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ORIGINAL RESEARCH

Association of Patient-Reported Outcome Patterns and Major Clinical Factors with Frailty in Stable COPD

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Purpose: Chronic obstructive pulmonary disease (COPD) exhibits heterogeneous symptom profiles across individuals. This study aimed to identify subgroups of patients with stable COPD according to physiological, psychological, and environmental symptoms; assess differences in their characteristics; and examine the association of symptom patterns with frailty.

Patients and Methods: We analyzed data from the second wave of a cohort study involving patients with COPD reassessed 6 months after hospitalization for acute exacerbations. Frailty and patient-reported outcomes were measured using the FRAIL and Modified COPD–Patient-Reported Outcome (mCOPD–PRO) scales. Latent profile analysis identified subgroups based on mCOPD–PRO symptom patterns. Differences across symptom severity subgroups were assessed using post-hoc trend analyses and chi-square tests for trends. Multinomial logistic regression quantified the magnitude of differences between subgroups. The relationship between subgroups, clinical factors, and frailty was examined through linear regression.

Results: Among 308 patients with stable COPD, three subgroups were identified: "low-symptom" (27.9%), "moderate-symptom" (51.3%), and "severe-symptom" (20.8%). Body mass index, Global Initiative for Chronic Obstructive Lung Disease stage (GOLD), COPD Assessment Test (CAT) score, modified Medical Research Council (mMRC) score, and physical activity exhibited significant linear trends across subgroups of increasing symptom severity. Frailty scores differed significantly: 0.50 ± 0.78 in the low-symptom group, 1.34 ± 0.96 in the moderate-symptom group, and 2.72 ± 0.95 in the severe-symptom group. Multivariate analysis identified severe-symptom group (β coefficient [β]=0.62, 95% confidence interval [CI]: 0.21–1.03), rural residence (β=0.21, 95% CI: 0.04–0.39), GOLD (β=0.23, 95% CI: 0.07–0.39), mMRC (β=0.17, 95% CI: 0.03–0.31), and CAT score (β=0.04, 95% CI: 0.02–0.06) associated with frailty.

Conclusion: Patients with stable COPD can be categorized based on patient-reported outcomes, with differences in demographic and disease characteristics across subgroups. Patients with severe COPD symptoms revealed higher levels of frailty compared to those with low symptoms.

Plain Language Summary: Patients with chronic obstructive pulmonary disease (COPD) often experience a variety of symptoms, including physical, psychological, and environmental challenges, which may affect their health status and increase frailty risk. Patient-reported outcomes (PROs) are valuable tools in clinical practice that allow patients to report their symptoms and thus reflect on their health status. However, the relationship between distinct symptom patterns, sociodemographic and disease-related factors, and frailty among patients with stable COPD remains unclear. This study conducted in a large tertiary care institution in Sichuan Province of China, analyzed data from 308 patients with stable COPD who were evaluated six months after discharged from the hospital for acute exacerbations. Frailty was assessed by the FRAIL scale, and symptom patterns were measured through the Modified COPD Patient-

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Reported Outcome (mCOPD-PRO). Latent profile analysis identified three subgroups: "low-symptom", "moderate-symptom", and "severe-symptom". The results of the study showed that the severe-symptom group had higher levels of frailty compared to the low-symptom group. Furthermore, patients in the severe-symptom group tend to be physically inactive and have poorer health characteristics, such as higher disease severity and symptom burden. These results emphasize the need for early screening and targeted interventions for patients with severe symptoms to mitigate frailty and its associated risks. By identifying symptom patterns and their relationship with frailty, this study highlights the importance of PROs in understanding patient experiences and guiding clinical strategies to improve care for patients with COPD.

Keywords: frailty, COPD, acute exacerbation, patient-report outcome, aging

Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent and burdensome respiratory disease, and has been the third leading cause of global disease burden since 2010.[1] Patients with COPD often experience various physical and psychological symptoms, including dyspnea, fatigue, appetite loss, pain, depression, and anxiety.[2,3] Notably, most patients with COPD experience multiple concurrent symptoms, which known as symptom clusters.[4,5] Furthermore, there is growing evidence that frailty is prevalent even in patients with stable COPD.[6] As a clinical syndrome associated with a decline in multi-system physiological reserve, frailty has been identified as an important risk factor for COPD exacerbation, hospitalization, extended hospital stays, readmission and mortality.[6–9] COPD is not only one of major contributor to global mortality and but also contributes to accelerated disability and impaired quality of life.[10,11] Previous studies reported that management strategies that target multiple symptoms rather than single symptoms are more effective for these patients.[4,5] Additionally, COPD shows heterogeneity in terms of disease progression, severity, and symptom presentation, which poses challenges for clinical management.[12,13]

