Re-exacerbation within 30 days of discharge is associated with poor prognosis in the following year among patients hospitalised with exacerbation of chronic obstructive pulmonary disease: a clinical cohort study

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ABSTRACT

Background Exacerbation of chronic obstructive pulmonary disease (ECOPD) is a complex phenomenon, with marked heterogeneity in the aetiology, pathophysiology and clinical manifestations. This study aimed to evaluate the clinical characteristics and long-term outcomes of patients with 30-day exacerbation among those hospitalised with ECOPD in China.

Methods Data from the Acute Exacerbations of Chronic Obstructive Pulmonary Disease Inpatient Registry were used in this study. The patients were divided into re-event and non-event groups based on the incidence of re-exacerbation within 30 days of discharge. Exacerbation, severe exacerbation and all-cause readmissions in the following 12 months were the outcomes of interest. The cumulative incidence rates and incidence densities were calculated. Multivariate hazard function models were used to determine the association between 30-day re-exacerbation and the long-term outcomes after accounting for the competing risk of death.

Results Re-exacerbation within 30 days of discharge was observed in 4.9% (n=242) of the patients (n=4963). The cumulative incidence rates and incidence densities of exacerbation, severe exacerbation and all-cause readmissions in the event group were significantly higher than those in the non-event group. After adjustment, re-exacerbation within 30 days of discharge was associated with increased risks of exacerbation, severe exacerbation and all-cause readmissions in the following 12 months (adjusted HR: 3.85 (95% CI: 3.09 to 4.80), 3.46 (2.66 to 4.25) accordingly).

Conclusion Re-exacerbation of COPD within 30 days of discharge is a significant predictor of long-term prognosis. In clinical practice, short-term re-exacerbation is a significant clinical phenotype of ECOPD that requires careful management at the earliest.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ The exacerbation of chronic obstructive pulmonary disease (ECOPD) is a frequent and major cause of mortality among patients with COPD. Previous studies have identified exacerbation history as a significant phenotype for future events. However, evidence regarding the association between short-term re-exacerbation after discharge and long-term prognosis remains limited.

WHAT THIS STUDY ADDS
⇒ Re-exacerbation within 30 days of discharge was a significant predictor of future 1-year outcomes, including exacerbation, severe exacerbation and all-cause readmission, in patients hospitalised with ECOPD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ This prospective clinical cohort study provides new evidence for identifying the phenotype associated with frequent exacerbation among patients with COPD. Our study emphasises the importance of in-hospital care and outpatient management.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a heterogeneous lung condition, is characterised by pathological damage to the airways (bronchitis and bronchiolitis) and/or alveoli (emphysema), leading to persistent, often progressive, airflow obstruction.1 Symptoms, such as dyspnoea, cough and sputum production, impair the quality of life of patients with COPD.2 Exacerbation of COPD (ECOPD) is defined as an event characterised by the worsening of dyspnoea, cough and/or sputum production over a period of <14 days,1 which is often associated with an increased risk of death.3 In recent years, ECOPD has been identified as a clinically important phenotype of COPD.
with distinct clinical features and prognosis. As one of the major phenotypes of COPD, it is associated with the progression of emphysema and irreversible airflow limitation. Moreover, it is the leading cause of COPD-related hospitalisation that results in increased overall morbidity. The ECOPD phenotype increases mortality and contributes to the high healthcare and socioeconomic burden of the disease. Several phenotypes of ECOPD have been described previously, and these phenotypes have varying impacts on the clinical outcomes of the patients. Eosinophilic exacerbation (15%) may benefit from corticosteroid therapy prior to admission, however, corticosteroid therapy increases the risk of infections. Bacterial exacerbation, characterised by the presence of airway bacteria in the sputum, attributes to a greater intensity of airway neutrophil inflammation and is directly correlated with longer duration of hospitalisation in patients with ECOPD. Thus, eosinophilic and bacterial exacerbation clusters represent distinct clusters with clinically important differences.

