International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

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ORIGINAL RESEARCH

Characterizing ECOPD Phenotypes: Associations with In-Hospital Outcomes and Immunoinflammatory Mechanisms

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Background: Hospitalization due to exacerbations of chronic obstructive pulmonary disease (ECOPD) is linked to substantial mortality rates.

Objective: This study aimed to identify the clinical and inflammatory phenotypes of patients with ECOPD, as well as to examine their associations with in-hospital outcomes. We sought to explore the underlying mechanisms that contribute to the relationship between ECOPD phenotypes and these outcomes.

Methods: A k-means cluster analysis was conducted on 20,890 recruited patients hospitalized for ECOPD. Logistic regression analyses were utilized to evaluate the associations between the identified phenotypes and in-hospital outcomes, such as mortality, invasive mechanical ventilation (IMV), and intensive care unit (ICU) admission. Additionally, a mediation analysis was performed to elucidate the immunoinflammatory mechanisms underlying the relationship between ECOPD phenotypes and in-hospital outcomes.

Results: Three distinct phenotypes were identified: Cluster 1 (n=4,944, 23.67%) exhibited a "Female Eosinophilic Phenotype", Cluster 2 (n=10,814, 51.77%) displayed a "Male Eosinophilic Phenotype", and Cluster 3 (n=5,132, 24.57%) presented as an "Geriatric Multimorbidity-Associated Neutrophilic Systemic Inflammatory Phenotype". Clusters 2 and 3 were associated with higher risks of in-hospital mortality (adjusted odds ratio [OR_{adj}]=1.88 and 17.07, respectively) and IMV (OR_{adj}=2.52 and 7.59, respectively) compared to Cluster 1. Patients in Cluster 3 also experienced an extended hospital stay (median of 13 days) and an increased risk of ICU admission (OR_{adj}=7.72). Additionally, blood eosinophils, neutrophils, CRP, and albumin played a mediating role in the relationship between ECOPD phenotypes and the composite outcome.

Conclusion: Our study identified three phenotypes stratified by sex, multimorbidity burden, and inflammatory endotypes, which advanced threshold definition for eosinophilic exacerbations and provided prognostic insights for ECOPD management.

Keywords: exacerbations of chronic obstructive pulmonary disease, ECOPD, phenotype, cluster analysis, in-hospital outcome, immunoinflammation, endotype

Received: 6 November 2024
Accepted: 4 May 2025
Published: 22 May 2025

Introduction

Exacerbation of chronic obstructive pulmonary disease (ECOPD) drives 20% of COPD-related hospitalizations.[1–4] ECOPD demonstrates marked heterogeneity in clinical presentations and immune-inflammatory signatures, contributing to elevated hospitalization, readmission rates and mortality risks. Hospitalized exacerbations demand vigilant monitoring for clinical deterioration, particularly for invasive mechanical ventilation (IMV) requirement, intensive care unit (ICU) transfer, and mortality prevention.[3,5–10]

Our previous study on asthma exacerbations identified three distinct phenotypes associated with disease progression and adverse in-hospital outcomes, highlighting the significant heterogeneity present even during exacerbations.[11] Similar to asthma, COPD is a heterogeneous airway disease. In stable COPD, cluster analyses have delineated distinct phenotypes, characterized by differing clinical features and progression trajectories.[5] This underscores the necessity for the implementation of phenotype-specific management strategies for COPD. For example, Burgel et al identified four COPD phenotypes, marked by variations in airflow limitation, symptoms, and comorbidities, aspects not encompassed by traditional GOLD classifications, thereby underscoring the imperative for a multidimensional assessment.[5] Castaldi et al characterized four COPD phenotypes among smokers based on baseline lung function and genetic variants; however, the absence of biomarker measurements, comorbidities, and follow-up outcomes constrained a thorough evaluation of their long-term clinical significance.[12] Furthermore, Gregory et al conducted a prospective cohort study integrating multi-omics biomarkers and comorbidities to assess subtypes over time, thus deepening our understanding of their progression and clinical significance.[13] Collectively, these studies have substantially deepened our understanding of stable COPD, offering crucial insights for clinical practice.[5,12,13] However, to our knowledge, a notable gap exists: few studies have categorized ECOPD patients into distinct phenotypes. Moreover, there is a lack of validation regarding these phenotypes and their associated immunoinflammatory mechanisms in the context of adverse outcomes during the index hospitalization.

This study proposes that patients with ECOPD can be categorized into distinct clinical and immunoinflammatory phenotypes. The objectives are: (1) to identify these phenotypes; (2) to investigate their influence on adverse outcomes during the index hospitalization; (3) to identify the associated immunoinflammatory factors and elucidate how these factors mediate the relationship between the identified phenotypes and adverse in-hospital outcomes.

