Hierarchical Clustering Analysis of Comorbidity Patterns in Patients with Chronic Obstructive Pulmonary Disease: Postprint

Authors: Cheng Zhuozhuo, Zhang Rui, Xu Haofeng, Huang Junting, Liang Zijing, Yan Ping, Yan Ping

Date: 2024-12-13T15:10:34+00:00

Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) often have multiple comorbidities, which increases the complexity of treatment and medical burden. The impact of comorbidities on COPD patient management is profound, but existing research mostly focuses on single comorbidities, lacking systematic analysis of multiple comorbidity patterns and hospitalization costs.

Objective: To explore the comorbidity characteristics and multiple comorbidity patterns in COPD patients, analyze the impact of different characteristics and comorbidity patterns on hospitalization costs, and provide a basis for personalized health management and resource allocation for COPD patients.

Methods: A retrospective analysis was conducted on 5,061 COPD patients hospitalized in a tertiary hospital in Guangzhou from 2020 to 2023. Systematic cluster analysis was used to draw a cluster dendrogram to study comorbidity patterns in COPD patients, and multi-group comparisons were performed to analyze the prevalence and characteristics of different patterns. Multiple linear regression was used to analyze the impact of each comorbidity pattern on total hospitalization costs, Western medicine costs, and antimicrobial drug costs.

Results: Systematic cluster analysis identified 6 clusters of comorbidity patterns, including a cardiometabolic disease pattern, liver-kidney disease pattern, digestive system disease pattern, joint disease pattern, cancer pattern, and respiratory disease pattern. The prevalence, gender, age, BMI, and smoking history among the 6 clusters showed statistically significant differences ($P<0.05$). Multiple linear regression analysis revealed that BMI, cancer pattern, and respiratory disease pattern all had significant effects on total hospitalization costs, Western

medicine costs, and antimicrobial drug costs (P<0.05), with the respiratory disease pattern having the greatest impact on total hospitalization costs (β=0.125, P<0.001).

Conclusion: The comorbidity patterns of COPD can be divided into 6 clusters, among which BMI, cancer pattern, and respiratory disease pattern are the main influencing factors of hospitalization costs.

Full Text

Systematic Cluster Analysis of Comorbidity Patterns in Patients with Chronic Obstructive Pulmonary Disease

CHENG Zhuozhuo[1], ZHANG Rui[1], XU Haofeng[1], HUANG Junting[2], LIANG Zijing[2], YAN Ping[1]*

[1]Department of General Practice, The First Affiliated Hospital, Guangzhou Medical University, Guangzhou 510120, China
[2]Department of Emergency Medicine, The First Affiliated Hospital, Guangzhou Medical University, Guangzhou 510120, China
*Corresponding author: YAN Ping, Chief physician, Master supervisor; E-mail: 173566555@qq.com

---

Abstract

Background Chronic obstructive pulmonary disease (COPD) patients often present with multiple comorbidities, which increase treatment complexity and healthcare burden. While comorbidities significantly impact COPD management, existing research primarily focuses on individual conditions, lacking systematic analysis of multiple comorbidity patterns and hospitalization costs. **Objective** This study aims to investigate comorbidity characteristics and patterns in COPD patients, analyzing how different features and comorbidity patterns affect hospitalization costs to provide evidence for personalized health management and resource allocation. **Methods** A retrospective analysis was conducted on 5,061 COPD inpatients at a tertiary hospital in Guangzhou from 2020–2023. Systematic clustering analysis was employed to construct dendrograms identifying comorbidity patterns, with multiple group comparisons assessing prevalence and characteristics. Multiple linear regression analysis evaluated the impact of each pattern on total hospitalization costs, western medicine costs, and antibacterial medication costs. **Results** Systematic clustering identified six comorbidity patterns: cardiovascular and metabolic diseases, hepatorenal diseases, digestive system diseases, arthropathy, cancer, and respiratory system diseases. The prevalence of these six patterns and differences in gender, age, BMI, and smoking history were statistically significant (P<0.05). Multiple linear regression revealed that BMI, cancer pattern, and respiratory system diseases pattern all significantly impacted total hospitalization costs, western medicine costs, and

antibacterial medication costs (P<0.05), with the respiratory system diseases pattern exerting the most substantial effect on total costs (β=0.125, P<0.001). **Conclusion** COPD comorbidity patterns can be categorized into six clusters, with BMI, cancer pattern, and respiratory system diseases pattern being the primary factors influencing hospitalization costs.

