Eosinophilic phenotype was associated with better clinical remission in elderly but not middle-aged patients with acute exacerbations of COPD

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Abstract

Background: There is limited evidence of the relationship between peripheral blood eosinophilia and clinical remission of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) at different ages, especially in elderly patients, which was the objective of the present study. Methods: This retrospective study stratified patients by age (>65 or [?]65 years) and analyzed the relationship between blood eosinophilia ([?]2% or <2%) and AECOPD clinical remission at observing time points of 7, 10, 14, 21, and 28 days. Results: Of 703 AECOPD cases analyzed, 616 were elderly (>65 years), 272 of whom had eosinophilic exacerbations. There were statistically significant differences in leukocyte count, high-sensitivity C-reactive protein levels (hs-CRP), and overall and daily hospital costs between eosinophilic and non-eosinophilic AECOPD patients ($p<0.05$, respectively). In the overall analysis, eosinophilic exacerbation was significantly associated with a higher remission rate at 7 (hazard ratio [HR]=1.457 [1.072, 1.982]), 10 (HR=1.316 [1.108, 1.562]), 14 (HR=1.334 [1.102, 1.615]), 21 (HR=1.326 [1.125, 1.562]), and 28 days (HR=1.254[1.078, 1.459]). The subgroup analysis showed that eosinophilic exacerbation yielded better clinical remission than non-eosinophilic exacerbation in elderly patients (>65 years old) at 7 (HR=1.521 [1.084, 2.136]), 10 (HR=1.319 [1.096, 1.588]), 14 (HR=1.374 [1.118, 1.689]), 21 (HR=1.326 [1.112, 1.582]), and 28 days (HR=1.234 [1.049, 1.451]), while no differences were observed in middle-aged patients (between 45 and 65 years) at all time points (all $p>0.05$). Conclusion: The eosinophilic phenotype was associated with better clinical remission at 7, 10, 14, 21, and 28 days among elderly but not in middle-aged patients with AECOPD.

Eosinophilic phenotype was associated with better clinical remission in elderly but not middle-aged patients with acute exacerbations of COPD

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What's known

* Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease with high morbidity and mortality.

* COPD causes great disease burden, mainly due to its acute exacerbation (AE).

* There was limited evidence of the relationship between blood eosinophilic phenotype and AECOPD clinical remission at different ages.

What's new

* Elderly AECOPD patients with higher blood eosinophils ([?]2%) gained better clinical remission than those with blood eosinophils lower than 2%.

* Eosinophilic phenotype was not associated with clinical remission in middle-aged AECOPD patients.

Abstract:

Background: There is limited evidence of the relationship between peripheral blood eosinophils and clinical remission of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) at different ages, especially in elderly patients, which was the objective of the present study. **Methods:** This retrospective study stratified patients by age (>65 or [?]65 years) and analyzed the relationship between blood eosinophils ([?]2% or <2%) and AECOPD clinical remission at observing time points of 7, 10, 14, 21, and 28 days.

Results: Of 703 AECOPD cases analyzed, 616 were elderly (>65 years), 272 of whom had eosinophilic exacerbations. There were statistically significant differences in leukocyte count, high-sensitivity C-reactive protein levels (hs-CRP), and hospital costs between eosinophilic and non-eosinophilic AECOPD patients (p <0.05, respectively). Among all AECOPD patients, eosinophilic exacerbation was significantly associated with a higher remission rate at 7 (hazard ratio [HR]=1.457 [1.072, 1.982]), 10 (HR=1.316 [1.108, 1.562]), 14 (HR=1.334 [1.102, 1.615]), 21 (HR=1.326 [1.125, 1.562]), and 28 days (HR=1.254[1.078, 1.459]). The subgroup analysis showed that eosinophilic exacerbation yielded better clinical remission than non-eosinophilic exacerbation in elderly patients (>65 years old) at 7 (HR=1.521 [1.084, 2.136]), 10 (HR=1.319 [1.096, 1.588]), 14 (HR=1.374 [1.118, 1.689]), 21 (HR=1.326 [1.112, 1.582]), and 28 days (HR=1.234 [1.049, 1.451]), while no differences were observed in middle-aged patients (between 45 and 65 years) at all time points (all$p$ >0.05).