Methods

Study Design and Patients

This study included two prospective observational cohort studies with a total of 29,844 inpatients. Cohort 1 (20,890 inpatients, training set) was conducted from December 2018 to October 2022, and Cohort 2 (8,954 inpatients, validation set) was conducted from November 2022 to January 2023 (Figure S1). Adult patients (age≥18 years) hospitalized for ECOPD, as defined by the Global Initiative for Obstructive Lung Diseases (GOLD), with a hospital stay longer than 24 hours, were prospectively recruited at West China Hospital, Sichuan University, China.[14,15] An ECOPD was defined according to the GOLD definition.[15] Patients with clinically and radiologically proven pneumonia and those who received any dose of systemic corticosteroids prior to admission were excluded. The patients were followed-up until discharge or death to assess prognosis. Cohort 1 (training set) was used for performing cluster analysis and cohort 2 (validation set) for validating the clusters. To assess whether the cluster analysis in training set had reproducibility, the same algorithm of cluster analysis in training set was used for the validation set. As this was a "real-world" study, patients management was guided by the consulting physicians based on GOLD. The study was approved by the Institutional Review Board (IRB) of West China Hospital, Sichuan University (Chengdu, China) (No. 2023–1882). All patients provided written informed consent. Additional details of the management of ECOPD are available in Methods section of the Supplementary Material.

Data Collection and Clinical Assessments at Baseline

Patients underwent a standardized assessment according to the GOLD within 24 hours of admission. This assessment collected comprehensive information, including demographic data, smoking status, body mass index (BMI), comorbidity, the COPD-specific co-morbidity test (COTE-index), oxygen therapy requirements, treatment history, GOLD staging, and spirometric data from clinical records prior to admission. Multimorbidity was defined as the co-existence of two or more

long-term health conditions.[16–18] Additional details of multidimensional assessment and data collection are available in Methods section of the Supplementary Material.

Laboratory Testing

Blood samples were collected within 24 hours of admission before in-hospital treatments for laboratory tests, including complete blood count, hematology, arterial blood gas analysis, inflammatory markers (C-reactive protein [CRP] and procalcitonin [PCT]), biochemistry, coagulation and electrolyte measurements. All measurements were completed within 2 hours of blood sampling.

In-Hospital Management of ECOPD

As a real-world study, ECOPD management adhered to GOLD under attending physicians' discretion. All patients received standardized evaluations including comprehensive medical history, physical exams, and systematic assessments (Table S1). In-hospital therapies were delayed until after baseline blood sampling to avoid confounding effects on eosinophil quantification.

Primary and Secondary in-Hospital Outcomes

To examine the associations between the identified clusters and in-hospital outcomes, all patients were followed up until hospital discharge or death. The analysis focused on events occurring during the hospital stay. The primary outcome was a composite outcome, defined as the occurrence of any of the following events during hospitalization: in-hospital all-cause death, ICU admission, or IMV. Secondary outcomes: individual components of the composite outcome. Additional details of definition of the outcomes are available in Methods section of the Supplementary Material.

Statistical Analyses and Cluster Analyses

Variable Selection

A comprehensive dataset of 130 variables was established. Variables with >10% missing data were excluded. For the remaining 86 variables, missing values were imputed using multilevel generalized linear models via multiple imputation. Dimensionality reduction was performed through exploratory factor analysis (continuous variables) and multiple correspondence analysis (categorical variables) to identify PCA candidates. Twelve variables were ultimately selected for PCA based on factor loadings (absolute value > 0.5), correlation coefficient < 0.6, and clinical relevance (Table S2), including: sex, age, BMI, smoking status, the presence of anemia and peripheral vascular disease, COTE-index, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), level of serum albumin, prior-year severe exacerbations, and level of CRP.[19]

Cluster Analysis

Cluster identification followed a two-stage approach using PCA-derived components, as described in our previous studies.[11,20] Methodological details are provided in the Methods section of Supplementary Materials.

Other Analysis

Categorical variables are presented as counts (%). Inter-cluster comparisons employed: ANOVA/Kruskal-Wallis tests for continuous variables (normality assessed via Shapiro-Wilk); χ^2-test/Fisher's exact tests for categorical variables, with Bonferroni-adjusted post hoc analyses. A decision-tree classifier (10-fold cross-validation) quantified cluster predictability, reporting misclassification rates.[21] Multivariable logistic regression adjusted for demographics (sex, age), clinical characteristics (exacerbation severity, COPD grade, BMI, mean arterial pressure [MAP], COTE index), treatment factors (non-invasive ventilation, pre-/in-hospital therapies), and smoking status when assessing phenotype-outcome associations. Statistical significance was set at α=0.05.

Guided by our causal inference framework (Figure S2), we implemented a four-phase mediation analysis to quantify how inflammatory mediators explain phenotype-outcome associations.[22–25] The pure indirect effect (PIE) was estimated through: 1) phenotype-mediator regressions, 2) mediator-outcome logistic models (covariate-adjusted), and 3) counterfactual decomposition using the mediation R package (v4.3.1). Age, sex, and smoking status were included as adjusted variables throughout. Methodological specifications are detailed in the Supplementary Methods.

