOPD in the year before starting treatment with azithromycin, which decreased to only 41 microorganisms during 65 AECOPD throughout the follow-up period. There was a significant reduction in frequent sputum isolates, such as *Haemophilus influenzae* ($p = 0.0128$) and *Moraxella catarrhalis* ($p = 0.0031$) (Table 4), and a significant increase in infrequent microorganisms, such as *Stenotrophomonas maltophilia* (from 2.2 to 10.3%; $p = 0.0448$). Microorganisms otherwise increased in the upper respiratory tract, and sputum isolates of *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* did not change.

Overall, the pattern of microbiological isolates changed with the intensity of AECOPD from before to after azithromycin therapy (Figure 3). In moderate AECOPD, *M. catarrhalis* decreased from 26.6 to 2.8% ($p = 0.0026$) and *S. maltophilia* increased from 0 to 11.1% ($p = 0.0026$), with a reset observed in the usual upper respiratory tract bacterial microbiota from 11.4 to 47.2% ($p < 0.0001$). In severe AECOPD, *P. aeruginosa* isolates increased from 1 to 3 ($p = 0.0075$) and

TABLE 1 Clinical and functional characteristics of study patients.

	Total	HUB	HGTiP	HPT	*p*-value
	n = 42	*n* = 15	*n* = 13	*n* = 14	
Age, years	72.2 (7.09)	71.5 (4.76)	72.2 (7.91)	73.1 (8.7)	0.838
Male, *n* (%)	38 (90.5)	13 (86.7)	12 (92.3)	13 (92.9)	0.947
BMI, kg/m^2	27 (5.31)	26.7 (4.48)	28.7 (5.01)	25.7 (6.2)	0.326
Charlson index	2 [1–3]	1 [1–2.75]	2.5 [1.75–4]	1 [1–2]	0.074
Current smokers, *n* (%)	4 (9.52)	0 (0)	3 (23.1)	1 (7.14)	0.174
Pack-years	57.9 (28.9)	59.6 (24.5)	60 (44)	53.9 (17.1)	0.865
FEV_1, % reference	44.5 (13.8)	40 (7.2)	47.3 (14.3)	49.2 (23.9)	0.407
FEV_1/FVC, % reference	45.4 (11.5)	39.5 (8.57)	54.7 (8.57)	39 (12)	0.003
RV, % reference	153 (43.5)	165 (46.5)	126 (36.9)	169.4 (30.3)	0.098
DLCO, % reference	45.6 (21)	46.8 (15.5)	54.5 (24.9)	28.8 (18)	0.092
6MWT, meters	341 (107)	326 (106)	371 (124)	333 (97)	0.562
PaO_2	69.2 (17.07)	72.2 (9.28)	69.3 (28.8)	66.1 (66.1)	0.675
$PaCO_2$	42.2 (8.39)	42.4 (6.69)	45.3 (11.3)	40.8 (6.6)	0.378
Dyspnea mMRC	2 [2–2]	2 [2–2]	2 [1–2]	2 [2–2.75]	0.007
CAT	16 [11–21]	16 [11.2–21]	14 [11–19]	17 [11.5–21]	0.749
LCADL	21 [17–29.5]	21 [17–24]	21.5 [18–24]	18 [14–30]	0.579
BQ index	4 [1–6]	2 [0–6.5]	2 [0–7.5]	6 [4.25–10.5]	0.061
Previous exacerbations	5 [4–6]	6 [4–7.5]	4 [4–5]	5 [4.75–5.75]	0.135

Data are presented as mean (SD) or median [25th–75th percentile]. 6MWT, 6-min walking test; BMI, body mass index; BQ index, bronchiectasis index; CAT, COPD Assessment Test; DLCO, diffusing lung capacity for carbon monoxide; Dyspnea mMRC, dyspnea scale modified Medical Research Council; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HUB, Hospital Universitari de Bellvitge; HGTiP, Hospital Germans Trias I Pujol; HPT, Hospital Parc Taulí; LCADL, London chest activity of daily living scale; PaO_2, partial arterial pressure of oxygen; $PaCO_2$, partial arterial pressure of carbon dioxide; RV, residual volume; SD, standard deviation; *$p < 0.05$ significant.

TABLE 2 Clinical and functional effects of continuous azithromycin in patients with severe COPD.

Parameters	Baseline	3 months	12 months	*p*-value
Dyspnea mMRC, *n* (%)				0.697
1	7 (18.9)	7 (18.9)	7 (19.4)	
2	26 (70.3)	23 (62.2)	23 (63.9)	
3	4 (10.8)	7 (18.9)	6 (16.67)	
CAT	16.2 (6.2)	14.5 (4.8)	13.9 (4.8)	0.059
LCADL	23.9 (12.7)	23.6 (12.4)	28.4 (12.7)	0.141
FEV_1, % reference	38.3 (14.3)	37 (14.5)	37 (13.8)	0.696
FVC, % reference	64.9 (17.2)	64.1 (17.2)	60.1 (20.8)	0.292
PaO_2, mmHg	69.2 (18.0)	74.7 (14.0)	79.2 (14.6)	**0.008***
$PaCO_2$, mmHg	43.2 (8.7)	42.9 (6.5)	43.3 (6.1)	0.944
6MWT				
Meters	345 (105)	354 (79)	352 (83.9)	0.539
$SatO_2$ initial, %	92.2 (4.0)	93.1 (3.5)	94.3 (1.9)	**0.002***
$SatO_2$ end, %	87 (7.8)	87.1 (8.6)	89.7 (5.5)	**0.035***

Data are expressed as mean (SD). *$p < 0.05$ significant (in bold). 6MWT, 6-min walking test; CAT, COPD Assessment Test; Dyspnea mMRC, dyspnea scale modified Medical Research Council; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LCADL, London Chest Activity of Daily Living scale; $PaCO_2$, partial arterial pressure of carbon dioxide; PaO_2, partial arterial pressure of oxygen.

S. pneumoniae isolates increased from 0 to 2 ($p = 0.0078$) after azithromycin therapy.

4. Discussion

This multicenter, prospective, observational study analyzed the systemic and functional real-life effects of continuous treatment with azithromycin in patients with severe COPD and frequent exacerbations managed in respiratory day hospitals. In addition to confirming that azithromycin effectively reduced the rate of moderate to severe COPD exacerbations, we provide the first evidence that treatment also improves gas exchange, both at rest and during exercise, after 1 year of treatment. Of the interleukin profiles analyzed in this study, IL-8 and TNFR2 presented as the major inflammatory mediators in the immunomodulatory response to azithromycin in patients with COPD. Baseline elevations of IL-8 in both blood and sputum samples predicted the therapeutic response and may indicate its potential utility as a biomarker. Changes were also observed in the microbial composition of subsequent AECOPD episodes after treatment, with the identification of potentially pathogenic microorganisms with unusual patterns of intrinsic antibiotic resistance that required treatment. This increases our knowledge about how azithromycin treatment affects the inflammatory response and bacteria selection in the airways, together with the implications for future COPD exacerbations.

TABLE 3 Inflammatory changes at baseline and after 3 and 12 months of treatment with azithromycin.

Parameters	SERUM				SPUTUM			
	Baseline	3 mo.	12 mo.	*p*-value	Baseline	3 mo.	12 mo.	*p*-value
Fibrinogen, mmol/L	4.53 (1.4)	3.85 (0.8)	2.91 (0.99)	0.168	–	–	–	–
CRP, mg/L	15.9 (30.2)	9.42 (21)	5.46 (6.08)	0.142	–	–	–	–
Leukocytes, cels/ μL	8,844 (3,128)	7,580 (1,830)	7,000 (1,480)	0.051	–	–	–	–
Eosinophils, cels/μL	188 (167)	200 (152)	223 (167)	0.801	–	–	–	–
TNFR2, pg/mL	1,386 (476)	1,246 (535)	1,148 (419)	**0.001***	1,590 (1,978)	1,073 (1,638)	624 (886)	**0.005***
IL-13, pg/mL	6.53 (12.5)	5.33 (8.64)	2.21 (2.42)	**0.021***	86.1 (83.6)	47.7 (44.1)	69.1 (102)	0.339
IL-5, pg/mL	2.71 (7.69)	2.06 (3.25)	2.24 (1.71)	0.65	58.1 (73.2)	61.8 (91.7)	94.5 (149)	0.124
IL-6, pg/mL	3.8 (4.70)	2.95 (2.81)	1.34 (3.14)	**0.003***	1,993 (3,744)	1,653 (1,869)	1,664 (1,969)	0.568
IL-8, pg/mL	9.17 (5.04)	8.88 (3.95)	8.23 (3.26)	0.26	212,852 (648,466)	97,954 (70,014)	98,734 (98,487)	0.169

Data are expressed as mean (SD). *$p < 0.05$ significant (in bold). CRP, C-reactive protein; IL, interleukin; Mo., months; TNFR2, tumor necrosis factor receptor 2.

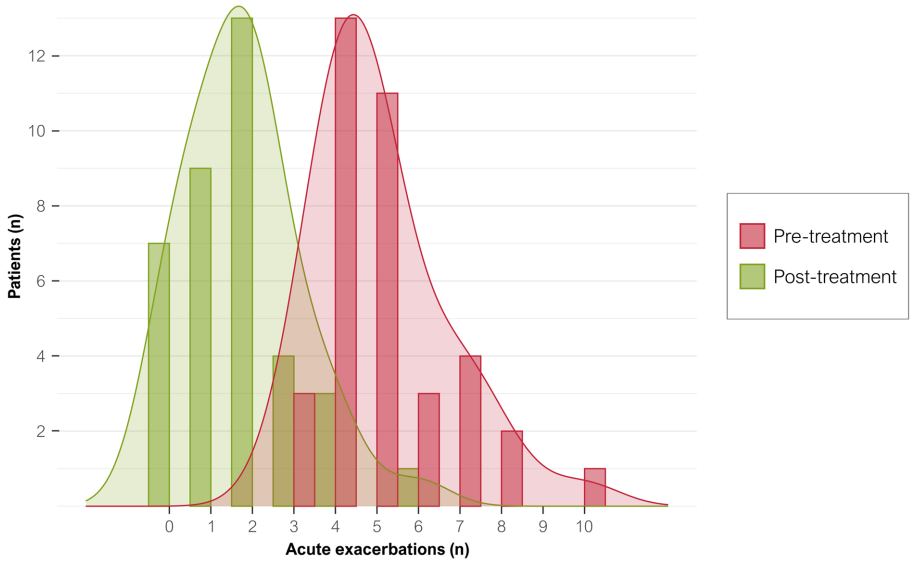

FIGURE 2
Distribution of exacerbations per patient before and after treatment. Graph shows the number of exacerbations in the year before starting azithromycin treatment (red bars) and after 12 months of treatment (green bars).

As expected, continuous azithromycin treatment in patients with severe COPD and frequent exacerbations led to fewer exacerbations (up to 66%) after 1 year of treatment, even using a dosage of 250 mg 3 times a week. From the limited published evidence available (only two clinical trials (5, 6), both carried out in a different profile of COPD patients) does not allow a categorical and unanimous recommendation for the type of patient chosen and the dose to be administered (8). In other chronic inflammatory respiratory diseases, such as bronchiectasis, the dosage of 250 mg 3 times a week for 1 year has been used successfully, minimizing side effects. Moreover, in airways of these patients, this dosage has demonstrated a significant reduction in host neutrophilic inflammatory response (11). The high effectiveness in the control of exacerbations achieved in this study and the few side effects also support the use of this dosage in clinical practice in COPD patients. Previous studies have shown that patients with more severe COPD and higher numbers of exacerbations during the previous year had higher reductions in AECOPD with azithromycin treatment (5–7). These results are consistent with the high effectiveness observed in this study and support the need to identify candidates for preventive therapy accurately and to avoid the use of azithromycin in patients with less severe disease who may not benefit. However, it was notable that neither baseline lung function nor the number of previous exacerbations predicted treatment response in this cohort. Instead, baseline elevations of IL-8 in both blood and sputum samples predicted the therapeutic response, suggesting that this could be a useful biomarker in clinical practice (12, 13).