Conclusion : The eosinophilic phenotype was associated with better clinical remission at 7, 10, 14, 21, and 28 days among elderly but not in middle-aged patients with AECOPD.

Keywords: chronic obstructive pulmonary disease; acute exacerbation; eosinophils; elderly; remission

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease with high morbidity and mortality[1]. It is becoming a global public health concern due to its high mortality, it was the fifth

leading cause of death in 2002 and is expected to rank third by 2030. COPD accounts for over half of the patients with chronic respiratory disease, making it the leading cause of global health care utilization and expenditure[2]. In China, nationwide epidemiology research showed that the overall prevalence of COPD was as high as 13.6% in people aged 40 years or older, implying there would be about 100 million COPD patients in China. [3]. Nationwide health policies have been promoted to improve COPD prevention and management to reduce economic burdens. However, the overall situation is still not as optimistic as expected[4, 5].

COPD significantly impacts quality of life and family income, mainly due to its acute exacerbation[6]. Acute exacerbation of COPD (AECOPD) is characterized by increased systemic and airway inflammation, leading to increased symptoms of dyspnea, sputum purulence, and sputum volume. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, AECOPD is one of the leading causes of hospitalization and contributes significantly to mortality[7]. In United States, AECOPD causes 726,000 hospitalizations annually[8]. In China, 44.4% of COPD patients developed one or more exacerbations in the 2-year observation period[9]. The impact of hospitalization on acute exacerbations in elderly COPD patients is significant, with readmission rates of 25–40% and mortality rates of 25–40% within 12 months after discharge[10-12].

Appropriate early assessment is fundamental for implementing proper initial treatment strategies and is associated with better outcomes and lower risk of treatment failure as well as the efficient and fair allocation of limited medical resources[13]. In the last decade, blood eosinophil count, an easy-to-use and easy-to-measure index which is economically efficient and provides rapid results, has been identified to be capable of measuring inflammatory response in AECOPD patients[14, 15]. The prevalence of eosinophilic COPD varies widely in different countries and regions, from 18.84% to 66.88%, with an average prevalence of 54.95%[16]. Compelling evidence has confirmed that patients with higher sputum or peripheral blood eosinophil counts are not only associated with better corticosteroid response and lower rate of AECOPD treatment failure[17, 18] but also with lower risk of all-cause mortality[19]. A study from Netherland reported that blood eosinophilia was associated with a higher short-term (10-day) treatment success rate in AECOPD patients[20], but the eosinophilic phenotype was also reported to be associated with increased risk of 12-month COPD-related readmission[21]. These studies indicated the diverse roles of blood eosinophil in AECOPD. However, limited evidence about the role of eosinophils in different age groups of AECOPD patients was reported. As COPD patients with eosinophil levels persistently >2% were more usual in older population[22]. However,. Thus, a better understanding of the relationship between eosinophilic phenotype and AECOPD clinical remission in different age groups, especially in elderly patients, is needed.

Therefore, this study investigated the role of peripheral blood eosinophil count in the prediction of AECOPD clinical remission in elderly and middle-aged patients.

2. Materials and Methods

AECOPD patients were retrospectively enrolled from the Department of Respiratory and Critical Care Medicine at the Affiliated Hospital of Chengdu University from July 1, 2014, to December 31, 2016. Patient data were extracted from the electronic medical record system; demographic, clinical, laboratory, and pulmonary function data were collected at the time of presentation. Data on clinical outcomes related to hospital admission and length of hospital stay were also collected. In-hospital remission was evaluated by defining five set time points (day 7, 10, 14, 21, and 28). The biological inflammatory state was assessed using high-sensitivity C-reactive protein (hs-CRP) level and peripheral blood count. Patients with missing information on peripheral blood count, including eosinophil counts, were excluded. The study was approved by the ethics community of the Affiliated Hospital of Chengdu University (NO.: PJ2018-012-02).

2.1 Inclusion and exclusion criteria

2.1.1 Inclusion criteria

AECOPD patients were enrolled according to the following criteria: (1) age [?]45 years; (2) a diagnosis of COPD based on the GOLD guidelines of corresponding years; and (3) a diagnosis of AECOPD based

on expert consensus on the acute exacerbation of chronic obstructive pulmonary disease in China; namely: worsening of respiratory symptoms (typically dyspnea, cough, increased sputum volume, and/or sputum purulence) beyond normal day-to-day variations and leading to a change in medication, without alternative specific causes for deterioration (such as pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism, and arrhythmia), as identified by clinical examination and/or corroborative testing[23, 24].