Readmission within 30 days of hospitalisation is a major concern among patients with ECOPD. It has a significant impact on the clinical course and accounts for approximately one-third of the costs related to COPD healthcare expenditure. Consequently, the Hospital Readmissions Reduction Program was developed to reduce the readmission rate. Several studies on COPD have reported that the incidence of 30-day readmission ranges from 8% to 26%, with great variation observed among countries and hospitals. However, short-term re-exacerbation after discharge is the main cause of rehospitalisation among patients with ECOPD. Thus, it is necessary to identify patients susceptible to re-exacerbation and provide them with additional medical resources.

Most previous studies were conducted in developed countries in Europe and North America. Thus, there is a need to identify the ECOPD phenotypes, especially short-term re-exacerbation within 30 days of discharge, in low/middle-income countries. Lowering short-term re-exacerbation is one of the key objectives of COPD treatment, and physicians can accomplish this goal through efficient recognition and therapeutic strategies. Therefore, this study aimed to determine and analyse the clinical features and long-term outcomes of patients with re-exacerbation of ECOPD in 30 days in a Chinese population. We hypothesised that further management of post-discharge support for COPD may be elucidated by gaining insights into the characteristics of short-term re-exacerbation in patients with ECOPD.

METHODS

Study design and participants

This was a prospective, multicentre, clinical cohort study. The data used in the present study were obtained from the Acute Exacerbations of Chronic Obstructive Pulmonary Disease Inpatient Registry (ACURE), an ongoing nationwide multicentre, prospective, observational study in China. This study was designed to investigate the clinical picture of patients hospitalised with ECOPD in China. The registry was created on 1 September 2017 and is expected to recruit 7600 patients from more than 170 hospitals across mainland China. Further details regarding ACURE have been described previously.

The present analysis included the data of patients enrolled until November 2021. The eligibility criteria were as follows: (1) age ≥18 years, (2) hospitalisation for confirmed diagnosis of ECOPD and (3) provided written informed consent for participation. The exclusion criteria included: (1) participation in other ongoing clinical trials or interventional drug studies and (2) loss to follow-up within 30 days of discharge. Among the 8372 subjects screened for eligibility from the ACURE dataset, 4963 patients were eligible for inclusion in this study (figure 1).

Procedures and measurements

The baseline demographic characteristics, disease history and clinical features of the patients were collected (ie, age, sex, education, body mass index (BMI), history of smoking, previous exacerbation, previous drug and non-drug treatments, modified British Medical Research Council (mMRC) Questionnaire and COPD Assessment Test (CAT) score at admission). The results of the pulmonary function and laboratory tests, treatments (drug and non-drug), complications/comorbidities and patient outcomes during hospitalisation were recorded.

The study protocol requires all enrolled patients to complete a face-to-face follow-up at the 1st, 3rd and 12th month after discharge. Within these intervals, follow-ups were performed by the physicians via telephone interviews at 6 and 9 months. Any self-reported and hospital-captured medical event (eg, exacerbation, rehospitalisation or death), the date of occurrence and other detailed
information were recorded at each visit or interview. As it was not possible to complete each patient’s follow-up on the exact calendar date, the data provided the opportunity to observe the long-term prognosis for >13 months after discharge.

As per the criteria endorsed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) scientific committee, exacerbation was defined as an acute episode of intensified dyspnoea and/or cough and sputum production within <14 days that required additional therapy. Severe exacerbation was defined as an acute episode that required emergency treatment or hospitalisation.1

The patients were divided into the event (re-exacerbation within 30 days of discharge) and non-event (no re-exacerbation within 30 days of discharge) groups according to the incidence of ECOPD. The outcomes of interest in this study were exacerbation, severe exacerbation and all-cause readmission during the 12 months following the 31st day after discharge. We also compared the all-cause mortality and ECOPD-related mortality between the event and non-event groups. As cardiovascular events were considered a significant outcome after exacerbation, we also compared the incidence of cardiovascular events between the two groups.

Patient and public involvement
The patients and public WERE NOT involved in the design, conduct, reporting or dissemination of the research.