Keywords COPD; Comorbidity patterns; Health management; Hospitalization costs; Systematic clustering

---

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung disease characterized by persistent chronic respiratory symptoms caused by airway and alveolar structural or functional abnormalities, leading to progressive airflow limitation. As a common chronic disease, COPD has become a major global health concern, currently ranking as the third leading cause of death worldwide and posing severe challenges to public health systems. While COPD primarily affects the lungs, its chronic systemic inflammatory characteristics can exert widespread effects on multiple systems and organs, often accompanied by various other chronic conditions. This phenomenon of multiple coexisting diseases is termed "comorbidity," referring to the additional health burden when a specific disease coexists with other conditions. Research indicates that 84.5% of COPD patients have at least one comorbidity, which not only significantly increases treatment complexity but also substantially elevates healthcare resource consumption, including higher hospitalization rates, medical expenses, and medication usage. Current comorbidity research predominantly focuses on single conditions, lacking systematic exploration of overall comorbidity patterns. This study employs systematic cluster analysis to identify comorbidity patterns in COPD patients and analyze their impact on hospitalization costs, aiming to provide reference evidence for personalized health management and resource allocation.

1. Methods

1.1 Study Population COPD patients hospitalized at The First Affiliated Hospital of Guangzhou Medical University between 2020–2023 were selected as study subjects. Inclusion criteria: met COPD diagnostic criteria in the "Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2021 Revision)" with COPD as the primary diagnosis; age $\geq$ 40 years. Exclusion criteria: patients who underwent lung transplantation during hospitalization. This retrospective study utilized broad informed consent signed by all participants upon admission, permitting use of their biological samples or data for other clinical research. The study was approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou Medical University (Approval No.: ES-2024-K085-01).

1.2 Data Collection and Definitions **1.2.1 General Data Collection.** Patient information was collected including gender, age, primary and all secondary diagnoses at discharge, smoking history, education level, Body Mass Index (BMI), total hospitalization costs, western medicine costs, antibacterial medication costs, number of hospitalizations, and length of stay. Smoking history was defined as any prior smoking experience. Education level was categorized as primary school or below, junior/high school, and college or above.

1.2.2 Grouping. Patients were divided into comorbidity and control groups based on secondary diagnoses at discharge. The comorbidity group included patients with at least one other chronic disease among the 15 common conditions listed in 1.2.3 in their secondary diagnoses, while the control group had none of these 15 chronic diseases diagnosed.

1.2.3 Comorbidity Classification. Based on the International Statistical Classification of Diseases and Related Health Problems (10th Revision) (ICD-10) classification method and referencing previous literature and disease prevalence, this study included 15 common chronic diseases for comorbidity analysis: hypertension, diabetes, cancer, heart disease (e.g., coronary heart disease, congestive heart failure), arrhythmia, cerebrovascular disease, emotional and mental disorders, arthritis or rheumatism, dyslipidemia, liver disease, kidney disease, digestive system diseases, other respiratory diseases (e.g., asthma, bronchiectasis, pulmonary hypertension), memory-related diseases (e.g., dementia, brain atrophy, Parkinson' s disease), and sleep disorders. All 15 diseases were confirmed by our hospital and met ICD-10 diagnostic criteria.

1.2.4 Comorbidity Pattern Cluster Analysis. The average linkage method in hierarchical cluster analysis was used, with Pearson correlation coefficient as the distance measure between clusters. Dendrograms were constructed to explore comorbidity patterns in elderly chronic disease patients.

1.3 Statistical Methods R 4.4.0 was used for multiple imputation of variables with missing values (smoking history, education level, and BMI had <10% missing rate). Statistical analysis was performed using SPSS 26.0. Categorical data were expressed as relative frequencies, with inter-group comparisons using ^{2} tests. Non-normally distributed continuous data were expressed as M(P25, P75), with two-group comparisons using Mann-Whitney U tests. Cluster analysis was conducted using R 4.4.0. Based on comorbidity patterns generated from dendrograms, ^{2} tests or Kruskal-Wallis H tests were used for prevalence and characteristic comparisons between groups, with Bonferroni correction for post-hoc tests. Multiple linear regression analysis was used to assess the impact of characteristics and comorbidity patterns on hospitalization costs. The significance level for post-hoc tests in multiple group comparisons was adjusted to α=0.003, while P<0.05 was considered statistically significant for other analyses.