2.1.2 Exclusion criteria

Patients were excluded if: (1) the presence of other respiratory diseases such as bronchial asthma, bronchiectasis, tuberculosis, lung cancer, and other allergic diseases such as allergic rhinitis; (2) missing information on peripheral blood counts and pulmonary function tests; or (3) pregnancy and lactation[25].

2.2 Definitions of eosinophilic exacerbation and clinical remission

2.2.1 Definition of elderly patients

This study defined elderly and middle-aged patients as those aged >65 years and those aged [?] 45 and [?] 65 years, respectively[26].

2.2.2 Eosinophilic exacerbation

This study defined eosinophilic exacerbation as a peripheral blood eosinophil count on admission of [?]2%[17].

2.2.3 Clinical remission

Clinical remission was defined as: (1) the resolution of symptoms and signs for 12–24 hours; (2) stable arterial blood gases for 12–24 hours; (3) patients with acceptable adherence to medication; (4) patients who would be able to be successfully managed at home without frequent dyspnea [20, 23].

2.2.4 Observation time points

The time of clinical remission for every patient was collected, and the observation time points were set for statistical analysis at 7, 10 (time point of early clinical remission evaluation), 14, 21, and 28 days.

2.3 Statistical analysis

Continuous variables are presented as means with standard deviation for normally distributed variables and as medians (interquartile range [IQR]) for non-normally distributed variables. For categorical variables, data are presented as percentages. Student's t-tests were used to compare continuous parametric variables, while Mann–Whitney-U tests were used to compare continuous non-parametrical variables. Chi-squared and Fisher's exact tests were used to compare categorical data. The Cox proportional hazards model was used to analyze the associations between blood eosinophilic levels and clinical remission at different time points. Two-side P -value <0.05 were considered statistically significant. R software (version 3.6.2, The R Foundation for Statistical Computing, Vienna, Austria) was used to perform the statistical analyses and draw the figures.

3. Results

3.1 Baseline characteristics

A total of 1427 cases were enrolled during the study period. After applying the exclusion criteria, 703 AECOPD cases (84.6% male) including 312 eosinophilic exacerbations and 391 non-eosinophilic exacerbations, were considered eligible for the final analysis (Figure 1). Of these patients, 616 were older than 65 years (272 eosinophilic exacerbations and 344 eosinophilic exacerbations) and 87 were middle-aged (40 eosinophilic exacerbations and 47 eosinophilic exacerbations).

The following indicators were significantly different between the eosinophilic and non-eosinophilic exacerbation groups: neutrophils, lymphocytes, monocytes, basophils, eosinophils, and hs-CRP levels (all$p$ <0.05). No statistically significant differences in the other factors were observed (p >0.05) (Table 1).

In elderly patients, there were statistically significant differences in neutrophils, lymphocytes, monocytes, basophils, and hs-CRP levels between eosinophilic and non-eosinophilic exacerbation groups (all$p$ <0.05). In middle-aged patients, statistically significant differences were observed in neutrophils, lymphocytes, monocytes, and basophils between the eosinophilic and non-eosinophilic exacerbation phenotypes, while no statistically significant differences of hs-CRP were observed between these two groups (Tables 1).

3.2 Treatment and medical costs in different groups

Referring to the treatment, the proportions of antibiotic and joint antibiotic use were higher in non-eosinophilic AECOPD patients, but the use of short-term steroids showed no difference between these two groups. Interestingly, lengths of stay (LOS) in eosinophilic AECOPD were shorter than those in non-eosinophilic AECOPD among elderly patients, but it showed no difference in middle-aged patients. Besides, the overall hospital costs (OHC) and daily hospital costs (DHC) was lower in elderly eosinophilic AECOPD patients. (Table 2).