Several studies have investigated the heterogeneity of clinical phenotypes or comorbidities among patients with COPD to promote personalized treatment and prognostication.[14–16] However, few studies have explored symptom clusters in this population.[5,17,18] Lim et al[17] identified clusters of common symptoms in Korean patients with COPD, including dyspnea, depression, anxiety, fatigue, sleep disturbances, dry mouth, and decreased physical function. Park et al[5,18] focused on clusters including dyspnea, anxiety, depression, and fatigue. Although these studies have provided valuable insights, the preselection of symptoms and use of multiple scales may lead to an incomplete or biased understanding of the symptom clusters experienced by patients with COPD in their daily lives.[4,19] Additionally, assessment of different symptoms often requires the use of multiple scales, which may increase the burden on patients.[20]

Patient-reported outcomes (PROs) comprise multiple measures of symptoms, including symptom severity, activity limitation, and quality of life, and are critical to the management of patients with COPD.[21] PROs allow patients to report the symptoms they experience without being limited to pre-defined measurements. Meanwhile, FRAIL scale[22] is a self-assessment tool developed by the International Task Force on Nutrition, Health, and Aging, which integrates functional, cumulative, and biological models of frailty and assesses physical frailty while also including disease factors. It is a widely used measure with five components, namely, fatigue, resistance, ambulation, illness, and weight loss.

A better understanding of PRO patterns in patients with COPD as well as their relationships with sociodemographic and disease-related characteristics and frailty could provide a basis for developing targeted interventions. Therefore, this study aimed to: (1) identify distinct patterns of symptom experience based on PROs among patients with stable COPD, (2) examine differences in sociodemographic and disease-related characteristics among these subgroups, and (3) investigate the relationship of PRO patterns with frailty.

Methods

Design and Participants

This study was the second wave of an ongoing cohort study of patients with COPD. Baseline data (wave 1) were collected between August 2022 and September 2023 from 500 patients with AECOPD admitted to the Respiratory and Critical Care Medicine Department of a large tertiary care institution in Sichuan Province of China.[23] Follow-up

assessments were conducted via telephone interview 6 months after hospital discharge. Of the 500 baseline participants, 324 (64.8%) completed the follow-up assessment. After excluding 16 patients who experienced acute exacerbations within 4 weeks and/or medication adjustments within 3 months prior to follow-up, 308 patients with stable COPD were included in the final analysis. The diagnosis and disease stage of COPD was determined based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[24]

PROs Measurement

PROs were assessed using the Modified Patient-reported Outcome Scale (mCOPD–PRO)[25] and divided into three domains: physiological, psychological, and environmental. The total and domain scores were averaged and obtained from the score/number of entries, with a resulting score ranging from 0 to 4. Higher scores indicated a more severe health condition. The detailed measurement of PROs was in Supplementary Figure 1.

Frailty Measurement

The frailty status was assessed using the FRAIL scale,[22] a clinical frailty screening tool that applies a simple self-reported questionnaire format comprising five components: fatigue, resistance, ambulation, illness, and loss of weight. The total scale score ranged from 0 to 5, with higher scores indicating a frailer status.

Descriptive Characteristics and Covariates

The patient-reported sociodemographic characteristics included age, sex (male or female), body mass index (BMI), living status (alone or else), marital status (married or else), education level (middle school or below, high school or above), residence (rural, urban), economic status (poor [<1000 Chinese Yuan/month] or better-off [≥1000 Chinese Yuan/month]), smoking status (never, former, or current), drinking status (never, daily, sometimes, or former), and physical activity (active [daily exercise or some exercise >3 times per week] or inactive [no activity or some exercise ≤3 times per week]).