Another novel finding was the improved arterial oxygenation in patients after 12 months of treatment with azithromycin, both at

TABLE 4 AECOPD characteristics before and after 1 year of azithromycin treatment.

	Pre-treatment	Post-treatment	*p*-value
Patients with AECOPD, *n* (%)	37 (100)	30 (81.1)	**0.0054***
AECOPD cases (mean ± SD)	188 (5.1 ± 1.6)	65 (1.8 ± 1.4)	**<0.0001***
AECOPD intensity, *n* (%)			
Severe	26 (13.8)	10 (15.4)	0.8370
Moderate	162 (86.2)	55 (84.6)	0.8370
Hospitalization, *n* (%)	26 (13.8)	10 (15.4)	0.8370
Days of hospital stay (mean ± SD)	184 (7.7 ± 3.7)	74 (12.3 ± 14.7)	0.0709
Microbiology pattern AECOPD, *n* (%)			
Cultured samples	91 (48.4)	39 (60.0)	0.1069
Uncultured samples**	97 (51.6)	26 (40.0)	0.1069
Potential pathogenic bacteria (%)#			
Haemophilus influenzae	28 (30.8)	4 (10.3)	**0.0128***
Moraxella catarrhalis	22 (24.2)	1 (2.6)	**0.0031***
Pseudomonas aeruginosa	12 (13.2)	5 (12.8)	0.9547
Streptococcus pneumoniae	6 (6.6)	5 (12.8)	0.2424
Stenotrophomonas maltophilia	2 (2.2)	4 (10.3)	**0.0448***
Achromobacter xylosoxidans	2 (2.2)	2 (5.1)	0.3753
Corynebacterium spp.	2 (2.2)	2 (5.1)	0.3753
Enterobacter spp.	2 (2.2)	0 (0)	0.3508
Escherichia coli	2 (2.2)	0 (0)	0.3508
Serratia marcescens	2 (2.2)	0 (0)	0.3508
Citrobacter freundii	1 (1.1)	0 (0)	0.5111
Klebsiella oxytoca	1 (1.1)	0 (0)	0.5111
Pasteurella multocida	1 (1.1)	0 (0)	0.5111
Haemophilus parainfluenzae	0 (0)	1 (2.6)	0.1252
Normal URT bacterial microbiota	12 (13.2)	17 (43.6)	**<0.0001***

**Low quality sputum or no expectoration; #more than one microorganism was isolated in some samples; *$p < 0.05$ significant (in bold). AECOPD, acute exacerbations of chronic obstructive pulmonary disease; URT, upper respiratory tract.

rest and after exercise, which was associated with effective control of AECOPD. To the best of our knowledge, gas exchange analysis has not been evaluated in studies of azithromycin in patients with COPD. Given that exercise tolerance and lung functional parameters did not improve with azithromycin therapy, this indicates a dissociation between systemic functional data and gas exchange. There are some mechanisms through which azithromycin may improve gas exchange in patients with COPD. The most important is provided by the drug's anti-inflammatory properties, which reduce the chronic inflammatory response that occurs in the lungs of COPD patients. The decrease in inflammatory markers in blood and sputum after starting prolonged treatment with azithromycin would indicate less airway inflammation and, as a result, an improvement in the pulmonary ventilation-perfusion ratios of treated patients, which presumably contributes to the improvement of gas exchange. In addition, azithromycin can modulate the immune response in the lungs, which may help reduce inflammation; finally, by reducing the frequency and severity of exacerbations, further lung damage can be prevented, leading to more effective lung function.

After analyzing the inflammatory parameters in serum and sputum samples, we observed a numerical improvement in most variables. This was particularly notable in the significant reductions of serum IL-13 and IL-6, as well as serum and sputum TNFR2, after 12 months of treatment. The decreased inflammatory response was more consistent in serial serum determinations than in sputum determinations. Moreover, our predictive models showed that high inflammatory marker and IL-8 levels at baseline predicted a good response to treatment. These immunomodulatory and anti-inflammatory effects of macrolides are well described in the literature (14, 15). Of the interleukin profiles analyzed in this study, IL-8 and TNFR2 presented as the major inflammatory mediators in the immunomodulatory response to azithromycin in patients with COPD. Studies indicate that macrolides take part in proinflammatory cytokine suppression (16–18) and inhibit the transcription and liberation of IL-8, which is important to neutrophil chemotaxis (19). Azithromycin has also been shown to inhibit TNFα-induced production of IL-8 via the JNK signaling pathway and to inhibit MUC5AC production and MMP9. These factors combine to reduce mucus production, which is beneficial for patients with COPD (18).

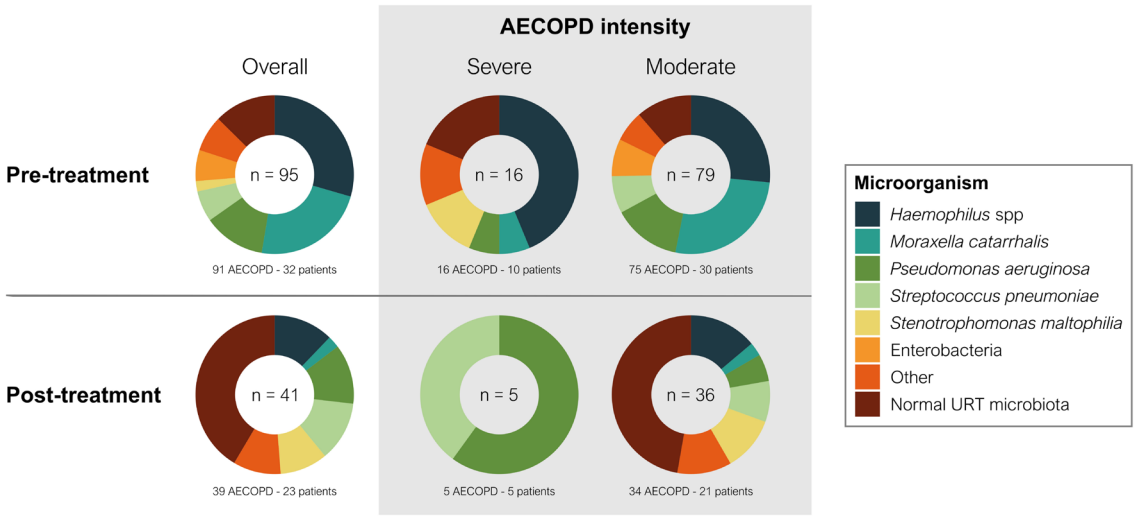

FIGURE 3
Change of microbiology by AECOPD severity during long-term azithromycin therapy. The number inside each donut chart indicates the number of bacterial isolates. Pre-treatment indicates the year before azithromycin treatment, and post-treatment indicates the first year of azithromycin treatment.

An animal model further showed that TNFα levels were reduced after macrolide treatment, and that this was associated with inhibited neutrophil recruitment in the lungs (12). Other effects of macrolides on cytokines include the modulation of dendritic cells by inhibiting IL-6 and stimulating IL-10 (13). In addition, a potential role of azithromycin in the T helper 2 (Th2) inflammatory pathway has been described, with evidence that it inhibits the expression of different IL- 13-induced genes to reduce mucus expression (i.e., MUC5AC) (20). Overall, our results therefore support previous findings, showing a reduction in cytokine levels associated with neutrophil and eosinophil inflammatory pathways. These help to resolve acute infections and reduce exacerbations in patients with chronic airway diseases.

Despite the significant reduction in exacerbations under continuous azithromycin treatment, some patients still had further AECOPD episodes. Although these patients had fewer hospitalizations, they required more days in hospital to treat severe AECOPD. They also showed changes in the patterns of microbiological isolates in sputum samples after continuous azithromycin treatment, with fewer frequent (*H. influenzae* and *M. catarrhalis*) and more potentially pathogenic microorganisms with unusual patterns of intrinsic antibiotic resistance that required treatment (e.g., *S. maltophilia* or *Achromobacter xylosoxidans* in 15% of isolates). This has clear implications when selecting empirical antibiotics for residual AECOPDs in patients receiving continuous azithromycin. Viral infections usually act as the trigger of the exacerbation, but no routine study of viral infections was performed in our study. Further research is therefore required.

Although it was not the scope of our study, many antibiotic resistance mechanisms have been described among the common microorganisms after continuous macrolide treatment (21–24). Indeed, the antimicrobial properties of azithromycin seem to affect the respiratory microbiota, and this may change the clinical evolution of COPD. Future studies should therefore look at the impact of limiting the use of some antibiotics in future AECOPD episodes based on the resistance mechanisms that develop after continuous azithromycin therapy.

The main limitation of the present study is the small sample size and absence of a control group. However, we did not want to demonstrate the efficacy of the treatment with azithromycin in a clinical trial. Instead, we wanted to analyze the effectiveness of azithromycin in real-world settings among patients with severe COPD (e.g., older, comorbidities, and frequent exacerbations), who clinical trials might miss, and to study the role of azithromycin on inflammation and bacterial isolates in these cases.

In conclusion, continuous azithromycin treatment for patients with severe COPD, comorbidities, and frequent exacerbations not only significantly reduces exacerbation and severity rates after 1 year of treatment but also improves gas exchange. Changes are also seen in microorganism patterns and inflammatory responses after treatment. Of note, high serum and sputum IL-8 levels at baseline also appear to predict a good clinical response to azithromycin and may indicate its potential utility as a biomarker. If proven, IL-8 as could be used to improve patient selection and reduce microbial resistance in clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by local ethics committee (Comité Ética Investigación Clínica, CEIC, ref. SSP-AZI-2016-01). The patients/participants

provided their written informed consent to participate in this study.

Author contributions

EC participated in patient's inclusion, statistical analysis, figure preparation, data interpretation, and manuscript drafting. DH participated in the study design, patient's inclusion, statistical analysis, data interpretation, and obtaining funding. CM and AM participated in the study design, patient's inclusion, and data interpretation. AC-S participated in sputum analysis, figure and table preparation, and data interpretation. XP participated patient's inclusion and data interpretation. MG-N participated in sputum analysis and ELISA experiments. SM participated in sputum analysis, data interpretation, and critical revision of the manuscript. SS contributed to the study concept and design, patient inclusion, funding, study supervision, data interpretation, manuscript drafting, and critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1229463/full#supplementary-material

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Prevalence, predictors, dynamic bone change, and treatment efficacy of osteoporosis among chronic obstructive pulmonary disease patients: a prospective cohort study

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Background: Osteoporosis is a silent chronic obstructive pulmonary disease (COPD) comorbidity that is often under-detected. We aimed to study the prevalence and potential predictors of osteoporosis in COPD. Dynamic changes in bone mass density (BMD) and treatment efficacy of bisphosphonate were also assessed.

