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Quantitative CT imaging characteristics of patients with chronic obstructive pulmonary disease with different eosinophil levels: a retrospective observational study using linked data from a tertiary hospital in China

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ABSTRACT

Objective To investigate the relationship between eosinophil (EOS) and CT imaging, we quantitatively evaluated the bronchial wall thickening, emphysema index (EI) and pulmonary vascular parameters in patients with chronic obstructive pulmonary disease (COPD) based on different EOS levels.

Design Retrospective observational study.

Setting A tertiary hospital in China.

Participants 448 patients with COPD from January 2020 to January 2023.

Main outcome measures Laboratory data, chest CT and pulmonary function based on different EOS levels: <150/µL, ≥150/µL; <100/µL, 100–300/µL, ≥300/µL; <2%, ≥2%.

Results We evaluated the records of 448 patients diagnosed with COPD. The prevalence of eosinophilia with EOS ≥2% was 41.1% (184 cases), 33.7% (151 cases) with EOS ≥150/µL and 9.4% (42 cases) with EOS ≥300/µL. A lower EOS (EOS <2% or EOS <150/µL) was associated with chronic pulmonary heart disease. The neutrophil count and percentage were significantly higher in the relatively lower EOS group (EOS <2%, EOS <150/µL or EOS <100/µL). When the groups were divided based on the two cut-off values of 2% of EOS percentage and 150/µL of absolute EOS value, no statistical significance was observed for the entire lung, left lung, right lung, lung lobe volume, lung index (EI), and lung emphysema heterogeneity index (HI). However, compared with the 100–300/µL group, the EI of the right upper lobe of the lung was lower in the EOS ≥300/µL group (0.32 vs 0.37, p<0.05). Airway wall thickness, wall area percentage and Pi10 in the EOS ≥2%, EOS ≥150/µL and 100–300/µL groups were lower than those in the EOS <2%, EOS <150/µL and EOS <100/µL groups, respectively. Compared with the EOS <100/µL group, Pi10 in the EOS ≥300/µL group was lower. According to the different cut-off values, such as percentage and absolute value of EOS, there was no significant difference in pulmonary vascular parameters, such as in cross-sectional area less than 5 mm^2 (BV5), total blood volume (TBV), BV5/TBV, network length, branchpoints and endpoints (p>0.05 for both). The per cent predicted diffusing lung capacity for carbon monoxide (DLCO%) of the EOS ≥2% group was higher than that of the EOS <2% group. Compared with patients with blood EOS <150/µL, patients with blood EOS ≥150/µL had lower residual volume and lung volume ratio and higher values for per cent predicted forced vital capacity and DLCO%. The values for per cent predicted forced expiratory volume in 1 s, maximal expiratory flow at 75%/50%/25% of lung volume (MEF75%,MEF50%, MEF25%) and DLCO% in the EOS ≥300/µL group were higher than those in the EOS <100/µL group and in the 100–300/µL group.

Conclusions Hypereosinophilic COPD (EOS ≥2% or EOS ≥150/µL or EOS ≥300/µL) appears to have less bronchial thickening and better lung function. Notably, in patients with EOS ≥300/µL, the EI of the right upper lobe is reduced. These findings provide valuable insights into the role of EOS in COPD pathophysiology.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study explores how blood eosinophil levels correlate with specific quantitative CT findings in patients with chronic obstructive pulmonary disease.
⇒ No restrictions on sex were imposed to enhance clinical practicability; however, this approach may increase the risk of confounding bias.
⇒ This study is a single-centre investigation with a relatively limited sample size.
⇒ Due to the inherent limitations of cross-sectional studies, this study was unable to establish the impact of eosinophil fluctuations on the study outcomes.
⇒ Owing to software constraints, we were unable to comprehensively incorporate a diverse range of quantitative CT chest indices.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic airway inflammatory condition characterised by significant

heterogeneity and has emerged as one of the leading causes of mortality worldwide.[1] Airway inflammation is a consistent feature of COPD, contributing to airway damage, remodelling, loss of small airways and emphysema (tissue damage with permanent dilation distal to the terminal bronchiole). Neutrophil-associated COPD represents the most common inflammatory phenotype; however, studies have shown that approximately 20%–40% of patients with COPD exhibit increased eosinophilic inflammation.[2–4]