2. Results

2.1 General Characteristics A total of 5,061 subjects were included, comprising 4,549 males (89.88%) and 512 females (10.12%), with a mean age of 69.2$±$9.2 years. The comorbidity group had significantly higher age, BMI, length of stay, number of hospitalizations, total hospitalization costs, western medicine costs, and antibacterial medication costs compared to the control group (P<0.05). No significant differences were observed between groups in gender, education level, or smoking history (P>0.05) .

2.2 Comorbidity Status The comorbidity group included 4,343 patients, with a prevalence of 85.81% and an average of 1.86$±$1.36 comorbidities per patient. The prevalence of the 15 comorbidities was: other respiratory diseases 2,277 cases (44.99%), hypertension 1,629 cases (32.19%), liver disease 1,156 cases (22.84%), heart disease 1,027 cases (20.29%), arrhythmia 622 cases (12.29%), diabetes 586 cases (11.58%), kidney disease 470 cases (9.29%), digestive system diseases 348 cases (6.88%), cerebrovascular disease 342 cases (6.76%), dyslipidemia 264 cases (5.22%), sleep disorders 228 cases (4.51%), malignant tumors 216 cases (4.27%), arthritis or rheumatism 120 cases (2.37%), memory-related diseases 68 cases (1.34%), and emotional/mental disorders 57 cases (1.13%).

2.3 Comorbidity Pattern Analysis Systematic cluster analysis using the average linkage method was performed on the 15 comorbidities, identifying six comorbidity patterns based on clinical and classification objectives, in order of clustering: cardiovascular and metabolic diseases pattern (hypertension, diabetes, heart disease, arrhythmia, cerebrovascular disease, memory-related diseases, emotional/mental disorders, sleep disorders), hepatorenal diseases pattern (kidney disease, liver disease, dyslipidemia), digestive system diseases pattern, arthropathy pattern, cancer pattern, and respiratory system diseases pattern [Figure 1: see original paper].

Statistically significant differences were found among the six patterns in prevalence, gender, age, BMI, and smoking history (P<0.05), but not in education level (P=0.054). Post-hoc tests with Bonferroni correction (adjusted significance level α=0.003) revealed: pairwise differences in prevalence among all six patterns (P<0.003); higher male proportion in the cancer pattern compared to cardiovascular metabolic, digestive system, and respiratory system patterns (P<0.003); older age in cardiovascular metabolic pattern compared to hepatorenal, digestive system, and respiratory system patterns, and older age in arthropathy and cancer patterns compared to hepatorenal and digestive system patterns (P<0.003); higher BMI in cardiovascular metabolic and hepatorenal patterns compared to cancer and respiratory system patterns (P<0.003); and higher smoking rate in hepatorenal pattern compared to cardiovascular metabolic and respiratory system patterns (P<0.003) .

2.5 Impact of Comorbidity Patterns on Hospitalization Costs
Univariate analysis was performed with independent variables including gender (male=1, female=2), age (40-49 years=1, 50-59 years=2, 60-69 years=3, 70-79 years=4, $ 80$years = 5), $smokinghistory(no = 0, yes = 1), BMI(< 18.5kg/m^{2}= 1, 18.5 - 23.9kg/m^{2}= 2, 24.0 - 27.9kg/m^{2}$=3, $ 28.0kg/m^{2}=4), education level (primary school or below=1, junior/high school=2, college or above=3), and the six comorbidity patterns (no=0, yes=1), with dependent variables of total hospitalization costs, western medicine costs, and antibacterial medication costs (all actual values). Results showed that age, BMI, smoking history, cardiovascular metabolic disease pattern, cancer pattern, and respiratory system diseases pattern influenced total hospitalization costs (P<0.05); gender, age, BMI, smoking history, cardiovascular metabolic disease pattern, hepatorenal disease pattern, digestive system disease pattern, cancer pattern, and respiratory system diseases pattern influenced western medicine costs (P<0.05); and gender, age, BMI, education level, smoking history, cardiovascular metabolic disease pattern, hepatorenal disease pattern, digestive system disease pattern, cancer pattern, and respiratory system diseases pattern influenced antibacterial medication costs (P<0.05) (see Supplementary Tables 1-3).