Methods: This prospective cohort study included COPD patients between January 2017 and January 2019. Demographics data, spirometric parameters, and C-reactive protein (CRP) were collected. Bone mineral density (BMD) at the lumbar spine (L2-4) and both femoral necks were measured after enrollment and the 12-month follow-up. Participants were categorized into three groups per the baseline BMD T-score: normal (≥ -1.0), osteopenia (between -1.0 and -2.5), and osteoporosis (≤ -2.5). In the osteoporosis group, alendronate 70 mg/week with vitamin D and calcium was prescribed.

Results: In total, 108 COPD patients were enrolled. The prevalence of osteoporosis and osteopenia were 31.5 and 32.4%, respectively. Advanced age, lower body mass index (BMI), history of exacerbation in the previous year, and high CRP levels were significant predictors of osteoporosis. After 12 months, 35.3% in the osteoporosis group reported new vertebral and femoral fractures, compared to none in the non-osteoporosis group ($p < 0.001$). In the normal BMD and osteopenia groups showed a further decline in BMD after 12-month. Conversely, the osteoporosis group showed a statistically significant improvement in BMD after anti-resorptive treatment ($p < 0.001$).

Conclusion: The prevalence of osteoporosis was high in Thai COPD patients. Advanced age, lower BMI, history of exacerbation, and high CRP levels were potential predictors. A rapid decline in BMD was observed in COPD patients without treatment.

KEYWORDS

chronic obstructive pulmonary disease (COPD), osteoporosis, bone mineral density (BMD), bisphosphonate, alendronate

1. Introduction

Chronic obstructive pulmonary disease (COPD) is common and causes progressive and persistent respiratory symptoms. In 2019, COPD was the third leading cause of death worldwide and will continue rising (1). COPD patients also have concomitant chronic diseases due to systemic involvement, including cardiovascular disease, skeletal muscle wasting, lung cancer, osteoporosis, metabolic syndrome, and anxiety/depression (2). Comorbidities often affect the progression, morbidity, and mortality of patients with COPD.

Osteoporosis is a silent COPD comorbidity that is closely related and often under-detected in the clinic; it leads to poor health status and mortality. Osteoporosis is characterized by a decrease in bone mass and microarchitectural deterioration of the bone tissue, leading to bone fragility and fracture (3). However, the pathophysiology of COPD-associated osteoporosis is still not well understood and requires further study. This hypothesis was based on low bone mineral density (BMD), abnormal bone changes, impaired bone quality, and low bone turnover due to systemic inflammation (4). Nowadays, there are much increasingly diverse data on the relationship between osteoporotic risk factors and COPD; including smoking, systemic inflammation, long-term corticosteroids used, decreased physical activity, smoking, and malnutrition (5). The molecular pathways of osteoporosis in COPD patients comprise of the interaction between risk factors and molecular pathways such as inflammatory cytokines, irisin, myostatin, osteoclast differentiation, osteoblast activity, etc. (6). These purposed pathways describe the mechanisms of bone loss and muscle loss in COPD patients. Meanwhile, osteoporosis can lead to fractures that have an enormous impact; vertebral fractures may reduce pulmonary function, and rib fractures can cause hypoventilation and interfere with expectorant secretion (7). In previously published studies, the prevalence of osteoporosis in patients was reported to be approximately 23–50% (8–12). A current meta-analysis reported that the pooled global prevalence of osteoporosis COPD was 38% and that COPD increased the likelihood of osteoporosis [odds ratio (OR) = 2.83] (8). Common risk factors for osteoporosis in patients were low body mass index (BMI) and muscle mass. Old age, female sex, severe airflow limitation, frequent exacerbations, advance COPD categories, and C-reactive protein (CRP) levels were also mentioned as potential risk factors (8–14).

The current recommendations for the treatment of osteoporosis (15–17) involve non-pharmacological and pharmacological management. Bisphosphonates, an antiresorptive therapy, are the most widely used treatment for osteoporosis. They have a clear benefit in postmenopausal and glucocorticoid-induced osteoporosis. However, there is limited evidence regarding patients with osteoporotic COPD. A previous randomized controlled trial (RCT) of airway disease demonstrated a significant improvement in lumbar spine BMD through daily intake of 10 mg alendronate (18).

Currently, only one study has reported the prevalence of osteoporosis in Thai COPD patients, (11) and there is limited evidence of dynamic BMD changes in COPD patients. In addition, the role of bisphosphonates in patients with osteoporotic COPD is not well established. This study aimed to investigate the prevalence of osteoporosis in Asian (Thai) COPD patients, define potential predictors of osteoporosis, evaluate dynamic bone changes, and explore the efficacy of bisphosphonate treatment in COPD patients.

2. Materials and methods

2.1. Study populations and design

This prospective cohort study was conducted at a single tertiary hospital, which is a major referral center for 14 provinces in southern Thailand, from January 2017 to January 2019. Patients were eligible for this study if they met the following criteria: age ≥ 40 years, stable COPD diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline 2017, and followed up at the outpatient department (19). Patients were excluded if they had acute exacerbation within 2 months, had comorbidities that could affect bone metabolism e.g., chronic kidney disease (CKD) ≥ stage 3, malignancy, chronic granulomatous disease, hyperparathyroidism, hepatic impairment or chronic liver disease, endocrinal disorders (type 1 diabetes mellitus, Addison's disease, Cushing's syndrome, and Graves' disease), bone metabolism disorders (Paget's disease and osteogenesis imperfect), mastocytosis, severe malabsorption, or received medication related to bone metabolism, including bisphosphonate, systemic glucocorticoids, and hormonal replacement.

Demographic data, including age, sex, BMI, underlying disease, smoking history, severity of COPD, exacerbation rates in the previous year, and inhaled corticosteroid use, were collected. C-reactive protein (CRP) levels were obtained and measured at the central laboratory of Songklanagarind Hospital, using turbidimetric/immunoturbidimetric methods (SENTINEL CH. S.p.A., Milano, Italy).

BMD measurements were performed in three areas: the lumbar spine (L2-4) and both femoral necks, using dual energy X-ray absorptiometry (DXA scan; PRODIGY Pro, GE healthcare/U.S.) after enrolment and a 12-month follow-up by a well-trained technician. Osteoporotic fracture events were also recorded during the follow-up period. All participants were categorized into three groups as follows: normal (≥ -1.0), osteopenia (between -1.0 and -2.5), and osteoporosis (≤ -2.5) according to the overall baseline BMD based on the World Health Organization (WHO) recommendations (20). COPD patients with osteoporosis were prescribed alendronate 70 mg/week, calcium 2,500 mg/day, and vitamin D 20,000 IU/week.

This study was approved by the Office of Human Research Ethics Committee at the Faculty of Medicine, Prince of Songkla University, Thailand (REC.57–225–14-1). All patients provided written informed consent prior to enrollment.

2.2. Outcomes

The primary outcome was the prevalence of osteoporosis in Thai COPD patients. Secondary outcomes were the potential predictors of osteoporosis and natural dynamic changes in BMD (the differences in baseline and 12-month follow-up BMD in the non-osteoporotic group) in patients with COPD. The treatment efficacy of bisphosphonate was also assessed by the percentage difference between the baseline and 12-month follow-up BMD in the osteoporotic group.

2.3. Statistical analyses

The sample size was calculated using an infinite population proportion from the application called n4Studies (21) according to

previously published studies on the prevalence of osteoporosis in patients with COPD (11). A total sample size of 103 patients, which included an additional 20% with missing data, was analyzed in this study.

Continuous demographic data are reported as mean ± standard deviation (SD) or median with interquartile range (IQR). Discrete parameters are presented as counts and percentages. Inferential statistics were used to compare the patient characteristics and outcomes. The chi-square test was used to compare differences in categorical variables, whereas Student's t-test (Kruskal-Wallis equality-of-populations rank test) was used for continuous variables.

Seemingly unrelated regression (SUR) analysis was used to minimize confounding factors of the results by adjusted according to GOLD classification, age, forced expiratory volume in 1 s (FEV_1), smoking status, body mass index, inhaled corticosteroids/long-acting β_2 agonist (ICS/LABA).

Factors with $p < 0.2$ in the univariate analysis were included in multivariate logistic regression analysis to determine the independent predictors of osteoporosis. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the Stata/MP 16.0 Mac.

3. Results

Altogether, 118 patients with stable COPD were screened, and 108 patients were included. After BMD measurement was performed, 34 (31.5%), 35 (32.4%), and 39 (36.1%) patients were categorized into the osteoporosis, osteopenia, and normal groups, respectively (Figure 1). The patients in the osteoporosis group received pharmacotherapy. All patients were followed up.

3.1. Prevalence of osteoporosis

The overall prevalence of osteoporosis and osteopenia according to the *T*-score at either L2–4 or both femoral necks were 31.5 and 32.4%, respectively.

3.2. Patient characteristics

The baseline characteristics are presented in Table 1. The median (IQR) age of the overall population was 72 (66.0, 78.5) years. The median age of the osteoporosis and osteopenia groups was similar but significantly older than that of the normal BMD group (76.0 (72.0, 80.0) vs. 76 (65.0, 82.0) vs. 69 (64.0, 72.0) years, $p = 0.001$, respectively). Most of the patients were men (97.4%). Interestingly, the median weight, height, and BMI were significantly lower in the osteoporosis group. Sixteen COPD patients (45.7%) with osteopenia also had diabetes mellitus, which was higher than in the other groups ($p < 0.001$).

In the osteoporosis group, 44.1% of the patients were classified as having a severe airflow limitation based on FEV_1, and 64.7% of the patients were categorized as group B based on the GOLD assessment. Most COPD patients with osteoporosis in our study (94.1%) had a modified Medical Research Council (mMRC) ≥2, and 55% of them had a history of exacerbation in the previous year, which was significantly higher than that in the osteopenia and normal groups (28.5 and 20.2%, respectively; $p = 0.041$).

The mean CRP level was significantly higher in the osteoporosis group, 4.78 ± 1.97 mg/L than in the osteopenia group, 1.62 ± 1.12 mg/L and the normal group, 0.92 ± 1.33 mg/L ($p = 0.047$). There were no other differences in the baseline characteristics.

3.3. Potential predictors of osteoporosis in COPD patients

From the univariate and multivariate analyses of all baseline characteristics, age > 60 years, BMI <18 kg/m^2, history of exacerbation in a previous year, and a CPR level > 0.6 mg/L were the significant potential predictors for osteoporosis, as shown in Table 2.

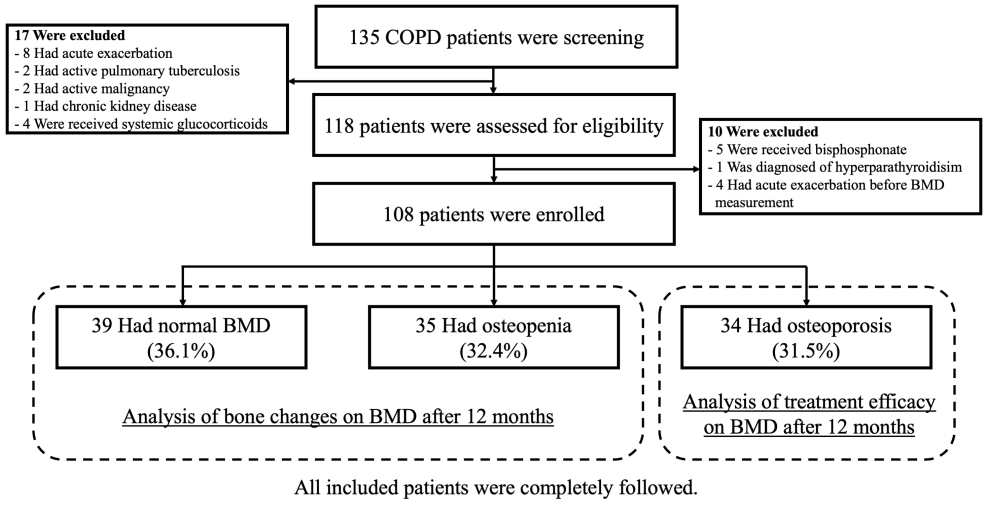

FIGURE 1
Patient enrollment and follow-up diagram.