Results

Subject Characteristics

The training cohort included 20,890 ECOPD patients (validation: n=8,954; Tables 1, S3 and S4). Patients had a median age of 72.3 years (IQR: 65.5–79.5) and BMI of 22.0 kg/m² (IQR: 19.49, 24.46), with 19.89% being female and 85.65%

Table 1 Demographic and Clinical Characteristics of ECOPD Patients by Cluster Analysis in the Training Cohort

Baseline Variables	Total	Cluster 1	Cluster 2	Cluster 3	P value
n	20890	4944 (23.67)	10,814 (51.77)	5132 (24.57)	
Age, years, median (Q1, Q3)	72.3 (65.5, 79.5)	73.10 (66.40, 79.70)[bc]	70.40 (63.80, 77.30)[ac]	76.20 (68.80, 83)[ab]	<0.001
Female, n (%)	4156 (19.89)	3229 (65.31)[bc]	58 (0.54)[ac]	859 (16.93)[ab]	<0.001
BMI, kg/m^2 median (Q1, Q3)	22.04 (19.49, 24.46)	22.96 (20.55, 25.53)[bc]	22.09 (19.68, 24.49)[ac]	20.52 (18.07, 23.38)[ab]	<0.001
<18.5 kg/m^2	3619 (17.32)	490 (9.91)[bc]	1668 (15.42)[ac]	1461 (28.47)[ab]	<0.001
>28 kg/m^2	1220 (5.84)	534 (10.80)[bc]	577 (5 0.34)[bc]	109 (2.12)[ab]	
MAP <70 mmHg, n (%)	228 (1.09)	33 (0.66)[c]	86 (0.79)[c]	109 (2.12)[ab]	<0.001
Smoking status, n (%)					
Never	2998 (14.35)	876 (17.72)[c]	2038 (18.85)[c]	84 (1.64)[ab]	<0.001
Ex-smoker and current smoker	17892 (85.65)	4068 (82.28)[c]	8776 (81.15)[c]	5048 (98.36)[ab]	
Arterial blood gas, n (%)					<0.001
$PaCO_2$, mmHg	45.5±16.6	38.5±27.1[bc]	44.5 ± 7.8[ac]	52.3 ± 13.7[ab]	<0.001
PH < 7.35, n (%)	2310 (11.05)	498 (10.07)[c]	1088 (10.06)[c]	724 (14.11)[ab]	<0.001
PaO_2, mmHg	62.5±18.1	68.8 ±15.4[bc]	66.5 ± 15.8[ac]	57.7 ± 19.3[ab]	<0.001
Pre-admission medication, n (%)					
LAMA	4888 (23.39)	1187 (24.01)	2498 (23.10)	1203 (23.44)	0.455
ICS-LABA	4377 (20.95)	1027 (20.77)	2238 (20.70)	1112 (21.67)	0.347
LABA-LAMA	6796 (32.53)	1585 (32.06)	3481 (32.19)	1730 (33.71)	0.115
LABA-LAMA-ICS	1695 (8.11)	395 (7.99)	859 (7.94)	441 (8.59)	0.349
Treatment during hospitalization, n (%)[†]					
ICS	16796 (80.40)	3985 (80.60)	8681 (80.28)	4130 (80.48)	0.880
SAMA	1754 (8.40)	398 (8.05)	935 (8.65)	421 (8.20)	0.387
SABA	16673 (78.91)	3899 (78.86)	8690 (80.36)	4084 (79.58)	0.084
Systemic corticosteroids	13767 (65.90)	2271 (55.04)[bc]	6571 (60.76)[ac]	4475 (87.20)[ab]	<0.001
Antibiotics	8528 (40.82)	2039 (41.24)	4432 (40.98)	2057 (40.08)	0.440
Oxygen therapy, n (%)[††]					
COT	18339 (87.79)	4387 (88.73)	9472 (87.59)	4480 (87.30)	0.058
NIV	2504 (11.98)	246 (4.97)[bc]	829 (7.66)[ac]	1429 (27.8)[ab]	<0.001
HFNC	1695 (8.11)	355 (7.18)[bc]	809 (7.48)[ac]	531 (10.35)[ab]	<0.001
Severe exacerbation in the preceding year, n (%)	8768 (41.97)	1093 (22.11)[bc]	3339 (30.88)[ac]	4336 (84.49)[ab]	<0.001

(*Continued*)

Table 1 (Continued).