Disease information assessed by the investigators based on patient self-reported information included duration of disease (<5 or ≥5 years), Charlson Comorbidity Index (CCI),[26] COPD pulmonary function classification (GOLD I–IV), COPD Assessment Test (CAT) score,[27] and modified Medical Research Council (mMRC) score.[28]

Statistical Analysis

First, the patterns of PROs were identified through latent profile analysis (LPA). The domains of mCOPD-PRO were used as observational indicators. We compared the robustness metrics of the models, including the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Bootstrapped Likelihood Ratio Test (BLRT), and the Vuong–LoMendell–Rubin likelihood ratio test (VLMR)[29] among the synthesized models to determine the number of latent classes, including the AIC, the BIC lower and different from lesser classes of model comparisons (BLRT, VLMR < 0.05), a minimum sample size of 5% or 50 cases,[30] and the relatively high entropy value of the models.[31]

Second, LPA analyses resulted in best-fit models for three subgroups with increasing symptom severity from low to high. We compared sociodemographic and disease-related characteristics between subgroups using descriptive statistics with one-way analysis of variance (ANOVA), Kruskal–Wallis tests, χ^2 and Fisher's exact tests. For multiple comparisons of PROs across subgroups, ANOVA followed by post hoc Tukey's multiple comparisons test was performed. For sociodemographic and disease-related variables which showed significant differences across subgroups, we used multinomial logistic regression to estimate odds ratios and 95% confidence intervals of belonging to moderate- and severe-symptom groups, while adjusted for age and sex. Subsequently, we used post-hoc trend analyses or chi-square test for trends to evaluate whether higher levels of these characteristics were associated with increasing symptom burden.

Finally, we computed univariate and multivariate linear regression models to explore the association between PRO subgroups, clinical factors, and frailty. Mplus (version 7.4) was used for the LPA, SPSS (version 26.0) was used for other statistical analyses, and GraphPad Prism 9.0.0 for graphing. Statistical significance was set at $P < 0.05$ (two-sided tests).

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles in the Declaration of Helsinki and approved by the Medical Ethics Committee of the Affiliated Hospital of North Sichuan Medical College (approval nos. 2022ER444-1 and 2023ER324-1). Informed consent was obtained from all participants for participation in the study.

Results

This study included 308 participants, with a mean age of 72.4 ± 8.7 years and 24.0% females.

Model Fitting

Table 1 shows the model fit indices for LPA based on lower AIC (1855.07) and BIC (1907.29), significant differences from models with one less category (BLRT, VLMR < 0.05), higher entropy values (0.85), and a minimum sample size >5% or 50 cases. The minimum sample size for the 4-profile model was less than 50 cases. Therefore, we selected a model with three profiles.

Patterns of Patient-Reported Outcomes

Three distinct PRO patterns were identified: low-symptom (27.9%), moderate-symptom (51.3%), and severe-symptom (20.8%) groups. Figure 1 and Table 2 show the scores for each domain of PROs across these subgroups. The low-symptom group had the lowest mean scores in physiological, psychological, and environmental domains. The moderate-symptom group scored close to the mean of all domains, whereas the severe-symptom group had the highest scores in all domains, which suggests that their symptom burden is the heaviest. As shown in Figure 1, the differences in PRO scores of all domains were statistically significant (all $P < 0.0001$).

Comparisons of Sociodemographic and Disease-Related Characteristics According to PRO Patterns

Table 2 shows the sociodemographic and disease-related characteristics of participants in each group. Significant differences were observed in BMI, GOLD stage, mMRC, CAT scores, and physical activity among the groups. Detailed comparisons of these variables across PRO patterns are shown in Supplementary Figure 2. Moreover, Table 3 presents the magnitude of the trend in terms of the difference in rank comparison between the moderate- and severe-symptom groups, with a reference to the low-symptom group. Compared to the low-symptom group, patients in the moderate- and severe-symptom groups had higher odds of advanced GOLD stages (OR = 3.47 [95% CI: 2.23–5.38] and 9.46 [5.49–16.29], respectively; $P < 0.001$), higher CAT scores (OR = 1.37 [1.26–1.48] and 1.84 [1.64–2.07]; $P < 0.001$), and higher mMRC scores (OR = 3.00 [2.12–4.25] and 12.63 [7.31–21.83]; $P < 0.001$). Conversely, BMI showed a protective association, with lower odds of belonging to the moderate- and severe-symptom groups (OR = 0.87 [0.81–0.94] and 0.88 [0.80–0.96]; $P = 0.002$). Physically active patients were less likely to be in the moderate- or severe-symptom groups (OR = 0.06 [0.02–0.27] and 0.01 [0.00–0.04], respectively; $P < 0.001$).