An increasing body of evidence suggests that eosinophilic COPD is recognised as a distinct phenotype within the spectrum of COPD.[5 6] Blood eosinophil (EOS) is an easily measurable and reliable biomarker that has been used to guide clinical treatment decisions.[7 8] Blood eosinophil count (BEC) not only serves as a predictor of future acute exacerbation risk,[9–12] but also functions as a biomarker to identify patients who are more likely to respond favourably to inhaled corticosteroids (ICS).[2] Moreover, researchers have found that hypoeosinophilia (EOS <100/μL) is associated with an increased risk of neutrophilic infectious inflammation.[13 14] The ECLIPSE study reported that hypereosinophilia (EOS ≥2% or 150/μL) was associated with higher forced expiratory volume in 1 s and lower scores on the St George's Respiratory Questionnaire and on the modified Medical Research Council scale.[15] However, there is currently no uniform criterion for the cut-off of blood EOS in COPD. Previous clinical trials have employed a variety of definitions based on both EOS percentage and absolute EOS count.[9 16–18] In our previous study, we adopted several commonly used classification methods. We found that patients with acute exacerbations of chronic obstructive pulmonary disease who had EOS levels below 2% or <100/μL exhibited poorer lung function and were at a higher risk for arrhythmia, respiratory failure, chronic cor pulmonale and increased 3-year mortality.[13] Therefore, EOS may serve as a valuable biomarker for predicting the clinical features and prognosis of patients with COPD.

Quantitative CT (QCT) has been investigated extensively for its role in respiratory system diseases. This imaging technology exhibits high sensitivity in diagnosing lung conditions such as COPD and the novel coronavirus pneumonia (COVID-19).[19 20] QCT is also valuable in phenotyping patients with COPD, as it provides detailed structural information on emphysematous changes, airway dimensions and lung volume. The utility of CT-based categorisation into emphysema-predominant, airway-predominant or mixed phenotypes is increasingly being recognised.[21 22] CT phenotypes have also been used to guide clinical treatment. Patients with bronchitis demonstrate more significant airway wall thickening and experience more frequent exacerbations, resulting in greater responsiveness to ICS and bronchodilators[23]; in contrast, patients with upper lobe-predominant emphysema and reduced exercise capacity may benefit from lung volume reduction surgery, which can improve quality of life and prognosis.[24] Patients with COPD with the mixed phenotype exhibit more severe dyspnoea and experience more frequent hospitalisations compared with those with each of the remaining CT-based phenotypes.[25 26] However, there are limited studies that have evaluated the CT profiles of patients with eosinophilic COPD, and it remains unclear whether airway eosinophilic inflammation in COPD contributes to bronchial remodelling or drives emphysema. In asthma, EOS is associated with bronchial wall thickening, potentially due to the release of cytokines, chemokines and leukotrienes by EOS, which promote bronchial remodelling.[27] In our previous study examining the clinical characteristics of patients with COPD with varying EOS levels, we observed that an EOS count of ≥100/μL appeared to be associated with emphysema or chronic bronchitis on chest CT. However, no indepth subgroup analysis was conducted.[13] The CanCOLD study[28] described that, in participants with COPD, EOS ≥300/μL had significantly increased estimated airway wall thickness (WT) for an idealised airway, with an internal perimeter of 10 mm (indicating airway wall thickening) and low attenuation area (LAA) <856 Hounsfield unit (HU) (indicating gas trapping), relative to the <150/μL EOS subgroup. The SPIROMICS cohort analysis demonstrated that the emphysema index (EI) in the upper left, lower and upper right lung lobes was significantly elevated when sputum EOS levels exceeded 1.25%. Additionally, in the high EOS group (EOS ≥200/μL), the airway WT of the right upper lobe apex segment (RB1) increased by 0.02 mm.[29] However, some research results show that emphysematous patients are characterised by lower levels of blood EOS, which leads to the hypothesis that the presence of emphysema is less likely to allow for significant T helper 2 cells (Th2)-type inflammation in the lungs.[15 30 31] Other studies[32] found no significant difference in emphysema scores or WT between hypereosinophilic and hypoeosinophilic patients with COPD. In summary, the relationship between EOS levels and CT findings in patients with COPD remains controversial and requires further investigation.

Therefore, based on our previous study, we used different EOS classifications (<2%, ≥2%; <150/μL, ≥150/μL; <100/μL, 100–300/μL, ≥300/μL) and further explored the CT imaging characteristics of COPD with different EOS levels, including bronchial wall thickening, emphysema and pulmonary vascular parameters.