Baseline Variables	Total	Cluster 1	Cluster 2	Cluster 3	P value
Severity of exacerbation, n (%)					
Mild	4012 (19.21)	2761 (55.85)[bc]	269 (2.49)[ac]	982 (19.13)[ab]	<0.001
Moderate	9113 (43.62)	1429 (28.90)[bc]	6621 (61.23)[ac]	1063 (20.71)[ab]	
Severe	7765 (37.17)	754 (15.25)[bc]	3924 (36.29)[ac]	3087 (60.15)[ab]	
Respiratory function, mean (SD)					
FEV_1, %pred.	42.30 (14.00)	44.00 (13.80)[bc]	41.70 (14.40)[ac]	32.80 (13.40)[ab]	<0.001
FEV_1/FVC, %	60.90 (15.60)	62.30 (15.40)[bc]	61.50 (15.50)[ac]	55.3 (15.60)[ab]	<0.001
COPD grades prior to acute exacerbation, n (%)					
1	4860 (23.26)	1542 (31.19)[bc]	2406 (22.25)[ac]	912 (17.77)[ab]	<0.001
2	6004 (28.74)	2255 (45.61)[bc]	2985 (27.60)[ac]	764 (14.89)[ab]	
3	7221 (34.57)	945 (19.11)[bc]	4045 (37.41)[ac]	2231 (43.47)[ab]	
4	2805 (13.43)	202 (4.09)[bc]	1378 (12.74)[ac]	1225 (23.87)[ab]	
COTE-index, mean (SD)	1 (0,2)	1.24 (1.85)[c]	1.26 (1.85)[c]	1.51 (2)[ab]	<0.001
COTE-index ≥ 4, n (%)	1949 (9.32)	422 (8.54)[c]	944 (8.73)[c]	583 (11.36)[ac]	<0.001
Comorbidities, n (%)					
Hypertension	8387 (40.15)	2155 (43.59)[b]	4000 (36.99)[ac]	2232 (43.49)[a]	<0.001
Diabetes	4139 (19.81)	988 (19.98)[c]	1987 (18.37)[c]	1164 (22.68)[a]	<0.001
Anemia	12072 (57.29)	2920 (59.06)[bc]	4025 (45.54)[ac]	4227 (82.36)[ab]	<0.001
Peripheral vascular disease	2525 (12.09)	442 (8.92)[bc]	635 (5.87)[ac]	1448 (28.22)[ab]	<0.001
Cognitive impairment	3669 (17.56)	675 (13.65)[bc]	1457 (13.47)[ac]	1537 (29.94)[ab]	<0.001
Frailty	3832 (18.34)	666 (13.47)[bc]	1094 (10.11)[ac]	2072 (40.37)[ab]	<0.001
Coagulopathy	3861 (18.48)	549 (11.10)[bc]	1560 (14.43)[ac]	1752 (34.14)[ab]	<0.001
CVD	7599 (36.38)	1678 (33.94)[bc]	3293 (30.45)[ac]	2628 (51.21)[ab]	<0.001
Chronic kidney disease	1332 (6.38)	305 (6.17)[bc]	446 (4.12)[ac]	581 (11.32)[ab]	<0.001
Hyperlipidemia	2001 (9.58)	642 (12.96)[bc]	1025 (9.48)[ac]	334 (6.51)[ab]	<0.001
In-hospital outcomes					
Composite outcome, n (%)	1816 (8.69)	146 (2.95)[bc]	525 (4.85)[ac]	1145 (22.31)[ab]	<0.001
Death, n (%)	426 (2.04)	12 (0.24)[c]	56 (0.51)[c]	358 (6.97)[ab]	<0.001
Invasive ventilation, n (%)	1587 (7.59)	140 (2.83)[bc]	487 (4.50)[ac]	960 (18.7)[ab]	<0.001
ICU admission, n (%)	1611 (7.71)	141 (2.85)[bc]	495 (4.57)[ac]	975 (18.99)[ab]	<0.001
Hospital LOS, median (Q1, Q3)	10 (7,15)	7 (4,14)[bc]	10 (7.11)[ac]	13 (9,20)[ab]	<0.001

Notes: Data are presented as n (%) for categorical variables and mean ± SD for continuous variables with normal distribution. For continuous variables not normally distributed, medians and interquartile ranges (IQR) are used. Intergroup comparisons were analyzed using one-way ANOVA (for continuous variables) or χ^2-tests (for categorical variables), followed by post hoc pairwise comparisons with Bonferroni correction. Significance thresholds were adjusted to α=0.0167 for pairwise tests. Superscripts denote significant differences: [a] vs Cluster 1, [b] vs Cluster 2, [c] vs Cluster 3. †All in-hospital therapies were initiated following baseline blood sampling to prevent interference with clinical measurements. ††The listed oxygen therapies are non-mutually exclusive and may overlap in clinical use, potentially resulting in combined utilization rates exceeding 100%.

Abbreviations: ECOPD, exacerbations of chronic pulmonary disease; BMI, body mass index; COT, conventional oxygen therapy; HFNC, high-Flow Nasal Cannula therapy; ICU, intensive care unit; ICS, inhaled corticosteroids; IQR, interquartile ranges IV, invasive ventilation; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; MAP, mean arterial pressure; NIV, non-invasive ventilation; $PaCO_2$, partial pressure of carbon dioxide; LOS, length of stay; SABA, short-acting beta-agonists; SAMA, short-acting beta-agonists.

https://doi.org/10.2147/COPD.S505016

current/ex-smokers. Clinically, 41.97% experienced ≥1 severe exacerbation in the prior year, while prevalent comorbidities included anemia (57.29%), hypertension (40.15%), cardiovascular disease (CVD; 36.38%), and diabetes (19.81%). Frailty and coagulopathy were observed in 18.34% and 18.48% of patients, respectively. Critical hospitalization outcomes comprised 2.04% (426) mortality, 7.59% (1,587) invasive ventilation events, 7.71% (1611) ICU admissions, and length of stay (median=10 days, IQR: 7–15).