Further multiple linear regression analysis was conducted using variables significant in univariate analysis as independent variables (assignments same as above) and hospitalization costs as dependent variables (actual values). Results showed that BMI, cardiovascular metabolic disease pattern, cancer pattern, and respiratory system diseases pattern influenced total hospitalization costs (P<0.05); gender, BMI, smoking history, cardiovascular metabolic disease pattern, cancer pattern, and respiratory system diseases pattern influenced western medicine costs (P<0.05); and gender, BMI, education level, cancer pattern, and respiratory system diseases pattern influenced antibacterial medication costs (P<0.05) .

3. Discussion

With population aging and changing disease patterns, multimorbidity has become increasingly prevalent among older adults. According to China Health and Retirement Longitudinal Study (CHARLS) data, 42.4% of older adults suffer from multiple chronic conditions. COPD often coexists with cardiovascular diseases, metabolic disorders, and psychological conditions, substantially increasing healthcare burden and management complexity while posing significant challenges to resource allocation. Given the growing importance of COPD comorbidities, increasing research attention has focused on this area. However, most studies examine single comorbidity effects, lacking systematic analysis of multiple comorbidity patterns. This study analyzed comorbidities and patterns in COPD patients aged 40 and above, exploring their impact on hospitalization costs to inform health management and prevention strategies.

Results showed that most COPD patients had at least one comorbidity, with a

prevalence of 85.81%, slightly higher than the 81% reported in a large Danish longitudinal cohort study of COPD patients. Another analysis of 939 middle-aged and elderly COPD inpatients in Beijing found 93.40% had at least one comorbidity. Variations in comorbidity prevalence across studies may be attributed to differences in measurement methods, data sources, and sample sizes. The top five comorbidities were other respiratory diseases, hypertension, liver disease, heart disease, and arrhythmia, consistent with multiple studies reporting respiratory and cardiovascular diseases as the most common COPD comorbidities. One study identified mood disorders, stress-related disorders, or anxiety as the most frequent COPD comorbidities, whereas our study found relatively lower proportions of emotional and mental issues, suggesting potential underrecognition of these aspects.

The comorbidity group was older than the control group, likely due to cumulative effects of lifestyle risk factors such as smoking, sedentary behavior, and unhealthy diet increasing comorbidity risk with age. An observational multicohort study found obesity (BMI \$ $30kg/m\hat{}\{2\}\$$) associated with 21 different diseases, with mechanisms including metabolic abnormalities, chronic inflammation, hormonal imbalance, and increased mechanical joint loading. Our study found comorbid COPD patients had higher hospitalization frequency, length of stay, total costs, western medicine costs, and antibacterial medication costs than the control group, possibly because comorbidities increase disease complexity and severity, requiring more frequent and complex medical interventions.

Different studies may identify varying comorbidity patterns due to methodological differences, sample characteristics, and chronic disease diversity. James et al. identified four major patterns in advanced COPD: cardiometabolic and anemia, malnutrition and low mood, obesity with metabolic and mood disorders, and fewer comorbidities. Hansen et al. identified three COPD comorbidity clusters using two-step clustering: heart disease-predominant, allergy-predominant, and other comorbidities excluding heart disease. Despite varying results, cardiovascular metabolic patterns remain prominent across studies. Our findings similarly show cardiovascular metabolic disease as the most common pattern in COPD patients. Complex interactions between COPD and cardiovascular disease include chronic hypoxemia, systemic inflammatory response, oxidative stress, shared risk factors, and medication effects, substantially increasing cardiovascular risk in COPD patients. The respiratory system diseases pattern ranked second in prevalence, encompassing asthma, bronchiectasis, and pulmonary hypertension. COPD-asthma comorbidity mechanisms involve Th1 and Th2 immune responses triggering systemic inflammation, airway remodeling, biomarker classification, gene-environment interactions, and epigenetic regulation. COPD-associated protease-antiprotease imbalance and uncontrolled protease activity such as neutrophil elastase can cause airway wall remodeling and bronchiectasis. Chronic hypoxemia and pulmonary vascular remodeling increase COPD patients' susceptibility to pulmonary hypertension. The hepatorenal diseases pattern (liver disease, kidney disease, dyslipidemia) may relate to non-alcoholic fatty liver disease and lipid metabolism disorders from chronic

smoking and inflammation. Studies show COPD patients have significantly elevated lung cancer risk, with shared pathological mechanisms including chronic inflammation, genetic susceptibility, epigenetic changes, telomere shortening, and protease-antiprotease imbalance.