Table 1 Model Comparison of Latent Profile Analysis Fit in PRO Patterns

No. Profiles	AIC	BIC	a-BIC	VLMR-LRT	BLRT	Entropy	Sample Proportion (%)
1	2375.23	2397.61	2378.58	-	-	1.00	100
2	2040.31	2077.61	2045.89	<0.001	<0.001	0.84	29/71
3	1855.07	1907.29	1862.89	0.012	<0.001	0.85	21/28/51
4	1814.45	1881.60	1824.51	0.040	<0.001	0.85	7/20/25/48
5	1793.30	1875.36	1805.59	0.450	<0.001	0.87	10/11/17/26/36

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; BLRT, Bootstrapped Likelihood Ratio Test; LRT, Likelihood Ratio Test; VLMR, Vuong–LoMendell–Rubin likelihood ratio.

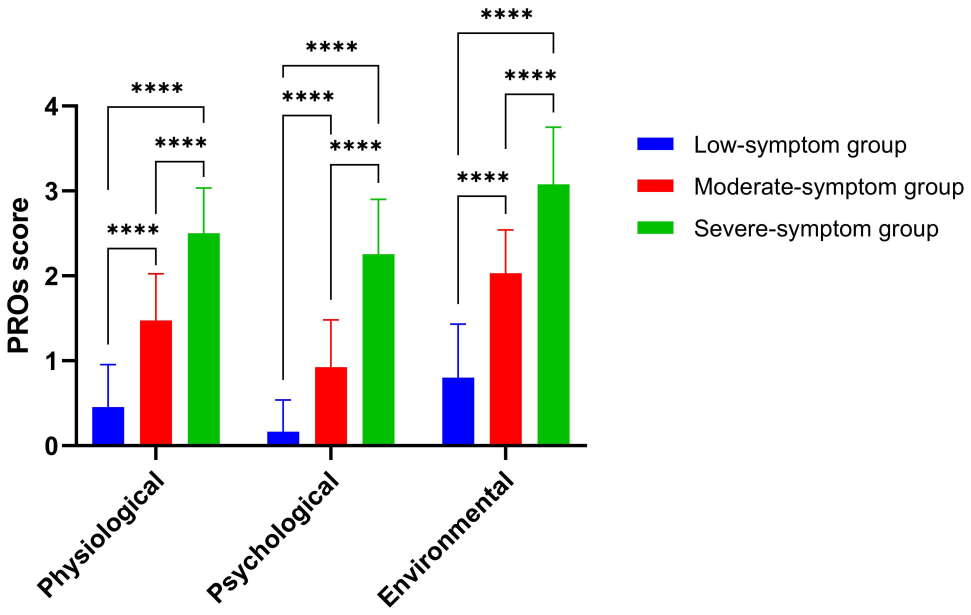

Figure 1 Scores for each domain of PROs in the three profiles.
Note: ****$P < 0.0001$.
Abbreviation: PRO, patient-reported outcome.

Association Between PRO Patterns, Clinical Factors, and Frailty

Participants' frailty scores differed significantly across subgroups: 0.50 ± 0.78 in the low-symptom group, 1.34 ± 0.96 in the moderate-symptom group, and 2.72 ± 0.95 in the severe-symptom group. Figure 2 shows the results of univariate and multivariate linear regression models examining the association between PRO patterns, clinical factors, and frailty. Univariate analysis identified several factors significantly associated with frailty level: PRO patterns (moderate-symptom and severe-symptom groups), age, BMI, residence, GOLD, mMRC, CAT score, and physical activity. The multivariate linear regression model revealed that the severe-symptom group (β coefficient [β] 0.62, 95% CI: 0.21–1.03, $P = 0.003$),

Table 2 Baseline Characteristics of the Study Population According to PRO Patterns