Cluster Profile

Cluster 1: Female Eosinophilic Phenotype

Cluster 1 comprised 4,944 patients (23.67%), characterized by female predominance (65.31%) and higher blood eosinophil counts (BEC; median 0.11×10^9/L [IQR: 0.05–0.20]) compared to Cluster 3 (0.05×10^9/L [IQR:0–0.15]; $P<0.001$). This cluster showed the fewer acute exacerbations (AEs) (22.11%) in the preceding year, in-hospital mortality (0.24%), and the composite outcome incidence (2.95%).

Cluster 2: Male Eosinophilic Phenotype

Cluster 2 (n=10,814, 51.77%) demonstrated male predominance (99.5%) with elevated eosinophilic markers: median eosinophil count 0.13×10^9/L [IQR:0.06–0.23] and eosinophil–basophil ratio (EBR) 5.25 [IQR:2.75–9], both significantly higher than Cluster 3 ($P<0.001$).

Cluster 3: Geriatric Multimorbidity-Associated Neutrophilic Systemic Inflammatory Phenotype

Cluster 3 comprised 5,132 patients (24.57%) and was characterized by older age (median 76.20 years [IQR: 68.8–83.0]), the highest COTE-index score, and extensive comorbidities, including hypertension (43.49%), anemia (82.36%), cognitive impairment (29.9%), frailty (40.4%), and CVD (51.21%). This phenotype exhibited more neutrophilic inflammation (7.28×10^9/L [IQR: 4.20–10.99] neutrophils vs 3.92×10^9/L [2.90–5.20] in Cluster 1; $P<0.001$) and systemic inflammation markers: CRP (44.50 mg/L [11.40–104.00]), PCT (0.15 ng/mL [0.06–0.54]), and D-Dimer (1.78 μg/mL [0.76–4.37] vs 0.62μg/mL [0.32–1.34] in Cluster 2). Cachexia prevalence (BMI < 18.5 kg/m²) was nearly 3-fold higher than Cluster 1 (28.47% vs 9.91%; $P<0.001$). Cluster 3 demonstrated the worst outcomes with 84.49% prior-year severe exacerbation, 22.31% in-hospital composite outcome rate, and 6.97% mortality.

In-Hospital Outcomes and Cluster Prediction

Cluster 3 exhibited the most severe in-hospital outcomes, with a composite outcome rate of 22.31% (n=1,145) versus 2.95% in Cluster 1, alongside significantly higher mortality (6.97%, n=358) and prolonged median hospitalization duration (13 days, IQR: 9–20). This cluster also demonstrated elevated critical care needs: 18.70% required IMV and 18.99% required ICU admission. Logistic regression analyses revealed substantially increased risks in Cluster 3 compared to Clusters 1–2, with adjusted odds ratios of 8.18 (95% CI: 6.72–10.14; $P<0.001$) for the composite outcome, 17.07 (95% CI: 9.45–30.66; P<0.001) for mortality, 7.59 (95% CI: 6.08–9.51; $P<0.001$) for IMV, and 7.72 (95% CI: 6.22–9.82; $P<0.001$) for ICU admission (Figure 1). A decision-tree model (sex, smoking status, prior severe exacerbation, neutrophil-to-lymphocyte ratio [NLR]) achieved 85.3% classification accuracy, comparable to models using all 12 variables (Figure 2). Detailed risk factor analyses are presented in Tables S5–S11.

Mediation Analysis Reveals Phenotype-Specific Immunoinflammatory Mechanisms in ECOPD

Mediation analysis investigated immunoinflammatory mechanisms linking ECOPD phenotypes to adverse outcomes (Figures S3–S6). Key mediators (eosinophils, neutrophils, CRP, and serum albumin) differentially modulated phenotype-outcome associations across clusters. In Cluster 2, eosinophils mediated 17.2–19.6% of adverse outcome risks: 17.2% for mortality, 19.2% for ICU admission, 19.6% for IMV, and 17.3% for composite outcomes. In contrast, composite outcome of Cluster 3 was predominantly driven by neutrophil-mediated pathways (33.6% risk elevation), systemic inflammation (CRP-mediated effects; 20.31%), and hypoalbuminemia (32.1%). Neutrophils mediated 34.7% of the effect of Cluster 3