Multiple linear regression analysis of hospitalization costs revealed significant effects of comorbidity patterns on total costs, western medicine costs, and antibacterial medication costs, with varying impact across patterns. A meta-analysis of 59 studies showed multimorbidity economic impact was most significant for cancer-mental health, diabetes-cardiovascular disease, and respiratory disease-mental health combinations, with costs substantially higher than other disease patterns. Our results showed the respiratory system diseases pattern significantly affected hospitalization costs, likely because COPD combined with other respiratory diseases increases recurrent infection and acute exacerbation risk, substantially increasing antibacterial and other medication needs. The cancer pattern' s impact on western medicine costs may relate to high cancer treatment expenses. Additionally, COPD patients with cancer may have increased antibacterial medication costs due to further lung function decline and infection risk. Cardiovascular metabolic comorbidities may increase total and western medicine costs through disease complexity, high incidence of cardiovascular events and metabolic disorders, and dependence on long-term medication.

This study has several limitations. First, as a single-center study from a Guangzhou tertiary hospital with relatively limited sample size, it may not fully represent broader population characteristics. Future research should expand sample size and conduct multicenter studies to enhance representativeness and generalizability. Second, as a retrospective study limited by data availability, we could not include potential influencing factors such as occupation and residence, which may limit comprehensiveness. Third, the analysis was based only on comorbidities with high frequency in previous literature and data, potentially omitting some low-frequency but important conditions and limiting pattern completeness. Fourth, single hierarchical cluster analysis may restrict comprehensive identification and interpretation of comorbidity patterns; future studies should employ more diverse statistical methods to enhance analytical accuracy and robustness.

In conclusion, this study identified six major comorbidity patterns in COPD patients through systematic cluster analysis. Multiple comorbidity patterns differentially impact hospitalization costs, with the respiratory system diseases pattern exerting particularly significant effects. Therefore, developing personalized health management strategies targeting high-frequency comorbidities is key to reducing disease burden in COPD patients.

Author Contributions: CHENG Zhuozhuo was responsible for drafting, data collection, and statistical analysis; ZHANG Rui and XU Haofeng produced figures and tables; HUANG Junting and LIANG Zijing contributed to research conceptualization and study design; YAN Ping was responsible for final version revision and overall accountability.

Conflict of Interest: The authors declare no conflict of interest.

ORCID IDs:
CHENG Zhuozhuo https://orcid.org/0009-0007-1703-5292
ZHANG Rui https://orcid.org/0009-0007-9433-7171
XU Haofeng https://orcid.org/0000-0002-3803-0286
HUANG Junting https://orcid.org/0000-0003-2582-2687
LIANG Zijing https://orcid.org/0000-0001-9759-9571
YAN Ping https://orcid.org/0000-0001-5238-4534

References

[1] AGUSTÍ A, CELLI B R, CRINER G J, et al. Global initiative for chronic obstructive lung disease 2023 report: gold executive summary[J]. Eur Respir J, 2023, 61(4): 2300239. DOI: 10.1183/13993003.00239-2023.

[2] HALPIN D M G. Mortality of patients with COPD[J]. Expert Rev Respir Med, 2024, 18(6): 381-395. DOI: 10.1080/17476348.2024.2375416.

[3] ADELOYE D, SONG P G, ZHU Y J, et al. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis[J]. Lancet Respir Med, 2022, 10(5): 447-458. DOI: 10.1016/S2213-2600(21)00511-7.

[4] MARINIELLO D F, D' AGNANO V, CENNAMO D, et al. Comorbidities in COPD: current and future treatment challenges[J]. J Clin Med, 2024, 13(3): 743. DOI: 10.3390/jcm13030743.

[5] FEINSTEIN A R. The pre-therapeutic classification of co-morbidity in chronic disease[J]. J Chronic Dis, 1970, 23(7): 455-468. DOI: 10.1016/0021-9681(70)90054-8.

[6] EROGLU S A, GUNEN, YAKAR H I, et al. Influence of comorbidities in long-term survival of chronic obstructive pulmonary disease patients[J]. J Thorac Dis, 2019, 11(4): 1379-1386. DOI: 10.21037/jtd.2019.03.78.

