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ORIGINAL RESEARCH

Symptom Network and Subgroup Analysis in Patients with Exacerbation of Chronic Obstructive Pulmonary Disease: A Cross-Sectional Study

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Purpose: This study aims to construct a contemporaneous symptom network of inpatients with Exacerbation of Chronic Obstructive Pulmonary Disease (ECOPD) based on the symptom cluster, identify core and bridge symptoms, and patient subgroups with different symptom clusters based on individual differences in the intensity of patient symptom experiences.

Patients and Methods: This study used convenience sampling to collect demographic, symptom, auxiliary examination, and prognosis information of 208 inpatients with ECOPD from April 2022 to October 2023. The data underwent exploratory factor analysis (EFA), symptom network analysis, latent class analysis (LCA), Spearman correlation analysis, Wilcoxon signed-rank test, single-factor regression and multiple-factor stepwise regression.

Results: In hospitalized patients with ECOPD, symptom network analysis revealed that loss of appetite was the core symptom, while chest distress was the bridge symptom. Through LCA analysis, two symptom subgroups were identified: a high-symptom group (53.8%) and a low-symptom group (46.2%). This suggests that there is significant heterogeneity in symptom experience among ECOPD individuals. Patients in the high-symptom group had a higher probability of experiencing symptom clusters related to nutrition-sleep.

Conclusion: The combination of symptom network analysis and LCA comprehensively captures the symptom/symptom cluster characteristics and accounts for the heterogeneity of ECOPD patients from both individual and group perspectives. This study identifies core symptoms, bridge symptoms, and symptom subgroups, offering valuable insights for precision symptom management in ECOPD.

Keywords: chronic obstructive pulmonary disease, COPD, exacerbation, precision care, network analysis, latent class analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic inflammatory lung disease with a high mortality rate.[1] It is a heterogeneous condition characterized by persistent respiratory symptoms, including dyspnea, cough, and sputum production, caused by chronic abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema). These abnormalities often lead to progressive airflow limitation.[2,3] It was estimated that by 2025, the global number of COPD cases will approach 600 million,[4] and by 2030, COPD will become the fourth leading cause of death worldwide.[5] The characteristics of exacerbation of COPD (ECOPD) include worsening respiratory symptoms such as

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dyspepsia, cough, and sputum production within 14 days, with other associated symptoms potentially including shortness of breath and tachycardia.[1]

There were approximately 100 million COPD patients in China, with an average of 0.5 to 3.5 exacerbations per person per year, making it the leading cause of death among COPD patients.[6] ECOPD accelerates the decline in lung function of COPD patients, leading to lower quality of life, limited activity, increased risk of death, and imposing a heavy burden on healthcare and the economy.[7–9]

Precision care mainly involves non-pharmacological, non-surgical nursing techniques to relieve symptoms and promote the physical and mental recovery of patients.[10,11] Symptom science is a key component of precision care, aiming to explore the underlying biological and behavioral mechanisms and influences of individual symptoms or symptom clusters.[12,13] In recent years, symptom management has gradually shifted from focusing on individual symptoms to addressing multiple symptoms. This is because the accumulation of symptoms can cause greater harm to patients, and identifying the relationships among multiple symptoms is more conducive to centralized symptom management and alleviating the symptom burden of patients.[14–16] This had already been revealed and summarized by some studies on symptom clusters in COPD.[17] Considering the heterogeneity and complexity of exacerbation of COPD, the severity of exacerbation varies, and the clinical symptoms or combinations of symptoms also exhibit diversity.[11] Furthermore, compared to stable COPD, patients with ECOPD experience a heavier symptom burden and worse prognosis. Therefore, it is necessary to explore the symptoms and mechanisms that COPD patients experience during exacerbation in order to provide more evidence for effectively alleviating and managing symptoms precisely.

Symptom network analysis is an emerging method for symptom analysis that has been used in various diseases such as schizophrenia,[18] Human Immunodeficiency Virus (HIV),[19] and childhood Attention-Deficit/Hyperactivity Disorder (ADHD).[20] Symptom networks[21] are based on the assumption that symptoms (nodes) interact with each other rather than existing independently. Building on this premise, symptom networks calculate and visualize the relationships between symptoms by representing their centrality with the position of nodes and the strength of connections with the thickness of lines. Compared to symptom cluster analysis, symptom network analysis offers distinct advantages. It not only provides a visual representation of symptom relationships but also helps healthcare providers identify core and bridge symptoms, enabling more precise symptom management. However, both symptom cluster analysis and symptom network analysis have limitations as they are variable-centered clustering methods that may overlook individual differences in symptom experience.[22] In contrast, latent class analysis (LCA) is a person-centered clustering method that can help identify patient subgroups with different symptom clusters and risk factors.[23] Previous studies have primarily used only one clustering method,[24] which may limit the comprehensiveness of symptom analysis. Therefore, this study combines symptom network analysis with LCA to provide a more complete analysis of ECOPD symptoms from both individual and group perspectives. The primary aim of this study is to use symptom network analysis to visualize the symptom clusters in ECOPD patients and identify key intervention targets. Additionally, LCA is used to uncover individual differences in symptom experience and identify symptom subgroups, further contributing to personalized and precise symptom management. A secondary goal is to explore the influencing factors and potential mechanisms of different symptom subgroups.