Variables	Total (n = 308)	Low-Symptom (n = 86)	Moderate- Symptom (n = 158)	Severe-Symptom (n = 64)	F/χ^2	P
PRO score, Mean ± SD	1.35 ± 0.78	0.45 ± 0.30	1.38 ± 0.33	2.46 ± 0.48	579.24	<0.001
Physiological domain, Mean ± SD	1.42 ± 0.82	0.48 ± 0.37	1.48 ± 0.44	2.53 ± 0.39	464.23	<0.001
Psychological domain, Mean ± SD	0.98 ± 0.86	0.19 ± 0.32	0.91 ± 0.51	2.22 ± 0.61	314.78	<0.001
Environmental domain, Mean ± SD	1.90 ± 0.95	0.84 ± 0.61	1.98 ± 0.47	3.08 ± 0.63	311.98	<0.001
Age, Mean ± SD	72.44 ± 8.73	70.72 ± 9.07	73.35 ± 9.00	72.48 ± 7.27	2.56	0.079
Sex, n (%)					1.66	0.435
Male	234 (76.0)	61 (70.9)	123 (77.9)	50 (78.1)		
Female	74 (24.0)	25 (29.1)	35 (22.2)	14 (21.9)		
BMI, Mean ± SD	21.23 ± 3.75	22.62 ± 3.98	20.67 ± 3.51	20.76 ± 3.60	8.54	<0.001
Disease duration, n(%)					1.83	0.401
<5 years	84 (27.3)	28 (32.6)	41 (26.0)	15 (23.4)		
≥5 years	224 (72.7)	58 (67.4)	117 (74.1)	49 (76.6)		
GOLD, M (Q_1, Q_3)	2.00 (1.00, 3.00)	1.00 (1.00, 2.00)	2.00 (2.00, 3.00)	3.00 (2.00, 4.00)	86.92#	<0.001
CAT score, M (Q_1, Q_3)	16.00 (9.00, 23.00)	6.00 (2.00, 9.00)	16.00 (12.00, 20.00)	26.00 (24.00, 29.00)	182.97#	<0.001
mMRC, M (Q_1, Q_3)	2.00 (1.00, 3.00)	1.00 (1.00, 2.00)	2.00 (2.00, 3.00)	3.50 (3.00, 4.00)	120.11#	<0.001
CCI, M (Q_1, Q_3)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.45#	0.800

(*Continued*)

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Table 2 (Continued).

Variables	Total (n = 308)	Low-Symptom (n = 86)	Moderate- Symptom (n = 158)	Severe-Symptom (n = 64)	F/χ^2	*P*
Living status, n(%)					5.26	0.072
Else	288 (93.8)	76 (89.4)	149 (94.3)	63 (98.4)		
Alone	19 (6.2)	9 (10.6)	9 (5.7)	1 (1.6)		
Marital status, n(%)					4.67	0.097
Married	270 (87.7)	75 (87.2)	134 (84.8)	61 (95.3)		
Else	38 (12.3)	11 (12.8)	24 (15.2)	3 (4.7)		
Education level, n(%)					0.48	0.788
Middle school or below	278 (90.3)	78 (90.7)	141 (89.2)	59 (92.2)		
High school or above	30 (9.7)	8 (9.3)	17 (10.8)	5 (7.8)		
Residence, n(%)					4.83	0.090
Rural	172 (55.8)	41 (47.7)	89 (56.3)	42 (65.6)		
Urban	136 (44.2)	45 (52.3)	69 (43.7)	22 (34.4)		
Economic status, n(%)					1.41	0.495
Better-off	222 (72.1)	66 (76.7)	110 (69.6)	46 (71.9)		
Poor	86 (27.9)	20 (23.3)	48 (30.4)	18 (28.1)		
Smoking status, n(%)					2.10	0.717
Never	81 (26.3)	25 (29.1)	43 (27.2)	13 (20.3)		
Former	194 (63.0)	51 (59.3)	98 (62.0)	45 (70.3)		
Current	33 (10.7)	10 (11.6)	17 (10.8)	6 (9.4)		
Drinking status, n(%)					-	0.556
Never	100 (32.5)	29 (33.7)	54 (34.2)	17 (26.6)		
Former	179 (58.1)	47 (54.7)	88 (55.7)	44 (68.8)		
Sometimes	25 (8.1)	8 (9.3)	14 (8.9)	3 (4.7)		
Daily	4 (1.3)	2 (2.3)	2 (1.3)	0 (0.0)		
Physical activity, n(%)					87.45	<0.001
Active	213 (69.2)	84 (97.7)	112 (70.9)	17 (26.6)		
Inactive	95 (30.8)	2 (2.3)	46 (29.1)	47 (73.4)		
Frail score, Mean ± SD	1.39 ± 1.19	0.50 ± 0.78	1.34 ± 0.96	2.72 ± 0.95	108.97	<0.001

Notes: F: ANOVA, χ^2: Chi-square test, #Kruskal–wallis test, -: Fisher's exact test.
Abbreviations: BMI, body mass index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; PRO, patient-reported outcome; M, Median; Q_1, 1st Quartile; Q_3, 3rd Quartile; SD, standard deviation.