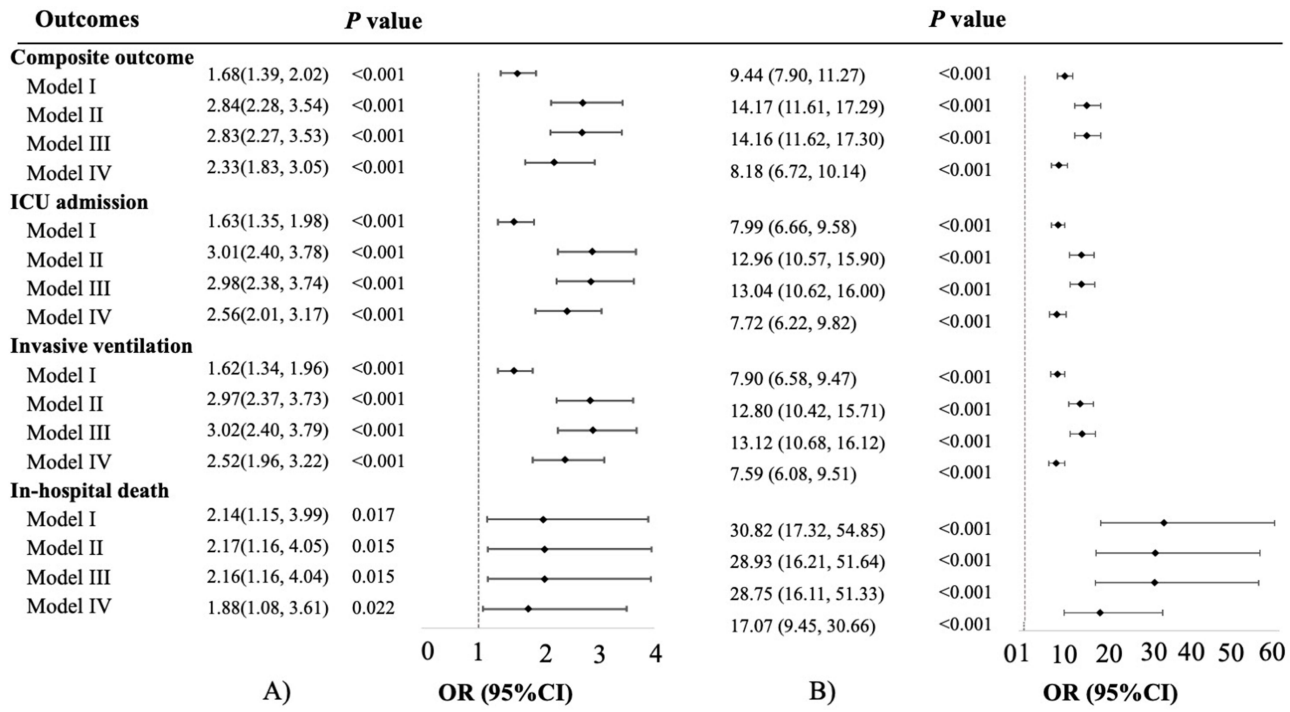

Figure 1 Forest plot illustrating the three identified clusters in relation to in-hospital outcomes.
Notes: This figure presents the correlations of the three clusters with death, ICU admission, invasive ventilation, and a composite outcome, using Cluster 1 as the reference. (**A**) Cluster 2 exhibited a significantly increased risk of in-hospital death, ICU admission, invasive ventilation, and the composite outcome compared to Cluster 1. The models are as follows: Model I = crude; Model II = adjusted for sex and age; Model III = Model II plus further adjustments for exacerbation severity, COPD grades, smoking status, BMI, and MAP; Model IV = Model III plus the COTE-index and prehospital and in-hospital treatments collected in our study. (**B**) Cluster 3 showed a significantly increased risk of in-hospital death, ICU admission, invasive ventilation, and the composite outcome compared to Cluster 1, with the models adjusted in the same manner as for Cluster 2.

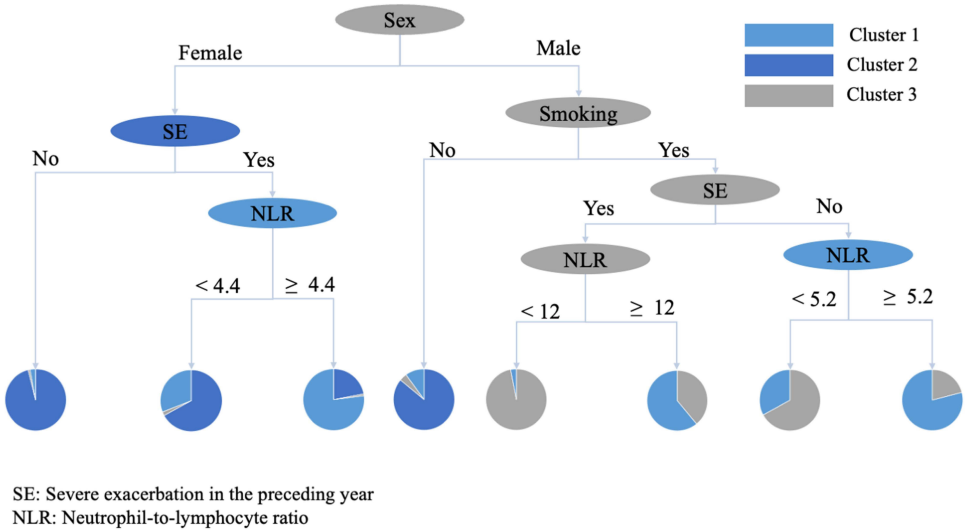

Figure 2 Decision tree analysis and classification of predicted clinical cluster assignments.
Notes: This figure illustrates a decision tree analysis and the classification of predicted clinical cluster assignments for patients. Patient assignments to the three clusters were based on four variables.
Abbreviations: SE, Severe exacerbation in the preceding year; NLR, Neutrophil-to-lymphocyte ratio.