[7] SHAH C H, ONUKWUGHA E, ZAFARI Z, et al. Economic burden of comorbidities among COPD patients hospitalized for acute exacerbations: an analysis of a commercially insured population[J]. Expert Rev Pharmacoecon Outcomes Res, 2022, 22(4): 683-690. DOI: 10.1080/14737167.2021.1981291.

[8] Chinese Thoracic Society COPD Group. Guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease (2007 revision)[J]. Chin J Tuberc Respir Dis, 2007, 30(1): 8-17. DOI: 10.3760/j:issn:1001-0937.2007.01.002.

[9] World Health Organization, WHO Collaborating Centre for the Family of International Classifications at Peking Union Medical College Hospital, DONG Jingwu. International statistical classification of diseases and related health

problems: ICD-10 Volume 2, Instruction manual[M]. Beijing: People' s Medical Publishing House, 2008.

[10] LIU Qian, ZHANG Jingyi, LI Yujing. Systematic cluster analysis of comorbidity patterns in elderly inpatients in Tangshan[J]. Chin J Prev Med, 2023, 24(12): 1333-1338. DOI: 10.16506/j.1009-6639.2023.12.011.

[11] HU Qianqian, ZHOU Tong, LIU Zhihui, et al. Analysis of comorbidity status and patterns in middle-aged and elderly ischemic stroke patients: based on data from a tertiary hospital in Henan Province[J]. Chin Gen Pract, 2024, 27(2): 201-207. DOI: 10.12114/j.issn.1007-9572.2023.0459.

[12] PAN Ye, LIU Zhihui, HU Qianqian, et al. Study on multimorbidity patterns in Chinese elderly[J]. Chin Gen Pract, 2023, 26(29): 3608-3615. DOI: 10.12114/j.issn.1007-9572.2023.0186.

[13] YAO S S, CAO G Y, HAN L, et al. Prevalence and patterns of multimorbidity in a nationally representative sample of older Chinese: results from the China health and retirement longitudinal study[J]. J Gerontol A Biol Sci Med Sci, 2020, 75(10): 1974-1980. DOI: 10.1093/gerona/glz185.

[14] CHEN S M, KUHN M, PRETTNER K, et al. The global economic burden of chronic obstructive pulmonary disease for 204 countries and territories in 2020-50: a health-augmented macroeconomic modelling study[J]. Lancet Glob Health, 2023, 11(8): e1183-e1193. DOI: 10.1016/S2214-109X(23)00217-6.

[15] CALABRIA S, RONCONI G, DONDI L, et al. Cardiovascular events after exacerbations of chronic obstructive pulmonary disease: results from the exacerbations of COPD and their outcomes in cardio vascular diseases study in Italy[J]. Eur J Intern Med, 2024, 127: 97-104. DOI: 10.1016/j.ejim.2024.04.021.

[16] FORDER A, ZHUANG R, SOUZA V G P, et al. Mechanisms contributing to the comorbidity of COPD and lung cancer[J]. Int J Mol Sci, 2023, 24(3): 2859. DOI: 10.3390/ijms24032859.

[17] HANSEN N S, ÄNGQUIST L, LANGE P, et al. Comorbidity clusters and healthcare use in individuals with COPD[J]. Respir Care, 2020, 65(8): 1120-1127. DOI: 10.4187/respcare.07136.

[18] CUI Jia, GUO Yanfei, TONG Yaqi, et al. Study on comorbidity status and patterns in middle-aged and elderly COPD patients in a Beijing hospital from 2012-2021[J]. Chin J Prev Med, 2023, 57(5): 701-709. DOI: 10.3760/cma.j.cn112150-20230216-00117.

[19] JUREVIČIENĖ E, BURNEIKAITĖ G, DAMBRAUSKAS L, et al. Epidemiology of chronic obstructive pulmonary disease (COPD) comorbidities in Lithuanian national database: a cluster analysis[J]. Int J Environ Res Public Health, 2022, 19(2): 970. DOI: 10.3390/ijerph19020970.

[20] SKAJAA N, LAUGESEN K, HORVÁTH-PUHÓ E, et al. Comorbidities and mortality among patients with chronic obstructive pulmonary disease[J]. BMJ

Open Respir Res, 2023, 10(1): e001798. DOI: 10.1136/bmjresp-2023-001798.

[21] ZOU X Y, ZOU S Y, ZHANG R L, et al. Association of lifestyle factors with multimorbidity risk in China: a national representative study[J]. Appl Res Qual Life, 2024, 19(3): 1411-1435. DOI: 10.1007/s11482-024-10291-3.