Table 3 Trend Analysis and Group Differences in Sociodemographic and Disease-Related Characteristics

Characteristics	OR (95% CI): Class 2 vs Class 1	OR (95% CI): Class 3 vs Class 1	*P* for Trend
BMI (Continuous)	0.87 (0.81, 0.94)	0.88 (0.80, 0.96)	0.002
GOLD stage (Continuous)	3.47 (2.23, 5.38)	9.46 (5.49, 16.29)	<0.001
CAT score (Continuous)	1.37 (1.26, 1.48)	1.84 (1.64, 2.07)	<0.001
mMRC (Continuous)	3.00 (2.12, 4.25)	12.63 (7.31, 21.83)	<0.001
Physical activity=Active (ref. Inactive)	0.06 (0.02, 0.27)	0.01 (0.00, 0.04)	<0.001

Note: The multinomial logistic regression model was adjusted for age and sex.
Abbreviations: BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; GOLD, Global Initiative for Chronic Obstructive Disease; mMRC, modified Medical Research Council; OR, odds ratio; CI, confidence interval.

rural residence (β 0.21, 95% CI: 0.04–0.39, $P = 0.018$), GOLD (β 0.23, 95% CI: 0.07–0.39, $P = 0.006$), mMRC (β 0.17, 95% CI: 0.03–0.31, $P = 0.018$), and CAT score (β 0.04, 95% CI: 0.02–0.06, $P < 0.001$) were associated with frailty, accounting for 57.9% of the variance.