Materials and Methods

Design and Subjects

This study included patients admitted to the respiratory ward or respiratory intensive care unit at a tertiary hospital in Wenzhou, Zhejiang Province, China, between April 2022 and October 2023. Inclusion criteria for participants were as follows: 1. Meet the diagnostic criteria related to ECOPD in the "Diagnosis and Treatment Guidelines for Chronic Obstructive Pulmonary Disease" (2021 revised edition).[25] 2. The primary diagnosis among the participants was ECOPD, leading to admission to either the respiratory department or the respiratory intensive care unit. 3. Willing to participate in the study and sign an informed consent form. Exclusion criteria were as follows: 1. Patients with impaired consciousness, mental illness, or inability to complete the questionnaire. 2. Patients with active pulmonary tuberculosis, bronchiectasis, or other restrictive ventilatory dysfunction. 3. Patients with asthma, pulmonary fibrosis, or pulmonary embolism. 4.

Patients with severe heart, liver, kidney failure, or malignancy. 5. Patients with a hospital stay of less than 72 hours were excluded from the study.

Sample Size

For Exploratory Factor Analysis (EFA), a sample size of 5–10 times the number of items is recommended.[26] This study involved 20 symptom items and factored in a 10% dropout rate, resulting in a targeted sample size of 111–222 cases. The study involved the distribution of 250 questionnaires, with 29 patients opting out of participation. Furthermore, eight patients were out because they developed conditions such as pulmonary embolism or heart failure after being hospitalized. Finally, 208[27] valid questionnaires were collected, with an effective rate of 97.7%.

Data Collection

This study assessed the symptoms of ECOPD patients during the four weeks before admission using the DESS questionnaire. Additionally, we designed forms to collect demographics, clinical treatment, physical examination, physiological and biochemical indicators, prognosis, and other information from the electronic medical records system upon patient admission. Additionally, to ensure the reliability and consistency of the questionnaire results, we provided standardized training for the data collectors. After the questionnaires were collected, two researchers independently verified and entered the data to ensure its completeness and accuracy. Our study was conducted in accordance with the Declaration of Helsinki. Ethical approval for this study was granted by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, Zhejiang Province, with the reference number KY2023-R084. All participants provided written informed consent.

Research Tools

Admission Basic Information Form

The researchers designed a demographic questionnaire that included statistical information such as age, gender, education level, severity of exacerbation,[6] smoking, alcohol consumption, history of occupational exposure, type of infection, medical history (allergy history, diabetes, hypertension, chronic obstructive pulmonary disease, coronary heart disease, cerebrovascular disease, cardiopulmonary disease, osteoporosis, respiratory failure).

Digital Evaluation Score System

This study used the Digital Evaluation Score System (DESS) developed by Professor Wang's[28] team to assess the symptoms and ancillary examination information of patients with ECOPD. The DESS incorporates a wide range of clinical indicators commonly used in ECOPD management, translating patients' clinical descriptions and examination information into standard scores of 0, 1, 2, or 4, with higher scores indicating greater severity. For a item where severity assessment is challenging, only scores of 0 and 1 are used to represent "no" and "yes", respectively. The scoring criteria for each item in the DESS were based on established systems such as the BODE index, acute physiology and chronic health evaluation (APACHE II), COPD assessment test (CAT) and current diagnostic guidelines to ensure the reliability of the scoring. Compared to standalone symptom assessment scales, the DESS can incorporate hundreds of clinical phenotype information, leveraging patients' clinical data more comprehensively.[29] The DESS version used in this study was modified from the original tool based on clinical expertise and existing literature to ensure it is more suitable for use by clinical nursing staff. In this study, we evaluated twenty symptoms using the DESS, including activity restriction, cough, shortness of breath, chest distress, expectoration, decreased exercise tolerance, loss of appetite, fatigue, insomnia, weight loss, constipation, orthopnea, anxiety, fever, pain, dysphoria, chills, muscle soreness, dysphagia, and diarrhea.