[22] KIVIMÄKI M, STRANDBERG T, PENTTI J, et al. Body-mass index and risk of obesity-related complex multimorbidity: an observational multicohort study[J]. Lancet Diabetes Endocrinol, 2022, 10(4): 253-263. DOI: 10.1016/S2213-8587(22)00033-X.

[23] BUSEBEE B, GHUSN W, CIFUENTES L, et al. Obesity: a review of pathophysiology and classification[J]. Mayo Clin Proc, 2023, 98(12): 1842-1857. DOI: 10.1016/j.mayocp.2023.05.026.

[24] LIAN H, KOU L, HAN X Z, et al. Comprehensive comorbidity assessment for the ECOPD: a long-term multi-centre retrospective study[J]. BMC Pulm Med, 2024, 24(1): 487. DOI: 10.1186/s12890-024-03257-6.

[25] JAMES B D, GREENING N J, TRACEY N, et al. Prognostication of co-morbidity clusters on hospitalisation and mortality in advanced COPD[J]. Respir Med, 2024, 222: 107525. DOI: 10.1016/j.rmed.2023.107525.

[26] BALBIRSINGH V, MOHAMMED A S, TURNER A M, et al. Cardiovascular disease in chronic obstructive pulmonary disease: a narrative review[J]. Thorax, 2022: thoraxjnl-thora2021-218333. DOI: 10.1136/thoraxjnl-2021-218333.

[27] CHEN Y C, CHANG Y P, HUANG K T, et al. Unraveling the pathogenesis of asthma and chronic obstructive pulmonary disease overlap: focusing on epigenetic mechanisms[J]. Cells, 2022, 11(11): 1728. DOI: 10.3390/cells11111728.

[28] SOBALA R, DE SOYZA A. Bronchiectasis and chronic obstructive pulmonary disease overlap syndrome[J]. Clin Chest Med, 2022, 43(1): 61-70. DOI: 10.1016/j.ccm.2021.11.005.

[29] GOEL K, EGERSDORF N, GILL A, et al. Characterization of pulmonary vascular remodeling and microRNA-126-targets in COPD-pulmonary hypertension[J]. Respir Res, 2022, 23(1): 349. DOI: 10.1186/s12931-022-02267-4.

[30] JUNDI B, AHMED H, REECE J, et al. The relationship of cholesterol responses to mitochondrial dysfunction and lung inflammation in chronic obstructive pulmonary disease[J]. Medicina, 2023, 59(2): 253. DOI: 10.3390/medicina59020253.

[31] VIGLINO D, JULLIAN-DESAYES I, MINOVES M, et al. Nonalcoholic fatty liver disease in chronic obstructive pulmonary disease[J]. Eur Respir J, 2017, 49(6): 1601923. DOI: 10.1183/13993003.01923-2016.

[32] PARK H Y, KANG D, SHIN S H, et al. Chronic obstructive pulmonary disease and lung cancer incidence in never smokers: a cohort study[J]. Thorax, 2020, 75(6): 506-509. DOI: 10.1136/thoraxjnl-2019-213732.

[33] CRINER G J, AGUSTI A, BORGHAEI H, et al. Chronic obstructive pulmonary disease and lung cancer: a review for clinicians[J]. Chronic Obstr Pulm Dis, 2022, 9(3): 454-476. DOI: 10.15326/jcopdf.2022.0296.

[34] TRAN P B, KAZIBWE J, NIKOLAIDIS G F, et al. Costs of multimorbidity: a systematic review and meta-analyses[J]. BMC Med, 2022, 20(1): 234. DOI: 10.1186/s12916-022-02427-9.

Supplementary Tables

Supplementary Table 1. Univariate Analysis of Total Hospitalization Costs

Variable	Total Hospitalization Costs [M(P25,P75), yuan]	Z(K) value	P value
Age (years)			
40-49	12765.24 (9783.79, 17427.97)	18.492a	<0.001
50-59	12489.42 (9756.53, 17446.68)		
60-69	12129.62 (8547.76, 18197.29)		
70-79	12246.90 (9293.56, 16550.07)		
$ 80|12469.98(9653.40, 17264.76)||||$BMI(kg/m^{2}$)			
<18.5	12884.66 (9999.69, 17462.38)	47.663a	<0.001
18.5-23.9	13566.81 (10160.13, 18278.35)		
24.0-27.9	13452.90 (10451.08, 18817.36)		
$ $28.0	12507.35 (9550.54, 17048.97)		
Education level			
Primary school or below	11996.25 (9407.65, 16422.41)	3.718a	<0.001
Junior/high school	12545.06 (9903.32, 17144.64)		
College or above	12461.50 (9758.95, 16758.10)		
Cardiovascular metabolic disease pattern	13162.04 (9814.15, 18210.87)	127.605a	<0.001
Hepatorenal disease pattern	12944.82 (9866.05, 17370.83)		