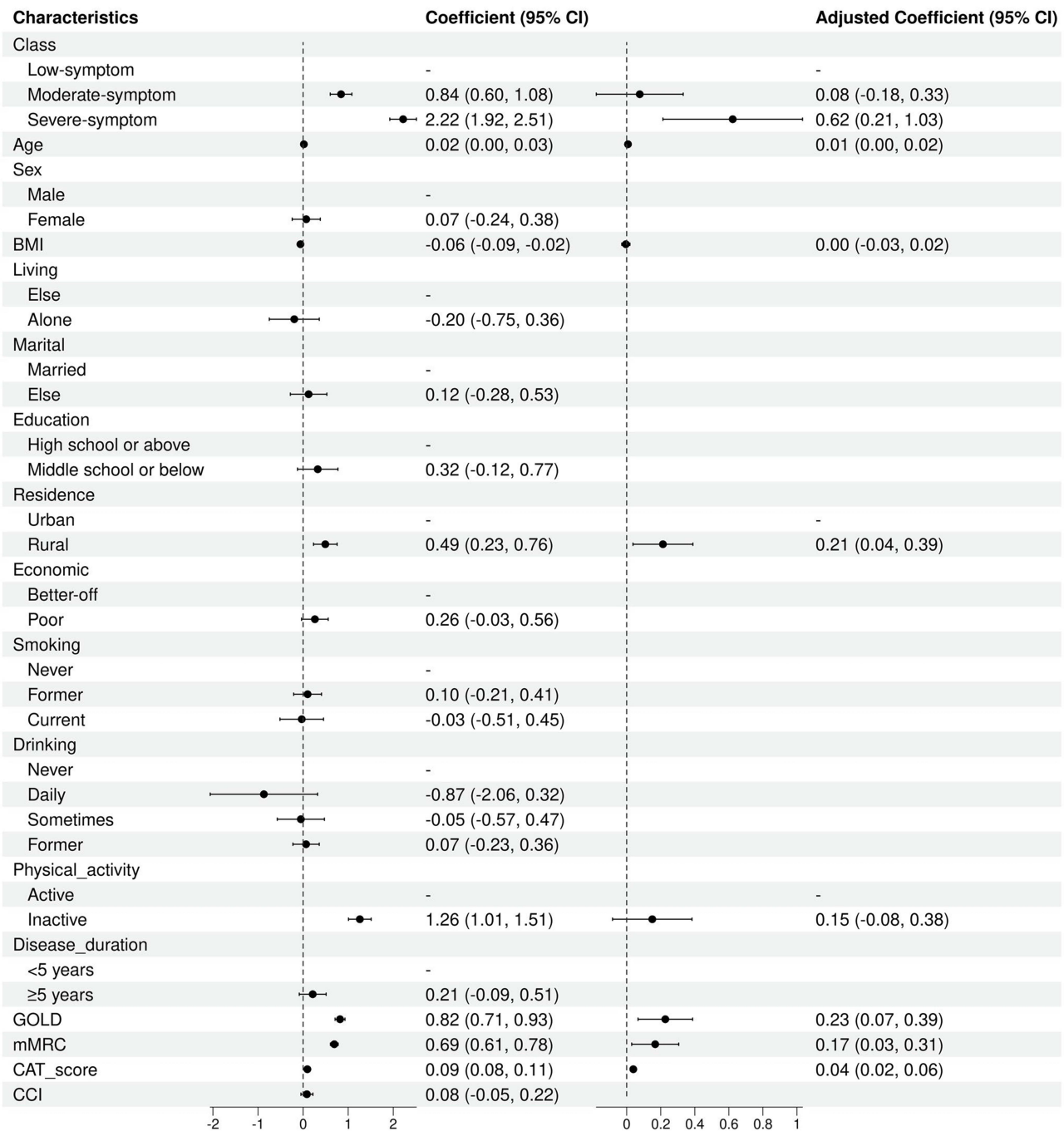

Figure 2 Association between PRO patterns, clinical factors, and frailty.
Note: Missing variables: CCI (n = 3) and living status (n = 1).
Abbreviations: PRO, patient-reported outcome; BMI, body mass index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council.

Discussion

This study identified three distinct PROs subgroups among patients with stable COPD who were heterogeneous in physiological, psychological and environmental domains, respectively. Our findings suggest that increasing symptom severity from the low-symptom to moderate-symptom to severe-symptom subgroups was associated with unfavorable sociodemographic and disease-related characteristics. In detail, the severe-symptom group had lower BMI, reduced

physical activity, poorer lung function, more severe dyspnea, and higher symptom burden. Additionally, the severe-symptom group, rural residence, GOLD, mMRC, and CAT score were associated with higher levels of frailty.

Although previous studies have explored the heterogeneity of COPD and attempted to categorize patients into different subgroups or clinical phenotypes, few studies have examined patient-reported symptom patterns. Existing studies have mainly focused on clustering based on a combination of clinical characteristics, including age, sex, BMI, lung function, physical activity, and quality of life measures.[14,15] In contrast, the current study focuses on patient-reported symptoms without the need for specialized physical measurements and laboratory tests. This approach not only simplifies the screening process for identifying vulnerable populations but also facilitates the practicality and feasibility of post-discharge evaluation of patients in clinical practice.

Among the limited number of studies on patient-reported symptoms, Lim et al[17] clustered participants according to physical and psychological symptoms including dyspnea, fatigue, depression, anxiety, sleep disorders, dry mouth, and physical functioning status, and identified them into three subgroups: respiratory functioning, emotional, and fatigue-sleep symptom. The results examined that these symptom patterns were associated with clinical features and negatively impacted quality of life. Similarly, Park and Larson[5] categorized patients into three patterns based on the symptoms of dyspnea, anxiety, depression, and fatigue. Subsequently, they assessed the differences between these patterns in terms of healthcare utilization and mortality, and found that patients with more severe symptoms used medical services more frequently and were more likely to die during the 5-year follow-up period than those with less severe symptoms.

The current study used a validated, multidimensional patient-reported outcome measure (mCOPD–PRO) rather than separate scales for individual symptoms, which reduced the assessment burden on patients. Furthermore, the mCOPD–PRO assesses not only physical and psychological symptoms but also includes the impact of environmental factors, thus provide a more accurate and comprehensive assessment of patients' health status. The relationship between symptom severity and disease burden is further supported by our findings that patients in the symptom-severe group had poorer disease characteristics, including advanced GOLD stage, more severe dyspnea (mMRC score), and higher symptom burden (CAT score), which further demonstrates the relationship between symptom severity and disease burden.