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TABLE 1 Demographic and baseline patient characteristics.

Patient's characteristics	Normal (n = 39)	Osteopenia (n = 35)	Osteoporosis (n = 34)	Total (n = 108)	value of p
Age (year), median (IQR)	69.0 (64.0, 72.0)	76.0 (65.0, 82.0)	76.0 (72.0, 80.0)	72.0 (66.0, 78.5)	0.001
Male, *n* (%)	38 (97.4)	32 (91.4)	30 (88.2)	100 (92.6)	0.310
Weight (kg), median (IQR)	68.0 (57.0, 74.0)	58.0 (52.0, 66.0)	47.9 (45.0, 55.0)	57.2 (48.9, 68.5)	<0.001
Height (cm), mean ± SD	163.0 ± 5.2	164.2 ± 6.4	159.3 ± 6.4	162.2 ± 6.3	0.001
BMI (kg/m^2), median (IQR)	24.8 (21.4, 27.4)	21.8 (19.0, 23.8)	19.6 (18.3, 21.3)	21.6 (19.2, 24.8)	<0.001
BMI, Categories					
<18.5, *n* (%)	1 (2.6)	5 (14.3)	9 (26.5)	15 (13.9)	0.020
18.5–23, *n* (%)	16 (41.0)	18 (51.4)	18 (52.9)	52 (48.1)	
23–25, *n* (%)	12 (30.8)	5 (14.3)	4 (11.8)	21 (19.4)	
≥25, *n* (%)	10 (25.6)	7 (20.0)	3 (8.8)	20 (18.5)	
FEV_1 (%), median (IQR)	71.0 (46.0, 82.0)	60.5 (47.0, 69.0)	49.5 (38.0, 61.0)	57.0 (46.0, 75.0)	0.106
FVC (%), median (IQR)	99.0 (78.0, 111.0)	86.5 (73.0, 98.0)	87.5 (74.0, 102.0)	90.0 (74.0, 103.0)	0.190
FEV_1/FVC, mean ± SD	54.3 ± 12.3	52.2 ± 10.6	47.7 ± 12.1	51.5 ± 11.9	0.077
GOLD (FEV_1classification), *n* (%)					
>80	14 (35.9)	4 (11.8)	6 (17.6)	24 (22.4)	0.012
50–80	13 (33.3)	23 (67.6)	11 (32.4)	47 (43.9)	
30–50	11 (28.2)	6 (17.6)	15 (44.1)	32 (29.9)	
<30	1 (2.6)	1 (2.9)	2 (5.9)	4 (3.7)	
GOLD group, *n* (%)					
A	15 (38.5)	12 (35.3)	2 (5.9)	29 (27.1)	0.001
B	14 (35.9)	16 (47.1)	22 (64.7)	52 (48.6)	
C	5 (12.8)	4 (11.8)	0 (0.0)	9 (8.4)	
D	5 (12.8)	2 (5.9)	10 (29.4)	17 (15.9)	
Smoking status					
current smoker, *n* (%)	38 (97.4)	30 (85.7)	28 (82.4)	96 (88.9)	0.095
ex-smoker, *n* (%)	1 (2.6)	5 (14.3)	6 (17.6)	12 (11.1)	
Underlying disease					
Dyslipidemia, *n* (%)	15 (38.5)	10 (28.6)	9 (26.5)	34 (31.5)	0.493
Hypertension, *n* (%)	18 (46.2)	14 (40.0)	10 (29.4)	42 (38.9)	0.338
Coronary disease, *n* (%)	4 (10.3)	5 (14.3)	6 (17.6)	15 (13.9)	0.658
Diabetes mellitus, *n* (%)	7 (17.9)	16 (45.7)	2 (5.9)	25 (23.1)	<0.001
Dose of steroid*(mg), mean ± SD	35.5	37.52	52.17	42.5	0.067
ICS used, *n* (%)	36 (92.3)	33 (94.3)	34 (100.0)	103 (95.4)	0.276
ICS dose (mg/day)					
Fluticasone 500, *n* (%)	24 (66.7)	21 (60.0)	27 (79.4)	72 (68.6)	0.196
Fluticasone 750, *n* (%)	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.0)	
Budesonide 640, *n* (%)	12 (33.3)	14 (40.0)	6 (17.6)	32 (30.5)	
CAT score, mean ± SD	17.1 ± 8.7	17.2 ± 8.4	18.4 ± 9.9	17.6 ± 8.3	0.158
mMRC dyspnea score					
1, *n* (%)	26 (66.7)	17 (48.6)	2 (5.9)	45 (41.7)	<0.001
2, *n* (%)	13 (33.3)	16 (45.7)	31 (91.2)	60 (55.6)	
3, *n* (%)	0 (0.0)	2 (5.7)	0 (0.0)	2 (1.9)	
4, *n* (%)	0 (0.0)	0 (0.0)	1 (2.9)	1 (0.9)	
History of exacerbation in a previous year, *n* (%)	8 (20.5)	10 (28.5)	19 (55.8)	37 (34.3)	0.041
CRP (mg/L), mean ± SD	0.92 ± 1.33	1.62 ± 1.12	4.78 ± 1.97	2.54 ± 2.96	0.047

*dose of steroid: dose of systemic corticosteroid in the previous year.

BMI, body mass index; CAT, COPD assessment test; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroid; IQR, interquartile range; mMRC, modified medical research council; SD, standard deviation; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified medical research council.

3.4. Association between BMD and GOLD groups

COPD patients in each group were classified into four GOLD groups, and the probabilities of osteoporosis and osteopenia were assessed according to age. Patients with COPD GOLD D had the highest probability of having osteoporosis, and a greater effect was seen in older age (Figure 2).

3.5. Dynamic changes in BMD and treatment efficacy of bisphosphonate

We examined the mean percentage change in BMD at 12 months in each group. In the normal and osteopenia groups, BMD at the lumbar spine and right and left femoral neck further declined (BMD values in the normal group were − 2.8, −4.3%, and − 3.2% and those in the osteopenia group were − 1.8, −5.1%, and − 3.8%, respectively). During the 12-month period, two COPD with osteopenia patients had declined BMD values at the vertebral body and turned to osteoporosis.

Conversely, the osteoporosis group that received alendronate 70 mg/week (with calcium and vitamin D) showed a statistically significant improvement in BMD of 6.7, 7.0, and 5.8% in the lumbar spine, right femur, and left femur, respectively ($p < 0.001$), as shown in Figure 3.

Over the 12-month study period, 12 patients (35.3%) in the osteoporosis group had new vertebral and femoral fractures, whereas no fracture was reported in the non-osteoporosis group ($p < 0.001$).

4. Discussion

This study has four important findings. First, the prevalence of osteoporosis in COPD was 31.5% and that of osteopenia was 32.5%. The second is that the potential risk factors for osteoporosis were age > 60 years, BMI <18 kg/m^2, history of exacerbation in the previous year, and a CRP level > 0.6 mg/L. Third, COPD GOLD D patients with older age had the highest probability of osteoporosis. Lastly, osteoporotic COPD patients who received anti-resorptive treatment had a statistically significant improvement in BMD after prospective follow-up.

To the best of our knowledge, osteoporosis is an important comorbidity of COPD that can lead to poor health status. This study found that one-third of Thai COPD patients had osteoporosis and nearly two-thirds had low BMD. The prevalence in our study was similar to that in other studies, which was reported as 31–40%, (8–10, 12) and also corresponded with a prior study in Thai COPD patients by Rittayamai et al. (11) However, our study also included women, which can cause a higher prevalence due to hormonal effects. The prevalence of the Thai male population was 12.6% as reported by Pongchiyakul et al. (22) However, we found a prevalence greater by 2.5 times; this difference might be attributed to the younger population in their study (mean age of 51 ± 16 years). The effect of aging on bone metabolism could result in a high prevalence of osteoporosis in the elderly, and most patients were diagnosed at an older age.

TABLE 2 Multivariate analysis of potential predictors for osteoporosis in COPD patients.

Variables	Odd ratio	95% CI	value of *p*
Age > 60 years	1.58	1.09–2.28	0.041
Low BMI (< 18 kg/m^2)	1.64	1.36–3.01	0.039
History of exacerbation in a previous year	1.92	1.25–4.79	0.036
High CRP level (> 0.6 mg/L)	1.52	1.12–2.34	0.048

BMI, body mass index; CRP, C-reactive protein.

Advanced age was also reported as an associated factor for osteoporosis in COPD in a previous study (23). Low BMI has also been documented as a risk factor for osteoporosis in numerous studies, (8, 10, 11, 24, 25) which could be explained by various mechanisms, including hormonal levels, changes in body composition, and mechanical loading on the weight-bearing bones that facilitate bone formation and are also correlated with systemic inflammation in COPD (7, 26, 27). History of exacerbation in the previous year increased the risk of osteoporosis in our patients. Although this factor remains controversial in most studies, a few trials have reported that COPD exacerbations are independently associated with osteoporosis progression (28, 29). COPD exacerbation is hypothesized to be a risk factor for osteoporosis because of important factors such as systemic inflammation, systemic corticosteroid prescription, and physical inactivity during acute exacerbation (30, 31). Systemic inflammation occurs at all stages of COPD, especially during acute exacerbations. To our knowledge, systemic corticosteroid usage is a common cause of osteoporosis and fracture according to a meta-analysis of 42,000 subjects (32). The inflammatory process is demonstrated by increased production of various cytokines, including the bone resorption marker collagen type I β-isomerized C-terminal telopeptide (beta CL), CRP, matrix metalloproteinase-9 (MMP-9), and tissue inhibitor of metalloproteinase-1 (TIMP-1). During exacerbation, the total oxidative status (TOS) was higher than that in the stable state ($p < 0.05$) (33). Unsurprisingly, we found that the CRP level, an inflammatory reactive cytokine, was higher in patients with osteoporosis than in those without osteoporosis. This factor is similar to that in another study in Thailand (11). Therefore, our results support the hypothesis that systemic inflammation is responsible for the high prevalence of osteoporosis in COPD patients.

Systemic and inhaled corticosteroid usage were not claimed as potential predictors of osteoporosis in this study, which is consistent with the TORCH study by Ferguson et al. (9) and the recent systematic and meta-analysis by Chen et al. (8) Severe COPD patients had a higher risk of osteoporosis about four times, as well as the lower FEV_1 and FEV_1/FVC ratio tended to have a higher risk of getting osteoporosis from a longitudinal study by Bitar et al. (13). However, the severity of airflow limitation could not be found as a significant risk factor for osteoporosis in our study, which was different from that reported in previous studies, (10, 12) but the same as that reported in two recent systematic and meta-analysis studies (8, 24).

Additionally, a more rapid decline in BMD was observed in the lumbar, right, and left femur in our COPD patients than in the non-COPD osteoporotic patients without treatment (34). Most patients in this study were males. Men have a slower bone mineral density loss than post-menopausal women because of hormonal effect. From the previous report, the loss of bone mineral density in men will occur after the sixth decade of life about 0.5–1% per year (35).