on mortality (PIE = 0.72, 95% CI: 0.46–0.94), 31.6% on ICU admission (PIE = 0.11, 95% CI: 0.02–0.21), and 32.2% on invasive mechanical ventilation (PIE = 0.12, 95% CI: 0.03–0.21).

https://doi.org/10.2147/COPD.S505016

Discussion

Our study is the first to employ cluster analysis for stratifying ECOPD patients into distinct clinical-inflammatory phenotypes at hospitalization and validate their association with adverse in-hospital outcomes. In a real-world cohort of 20,890 patients, we identified three phenotypes, with the "Geriatric Multimorbidity-Associated Neutrophilic Systemic Inflammatory Phenotype" (Cluster 3) demonstrating poor outcomes: 6.97% mortality, 22.31% the composite adverse outcome (IMV, ICU admission, or death), and 18.99% ICU admission rates. These figures fall within the ranges reposted in prior ECOPD studies, which document mortality of 1.0–11.8% and ICU admission rates of 17.4–24.4%, underscoring the limitations of existing etiology-based classifications (eg, viral vs bacterial) that fail to adequately stratify risk in multidimensional clinical-inflammatory profiles.[26–29]

Our study reveals that blood eosinophils significantly moderate the influence of ECOPD phenotypes on several in-hospital outcomes, including a diminished risk of the composite outcome, IMV, ICU admission, and in-hospital mortality. Mechanically, elevated eosinophils during exacerbations likely indicate the persistence of Type 2 inflammation.[30] In our study, the BEC threshold for defining eosinophilic ECOPD ($\geq 0.11\times10^9$/L) is lower than the established stable-phase cutoff ($\geq 0.3\times10^9$/L) associated with ICS efficacy. This threshold discrepancy likely reflects acute-phase eosinophil depletion, evidenced by Bafadhel et al's study of median BEC declines at 0.11×10^9/L (IQR: 0.10–0.13) during ECOPD.[31] Whether such changes can adequately predict ICS responsiveness during hospitalization remains unproven, necessitating prospective trials to correlate acute-phase BEC with post-ICS or targeted eosinophil therapy outcomes. Mechanistic studies are essential to verify whether eosinophil-rich exacerbations display elevated glucocorticoid receptor-α expression in the airway.[31–33] Our findings support the GOLD guideline's recommendation to consider ICS for stable COPD patients with BEC of ≥100 cells/μL, particularly when this aligns with their history of exacerbations.[14] Future research should verify if acute-phase thresholds for BEC need to be adjusted downward relative to stable-phase criteria, ensuring a balance between therapeutic benefits and the risks of excessive ICS and targeted eosinophil therapy use in non-eosinophilic phenotypes.

Besides, our additional analysis revealed significant sex-based differences in eosinophil counts, with male patients demonstrating higher median blood eosinophil levels (0.12×10^9/L) compared to females (0.08×10^9/L; $P<0.001$), a finding consistent with prior studies.[34–36] Experimental models indicate estrogen suppresses eosinophilopoiesis through ERα-mediated inhibition of IL-5/IL-13 signaling in bone marrow progenitors, while clinical data show premenopausal women exhibit 32–41% lower eosinophil counts than age-matched men, potentially reflecting estradiol's attenuation of eosinophil peroxidase release and leukotriene synthesis.[37] However, the precise mechanisms underlying sex hormone-eosinophil interactions in COPD remain elusive, particularly regarding androgen receptor modulation of eosinophil survival, menopause-related hormonal shifts, and tissue-specific inflammatory regulation.[38,39] Future investigations integrating hormone profiling with single-cell transcriptomic analysis of airway eosinophils are warranted to delineate these pathways and their therapeutic implications.

Our study identifies an ECOPD phenotype distinguished by reduced eosinophil counts (Cluster 3), which correlates with inferior hospital outcomes. The data indicate that low eosinophil levels are associated with more severe exacerbation and elevated hospitalization rates, thereby serving as prognostic indicators for clinical deterioration.[40] It has confirmed that non-eosinophilic patients exhibit higher mortality rates compared to their eosinophilic counterparts, thereby reinforcing our findings from Cluster 3.[41] Furthermore, patients in Cluster 3 display a substantial morbidity burden, signifying a complex profile marked by systemic inflammatory responses and multiple comorbidities. The effective management of these patients requires a comprehensive approach that tackles both pulmonary and systemic issues.