Outcomes

We selected multiple outcome measures, including the use of a non-invasive ventilator, types and days of antibiotic use, types and days of nebulized inhalation therapy drug use, duration of glucocorticoid use, whether admitted to the intensive care unit, number of days in critical care, total hospital days, total hospital costs, and readmission within three months.

Statistical Analysis

Categorical variables in this study were described as frequencies (percentages). Wilcoxon rank-sum test was used to compare between groups. The Kolmogorov–Smirnov (K-S) test was employed to assess the normality of continuous variables. Normally distributed continuous variables were expressed as means with standard deviations (SD) and compared between groups using the *t*-test. Non-normally distributed continuous variables were reported as medians with interquartile ranges (IQR) and compared between groups using the Wilcoxon rank-sum test. The data analysis process of this study utilized three statistical software programs: SPSS 26.0, Mplus 8.0, and R 4.3.2. A two-tailed p-value < 0.05 was considered statistically significant.

Contemporaneous Symptom Network Analysis

To ensure clinical significance, symptoms with occurrence probability greater than 40% were selected for symptom cluster analysis using EFA. The number of factors is determined based on an eigenvalue greater than 1, and for each factor, the factor loading of symptoms should exceed 0.40. Subsequently, we utilized the "qgraph" package in R language to construct a symptom network for ECOPD. The network was based on the Gaussian Graphical Model (GGM),[30] which estimates conditional relationships between nodes. To produce a sparse and interpretable network, we applied the graphical Least Absolute Shrinkage and Selection Operator (gLASSO), combined with the Extended Bayesian Information Criterion (EBIC) to select optimal tuning parameters. In the symptom network, each symptom serves as a node, with edges connecting the nodes. Thicker and darker edges indicate stronger associations between symptoms. The positions of nodes in the network were determined using the Fruchterman-Reingold algorithm, which places nodes with stronger associations closer to each other. Different edge colors are used to differentiate positive and negative associations, with blue indicating positive and red indicating negative correlations. Calculate the centrality indicators of nodes, including strength centrality, closeness centrality, betweenness centrality, and expected influence (EI) to objectively assess the strength, closeness, centrality, and expected impact of each symptom node, respectively, to measure the influence and importance of each symptom node and determine the core symptoms. Bridge symptoms were primarily identified by calculating and comparing the bridge centrality indicators of nodes. Finally, we used the "bootnet" package in R to assess the stability of centrality indicators by calculating the correlation stability coefficient (CS-coefficient) and evaluated the accuracy of edge weights through their 95% confidence intervals.

Subgroup Analysis and Differential Analysis

Latent Class Analysis (LCA) is a modern statistical technique that can identify homogeneous subgroups from multivariate categorical data, grouping individuals with similar or identical symptom features into the same subtype.[31] By considering the Bayesian Information Criterion (BIC), adjusted BIC (aBIC), Akaike Information Criterion (AIC), Lo-Mendell-Rubin likelihood ratio test (LMRT), Bootstrap Likelihood Ratio Test (BLRT), and entropy, the optimal latent class model was selected. After determining the best latent categories, single-factor regression and multiple-factor stepwise regression were used to evaluate patient characteristic factors contributing to classification. The odds ratios (OR) and 95% confidence intervals (CI) were calculated to assess the effect size and the precision of the estimates. Additionally, differences between auxiliary examinations of different subgroups were analyzed using the Wilcoxon signed-rank test. To further clarify the relationship between auxiliary examinations of each subgroup and the severity of specific symptoms, a correlation heatmap was created using Spearman correlation analysis. Finally, the Wilcoxon signed-rank test was employed to compare outcomes among different subgroups.

Results

Symptom Network Analysis in Patients with ECOPD

The results (Figure S1) revealed the presence of three symptom clusters in hospitalized patients with ECOPD: fatigue-activity, nutrition-sleep, and cough-sputum symptom cluster (Table S1). The constructed symptom network analysis graph provided a more intuitive display of the relationships between symptoms in patients with ECOPD. As shown in Figure 1, almost all symptoms are positively correlated. Analysis of centrality indicators (Figure 2) showed that loss of appetite (B1, r_s=4.239) has the highest strength centrality, indicating that it is the most influential symptom in the entire network. Figure 3 demonstrated that chest distress (C3) was the most probable bridge symptom since it had the highest