We also assessed the treatment efficacy of bisphosphonate; alendronate has a beneficial effect on BMD, including that in the lumbar spine and both femurs, which was similar to that reported in

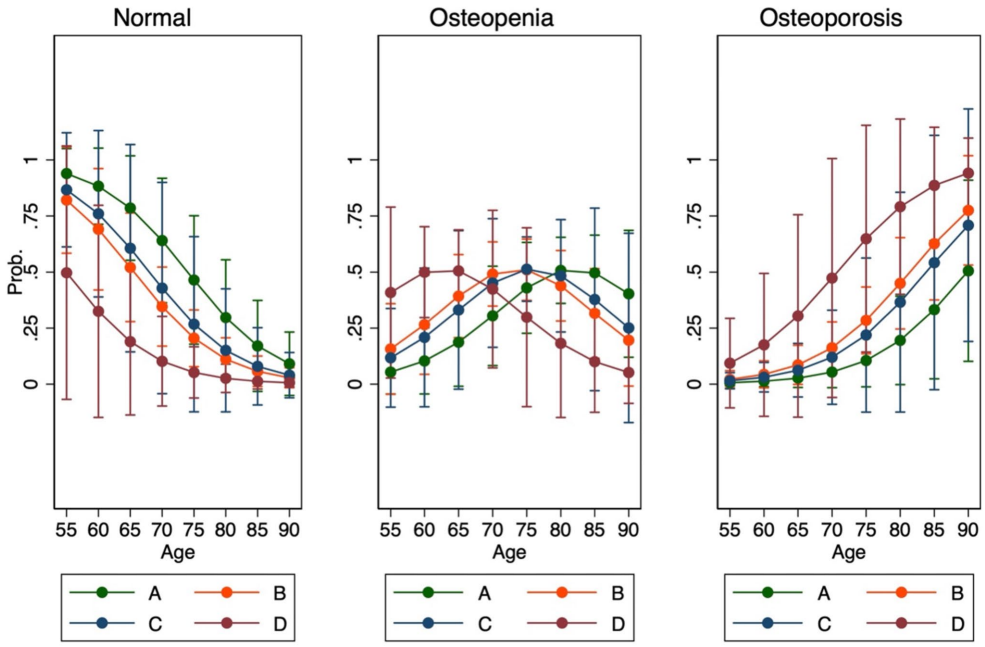

FIGURE 2
Association between BMD and GOLD groups according to age.

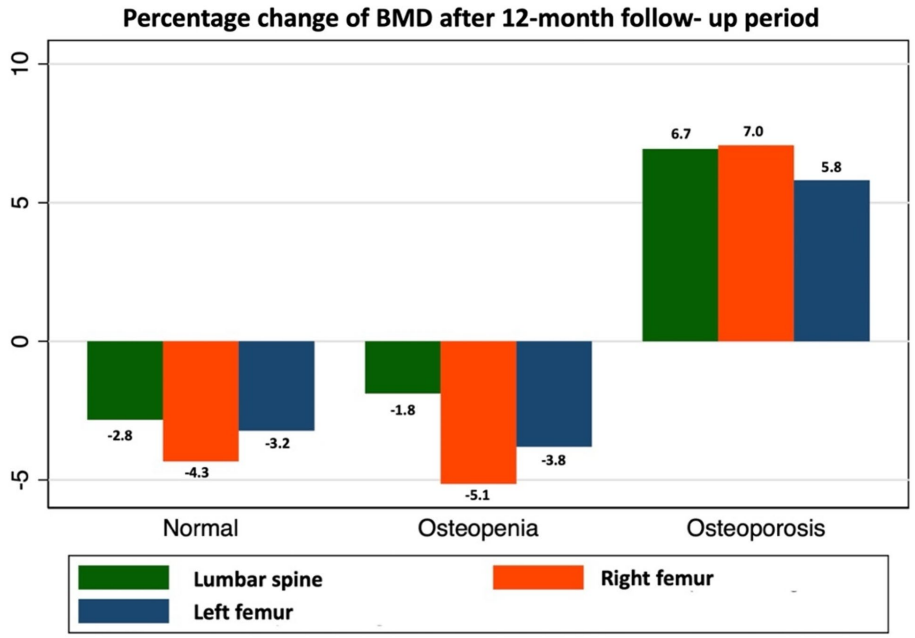

FIGURE 3
Dynamic changes in BMD in COPD patients.

a prospective observational study from Japan (36). An earlier RCT by Smith et al. (18) evaluated the effect of bisphosphonate in patients with airway disease (mostly asthma patients), and the results demonstrated a significant benefit on BMD only at the lumbar spine. These results could reflect the benefit of alendronate in preventing rapid bone decline in COPD as well as in postmenopausal, male, and glucocorticoid-induced osteoporosis. From our study, in COPD patients with normal BMD and osteopenia group also showed a significant decline after only 1 year period. These findings could be implied to general practice such as routine BMD screening and close follow-up, early initiation of vitamin D and calcium supplements, early considering anti-resorptive drugs if possible.

To our knowledge, this is the first prospective cohort study to demonstrate many aspects of osteoporosis in Thai COPD patients. In

this study, we minimized confounding factors as much as we could by using seemingly unrelated regression (SUR) analysis. The confounders including GOLD classification, age, FEV_1, smoking status, body mass index, ICS/LABA used were already adjusted. However, gender was not adjusted due to the small number of females in our study. These results could alert pulmonologists to the importance of osteoporosis. Routine BMD screening can lead to early diagnosis and initiation of treatment. This issue will prevent fractures and improve the quality of life and prognosis. However, our study has some limitations. First, our study was not population-based with age-and sex-matched controls. Second, a 1-year-follow up period might not be sufficient to represent the BMD change, but it can display a trend of changes, as well as this period was not long enough to confirm the long-term benefit of bisphosphonate and observe its side effects. Therefore, further studies should be conducted on population-based age-sex-matched control patients and extend the duration of treatment to confirm long-term benefits and side effects.

5. Conclusion

The overall prevalence of osteoporosis is high in Thai COPD patients. Advanced age, lower BMI, history of exacerbation, and high CRP levels were potential predictors. A rapid decline in BMD was observed in COPD patients without treatment, whereas alendronate prevented further BMD decline in osteoporotic COPD patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Office of Human Research Ethics Committee at the Faculty of Medicine, Prince of Songkla University, Thailand (REC.57-225-14-1). All patients provided written informed consent to participate in this study prior to enrollment.

Author contributions

PK, WK, and SG: conceptualisation, methodology, and data interpretation. NC and PS: data collection and investigation. PK and SG: data analysis. PK and WK: validation. PK: data curation and writing-original draft preparation. WK: writing – review and editing, supervision, and project administration. All authors contributed to the article and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Remote patient monitoring strategies and wearable technology in chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is highly prevalent and is associated with a heavy burden on patients and health systems alike. Exacerbations of COPD (ECOPDs) are a leading cause of acute hospitalization among all adult chronic diseases. There is currently a paradigm shift in the way that ECOPDs are conceptualized. For the first time, objective physiological parameters are being used to define/classify what an ECOPD is (including heart rate, respiratory rate, and oxygen saturation criteria) and therefore a mechanism to monitor and measure their changes, particularly in an outpatient ambulatory setting, are now of great value. In addition to pre-existing challenges on traditional 'in-person' health models such as geography and seasonal (ex. winter) impacts on the ability to deliver in-person visit-based care, the COVID-19 pandemic imposed additional stressors including lockdowns, social distancing, and the closure of pulmonary function labs. These health system stressors, combined with the new conceptualization of ECOPDs, rapid advances in sophistication of hardware and software, and a general openness by stakeholders to embrace this technology, have all influenced the propulsion of remote patient monitoring (RPM) and wearable technology in the modern care of COPD. The present article reviews the use of RPM and wearable technology in COPD. Context on the influences, factors and forces which have helped shape this health system innovation is provided. A focused summary of the literature of RPM in COPD is presented. Finally, the practical and ethical principles which must guide the transition of RPM in COPD into real-world clinical use are reviewed.

KEYWORDS

chronic obstructive pulmonary disease, exacerbations of COPD, remote patient monitoring, wearable electronic devices, COVID-19 pandemic

Introduction

We are in an unprecedented period in human history marked by a longer life expectancy and a global aging of the human population. With this remarkable basic sanitary, public health and healthcare-driven success, however, come new pressures and challenges for these same health systems. The accruement in the number and severity of chronic diseases with age has led to multimorbidity and increased complexity of care (1). There is a remarkable increase in the

burden of chronic medical conditions (2), which will require innovation and revision to the traditional care model.

Remote patient monitoring (RPM) enables the collection of patient health data using peripheral measurement devices or specific questionnaires about their condition without necessitating an in-person visit to obtain these measurements. Typically used in the comfort of the patient's home environment, this form of monitoring involves the real-time transfer of data to a dedicated platform where healthcare professionals can receive and/or access it. Remote patient monitoring solutions may therefore possess the potential to reduce healthcare costs and increase patient quality of life (3).

Chronic obstructive pulmonary disease (COPD) and exacerbations of COPD (ECOPDs): a paradigm shift

Chronic obstructive pulmonary disease (COPD) is a very common and progressive respiratory condition characterized by chronic breathlessness, a gradual decline in lung function, and reduced quality of life (4). COPD alone was responsible for 3.23 million deaths worldwide in 2019 and has become the third-leading cause of death (5). The global estimated prevalence is 11.7%, and this estimate is projected to increase due to global population aging and due to the growing rates of both smoking and non-smoking exposures in low-and middle-income countries (LMICs) (6). Cigarette smoke (7), occupational exposure to toxic particles, and outdoor and indoor air pollution are all relevant risk factors (6).

The natural history of COPD is characterized by a progressive decline in lung function over time and is also marked by acute episodes of increased symptoms and physiological alterations known as *exacerbations of COPD (ECOPDs)*. While in the acute setting ECOPDs are clinically important events, frequent and severe ECOPDs can also lead to irreversible airway damage and worsening in chronic lung function (8, 9). The overall rate of ECOPDs and COPD hospitalizations continues to increase, partly due to increasing COPD prevalence and more severe forms of disease associated with longer lifespans (6, 10). For example, from 2010 to 2015, the rate of hospitalization for ECOPDs increased from 83 to 86 per 100,000 individuals (10), and COPD remains a top cause of hospitalization amongst all adult chronic diseases. The significant contribution of hospitalizations to the total cost of COPD, amounting to a staggering $50 billion in the United States alone, clearly indicates that COPD poses a substantial burden on healthcare systems (11).

A new ECOPD definition and classification was recently put forth by Celli et al. (12) in the *Rome Proposal*, in part to address issues with the pre-existing framework which had retrospectively classified exacerbations by the way the treating clinician managed the patient rather than using, for example, objective physiological criteria. Using six objectively measured variables in addition to symptom scores, clinicians can use the more 'objective' criteria presented in the Rome Proposal to classify ECOPDs as 'mild', 'moderate' or 'severe'. These variables include not only dyspnea but also *oxygen saturation (SpO_2)*, *respiratory rate (RR)* and *heart rate (HR)*, as well as serum C-reactive protein (CRP), and in some cases, arterial blood gas (ABG) values (12). While this will require prospective validation, early enthusiasm and support for this new definition/classification criteria by the international COPD community is reflected by its inclusion in the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 Report (6).