Statistical analysis
Descriptive statistics were stratified according to the group. Continuous variables are presented as means±SD if normally distributed or as median (quartiles) if they had skewed distribution. Student’s t-test or the Kruskal-Wallis test was used for comparisons when appropriate. Categorical variables are presented as frequency (percentage (%)) and were compared using the χ² test.

Time-to-event analyses were used to assess the long-term outcomes. The cumulative incidence rates of 12-month exacerbation, severe exacerbation and all-cause readmission since the 31st day after discharge were generated using the cumulative incidence function 26 after accounting for competing risk caused by death during follow-up. The 12-month incidence densities of exacerbation, severe exacerbation and all-cause readmission were calculated based on the sum of events and cumulative person-years of follow-up.

Fine-Gray subdistribution hazard models that simultaneously account for competing risks were used to calculate the HR and 95% CIs to determine the association between the 30-day events and long-term outcomes.21 To reduce potential confounding factors, demographic characteristics (age, BMI, smoking and education) and clinical features (previous exacerbation and treatment, CAT score at admission, complications/comorbidities and treatment during hospitalisation) were included in the models for adjustment. Lung function is recognised as a predictor of exacerbation; however, post-bronchodilator percentage-predicted forced expiratory volume in 1 s (FEV₁, %pred) was not included in the models as a notable proportion of patients had missing FEV₁, %pred values (1099 of 4963, 22.1%). The association was further evaluated by deleting data with missing FEV₁, %pred values and including the FEV₁, %pred values in the models. In addition, multiple interactions between 30-day events and other risk factors were detected by adding an interaction term to the multivariable models. A p value of <0.05 of the interaction term indicates a significant interaction. Stratification analysis of the risk factors was performed subsequently.

All analyses were performed using SAS statistical software (V.9.4; SAS Institute). A two-tailed p value of <0.05 was considered statistically significant for all analyses.

RESULTS
Baseline and 30-day characteristics
Among the 8372 patients included in the ACURE Study, 4963 were eligible for inclusion in the analysis of the present study. Among the included patients, 242 (4.9%) experienced at least one re-exacerbation within 30 days of discharge (figure 1).

The mean age of the patients was 68.89±9.50 years, and 78.64% of the patients were men. The proportions of smokers, severe exacerbation in the past year, previous treatment with home oxygen, complications/comorbidities and treatment during hospitalisation differed significantly between the two groups. The event group had significantly lower FEV₁, %pred values, higher mMRC and CAT scores at admission, and higher PaCO₂ (artery carbon dioxide pressure) and neutrophil counts (table 1).

The clinical characteristics on the 30th day of follow-up are presented in online supplemental table 1. The mMRC and CAT scores in the event group were significantly higher than those in the non-event group. The patients in the event group were more likely to receive home oxygen therapy during the 30-day follow-up period.

Incidence rates of the 12-month outcomes
Since the 31st day of discharge, the cumulative incidences of exacerbation, severe exacerbation and all-cause readmission during the following 12 months in the event group were significantly higher than those in the non-event group (figure 2). The cumulative incidence rates of exacerbation, severe exacerbation and all-cause readmission in the event group were 49.1% (41.6% to 56.1%), 33.9% (27.2% to 40.8%) and 34.1% (27.4% to 41.0%), respectively. In contrast, the incidence rates in the non-event group were 15.2% (14.0% to 16.5%), 12.4% (11.1% to 13.7%) and 14.0% (12.7% to 15.5%), respectively.