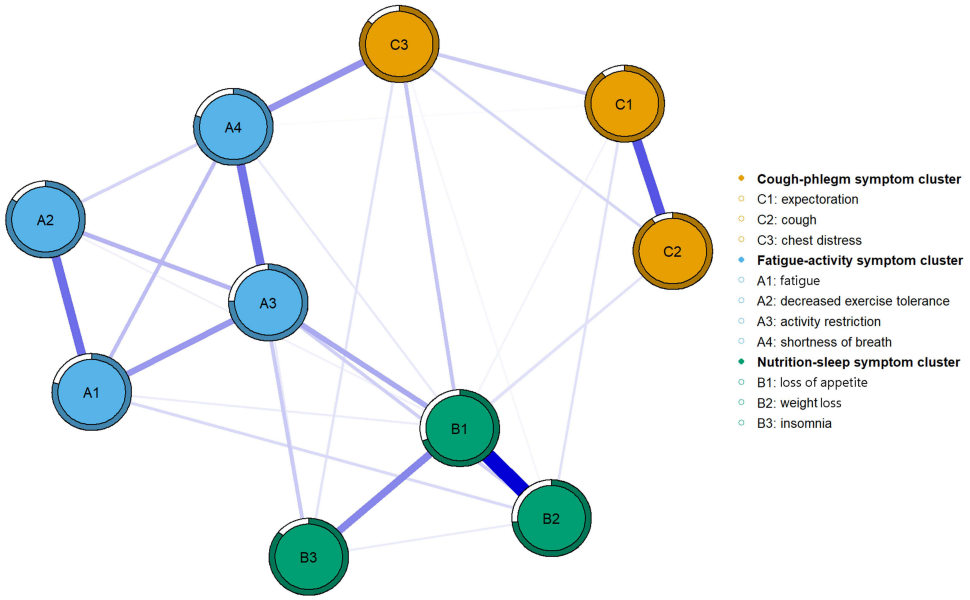

Figure 1 Symptom network diagram of patients with ECOPD.