The COVID-19 pandemic

Even predating the reporting of the first observed COVID-19 cases (13) and the global pandemic that followed, there had been notable technological advancements in the development of increasingly precise and compact devices with extended battery life. The COVID-19 pandemic itself then further complicated the delivery of healthcare, including challenging the conventional chronic management of patients with COPD through decreased availability of in-person clinics and recurrent pulmonary function lab testing closures. From a therapeutic perspective, temporary shortages in inhaled medications and the absence of in-person pulmonary rehabilitation programs compounded these difficulties (14). These COPD-specific challenges, combined with challenges which affected all patients with chronic disease including social distancing, isolation, and area-wide lockdowns, led to a recognition of the need to develop new disease monitoring approaches (6, 15). This was embraced also by health systems. In 2019, for example, the Centers for Medicare and Medicaid Services (CMS) established billing codes for remote monitoring (16), and in 2021 the use of remote monitoring platforms in traditional Medicare had increased by six-fold compared to pre-pandemic levels (17).

Remote patient monitoring

Remote patient monitoring (RPM) presents an interesting and innovative approach to address the multiple challenges faced by burdened health systems around the world, both newer issues (pandemic-associated) and more longstanding ones (geographic issues with rural/underserved regions, the ever-growing burden of effective in-person chronic disease management for the aging global population, and so on). Applications in the effective management of COPD span across the 'chronic' (regular respiratory monitoring and remote pulmonary rehabilitation delivery) and 'acute' (early detection of new exacerbations and ensuring adequate recovery) conditions.

RPM in COPD thus far has encompassed a variety of equipment, platforms, and strategies. Conventional approaches have included remote lung function testing on fixed/stationary devices such as peak flow meters and oscillometers, closely resembling the data collection process employed in hospitals and ambulatory clinics, which typically yields one measurement per day (3). More recent emerging approaches have incorporated 'wearables', biometric devices which can be worn for prolonged periods while collecting relevant physiological parameters in daily life (17, 18). These wireless, non-invasive, and self-contained devices can be attached to the human body or to clothing (19). The incorporation of wearables within RPM platforms has facilitated near-continuous remote collection and transmission of physiological data in ambulatory patients, enhancing the richness and resolution of data collected when compared to more traditional approaches and ushering in an era of sophisticated personalized medicine (17, 20–22). A semi-structured approach was followed in order to extract articles from the existing literature (see Supplementary material). The following is a focused summary of RPM in COPD following an independent review and appraisal of each article. A concise summary of the most relevant articles featured in this review can be found in the Supplementary Table 1.

Discussion

Current 'medical', 'research-grade' and 'consumer-facing' wearable biometric devices are worn on various parts of the human body, including the head, limbs, and torso (23). Wristbands (24, 25), armbands (26), vests (27, 28), upper thorax stamps and bands (29), and rings (30) are all commercially available. The types of physiological data collected can include blood pressure, HR and its variability (HRV), RR and its variability (RRV), SpO_2, activity, body temperature and metabolic function, sleep metrics and autonomic function including electrodermal activity (31).

There are pros and cons to each type of device as it relates to technical performance (quality/quantity of data collected), patient satisfaction, and ease of overall use. Wristbands, smartwatches, and rings are highly user-friendly, comfortable to wear, and possess versatile functionality which makes them highly suitable for prolonged use (32). These devices largely utilize optically obtained photoplethysmographic (PPG) signals which measure the intensity of light that penetrates through the skin to estimate the frequency and amplitude modulation of the cardiac pulse. Indirect estimations of RR are possible through frequency modulation (FM), by analyzing the variation in pulse frequency (33, 34). While this method offers several advantages, the indirect measurement of RR through the derivation of the PPG waveform may risk limiting precision compared with devices capable of directly measuring thoracic expansion, especially during strenuous movements or during exercises which can induce movement artifact (35).

Wearable vests, shirts, and bands are highly accurate in measuring cardiac and respiratory parameters in patients with COPD given the proximity to the heart to detect electrical activity and the use of chest expansion for detailed respiratory measurement. They are, however, limited by a sensation in some patients of discomfort by being mechanically restrained particularly during inspiration/expansion of the thorax (28). Given the diverse range of devices available and under continuous redevelopment, clinical researchers have a variety of options available to choose from. The clinical condition, setting, individual/patient-specific characteristics, anticipated duration of wear and desired parameters can inform device selection.

RPM and wearables have been studied in non-COPD respiratory diseases such as in pediatric asthma and during acute viral illness. Depending on the age of the pediatric patient, the forced maneuvers and coordination required for conventional spirometry are difficult for children to complete reproducibly (36). A study by Lundblad et al. (37) demonstrated that respiratory resistance measured during normal (tidal) breathing using a novel handheld portable oscillometer device correlated closely with estimates obtained by conventional oscillometry in children with asthma. User experience questionnaires were favorable, including perceptions by children and their parents that the test was 'easy' and that they 'would use it at home if recommended by their health care provider', supporting the feasibility of remote lung function monitoring even in children with asthma.

Remote patient monitoring and wearables in COPD

The development of RPM solutions specifically for patients with COPD is a very active field of clinical research and one that holds great promise. An important foundational 2012 study in this modern field by Yanez et al. (38) utilized existing domiciliary oxygen therapy equipment to detect subtle changes in RR preceding exacerbation. In more than two-thirds of detected exacerbations, the average RR was found to increase as early as 5 days prior to hospitalization and RR closer to hospitalization was increasingly accurate and specific as a predictive 'biomarker'. In 2015, Borel et al. (39) again leveraged existing patient equipment by analyzing COPD non-invasive ventilation (NIV) recipient data RR and percentage of respiratory cycles triggered (%Trigg) > 75th percentile for two or more of the preceding 5 days were associated with an increased risk of subsequent exacerbation. Daily NIV adherence variations (either > 75th or < 25th percentile) were also linked to subsequent exacerbations (39). This important 'early' work laid the foundation for subsequent studies on physiology-based RPM strategies in the ambulatory COPD outpatient population.

A 2017 study by Rubio et al. (40) transported RR into the realm of 'wearables' by demonstrating that wearable accelerometers and chest bands provide accurate measures of RR comparable to a gold standard. These were sensitive enough to detect a decrease in RR after an exacerbation, and likewise an increase in RR before a future exacerbation in ambulatory outpatients with COPD (40). To determine whether accurate data collection and good COPD-specific adherence with wearable biometric smartwatches were possible, Wu et al. (41) used quantitative and qualitative methods to demonstrate the feasibility and willingness of participants with COPD to wear smartwatches that collect physiological data. Participants reported desiring active engagement and feedback on their activity, HR, and COPD management.

Walker et al. (3) hypothesized in a 2018 study that remote monitoring of lung function using daily oscillometry measurements was not only possible but moreover would reduce the time to first hospitalization, reduce healthcare costs, and increase quality of life in older patients with COPD and prevalent comorbidities. An advantage of oscillometry, when compared to conventional spirometry, is that patients with COPD can perform this test autonomously and reliably at home without the need for a respiratory therapist (36). Mechanical properties of the lungs during tidal breathing were collected and transmitted remotely (3). While the time to first hospitalization, EQ-5D utility score and quality-adjusted life years (QALYs) were not different between intervention and control groups, the per-patient cost was lower for all subgroups of the intervention group except for those with severe/very severe COPD (3). While potentially underpowered by a low number of events (hospitalizations), these hypothesis-generating secondary outcomes in addition to having demonstrated the acceptability, tolerability, and practicality of remote lung monitoring using oscillometry in older patients with COPD with cardiac comorbidities contributed to the field of RPM in more advanced forms of COPD (3).

Hawthorne et al. (28) investigated the usability and acceptability of a sophisticated biometric wearable vest in patients with COPD both in stable and in acute (peri-exacerbation) conditions. This 2022 study found that while most participants experienced no vest-associated discomfort, a subset of peri-/post-exacerbation participants expressed occasional feelings of restriction and breathlessness thereby influencing their acceptance of the vest (28). The conventional 'trade-off' between capturing artifact-free data, versus the patient discomfort associated with some wearable thoracic bands, shirts, and vests, was well-demonstrated in this study. PPG-derived parameters from wearable devices in other COPD-specific studies have demonstrated a reassuringly close correlation between RR and HR with gold-standard acquired measurements (40, 42).

In the same year, Park et al. (43) investigated the feasibility of HR monitoring in COPD using a chest-worn biosensor. As previously reported, this study concluded that HRV was in fact reduced in COPD. Interestingly, this variation was independent of the severity of airflow obstruction, however a correlation between lower HRV and poorer overall health or functional status was observed. Finally, a notable strong variation signal was observed in long-acting inhaled bronchodilator (β-agonist and muscarinic-antagonist) users given the overlapping mechanism of action on the autonomic nervous system, which underscores the sensitivity of these devices and the relevance of accounting for these factors in general in the field of RPM data interpretation.

Most recently, Polsky et al. (44) performed a *retrospective*, non-randomized study on an RPM 'service' in patients with COPD which included an undergarment-adhered cardiorespiratory physiologic monitor linked via data capture 'hub' to a web-based clinical dashboard. This 2023 study demonstrated that RPM recipients experienced significantly fewer unplanned hospitalizations when compared with usual care. This important study further demonstrates the potential for RPM and wearables to assist in the early detection of ECOPDs. This technology also has the potential to be leveraged towards a better understanding of the physiology (and pathophysiology) of ECOPDs in ambulatory outpatients with COPD, which might help inform future *prospective* large-scale randomized clinical trials evaluating wearable-based RPM interventions in the COPD patient population.

Emerging artificial intelligence and machine learning applications

Artificial intelligence (AI) has been described as a computer framework which displays 'human-like intelligence', whereas machine learning (ML) is a subset of AI that uses statistical models to 'learn' from data for designated tasks (45, 46). These methodologies can be leveraged to process, categorize, and analyze substantial amounts of data (45), with a performance which can be autonomously optimized. These properties render AI/ML methodologies ideal for processing substantial physiological datasets, and in keeping with this, the more recent RPM literature has increasingly gravitated towards AI/ML incorporation. In a recent non-COPD study by Grzesiak et al. (24), the capacity of ML models using data obtained from healthy participants who were inoculated with respiratory viruses and wearing a non-invasive 'wearable' wristband could accurately predict viral infection status and severity even before symptom onset using ML models. Binary and multiclass random forest classification models, each addressing a distinct time period following inoculation or adopting different criteria to distinguish between 'infected' and 'non-infected' subjects, were developed. Remarkably, by combining near-continuous wearable-obtained physiologic data with robust ML modelling, it was possible to predict the subsequent severity (mild vs. moderate) of infection at a timepoint which preceded symptom onset by 24 h (24).

Pertaining specifically to the COPD RPM literature, Shah et al. (47) collected data from a large cohort of 110 individuals with COPD over the course of 1 year in order to assess the feasibility of developing a COPD digital health system. A Bluetooth pulse oximeter was paired with a comprehensive questionnaire which obtained near-daily symptom scores and medication use. A finite-state machine learning approach was used to process this extensive dataset, and the model developed was able to effectively classify the health condition of study participants. This study also found that, amongst the parameters collected (HR, RR, and SpO_2), that SpO_2 emerged as the most useful in predicting exacerbations.

The applications of AI/ML methodologies towards the development of effective COPD remote monitoring platforms are gaining attention. A recent review (48) details the superior approach of combining AI/ML with remotely acquired data when compared to pre-existing models, platforms and algorithms. Included in this review, Orchard et al. (49), Wu et al. (50) and Fernandez-Granero et al. (51) all place a particular emphasis on the applicability of ML-based approaches in producing sophisticated platforms capable of detecting the very early onset of exacerbations. This predictive capacity, once launched in a real-world clinical setting, could have a substantial impact on disease management in COPD.