3.3 Association between eosinophilic exacerbation and clinical remission

Compared to patients with non-eosinophilic exacerbation, patients with eosinophilic exacerbation had an higher probability of clinical remission at the time point of 7 (p =0.020), 10(p =0.002) and, 14 (p =0.003), 21 (p< 0.001), and 28 days (p =0.003) (Table 3). Figure 2 shows and the changes of cumulative remission rates along with hospital days, with the horizontal axis (x-axis) representing time in days and the vertical axis (y-axis) the cumulative proportion of clinical remission at the different time points. The higher rate of clinical remission was observed in eosinophilic AECOPD patients at most of the time point when comparing with non-eosinophilic patients (Figure 2a).

In elderly patients, the Cox proportional hazards model showed that eosinophilic exacerbation was significantly associated with in-hospital clinical stability and eosinophilic exacerbation tended to have a higher rate of clinical remission compared to non-eosinophilic exacerbation at 7 (p =0.003), 10 (p =0.040), 14 (p =0.003), 21 (p= 0.020), and 28 (p =0.010) day time points. In contrast, no statistically significant differences were observed at all time points (all p >0.05) in the middle-aged patients (Table 3 and Figure 2b, 2c).

4. Discussion

Earlier and accurate individual risk assessment of patients is important for successful disease management[27]. Despite recent technical progress in diagnosis and treatment, the management of AECOPD remains difficult; thus, it is necessary to identify clinically meaningful predictors for successful management[28]. This retrospective study investigated the relationship between eosinophils and clinical remission of AECOPD and demonstrated several new findings. First, we observed a lower medical cost in eosinophilic AECOPD patients. Second, subgroup analysis stratified by age groups revealed a higher rate of clinical remission observed among elderly but not in middle-aged eosinophilic patients. In the baseline analysis, we found that neutrophils, hs-CRP level, and OHC in eosinophilic cases were lower and hospital time was shorter than those in non-eosinophilic cases. These findings are consistent with those of previous studies despite different clinical settings, enrollment criteria, and definitions of disease severity and exacerbation[17, 26, 29]. Our findings of statistically significant differences in LOS and OHC between groups was consistent with those of a previous study [30]. Furthermore, the Cox proportional hazards model used to assess and explore the risk of eosinophilic exacerbation to in-hospital remission of AECOPD patients, showed that eosinophilic group tended to show higher rates of clinical remission at all time points (7, 10, 14, 21, and 28 day time points). In the subgroup analysis assessing the association between eosinophilic exacerbation and remission, eosinophilic exacerbation group in elderly patients showed a higher clinical remission rate at all time points. In contrast to these findings in elderly patients, no significant differences in middle-aged patients were observed.

Eosinophilic exacerbation is associated with eosinophilic airway inflammation which was associated with T-helper cell type 2 (Th2) inflammation. Increasing evidence in recent years has shown that eosinophilic airway inflammation might play an important role in COPD[31]. Subsequent infiltration of eosinophils in the airways of COPD patients regulates the immunoglobulin E (IgE)-dependent mechanism, which is con-

sidered as an important part of Th2 cell cytokine production process[32], with an irregular Th1/Th2 ratio and interleukin-17/IgE ratio that may be caused by imbalanced Th2 cell production[33]. Previous clinical trials have explored the relationship between blood eosinophil counts over time and in-hospital management outcomes[16]. Eosinophilia has been observed both in COPD and AECOPD patients and represents a novel pathological mechanism of a special clinical phenotype in COPD. Moreover, eosinophilic exacerbation also affects COPD outcomes. Previous studies reported an association between COPD patients with persistently increased blood eosinophil counts and better outcomes; furthermore, evidence from randomized clinical trials has shown that patient blood eosinophil counts are crucial for predicting a good response to corticosteroid administration[34, 35]. Corticosteroid treatment at the time of an exacerbation may yield better interventional outcomes with shorter LOS and better treatment responses[36]. In the current study, with the similar rate of steroids use, elderly patients with eosinophilic AECOPD gained higher clinical remission rate than non-eosinophilic elderly patients, which implied that steroids acted better in elderly eosinophilic patients, highlighting the value of steroids in AECOPD patients.