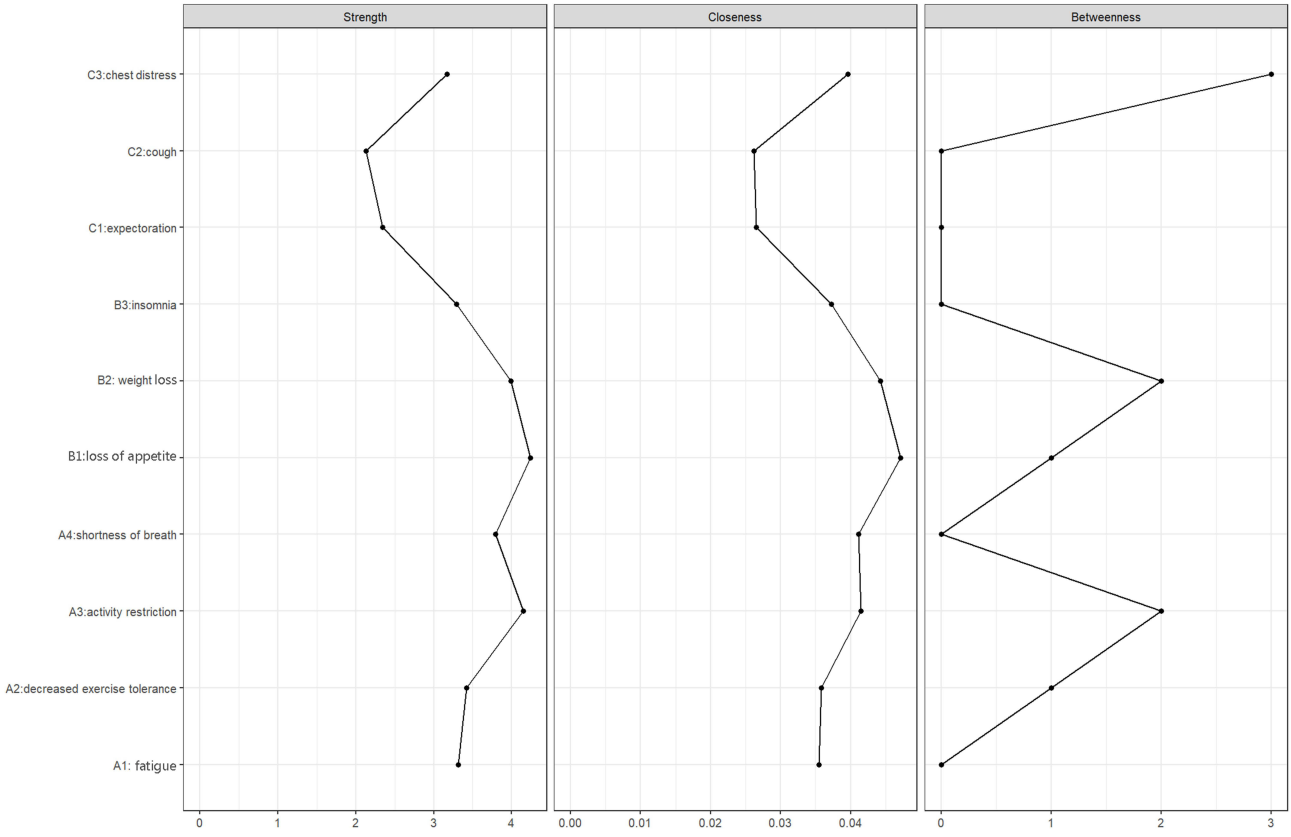

Figure 2 Analysis of centrality indicators in symptom network analysis of patients with ECOPD.

bridge strength centrality (r_{bs}=0.460). This suggested that chest tightness is a key symptom connecting the cough-sputum symptom cluster with other symptom clusters, and its presence could drive the occurrence of other symptoms, making it a crucial target for symptom improvement. Figure S2A and S2B demonstrate the accuracy and stability of the symptom cluster network, while Figure S3 illustrates the stability of bridge centrality, all within acceptable ranges.

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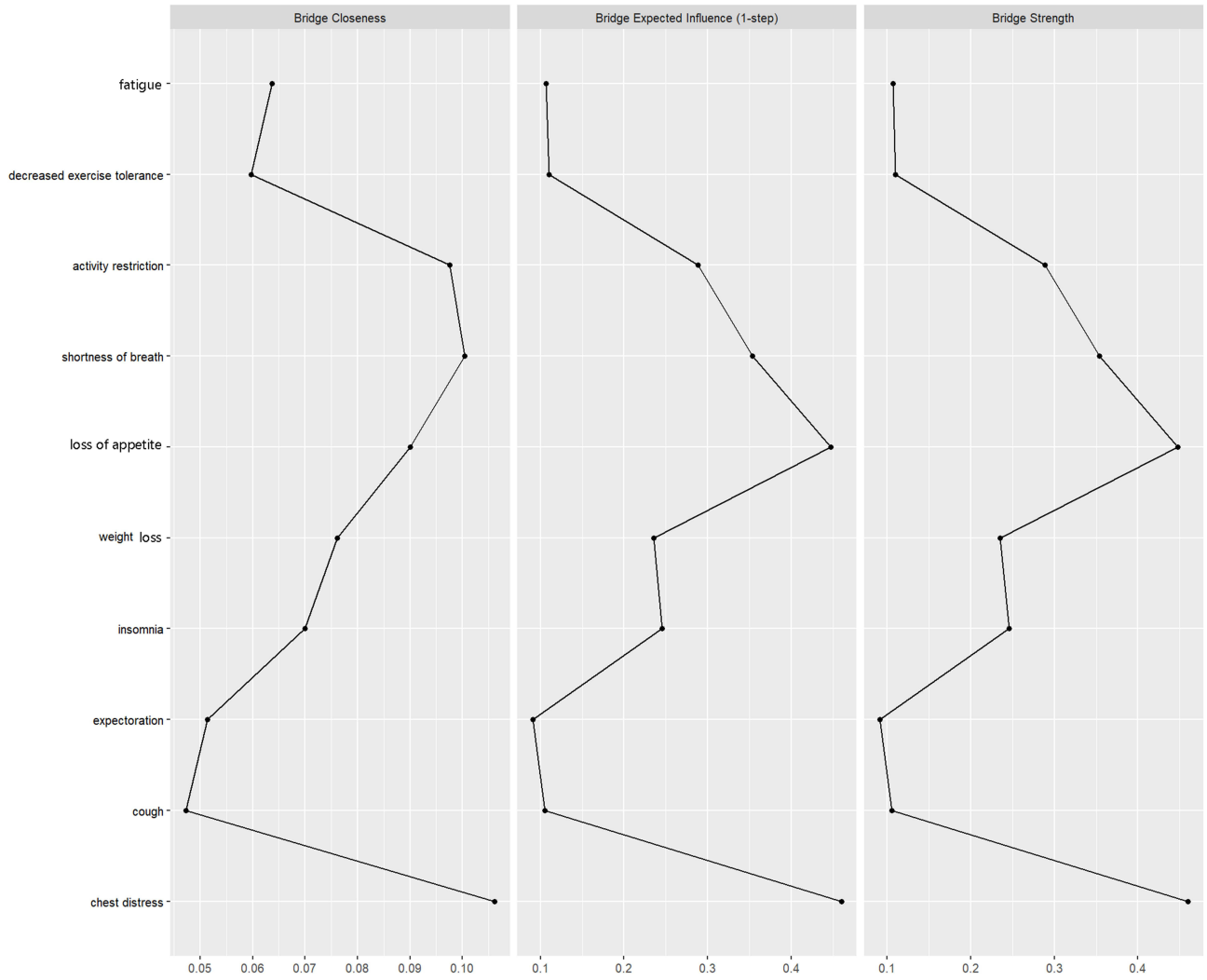


Figure 3 Bridge symptom analysis in symptom network analysis of patients with ECOPD.