The incidence densities differed significantly between the two groups, as shown in figure 3. The incidence
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N=4963)</th>
<th>Event (N=242)</th>
<th>Non-event (N=4721)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>68.89±9.50</td>
<td>68.88±9.82</td>
<td>68.89±9.48</td>
<td>0.988</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>3903 (78.64)</td>
<td>182 (75.21)</td>
<td>3721 (78.82)</td>
<td>0.181</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>Primary school and below</td>
<td>2331 (46.97)</td>
<td>132 (54.55)</td>
<td>2199 (46.58)</td>
<td></td>
</tr>
<tr>
<td>Junior high school</td>
<td>1620 (32.64)</td>
<td>67 (27.69)</td>
<td>1553 (32.9)</td>
<td></td>
</tr>
<tr>
<td>Senior high school and above</td>
<td>1012 (20.39)</td>
<td>43 (17.77)</td>
<td>969 (20.53)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²), mean±SD</td>
<td>22.24±3.82</td>
<td>21.81±3.98</td>
<td>22.26±3.81</td>
<td>0.073</td>
</tr>
<tr>
<td>Smoking status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Never smoking</td>
<td>1594 (32.12)</td>
<td>92 (38.02)</td>
<td>1502 (31.82)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>2152 (43.36)</td>
<td>116 (47.93)</td>
<td>2036 (43.13)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>1217 (24.52)</td>
<td>34 (14.05)</td>
<td>1183 (25.06)</td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td>0.022</td>
</tr>
<tr>
<td>Severe exacerbation in the past year</td>
<td>2869 (57.81)</td>
<td>157 (64.88)</td>
<td>2712 (57.45)</td>
<td></td>
</tr>
<tr>
<td>Ever regular long-acting bronchodilator treatment (≥3 months)</td>
<td>1204 (24.26)</td>
<td>65 (26.86)</td>
<td>1139 (24.13)</td>
<td>0.333</td>
</tr>
<tr>
<td>Ever regular inhaled corticosteroid treatment (≥3 months)</td>
<td>1154 (23.25)</td>
<td>64 (26.45)</td>
<td>1090 (23.09)</td>
<td>0.228</td>
</tr>
<tr>
<td>Ever home oxygen therapy</td>
<td>800 (16.12)</td>
<td>52 (21.49)</td>
<td>748 (15.84)</td>
<td>0.020</td>
</tr>
<tr>
<td>Ever pulmonary rehabilitation</td>
<td>534 (10.76)</td>
<td>35 (14.46)</td>
<td>499 (10.57)</td>
<td>0.057</td>
</tr>
<tr>
<td>FEV₁%pred, median (quartile)</td>
<td>43.51 (32.19, 60.34)</td>
<td>38.57 (28.15, 53.56)</td>
<td>43.78 (32.31, 60.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mMRC at admission, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.084</td>
</tr>
<tr>
<td>&lt;2</td>
<td>769 (15.49)</td>
<td>28 (11.57)</td>
<td>741 (15.70)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>4194 (84.51)</td>
<td>214 (88.43)</td>
<td>3980 (84.30)</td>
<td></td>
</tr>
<tr>
<td>CAT score at admission, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>&lt;10</td>
<td>392 (7.90)</td>
<td>7 (2.89)</td>
<td>385 (8.16)</td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>4571 (92.10)</td>
<td>235 (97.11)</td>
<td>4336 (91.84)</td>
<td></td>
</tr>
<tr>
<td>Laboratory test</td>
<td></td>
<td></td>
<td></td>
<td>0.582</td>
</tr>
<tr>
<td>pH, mean±SD</td>
<td>7.40±0.14</td>
<td>7.40±0.06</td>
<td>7.40±0.15</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mm Hg), mean±SD</td>
<td>77.93±26.95</td>
<td>75.66±24.65</td>
<td>78.06±27.06</td>
<td>0.210</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg), mean±SD</td>
<td>45.08±12.87</td>
<td>47.76±14.24</td>
<td>44.93±12.78</td>
<td>0.002</td>
</tr>
<tr>
<td>Neutrophil, median (quartile)</td>
<td>5.00 (3.61, 7.12)</td>
<td>5.42 (4.11, 8.24)</td>
<td>4.97 (3.58, 7.07)</td>
<td>0.001</td>
</tr>
<tr>
<td>Eosinophil, median (quartile)</td>
<td>0.10 (0.03, 0.22)</td>
<td>0.10 (0.02, 0.23)</td>
<td>0.10 (0.03, 0.22)</td>
<td>0.517</td>
</tr>
<tr>
<td>Lymphocytes, median (quartile)</td>
<td>1.28 (0.90, 1.77)</td>
<td>1.19 (0.82, 1.68)</td>
<td>1.29 (0.90, 1.77)</td>
<td>0.086</td>
</tr>
<tr>
<td>Comorbidity/complication, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.588</td>
</tr>
<tr>
<td>Asthma</td>
<td>459 (9.25)</td>
<td>20 (8.26)</td>
<td>439 (9.30)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1239 (24.96)</td>
<td>84 (34.71)</td>
<td>1155 (24.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1465 (29.52)</td>
<td>102 (42.15)</td>
<td>1363 (28.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic cor pulmonale</td>
<td>1057 (21.30)</td>
<td>88 (36.36)</td>
<td>969 (20.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>889 (17.91)</td>
<td>52 (21.49)</td>
<td>837 (17.73)</td>
<td>0.137</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1652 (33.29)</td>
<td>77 (31.82)</td>
<td>1575 (33.36)</td>
<td>0.619</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>280 (5.64)</td>
<td>25 (10.33)</td>
<td>255 (5.40)</td>
<td>0.001</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>341 (6.87)</td>
<td>18 (7.44)</td>
<td>323 (6.84)</td>
<td>0.721</td>
</tr>
<tr>
<td>Diabetes</td>
<td>537 (10.82)</td>
<td>27 (11.16)</td>
<td>510 (10.80)</td>
<td>0.863</td>
</tr>
<tr>
<td>Treatment during hospitalisation, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Multivariate analysis of the 12-month outcomes
Multivariate analysis of the long-term prognosis revealed that compared with patients without an event, re-exacerbation within 30 days of discharge was significantly associated with a 3.85-fold, 3.46-fold, and 3.28-fold risk of exacerbation, severe exacerbation, and all-cause readmission during the following 12 months, respectively (figure 4). Stratification analysis revealed consistent associations across demographic and clinical features except for home oxygen therapy and CAT scores at admission (online supplemental table 2). A sensitivity multivariate analysis performed after including the GOLD stage in the models revealed that the association between 30-day events and long-term prognosis remained significant (online supplemental table 3).