Age is always listed as a risk factor for COPD; elderly patients are often accompanied by other typical comorbidities that negatively impact prognosis and health status, and the number of comorbidities is associated with the risk of COPD exacerbation[11, 37]. However, although COPD is common in older people, whether there is difference between elderly patients and middle-aged patients in terms of eosinophilic phenotype-related COPD outcomes remains unclear. Previous study reported the value of blood eosinophilia for predicting clinical remission of AECOPD by setting 10 days as the observation time point; due to the design and information collected by the study, observing the association at more set time points or adjusting for age were not possible. In this study, we were able to further demonstrate this phenomenon by setting more observation time points (at 7, 10, 14, 21, and 28 days in hospital), and patients were divided into different age groups, which would make the difference between middle-aged and elderly patients more visible. We found a significant difference in clinical remission between elderly patients and middle-aged adults over all the observation time points.

The current study has some limitations. First, although 703 patients were enrolled, this study was a single-center retrospective study. Further multi-center prospective studies evaluating the value of blood esinophils are needed. Second, patient follow-up after discharge was not performed in this study, as the data were collected from electronic medical records, and readmissions and other follow-up-related information of these patients could not be identified. To better understand the relationship between eosinophils and elderly ages, additional eosinophilic phenotype-related clinical and basic studies focusing on AECOPD at different ages might be performed

5. Conclusion:

In this study, the eosinophilic phenotype was associated with better clinical remission at 7, 10, 14, 21, and 28 days in the hospital among elderly but not middle-aged patients with AECOPD. Early identification of this special phenotype in elderly patients may be valuable in better personalized management for AECOPD.

Declarations: The authors declare no conflict of interest.

Abbreviations: AECOPD: acute exacerbations of chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease; DHC: daily hospital costs; GOLD: global initiative for chronic obstructive pulmonary disease; HR: Hazard ratio; Hs-CRP: hypersensitive C-reactive protein; mMRC: Modified Medical Research Council; CNY: Chinese Yuan; DHC: daily hospital costs; LOS: Length of stay; OHC: overall hospital costs; Th2:T-helper cell type 2;

Authors' contributions: (I) Conception and design: T.W and F.Q.; (II) Administrative support: H.Z. and F.Q.; (III) Provision of study materials or patients: Q.Z, H.Z.; (IV) Collection and assembly of data: Q.Z, H.W, and K.W.; (V) Data analysis and interpretation: Q.Z, and H.W.; (VI) Manuscript writing: Q.Z., and H.W.;; (VII) Final approval of manuscript: All authors; (VIII) Guarantor of the paper: F.Q.; All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials :The datasets during the current study are available from the corresponding author on reasonable request.**Consent for publication:** Not applicable.

Ethics approval and consent to participate: The study was approved by the ethics community of the Affiliated Hospital of Chengdu University (NO: PJ2018-012-02).

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Data availability statement : The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1 Baseline characteristics between eosinophilic and non-eosinophilic patients

	Overall analysis (n=703)	**Overall analysis (n=703)**	**Overall analysis (n=703)**	**Elderly patients (n=616)**	**Elderly patients (n=616)**	**Elderly patients (n=616)**	**Middle-aged patients (n=87)**	**Middle-aged patients (n=87)**	**M ag pa tie (n**
Variables	**Eosinophilic (n=312)**	**Non-eosinophilic (n=391)**	*p* **value**	**Eosinophilic (n=272)**	**Non-eosinophilic (n=344)**	*p* **value**	**Eosinophilic (n=40)**	**Non-eosinophilic (n=47)**	*p*
Age (year)	75.81±9.68	76.15±9.17	0.631	78.32±7.40	78.30±7.42	0.974	58.78±5.05	60.47±4.11	0.0
Gender (Male n/%)	272(87.2%)	344 (88.0%)	0.749	222(81.6%)	293(85.2%)	0.236	39(97.5%)	41(87.2%)	0.0
Smoke (Yes , n/%)	226 (74.8)	290 (77.5)	0.411	194(72.7%)	258(77.5%)	0.080	32(91.4%)	32(78.0%)	0.1
Give up smoke(n/%)	123(54.4)	164 (56.7)	0.598	111(57.5%)	152(59.1%)	0.728	12(36.4%)	12(37.5%)	0.9
Leukocytes (10^9/L)	5.75(4.68, 6.94)	7.29(5.59, 9.68)	0.000	5.64(4.56,6.93)	7.23(5.51,9.72)	0.000	6.37(5.16,6.99)	7.34(5.83,9.67)	0.0
Neutrophils (10^9/L)	3.72(2.92, 4.77)	5.38(4.03, 8.12)	0.000	3.7(2.87,4.86)	5.44(4.01,8.13)	0.000	3.79(3.09,4.37)	5.2(4.1,7.85)	0.0