The mechanisms underlying the association between severe COPD symptoms and frailty are complex. According to the results of previous studies, the chronic inflammatory state associated with COPD causes muscle wasting and catabolism, leading to sarcopenia, which is a key component of frailty.[32,33] Moreover, increased respiratory workload and respiratory dysfunction in patients with COPD can further exacerbate muscle weakness and impair physical performance.[34,35] In addition, severe respiratory symptoms such as dyspnea and fatigue can limit physical activity and promote a sedentary lifestyle, that resulted in decreased physical performance and further muscle atrophy.[17,20] Meanwhile, the commonly psychological symptoms of anxiety and depression can also negatively impact patient motivation as well as adherence to treatment and self-management, which contribute to functional decline and frailty.[36,37]

Environmental factors are also important in exacerbating COPD symptoms and may contribute to frailty. Exposure to confined or poorly ventilated environments can increase the concentration of indoor air pollutants, which can further exacerbate patients' respiratory symptoms and systemic inflammation.[38] As a result of worsening respiratory symptoms or limited in their daily living abilities, it could reduce patients' ability to interact with friends, colleagues, and neighbors, and leads to reduced physical activity and social isolation.[35,39] Furthermore, changes in weather conditions can trigger respiratory symptoms and exacerbations in patients with COPD, such as cloudiness, haze, humidity, or sudden temperature fluctuations.[40]

The observed association between patient-reported patterns and frailty has important implications for clinical practice. First, it emphasizes the need for comprehensive symptom assessment using validated PROs, which can provide valuable insights into the multidimensional nature of symptom experiences in COPD.[24] By identifying patients with severe symptom patterns, clinicians can prioritize targeted interventions to reduce symptom burden and potentially mitigate the development or worsening of frailty.[41] Second, the findings underscore the importance of routine screening for frailty among patients with COPD, especially those with severe symptoms. Early identification of people at high risk of frailty and implementation of interventions is particularly beneficial for this vulnerable population.[42]

The strengths of this study are the validation of the existence of heterogeneity of symptoms in patients with stable COPD and categorize them according to their PROs, thus identifying different symptom patterns in the population and

revealing the possible benefits of risk-stratified interventions rather than uniform disease management. In addition, this study explored the relationship between these symptom patterns, clinical factors, and frailty to inform the identification of vulnerable populations and the development of interventions. Furthermore, this study used validated, multidimensional patient-reported measures rather than categorizing patients based on a single or few symptoms, and the association with level of frailty further reveals the validity of using patient-reported outcome measures in clinical practice.

However, this study has several limitations. Due to the complex and dynamic nature of COPD, participants' PRO patterns may change over time. Therefore, further longitudinal or trajectory studies are necessary to assess these dynamic changes and their relationship with frailty. In addition, the study was conducted at a single center with relatively small sample sizes for each PRO pattern subgroup, which may limit the generalizability of the findings. Future multi-center studies with larger sample sizes are needed to validate these findings and enhance the generalizability of the results.

Conclusion

This study identified three distinct subgroups of patients with stable COPD based on patient-reported outcomes of physiological, psychological, and environmental domains: low-symptom (27.9%), moderate-symptom (51.3%), and severe-symptom (20.8%). Furthermore, BMI, GOLD, mMRC, CAT score, and physical activity were associated with symptom severity. Notably, the severe-symptom pattern, rural residence, GOLD, mMRC, and CAT score were associated with higher frailty levels. These findings highlight the importance of symptoms assessment for early identification of patients at risk for frailty and implementation of targeted interventions to prevent or delay its progression in vulnerable individuals.

Abbreviations

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; VLMR, Vuong–LoMendell–Rubin likelihood ratio; BLRT, Bootstrapped Likelihood Ratio Test; BMI, body mass index; CAT, COPD Assessment Test; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mCOPD-PRO, Modified COPD Patient-Reported Outcome; LPA, latent profile analysis; mMRC, modified Medical Research Council; SD, standard deviation; OR, odds ratio; CI, confidence interval.

Data Sharing Statement

The datasets are available from the corresponding author upon reasonable request.

Consent for Publication

Informed consent was obtained from all participants for participation in the study and publication of information.

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Author Contributions

All authors contributed significantly to the work, including conception, study design, execution, data acquisition, analysis, and interpretation. They participated in drafting, revising, or critically reviewing the article; approved the final version for publication; agreed on the submission; and accepted responsibility for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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