Subgroup Analysis and Differential Analysis of Patients with ECOPD

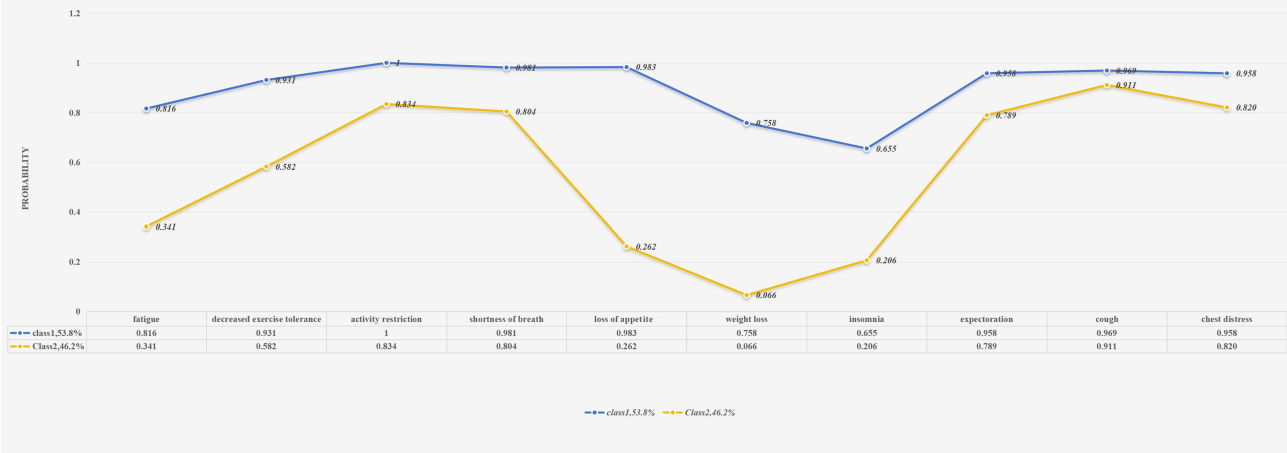
Subgroup Analysis

Table 1 showed that when the latent class is binary, the BIC value is the lowest, with statistically significant LMRT and BLRT values ($p < 0.001$), and an entropy greater than 0.8, indicating a classification accuracy of over 90%. Therefore, we believe that dividing them into two subgroups is most appropriate. The occurrence probabilities of all symptoms in class 1 were higher than in class 2, so we named class 1 the high-symptom group and class 2 the low-symptom group, with the

Table 1 Results of Latent Class Analysis

N classes	AIC	BIC	aBIC	Entropy	LMR	BLRT	Class probability
1	4079.578	4159.679	4083.636	–	–	–	1
2	3752.003	3915.542	3760.286	0.874	<0.001	<0.001	0.538/0.462
3	3669.206	3916.184	3681.716	0.869	0.289	0.286	0.409/0.370/0.221
4	3632.680	3963.097	3649.417	0.872	1.000	1.000	0.235/0.313/0.332/0.120
5	3613.583	4027.438	3634.545	0.886	0.761	0.761	0.293/0.202/0.125/0.164/0.216

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; aBIC, Ajusted BIC; LMRm Lo-Mendel-Rubin; BLRT, Bootstrap likelihood ratio test.



	fatigue	decreased exercise tolerance	activity restriction	shortness of breath	loss of appetite	weight loss	insomnia	expectoration	cough	chest distress
class1,53.8%	0.816	0.931	1	0.981	0.983	0.758	0.655	0.958	0.969	0.958
Class2,46.2%	0.341	0.582	0.834	0.804	0.262	0.066	0.206	0.789	0.911	0.820

Figure 4 Probability distribution of symptom occurrence in two subgroups.

low-symptom group as the reference group (Figure 4). It could be observed that both groups have relatively high probabilities of respiratory symptoms. Compared to the low-symptom group, individuals in the high-symptom group have a higher probability of experiencing the nutritional-sleep symptom cluster, followed by the fatigue-activity symptom cluster.