Systemic inflammation, which is directly correlated with adverse clinical outcomes, serves as an indicator of the severity of COPD.[42] Elevated CRP levels are particularly noteworthy in patients with severe COPD, signifying not only the occurrence of exacerbations but also persistent chronic inflammation.[43,44] The elevated CRP levels in Cluster 3 patients are associated with poorer in-hospital adverse outcomes compared to other clusters, likely attributable to their heightened systemic inflammatory responses exacerbated by multiple comorbidities. Mediation analysis further elucidates that elevated CRP levels significantly mediate the relationship between ECOPD phenotypes and in-hospital mortality. Consequently, CRP emerges as a crucial prognostic biomarker in ECOPD.[45–47] Further research is essential to comprehensively understand these relationships and assess the potential impact of interventions designed to reduce CRP, particularly in high-risk groups such as Cluster 3. Moreover, there is a pressing need for personalized management strategies that concurrently address systemic inflammation

and associated comorbidities. Besides, albumin is a crucial biomarker for assessing health status in ECOPD patients. In Cluster 3, more than 90% of patients exhibit levels below 40 g/L.[48] This reduced albumin level indicates inadequate nutrition, thereby exacerbating clinical outcomes.[49] Hypoalbuminemia in Cluster 3 may arise due to inadequate dietary intake and persistent inflammation, exacerbated by respiratory stress and recurrent exacerbations.[50] This cycle of declining health extends beyond malnutrition, impacting nutritional status, immune response, and tissue repair, thereby heightening the risk of severe outcomes.[51]

This study's strengths include a large, rigorously curated cohort of 20,890 hospitalized ECOPD patients, enabling robust phenotype identification through multidimensional data integration. We systematically addressed high-dimensional complexity by applying exploratory factor analysis and multiple correspondence analysis, distilling 130 parameters to 12 clinically interpretable biomarkers, thereby balancing methodological transparency with replicability. However, our study has several limitations. Firstly, we used blood eosinophil counts as a surrogate for sputum eosinophils to predict the eosinophilic phenotype, although this method has been validated.[52] Secondly, despite employing a broad range of variables and objective statistical methods, some subjectivity in variable selection remains.[53] Additionally, we did not identify the causes of exacerbation, including viral and bacterial profiles.[54] Lastly, the generalizability of our findings is limited since patient phenotypes were identified from a single center without external validation, despite the robust sample size.

Conclusion

This study defines three ECOPD phenotypes stratified by sex, multimorbidity, and inflammatory endotypes, advancing eosinophil-guided exacerbation thresholds and prognostic risk stratification. We establish a framework integrating acute-phase eosinophil dynamics with systemic inflammation to personalize management, considering neutrophilic inflammation and multimorbidity as therapeutic targets. Our findings could optimize acute-care precision and phenotype-driven resource allocation.

Abbreviations

ECOPD, Exacerbations of chronic obstructive pulmonary disease; ALB, Albumin; BMI, Body mass index; COT, conventional oxygen therapy; COTE, index -the COPD, specific co-morbidity test; CVD, cardiovascular disease; CRP, C-reactive protein; CI, Confidence interval; HFNC, high-Flow Nasal Cannula therapy; IMV, invasive mechanical ventilation; ICU, Intensive care unit; ICS, inhaled corticosteroids; GOLD, the Global Initiative for Obstructive Lung Diseases; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonists; LOS, Length of stay; MAP, mean arterial pressure; NIV, non-invasive ventilation; NLR, Neutrophil-to-lymphocyte ratio; PCA, Principal component analysis; PLR, Platelet-to-lymphocyte ratio; PIE, the pure indirect effect; PaO2, Partial pressure of oxygen; OR, Odds ratio; OR_{adj}, Odds ratio after adjusting for confounders; SABA, short-acting beta-agonists; SAMA, short-acting beta-agonists; SE, Severe exacerbation in the preceding year.

Data Sharing Statement

Supplementary data to this article can be found online. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

The study was approved by the Institutional Review Board (IRB) of West China Hospital, Sichuan University (Chengdu, China) (No. 2023–1882). All patients provided written informed consent.

Acknowledgments

We thank all participating patients and all departments, healthcare providers and professionals involved in this study.

Author Contributions

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

Funding

This study was supported by 1.3.5 project for disciplines of excellence-Clinical Research Fund, West China Hospital, Sichuan University (2023HXFH045), 1.3.5 project for disciplines of excellence, West China Hospital, Sichuan University (ZYGD23002), Science and Technology Foundation of Sichuan Province (2022NSFSC1278), National Natural Science Foundation of China (82100032, 82300036, 82200037), Post-Doctor Research Project, West China Hospital, Sichuan University (2023HXBH093), China Postdoctoral Science Foundation (2022M722294), and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Z20192005).

Disclosure

The authors declare that they have no conflicts of interest to disclose.

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