DISCUSSION
ECOPD is a major global concern as it has a significant effect on the prognosis of the patient. The clinical presentation of ECOPD is heterogeneous.22 The present study aimed to determine 30-day re-exacerbation in patients with ECOPD after discharge, and it was observed that patients with repeated 30-day re-exacerbation had more severe respiratory symptoms and poorer clinical prognosis at the 30-day and 12-month follow-ups.

COPD is a heterogeneous condition with various underlying mechanisms in different subsets of patients. ECOPD has been identified as a major clinical phenotype of COPD, which is responsible for disease progression, disease-related healthcare costs, morbidity and mortality.25 As reported by previous studies, patients with ECOPD can be classified into different exacerbation clusters (such as bacterial, viral and eosinophilic). Bacteria have been implicated as a major cause of ECOPD and are detected in approximately half of the patients with ECOPD.24 Viruses are also considered to play a key role in up to 50% of cases with ECOPD.25 Severe eosinophilic exacerbation presents with variable phenotypes. Thus, marked heterogeneity exists in the aetiology of ECOPD.26 Some studies have focused on the findings of clinical assessments, indicating the role of the frequency of exacerbation.27 In the present study, re-exacerbation within 30 days of discharge was identified as a significant clinical phenotype of ECOPD that is associated with clinically meaningful outcomes.

An abundance of data indicates that neutrophils play a key role in the pathogenesis of COPD and are related to lung destruction and remodelling.29 ECOPD is characterised by impaired neutrophil function and decreased receptor-dependent reactive oxygen species production.30 The present study showed that the neutrophil count in patients with ECOPD with re-exacerbation within 30 days of discharge was higher than that in the patients without ECOPD. Similarly, several other studies have indicated that increased disease severity is associated with an increase in the inflammatory cell count but a downregulation of activity.

The main causes and risk factors for COPD are environmental exposure, including tobacco smoking, household gases, outdoor air pollution and inhalation of toxic
particles. Although smoking is a key risk factor for COPD, less than 50% of heavy smokers develop COPD.