Analyzing Differences in Different Subgroups

Analysis of Characteristic Factors in Different Subgroups

Single-factor regression (Table S2) and multiple-factor regression results (Table S3) showed that patients with poorer daily activity capacity (OR=4.50, $p<0.001$) and a history of coronary heart disease of more than 5 years (OR=8.04, $p=0.049$) are more likely to be classified into the high-symptom group, with a higher symptom burden.

Differential Analysis of Auxiliary Examinations in Different Subgroups

Abnormalities in C-reactive protein (CRP) levels were positively correlated with the presence of cough (r = 0.210, p = 0.027) and expectoration (r = 0.321, p = 0.001) in the high-symptom group (Table S4). The high-symptom group was more likely to have abnormalities in serum calcium ion levels, which may be related to decreased exercise tolerance (r=0.196, P=0.038) (Figure S4).

Comparison of Outcomes in Different Subgroups

Table S5 showed that in terms of treatment, the high-symptom group had a longer duration and variety of antibiotic usage, as well as a longer duration of inhalant use. Additionally, the high-symptom group had a higher probability of being admitted to the intensive care unit, requiring a higher level of care, longer overall hospital stay, and incurring higher medical expenses.

Discussion

Unlike previous studies on COPD[24] or ECOPD[32] symptoms that primarily employed various clustering methods to explore symptom clusters, this study, for the first time, visually presented the internal network structure of symptoms frequently reported by ECOPD patients in a graphical format and calculated specific indicators such as centrality/bridge centrality to provide objective basis for precise symptom management.[19] Based on the symptom network, loss of appetite and chest distress were identified as the core and bridge symptoms of hospitalized ECOPD patients. Additionally, this study utilized LCA to fully uncover the individuality of symptom experiences,[33] revealing that the ECOPD population can be broadly divided into two symptom subgroups: a high-symptom group (53.8%) and a low-symptom group (46.2%). Symptom network analysis and LCA complement each other in providing a comprehensive understanding of the

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heterogeneity of ECOPD symptoms from both individual and group perspectives. These findings offer additional references for prioritizing symptoms and developing personalized symptom management strategies for ECOPD.

Our study found that exacerbation of respiratory symptoms, especially cough, expectoration, shortness of breath, chest distress, and deteriorating respiratory function, resulted in activity limitation and decreased exercise tolerance, which were the main symptoms troubling patients with ECOPD. Additionally, symptoms such as loss of appetite, fatigue, insomnia, and weight loss were frequently reported by our patients. These research findings were consistent with previous studies.[34,35] However, anxiety and other psychological symptoms were not prominent in the population we surveyed, which may be related to the fact that the majority of our respondents were Asian males.[17] We explored and identified three symptom clusters in ECOPD patients: fatigue-activity cluster, nutrition-sleep cluster, and cough-sputum cluster. These findings differ slightly from our previous research results.[36] By employing a larger sample size in this study, previously undiscovered relationships between nutrition and sleep were uncovered, suggesting that nutritional status and sleep quality may be interconnected aspects of daily life. Sleep disturbances are common in COPD patients and may contribute to increased risk of acute exacerbation.[37] Similarly, loss of appetite and malnutrition are commonly observed during the progression of COPD.[38] Increasing evidence suggested that diet and sleep are intertwined factors; inadequate sleep could have a detrimental impact on food choices and intake, while adopting a balanced dietary regimen may be a crucial measure for enhancing both sleep and nutrition.[39] Based on the symptom cluster study, we have further identified loss of appetite as a core symptom in patients with ECOPD. This suggests that healthcare providers should prioritize improving appetite and nutrition in ECOPD patients. Research indicated that decreased appetite in individuals with COPD can lead to reduced food intake and inadequate nutrition,[40] subsequently worsening lung function[41] and accelerating the progression of COPD.[42] The loss of appetite among COPD patients is multifactorial, potentially related to dry mouth, gastric pain or discomfort, and constipation.[43] Previous research indicates that dry mouth was the most prominent reason for changes in appetite among patients with COPD, possibly linked to damage to oral thermoreceptors and taste receptors due to the prolonged use of inhaled medications in COPD patients.[43,44] However, further exploration and evidence are required to determine how to enhance appetite in COPD patients and to identify the appropriate timing during exacerbations in hospital settings for correcting poor nutritional status.[45,46] Additionally, this study revealed that chest distress was a crucial bridge symptom in patients with ECOPD, suggesting that chest distress can serve as a bridge among the three symptom clusters, which is significant for maintaining the integrity of the ECOPD symptom network.[47] Chest distress is a common unpleasant respiratory experience in COPD patients, leading many to reduce physical activity to avoid such discomfort, yet this behavior also brings about a range of adverse effects, including broader impairments in skeletal muscle function and negative psychological emotions.[48] Thus, interventions targeting chest distress represent the primary goal in disrupting this vicious cycle, where the overall benefits obtained may far exceed alleviating the chest tightness symptoms themselves. The mechanisms underlying respiratory distress are complex, and a single intervention often falls short of meeting demands. Improving respiratory distress necessitates the implementation of multidisciplinary interventions and personalized customization based on individual needs.[49] In conclusion, the symptoms of patients with ECOPD in clinical settings are intricate and diverse. Selecting and addressing key, appropriate symptoms for priority identification and management within limited time and urgent environments might significantly amplify the effectiveness of our nursing interventions.