Remote patient monitoring and wearables in COPD: additional applications

Beyond daily outpatient monitoring and ECOPD detection, innovations in RPM and wearable technology can also support and complement longstanding evidence-based standard-of-care interventions in COPD including *pulmonary rehabilitation (PR)* delivery and in reinforcing *self-management behaviors*. Advances in technology now permit the possibility of near-completely 'remote' PR delivery, which was particularly important during the COVID-19 pandemic when most in-person PR programs were closed (52). Home-based PR for COPD has been shown to be as effective as center-based PR in improving functional exercise capacity and quality of life (53), and patients with chronic respiratory disease achieved similar effectiveness and safety outcomes to center-based PR as they did with telerehabilitation (53). COPD telerehabilitation may even be able to increase and maintain the persisting benefits of PR (54).

Remote patient monitoring technology can reinforce and support COPD-specific self-management adoption. Real-time feedback on activities, behaviors and physiological changes can make patients with COPD more involved and engaged in their own care and more aware of their condition (40, 55). Patients with COPD have described that this data would empower them by allowing them to link how they feel, a 'subjective' experience, to an 'objective' measurement such as real-time vital sign information. This may increase awareness, and in some instances, can reassure them about the status of their condition at any given time (55).

Practical considerations in COPD

While the literature to date on device-based RPM solutions in COPD are encouraging, the 'real-world' clinical launch and operation of these platforms remain associated with sizeable challenges. These need to be considered at the earliest stages of platform development/validation (i.e., during the 'clinical research' phase) to ensure that the downstream COPD target subpopulations and intended clinical purposes of the platform are maintained. Firstly, the RPM platform device(s) would need to effectively measure the main outcome of interest. Second, the intended patient population and the setting of

data collection should be considered (32). COPD-specific factors include patient age (56) and technology 'literacy', which might favor the use of simpler devices and interfaces. Generational divides in comfort with technology (software and hardware) may adversely affect patient access to RPM platforms in a notable proportion of the COPD population. Beyond age and generation, individual educational background, professional work experience, and personal experience with technology are relevant (57). Moreover, because the goal of RPM is real-time near-continuous data collection, the devices should be as comfortable as possible for prolonged wear. Finally, an extensive battery life, intuitive or even automatic data upload processes, and convenient platform access by the treating clinical team must all be factored into the design of wearable device-based RPM platforms intended for 'real-world' clinical use.

Ethical considerations in COPD

Beyond the practical issues in developing, testing, and launching device-based RPM platforms in the COPD patient population, there are also ethical principles which are paramount. Firstly, while it might be challenging for the 'highest risk' patients or those with the most advanced forms of COPD to participate in clinical research studies, researchers must find ways to include these patients in particular given that RPM strategies are most likely to be useful and cost-effective in this clinical subpopulation as it relates to reducing patient and health system burden. For example, if the platform intends to detect new exacerbations in those patients at highest risk, then this high-risk subpopulation (rather than, for example, patients with milder disease or infrequent exacerbations) must be enrolled and studied in these trials. Likewise, the intention to serve traditionally vulnerable and marginalized populations through these technological advances (58) must be met with a purposeful and equitable commitment of the clinical investigator to include these patients in RPM clinical research studies, to minimize the risk of their subsequent exclusion at the time of downstream clinical launch. Finally, an ongoing and organized strategy at hospital administrative, governmental, and even international levels in order to oversee and regulate ethical aspects and best practices in the utilization of RPM technologies and patient data is critical. The priority must always be the patient, their well-being, their right to confidentiality and privacy, and their right to autonomy. The highly sensitive data that can be collected by these platforms must be protected, anonymized, and safely stored.

Conclusion: current landscape and future directions

Although significant progress has been made, there remains a need to continually develop and refine existing versions of device-based RPM platforms such that ever-improving sensors, longer battery lives, smaller sizes, more efficient and precise computational algorithms, and enhanced data security features can be harnessed to effectively face the many challenges in the modern care of COPD (15). Research dedicated to the bottom-line clinical efficacy of these platforms in COPD in a prospective manner is necessary before more widespread adoption in the clinical sphere can occur. The future interaction between wearable biometric devices, sophisticated platforms, and harnessing the power of 'big data' and AI/ML methods (48–51) makes this an exciting and promising field which will no doubt shape the future of healthcare.

Author contributions

F-AC, OI, and BR developed the manuscript template, performed the literature review, finalized the content and relevant themes, and wrote the manuscript. All authors have given agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

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Conflict of interest

BR reports the following Conflicts of Interest: *Honoraria* from the Canadian Thoracic Society (CTS—presenter and educational content creator), CHEST (educational content creator), Respiplus non-profit (educational content creator), Alberta Kinesiology Association (AKA—educational webinar presenter), Association des Pneumologues de la Province du Québec (APPQ—presenter), McGill University Continuing Professional Development (CPD—presenter) and from GSK (educational session moderator); *Research funding* as Principal Investigator from the McGill University Health Centre (MUHC) Department of Medicine Contract Academic Staff (CAS) Research Award, the Quebec Respiratory Health Network (QHRN), the *Ministère de l'Éducation et le Ministère de l'Enseignement Supérieur* Innovation and Partnership Program (McGill University and Thorasys, Inc.), and the MUHC Foundation/MCI Respiratory Research Campaign Innovation Grant.

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Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1236598/full#supplementary-material

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Sex-differences in COPD: from biological mechanisms to therapeutic considerations

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory condition characterized by symptoms of dyspnea, cough, and sputum production. We review sex-differences in disease mechanisms, structure-function-symptom relationships, responses to therapies, and clinical outcomes in COPD with a specific focus on dyspnea. Females with COPD experience greater dyspnea and higher morbidity compared to males. Imaging studies using chest computed tomography scans have demonstrated that females with COPD tend to have smaller airways than males as well as a lower burden of emphysema. Sex-differences in lung and airway structure lead to critical respiratory mechanical constraints during exercise at a lower absolute ventilation in females compared to males, which is largely explained by sex differences in maximum ventilatory capacity. Females experience similar benefit with respect to inhaled COPD therapies, pulmonary rehabilitation, and smoking cessation compared to males. Ongoing re-assessment of potential sex-differences in COPD may offer insights into the evolution of patterns of care and clinical outcomes in COPD patients over time.

KEYWORDS

chronic obstructive pulmonary disease, dyspnea, exercise physiology, sex-differences, exercise testing

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory condition with hallmark chronic symptoms that include dyspnea, cough, and sputum production. It is characterized by airway remodeling and lung parenchymal destruction, resulting from a combination of environmental exposures and individual factors that ultimately alter the trajectory of normal lung development and aging, manifesting in disease (1). COPD is currently defined by the combination of symptoms, risk factors for disease, and airflow obstruction measured on spirometry (1). Dyspnea, reduced exercise capacity, and low quality of life frequently characterize the lives of COPD patients. The estimated global prevalence of COPD is approximately 12% and the prevalence and burden of COPD is increasing (1, 2). Due to multiple factors, the prevalence of COPD in females has increased and the number of females diagnosed with COPD in the United States now outnumbers males (3). COPD has also become the leading cause of death among

female smokers (4). In females with COPD, dyspnea severity is greater and associated with increased morbidity compared to males (5–7). By comparison, data are mixed with some studies demonstrating that either males or females may be more likely to have symptoms of cough (8, 9). We review biological mechanisms underpinning sex-differences in COPD, the impacts of dyspnea in females with COPD, and structure-function-symptom interactions uncovered through use of imaging and cardiopulmonary exercise testing. Finally, we consider available evidence of clinical outcomes and treatment in females with COPD.

2 Sex in COPD

Sex is defined as the different biological and physiological characteristics of females, males, and intersex persons (10). Gender refers to the socially constructed characteristics of women and men that determine roles and relationships across an individual lifetime (10, 11). Understanding sex- and gender-differences and similarities in COPD is increasingly relevant given the growing focus on "treatable traits" and phenotyping patients (12, 13). There is mounting awareness that COPD is a heterogenous disease and that sex may play a role in the symptoms, clinical presentation, and outcomes of patients. The understanding of COPD in females and women has increased in recent decades, offering insights into observed differences in symptoms and clinical outcomes.

Biological differences between females and males include differences in airway growth leading to differential susceptibility to inhaled substances such as tobacco smoke, alterations in inflammatory responses in the lungs, and hormonal factors (14). Smaller airways relative to lung volume has been described in females (15). As a consequence, particle deposition from noxious substances, including cigarette smoke, may be greater in the proximal airways of females (16). Females experience greater small airways disease compared to males for a similar tobacco smoke exposure (5). Female smokers also experience a faster annual loss of forced expiratory volume in 1 s (FEV_1) than male smokers (17). Female smokers tend to present at a younger age and lower pack-year smoking history, compared to males with the same degree of lung function impairment (18). This suggests that females may be more susceptible to the effects of cigarettes compares to males (19). Susceptibility to air contaminants is not limited to cigarettes and often non-smoking COPD patients are female (20). Exposures and risk factors associated with non-smoking COPD vary by geographic region and include exposure to biomass fuels, passive smoking, occupational exposures, infections, and air pollution (20–22).

The greater degree of small airways disease in females and increased emphysema in males may have a basis in sex hormones (11). In humans, testosterone level is associated with higher FEV_1 after adjustment for age, height, and smoking (23). In mice models, females develop more small airways disease compared to males who develop more emphysema for the same level of cigarette smoke exposure (24). In female mice treated with tamoxifen or ovariectomy, greater emphysema developed, suggesting that estrogen may contribute to these observed sex-differences in mice (24). The Multi-Ethnic Study of Atherosclerosis Lung Study observed an association between male sex and paraseptal emphysema subtype visualized on computed tomography (CT) chest imaging (25) and an association between male sex and a diffuse emphysema subtype has also been described in a machine learning analysis of the Subpopulations and Intermediate Outcome Measures in COPD Study (26).

Despite the aforementioned insights, defining the role of sex-hormones in COPD and changes throughout the life cycle such as menopause in humans remains complex. Interestingly, early menopause has been associated with a lower risk of airflow obstruction, although other pulmonary function abnormalities such as a non-specific restrictive pattern, may develop in the peri-menopause period (27). Unlike the study of sex in respiratory health and disease, there is limited evidence to date regarding the potential role of gender in lung disease, as many studies to date have not included systematic gender assessment distinct from considering biological sex.

3 Dyspnea in females with COPD

Females with COPD experience more dyspnea compared to males, matched for relative lung function (14). Females less than 65 years of age have a higher exacerbation risk and higher odds of severe airflow obstruction in comparison to males (28). Females with COPD also experience increased depression and anxiety as well as reduced quality of life in comparison to their male counterparts (29–31). Importantly, dyspnea is strongly associated with depression in COPD (29). Anxiety and depression are associated with reduced smoking cessation (32), increased dyspnea (33), and reduced sleep quality (34, 35). Even after controlling for percent predicted lung function, age, smoking history, and extent of emphysema on chest CT, females still experience a greater dyspnea burden, more depression, and reduced quality of life relative to males (5). Female sex, depression, and anxiety are associated with increased risk of exacerbations and mortality (36–39). Recent population-based studies have demonstrated that sex-differences in dyspnea are accounted for by sex-differences in absolute values of lung function measurements [FEV_1, forced vital capacity (FVC) or diffusing capacity of the lungs for carbon monoxide (D_LCO)] (40–42). The complex interrelationships between dyspnea, mental health symptoms, and clinical outcomes are likely multidirectional. Dyspnea is central to the experience of both females and males with COPD, emphasizing the importance of understanding the underlying mechanisms of this symptom.