Variable	Total Hospitalization Costs [M(P25,P75), yuan]	Z(K) value	P value
Digestive system disease pattern	12499.50 (9721.94, 17198.38)		
Arthropathy pattern	13155.02 (9662.31, 19054.47)		
Cancer pattern	13296.30 (10216.64, 18114.28)		
Respiratory system diseases pattern	12111.52 (9287.14, 16427.83)		

Note: a represents K value, remaining test statistics are Z values.

Supplementary Table 2. Univariate Analysis of Western Medicine Costs

Variable	Western Medicine Costs [M(P25,P75), yuan]	Z(K) value	P value
Age (years)			
40-49	2223.24 (1368.06, 3768.59)	101.944a	<0.001
50-59	1938.15 (1206.72, 3263.31)		
60-69	1625.18 (937.82, 3008.81)		
70-79	1786.95 (1109.06, 3077.42)		
$ 80|2098.12(1289.86, 3522.54)||||$BMI(kg/m^{2}$)			
<18.5	2297.63 (1460.85, 3841.88)	74.781a	<0.001
18.5-23.9	2673.24 (1577.45, 4466.39)		
24.0-27.9	2533.78 (1565.99, 4241.89)		
$ $28.0	2112.21 (1296.73, 3553.16)		
Education level			
Primary school or below	1980.57 (1145.06, 3287.42)	5.864a	<0.001
Junior/high school	2118.76 (1389.05, 3512.36)		
College or above	2039.62 (1323.32, 3345.92)		

Variable	Western Medicine Costs [M(P25,P75), yuan]	Z(K) value	P value
Cardiovascular-metabolic disease pattern	2476.42 (1377.01, 4248.98)	108.685a	<0.001
Hepatorenal disease pattern	2275.30 (1383.63, 3725.45)		
Digestive system disease pattern	2141.78 (1339.73, 3689.39)		
Arthropathy pattern	2069.28 (1122.39, 3924.74)		
Cancer pattern	2372.74 (1433.12, 3939.05)		
Respiratory system diseases pattern	2021.81 (1247.31, 3456.25)		

Note: a represents K value, remaining test statistics are Z values.

Supplementary Table 3. Univariate Analysis of Antibacterial Medication Costs

Variable	Antibacterial Medication Costs [M(P25,P75), yuan]	Z(K) value	P value
Age (years)			
40-49	467.16 (3.62, 1017.19)	125.676a	<0.001
50-59	386.64 (3.95, 813.79)		
60-69	17.87 (0.00, 544.32)		
70-79	241.55 (0.00, 728.52)		
$ 80|410.56	(0.00, 929.27)||||$BMI(kg/m^{2}$)		
<18.5	507.54 (78.40, 1076.40)	72.660a	<0.001
18.5-23.9	615.75 (197.60, 1215.81)		
24.0-27.9	594.66 (137.20, 1287.61)		
$ $28.0	429.66 (0.00, 932.75)		
Education level			

Variable	Antibacterial Medication Costs [M(P25,P75), yuan]	Z(K) value	P value
Primary school or below	329.72 (0.00, 842.40)	14.166a	<0.001
Junior/high school	455.03 (0.00, 751.40)		
College or above	418.00 (15.96, 858.36)		
Cardiovascular metabolic disease pattern	537.92 (0.00, 1211.07)	101.944a	<0.001
Hepatorenal disease pattern	492.23 (39.55, 1040.35)		
Digestive system disease pattern	439.54 (2.23, 960.70)		
Arthropathy pattern	307.90 (0.00, 982.80)		
Cancer pattern	493.88 (13.32, 1057.23)		
Respiratory system diseases pattern	405.29 (0.00, 919.09)		

Note: a represents K value, remaining test statistics are Z values.

Note: Figure translations are in progress. See original paper for figures.