Symptom network analysis revealed connections among symptom clusters in ECOPD, based on the average intensity of the overall symptoms experienced by the ECOPD population, which may not adequately reflect individual differences. Therefore, this study employed a person-centered clustering approach to explore the heterogeneity of symptom phenotypes within individual ECOPD patients, differentiate patient subgroups with distinct symptom clusters, and refine the patterns of symptom occurrence for betterment. LCA was our preferred clustering method, as it has been successfully utilized in patients with asthma and acute respiratory distress syndrome (ARDS).[50,51] Through LCA analysis, we identified two symptom expression patterns in ECOPD patients: the high-symptom group and the low-symptom group. Both groups demonstrated a high prevalence of respiratory symptoms, yet the high-symptom group had a higher probability of experiencing the nutritional-sleep cluster. Therefore, we recommend incorporating the assessment of nutrition and sleep status in hospitalized ECOPD patients as a routine procedure to promptly identify individuals in the high-symptom group and promptly

offer effective strategies for improving nutrition and sleep, aiming to alleviate both symptom burden and disease impact on patients and expedite their health recovery.[52] In short, prompt recognition and management of the high-symptom group could lead to a more rational allocation of nursing resources and personalized care services for the patients.

Furthermore, individuals with poorer daily activity abilities and a history of coronary heart disease for over 5 years may represent important demographic characteristics of the high-symptom group. This finding may suggest a potential association between these characteristics and nutritional risks. Previous research has indicated that limitations in ADL may result from physical frailty in patients,[53] and frailty and nutritional risks share highly similar risk factors. The coexistence of coronary heart disease exacerbates pulmonary function impairment in COPD patients, as highlighted by Zhang,[54] suggesting that ECOPD and coronary heart disease patients should proactively and appropriately supplement vitamin D to maintain optimal nutritional status and internal stability. While our study did not identify specific biological markers representing loss of appetite or chest distress, we found a correlation between serum calcium levels and reduced physical activity in the high-symptom group and a close association of CRP levels with cough and sputum production. These biochemical abnormalities may serve as objective indicators to distinguish between the two subgroups and potentially reflect the underlying physiological mechanisms of these high-symptom occurrences. In conclusion, understanding the physiological mechanisms behind symptoms in ECOPD patients and identifying biomarkers that can substitute subjective symptom assessments are crucial aims of precise symptom management, necessitating further in-depth exploration and broader validation.

Limitations

Our study has several acknowledged limitations: 1. It is a cross-sectional study, which means that causal inferences cannot be drawn; future longitudinal, prospective studies should be conducted to clarify the specific causal relationships between the occurrence and development trajectories of symptom clusters, their influencing factors, and prognosis. 2. Although the participants included in this study were primarily diagnosed with ECOPD, we acknowledge that this does not completely eliminate the potential influence of other comorbidities on individual symptoms. 3. Conducting a single-center study may restrict sample representativeness. 4. The sample size in this study is limited, and future research should involve larger-scale studies.

Conclusion

Our study integrates the results of symptom network analysis and LCA, providing a comprehensive depiction of symptom/symptom cluster characteristics at both individual and group levels, thereby offering a significant contribution to the understanding of ECOPD symptom heterogeneity. Our findings suggest that loss of appetite and chest distress may be potential intervention targets for precision symptom management. The identification of distinct symptom subgroups lays a foundation for implementing personalized care, with the sleep-nutrition symptom cluster potentially serving as a critical marker for differentiating high-symptom and low-symptom subgroups. Exploring the underlying pathophysiological mechanisms of symptom heterogeneity in patients will be a key direction for future scientific research on ECOPD symptom management.

Data Sharing Statement

Data will be made available on request.

Ethics Approval Statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval for this study was granted by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, Zhejiang Province, with the reference number KY2023-R084.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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