	Overall analysis (n=703)	**Overall analysis (n=703)**	**Overall analysis (n=703)**	**Elderly patients (n=616)**	**Elderly patients (n=616)**	**Elderly patients (n=616)**	**Middle-aged patients (n=87)**	**Middle-aged patients (n=87)**	**M ag pa tie (n**
Lymphocytes (10^9/L)	1.13(0.88, 1.63)	0.99(0.67, 1.41)	0.000	1.1(0.87,1.51)	0.96(0.65,1.36)	0.000	1.76(1.26,2.13)	1.22(0.89,1.72)	0.0
Monocytosis (10^9/L)	0.41(0.33, 0.55)	0.47(0.33, 0.64)	0.008	0.42(0.32,0.55)	0.47(0.33,0.64)	0.033	0.4(0.33,0.49)	0.46(0.32,0.67)	0.0
Basophils (10^9/L)	0.04(0.02, 0.05)	0.02(0.01, 0.04)	0.000	0.03(0.02,0.05)	0.02(0.01,0.04)	0.000	0.04(0.03,0.06)	0.02(0.02,0.04)	0.0
Pymphocyte (10^9/L)	149(113, 192)	147(113, 191)	0.997	169.5 (121.25, 203)	157(123,191)	0.845	169.5(121.25,203)	157(123, 191)	0.8
Hemoglobin (g/L)	130(119, 143)	130(120, 142)	0.579	128(117,142)	129(119,141)	0.200	141.5(135.25,148.75)	139(124,150)	0.2
Hs-CRP (mg/L)	11.67(4.18, 30.93)	22.8(6.05, 73.1)	0.009	12(4.99,29.17)	24.84(6.54,74.4)	0.004	4.05(1.44,55.15)	5.8(1.44,75.13)	0.5
Lung function									
GOLD I n (%)	36(11.5%)	33 (8.4%)	0.260	34(12.5%)	32 (9.3%)	0.458	2(5.0%)	1 (2.1%)	0.3
GOLD II n (%)	99 (31.7%)	134 (34.3%)		88 (32.4%)	123 (35.8%)		11 (27.5%)	11 (23.4%)	
GOLD III n (%)	121 (38.8%)	138 (35.3%)		103 (37.9%)	122 (35.5%)		18 (45.0%)	18 (34.0%)	
GOLD IV n (%)	56 (17.9%)	86 (12.0%)		47 (17.3%)	67 (19.5%)		9 (22.5%)	19 (40.4%)	
mMRC scale	2.24±0.98	2.24±1.05	0.986	2.29±0.96	2.30±1.02	0.889	1.89±1.05	1.78±1.17	0.6

DHC: daily hospital costs; GOLD: global initiative for chronic obstructive pulmonary disease; Hs-CRP: hypersensitive C-reactive protein; mMRC: Modified Medical Research Council

Table 2 Antibiotic treatments, short-term steroid administrations, and economic burdens between eosinophilic and non-eosinophilic patients

	Overall analysis (n=703)	**Overall analysis (n=703)**	**Overall analysis (n=703)**	**Elderly patients (n=616)**	**Elderly patients (n=616)**	**Elderly patients (n=616)**	**Middle-aged patients (n=87)**	**Middle-aged patients (n=87)**	**M ag pa tie (n**
Variables	**Eosinophilic (n=312)**	**Non-eosinophilic (n=391)**	***p* value**	**Eosinophilic (n=272)**	**Non-eosinophilic (n=344)**	***p* value**	**Eosinophilic (n=40)**	**Non-eosinophilic (n=47)**	***p* v**