Thus, it has been estimated that 50% of COPD cases are caused by other environmental risk factors, such as biomass exposure, occupational exposure and air pollution. Environmental exposure also increases the risk of ECOPD, hospitalisation and mortality. Our findings on exposure among patients with ECOPD showed that non-smoking COPD is more common and that risk factors other than smoking may contribute to a greater burden of COPD in China. Therefore, further research is warranted to better understand the characteristics of non-smokers with COPD.

Most studies have reported a beneficial effect of inhaled corticosteroids (ICS) combined with long-acting beta₂-agonists (LABAs)/long-acting muscarinic antagonists (LAMAs) over LABA/LAMA alone in improving symptoms and lung function and reducing exacerbation in patients with moderate-to-very severe COPD and frequent exacerbation. However, treatment with ICS modifies the lung microbiome, resulting in a high risk of developing pneumonia. Pavord et al reported that a lower blood eosinophil count increased the risk of developing pneumonia in patients with COPD receiving ICS at low doses. Similarly, although there was no difference in ICS use before or during hospitalisation between the two groups, patients in the non-event group had a significantly higher incidence of pneumonia during hospitalisation in our study, accompanied by a higher blood neutrophil count but not eosinophil count. Further, the comorbidity of pneumonia during hospitalisation was not associated with exacerbation, severe exacerbation or all-cause readmission during the following 12 months, which may be due to the standard use of ICS after discharge. Therefore, the use of ICS should be studied further. Moreover, ICS should be used cautiously, particularly in patients with COPD without high eosinophil counts.

An association between exacerbation-related rehospitalisation and follow-up visits after discharge was confirmed. Furthermore, hospitalisation for the disease had a strong negative impact on the quality of life of patients with COPD, leading to increased all-cause mortality. However, no standard profile can be applied to the timing of follow-up visits after discharge. Early follow-up (within 1 month) after discharge should be undertaken, as it has been associated with fewer exacerbation-related readmissions. Consistent with the results of previous studies, we also observed that the median time of re-exacerbation was 19 days in patients with ECOPD with re-exacerbation.
within 30 days of discharge. Therefore, a careful review of discharge therapy must be performed approximately 2 weeks after discharge from the hospital, and changes in therapy must be made to delay the deterioration of disease and maintain the quality of life in patients with COPD.

To the best of our knowledge, this is one of the most extensive studies on the prognosis of 30-day re-exacerbation in patients with ECOPD in China. However, the present study has some limitations. First, no clear information on non-smoking, which plays a central role in the exacerbation of COPD, was available. In addition, other types of exposures, such as biomass and occupational exposure, were not investigated. Second, some clinical information, such as eosinophil count, was not included in the present study. A notable proportion of patients had missing eosinophil count values in the dataset (1732 of 4963, 34.9%), and a risk of bias may have occurred if all data with missing values were deleted. Similarly, the prevalence of bacterial exposure was not available, and lung function parameters were excluded from the model due to non-negligible missing values. However, the lung function was analysed using sensitivity analysis. Lastly, mild and moderate exacerbation of COPD may also negatively affect the rates of hospitalisation, readmission and disease progression, which were not reported in the present study. In the future, more clinical indices, such as eosinophil count, were not investigated. Second, some clinical information, such as eosinophil count, was not included in the present study. A notable proportion of patients had missing eosinophil count values in the dataset (1732 of 4963, 34.9%), and a risk of bias may have occurred if all data with missing values were deleted. Similarly, the prevalence of bacterial exposure was not available, and lung function parameters were excluded from the model due to non-negligible missing values. However, the lung function was analysed using sensitivity analysis. Lastly, mild and moderate exacerbation of COPD may also negatively affect the rates of hospitalisation, readmission and disease progression, which were not reported in the present study. In the future, more clinical indices, such as the severity of ECOPD (including mild and moderate exacerbation), and risk factors other than smoking and lung function trajectory should be investigated as it may help identify ECOPD phenotypes with even greater resolution.

In conclusion, the present study revealed a significant phenotype of ECOPD: re-exacerbation within 30 days of discharge. Patients with this phenotype had poor clinical outcomes at the 12-month follow-up. A better understanding of ECOPD phenotypes could contribute to better and more precise management of COPD exacerbation events.

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