4 Structure-function-symptom relationships underpinning dyspnea in COPD

Quantitative chest CT scans enable sex-based comparisons of lung structure in people with COPD. Imaging studies using chest CT scans have demonstrated that females with COPD, matched for percentage predicted FEV_1, tend to have smaller airways than males as well as a lower burden of parenchymal lung tissue destruction (5). Smaller airways on CT are measured as reduced airway luminal area and diameter, reduced wall thickness, and increased airway wall area (43, 44). Female smokers without

established COPD as well as females with severe COPD have less emphysema compared to males (5, 45). Although the precise mechanisms underlying anatomical differences are an area of ongoing research, examining the functional consequences of these structural differences, relative to health, under the stress of exercise with cardiopulmonary exercise testing (CPET), enables integration of structural differences with differences in symptoms, specifically exertional dyspnea.

The current understanding of mechanisms of dyspnea in females with COPD is partially informed by data examining sex-differences in dyspnea in healthy individuals. The Burden of Obstructive Lung Diseases international population-based study describes a greater prevalence of dyspnea in females compared to males, including in a subpopulation of participants without self-reported diseases associated with dyspnea or abnormal spirometry (46). Males have larger conducting airways and lung volumes in comparison to females, even when accounting for differences in height (47–49). Healthy females also have reduced respiratory muscle strength compared to height-matched males (50). These differences may predispose females to developing greater ventilatory abnormalities and increases in both neural respiratory drive, the signal to breathe from the brain to the respiratory muscles, and dyspnea intensity during exercise relative to males (51, 52). There are also sex differences in qualitative descriptors of dyspnea, with healthy females being more likely to select unpleasant dyspnea descriptors related to inspiratory difficulty, shallow breathing, and unsatisfied inspiration than males (52). Sex-differences in dyspnea quality in health are likely a manifestation of relatively greater respiratory mechanical constraints and neural respiratory drive at a given absolute ventilation in females (51, 52).

Dyspnea in COPD is closely related to the physiological consequences of the disease and can be systematically studied using CPET. Airway remodeling and lung parenchymal destruction in COPD leads to airflow limitation, increased lung compliance, and impaired gas exchange. During CPET, the consequences of these abnormalities manifest as dynamic hyperinflation, respiratory muscle weakness, ventilatory inefficiency, and hypoxemia (53–55). Abnormal responses to exercise provide a powerful stimulus for increased neural respiratory drive to the diaphragm in an effort to increase ventilation commensurate with the metabolic demands of exercise (53–55). Neural respiratory drive can be estimated using diaphragm electromyography during CPET and is highly correlated with dyspnea in COPD (53–55).

In a detailed physiology study in females and males with mild COPD, matched for % predicted FEV_1, females experienced significantly greater dyspnea intensity ratings during exercise (**Figure 1A**), constraints on tidal volume expansion (**Figure 1C**), and a more rapid breathing pattern (**Figure 1D**) at a given absolute work rate in comparison to males (6). However, when dyspnea was assessed relative to maximum ventilatory capacity (**Figure 1B**), sex differences in dyspnea between males and females with COPD disappeared, suggesting that increased intensity of exertional dyspnea in females is largely driven by females using a greater fraction of their ventilatory capacity to achieve the same absolute exercise intensity and ventilation compared with males (6).

Differences in absolute lung function between males and females in relation to dyspnea has also been examined in several recent population-based studies. The European Community Respiratory Health Survey, a general population-based study, found that dyspnea was twice as common in females and was explained by differences in absolute FEV_1 and FVC values, demonstrating that lower absolute lung function accounts for dyspnea in females (41). In the population-based Swedish CArdioPulmonarybioImage Study, similar results were found with respect to absolute diffusing capacity and static lung volumes as well as in obese females (42, 56). Similar findings have been described in individuals with COPD in the COPDGene study, demonstrating that sex-based differences in absolute FEV_1 accounted for the difference in dyspnea between females and males (40).

Taken together, detailed physiological studies and larger scale population-based studies demonstrate that differences in exertional dyspnea intensity between females and males are largely explained by differences in absolute measures of lung function and the relatively higher ventilation needed in females to perform a given absolute task compared to males. However, the underlying physiologic explanations for differences in dyspnea quality and unpleasantness across the spectrum of COPD disease severity and any potential association with observed higher anxiety and depression in females with COPD, remains unknown and an important area for future research.

5 COPD therapies

Major classes of inhaled medications for COPD include long-acting muscarinic antagonists (LAMA), long-acting beta agonists (LABA), combination LABA-LAMA, and combination inhaled corticosteroid (ICS)-LABA. A recent systematic review of randomized controlled trials and observational studies found that there is limited data directly comparing treatment effectiveness between sexes in COPD; however, there is evidence from retrospective and sub-group analyses of large randomized controlled trials (57). When clinical trials report sex-differences, they are frequently not found; however, some trials may not be powered to detect differences in treatment response between females and males. Tiotropium demonstrates a similar improvement in exercise capacity, trough FEV_1, reduced exacerbations, and improved quality of life in males and females (58, 59). Females experience improvements in dyspnea with LABA-LAMA similar to males in comparison to either LAMA or LABA alone (60, 61). Comparing LABA-LAMA to ICS-LABA, improvement in FEV_1 are observed in both males and females to varying degrees (60–62). Only males had a significant reduction in exacerbations (62), but females had better responses with regards to dyspnea and quality of life with LABA-LAMA compared to ICS-LABA (61). Taken together, there is no evidence to support treating females with COPD differently from their male peers in terms of inhaled therapies.

There is similarly no evidence to support differential non-pharmacologic management of individuals with COPD based on sex. Despite greater benefits of smoking cessation with respect to lung function in females compared to males, females find it harder to quit and are more likely to relapse (63). However, upon smoking cessation, the gain in FEV_1 in female ex-smokers is greater than males (63). Long term oxygen therapy in females with COPD affords benefits with respect to survival similar to males (64, 65).

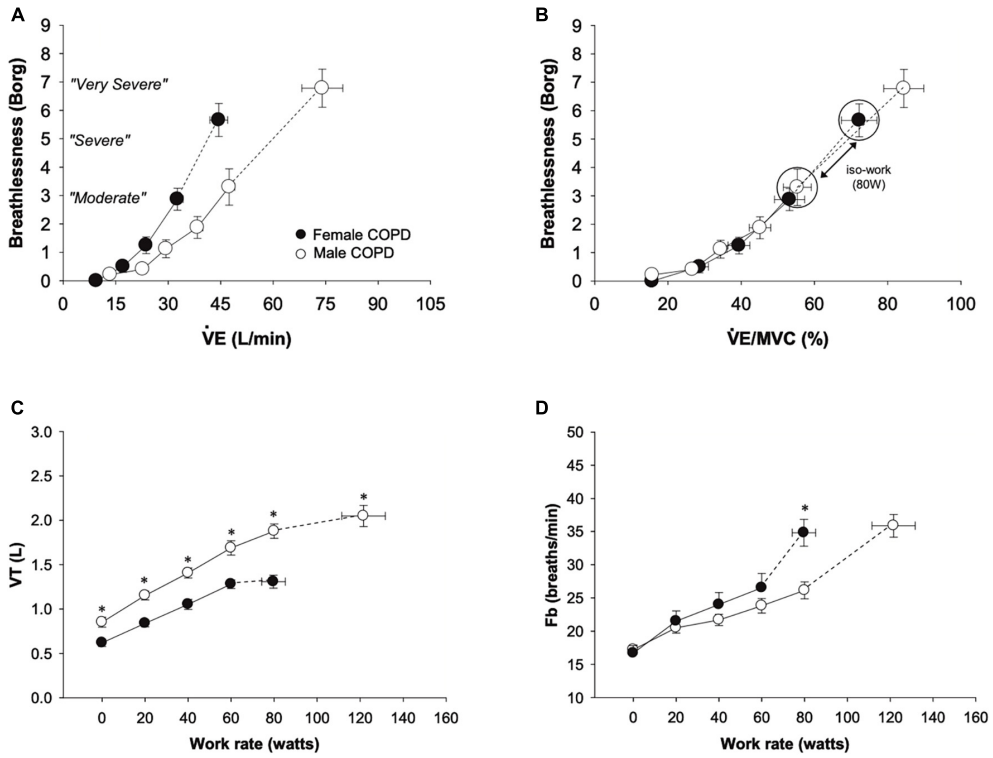

FIGURE 1
Comparison from rest to peak exercise between males and females with mild COPD in **(A)** dyspnea, **(B)** dyspnea relative to ventilation as a percentage of estimated maximum ventilatory capacity, **(C)** tidal volume, and **(D)** breathing frequency. Females with COPD experienced greater dyspnea for a given absolute ventilation during exercise and had reduced tidal volume expansion and consequent increased breathing frequency compared to males. At a work rate of 80 W (the highest absolute work rate comparison between males and females with COPD), the V_E/MVC ratio and dyspnea were greater in females. Values are mean ± SE. *$p < 0.05$. Fb, breathing frequency; MVC, maximum ventilatory capacity; V_E, minute ventilation; V_T, tidal volume. Reprinted from Guenette et al. (6) with permission from Elsevier.

There are no established sex-differences in exercise capacity and quality of life improvement following pulmonary rehabilitation in females compared to males, although benefits of pulmonary rehabilitation may not be sustained in females (66).

6 COPD outcomes in females

Previously described significant disparities in the accurate diagnosis and clinical outcomes of females with COPD may be changing (67–69). Ongoing prospective re-evaluation of potential sex-differences in females and women with COPD is valuable to understanding how patterns of care may change over time. Females with COPD also present with different comorbidities compared to their male counterparts. Females more often have heart failure, osteoporosis, and diabetes (70). Interestingly, different combinations of comorbidities in COPD are associated with mortality between sexes (71). Healthcare related costs for those living with COPD account for the majority of expenditures in respiratory disease in Europe and are expected to increase in the United States (1). Females incur greater healthcare costs than males and lose more quality-adjusted life years (72). Females with COPD have a higher BODE index (body mass index, airflow obstruction, dyspnea, and exercise capacity) suggesting a worse prognosis (73). Females have also been at greater risk of hospitalization and death (74). Female sex has additionally been identified as a risk factor for acute exacerbations of COPD in the large COPDGene cohort study (39).

7 Conclusion

Sex and gender have the potential to influence biological mechanisms, symptoms, and clinical outcomes. Several mechanisms may contribute to sex-differences in COPD including differences in airway and lung structure, differential consequent susceptibility to inhaled pollutants, and sex-hormones. Females with COPD experience significantly greater dyspnea compared to males. In mild COPD, females have greater respiratory mechanical constraints at a lower work rate compared to males, which is associated with greater neural respiratory drive and dyspnea (6). However, differences in exertional dyspnea intensity have been demonstrated to be related to differences in absolute measures of lung function and consequent differences in ventilatory capacity between sexes.

Insights into sex-differences and similarities in lung structure, exercise physiology, and responses to mainstay COPD therapies has advanced over the past decade. In contrast, our understanding of gender-differences in COPD remains limited, as studies either frequently neglect to systematically assess gender, or conflate

gender related factors with sex. Considering the multidimensional nature of dyspnea, our collective understanding of differences in dyspnea quality between sexes and genders in COPD remains an area of future research.

Author contributions

KM: Conceptualization, Writing – original draft, Writing – review & editing. RM: Writing – review & editing. OF: Writing – review & editing. AH: Writing – review & editing. JG: Conceptualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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