	Overall analysis (n=703)	**Overall analysis (n=703)**	**Overall analysis (n=703)**	**Elderly patients (n=616)**	**Elderly patients (n=616)**	**Elderly patients (n=616)**	**Middle-aged patients (n=87)**	**Middle-aged patients (n=87)**	**M ag pa tie (n**
Antibiotic treatment n (%)	270(86.2%)	358(91.6%)	0.032	244 (89.7%)	319 (92.7%)	0.183	26(65.0%)	39(83.0%)	0.0
Joint antibiotic treatment n (%)	11 (4.1%)	30 (8.4%)	0.032	11 (4.5)	27 (8.5)	0.065	0 (0.0)	3 (7.7)	0.4
Short-term steroids n (%)	67 (21.5%)	109 (27.9%)	0.052	66 (24.3)	101(29.4)	0.158	1(2.5%)	8(17.0)	0.0
LOS	10(7,12)	10(8,14)	0.001	10(7,13)	11(8,14)	0.001	9(7,11)	9(7,12)	0.4
OHC (CNY)	9645.74 (7342.45, 14343.71)	11871.32 (8579.02, 17349.46)	0.000	10420.18(783	1292	32	7192.28(5860. 9606.6)	9944.53(6633. 13469.05)	92
DHC (CNY)	1047.16 (879, 1343.51)	1153.75 (904.54, 1473.19)	0.004	1069.25(899.2	1153.93(9	5.013	933.08(786.8, 1059.36)	977.66(755.1, 1268.82)	0.2

CNY: Chinese Yuan; DHC: daily hospital costs; LOS: Length of stay; OHC: overall hospital costs

Table 3 Hazard ratio of eosinophilic exacerbation phenotype in clinical remission

	Time points	**Hazard ratio**	**Wald**	***p* value**
Overall analysis	7^{th} day	1.457 [1.072, 1.982]	5.770	0.020
	10^{th} day	1.316 [1.108, 1.562]	9.820	0.002
	14^{th} day	1.334 [1.102, 1.615]	8.760	0.003
	21^{th} day	1.326 [1.125, 1.562]	11.380	<0.001
	28^{th} day	1.254[1.078, 1.459]	8.570	0.003
Elderly patients	7^{th} day	1.521 [1.084, 2.136]	5.88	0.020
	10^{th} day	1.319 [1.096, 1.588]	8.570	0.003
	14^{th} day	1.374 [1.118, 1.689]	9.110	0.003
	21^{th} day	1.326 [1.112, 1.582]	9.880	0.002
	28^{th} day	1.234 [1.049, 1.451]	6.470	0.010
Middle-aged patients	7^{th} day	1.163 [0.562, 2.410]	0.170	0.700
	10^{th} day	1.265 [0.800, 1.998]	1.010	0.300
	14^{th} day	1.092 [0.916, 1.809]	0.120	0.700
	21^{th} day	1.284 [0.779, 2.009]	1.190	0.300
	28^{th} day	01.321 [0.757, 2.043]	1.560	0.200

Figure legends

Figure 1. Study consort diagram.

Figure 2. Hazard ratios (HR) and 95% confidence intervals (CI) of remission rates of COPD patients with eosinophilic or non-eosinophilic acute exacerbation ([?] 2% vs <2%). COPD: chronic obstructive pulmonary disease: (**a**) Overall analysis of all ages; (**b**) Subgroup analysis of elderly patients; (**c**) Subgroup analysis of middle-aged patients.

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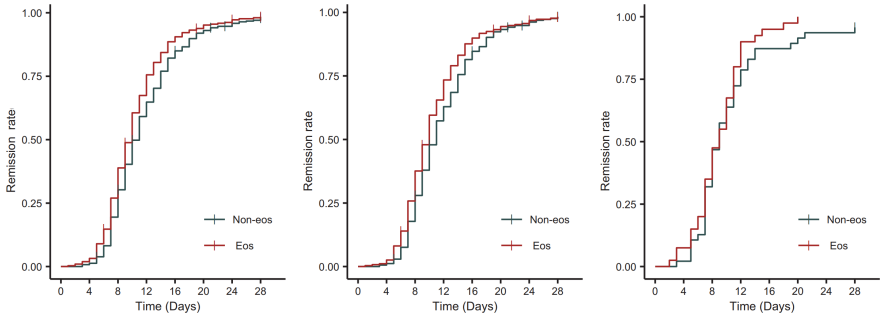
`Figure 01.pdf` available at https://authorea.com/users/375400/articles/492650-eosinophilic-phenotype-was-associated-with-better-clinical-remission-in-elderly-but-not-middle-aged-patients-with-acute-exacerbations-of-copd



(a) Overall analysis (b) Elderly patients (c) Middle aged patients