METHODS

Study population

This was a retrospective and cross-sectional observational study. The medical records of 820 patients with COPD from January 2020 to January 2023 at Shanxi Bethune Hospital were collected. All participants provided informed consent. The inclusion criteria were as follows: patients with clinical symptoms (such as dyspnoea, cough, or sputum production) and risk factors (including environmental exposures like smoking or biofuel use), as well as those whose lung function tests met the diagnostic

criteria for COPD. Specifically, a post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio of less than 0.7 after inhaling bronchodilators, according to the 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[33] The exclusion criteria were (1) combination of asthma, allergic diseases, hypereosinophilia, parasitic infections, blood system-related diseases and other diseases that can cause increased EOS; (2) combination of diseases that affect changes in lung volume: history of thoracic surgery, thoracic deformity, massive pleural effusion, etc; (3) combination of severe cardiac, brain, hepatic and renal diseases; (4) complicated by other obvious respiratory diseases, such as large area pulmonary infection, pulmonary interstitial fibrosis, pulmonary tuberculosis, bronchiectasis, lung cancer, pneumoconiosis, etc; and (5) use of long-term oral corticosteroids or had used oral or intravenous corticosteroids within 48 hours before the visit.

General information and laboratory data collection

Information on medical history provided by the subjects was collected, including gender, age, body mass index (BMI), smoking history and comorbidities. Blood test parameters included EOS count, EOS percentage, white cell count, neutrophil count and percentage, lymphocyte count and percentage, haemoglobin and platelets. Pulmonary function parameters included FEV_1%, FVC%, FEV_1/FVC, maximal expiratory flow at 25%/50%/75% of lung volume(MEF25%, MEF50%, MEF75%), inspiratory capacity (IC), per cent predicted residual volume (RV%), per cent predicted total lung capacity (TLC%), residual volume to total lung capacity ratio (RV:TLC) and per cent predicted diffusing lung capacity for carbon monoxide (DLCO%).

EOS grouping

Based on our previous study[13] and commonly used classification methods, this study employed three different EOS categorisation schemes. First, subjects were classified based on the percentage of EOS, using 2% as the cut-off value: EOS <2% or ≥2%. Second, subjects were categorised according to absolute EOS counts: EOS <150/µL or ≥150/µL. Finally, a more detailed classification was applied: EOS <100/µL, 100-300/µL and EOS ≥300/µL.

Processing of chest CT scans

All patients underwent chest scans at the end of inspirations using the Siemens SOMATOM Definition Flash and SOMATOM Definition AS CT scanners at Shanxi Bethune Hospital. During CT examination, the patient was placed in a supine position, with arms raised and head held, and scanned from head to toe, with the following parameters: tube voltage 120 kV, automatic tube current, layer thickness 1.25 mm, collimation 0.6×128 mm, spiral time 0.5 s/turn and pitch factor 0.9; and with reconstruction using lung window: reconstruction layer thickness 1 mm, layer spacing 0.7 mm, convolutional kernel I70f, lung window position −500 HU and window width 1500 HU. According to the method proposed in the literature,[34–36] an in-house developed software (a respiratory disease artificial intelligence imaging analysis software; Northeastern University, China) was used to segment the pulmonary airway tree, vessel tree, pulmonary lobes and pulmonary emphysema distribution on inspiratory CT images in an automated way (online supplemental figure 1).

QCT analysis

Consistent with other studies, the LAA was defined as the volume of image voxels with HU values lower than −950 HU.[37] Emphysema measurements were obtained, including the percentage of LAA with attenuation less than −950 HU (%LAA −950) for the whole lung and for each lobe separately: right upper lobe, right middle lobe, right lower lobe, left upper lobe and left lower lobe. Following the identification of emphysematous regions, the heterogeneity index (HI) between the upper and lower lobes was calculated to indicate the distribution of emphysema. The emphysema HI quantifies the distribution and variability of emphysema, spanning from 1 to +1. The formula for HI is given by: HI=(upper lobe emphysema index−lower lobe emphysema index)/(upper lobe emphysema index+lower lobe emphysema index)×100%. A value near +1 signifies a preponderance of upper lobe emphysema, a value near −1 indicates a predominance of lower lobe emphysema, and a value near 0 suggests a uniform distribution of emphysema across both the upper and lower lobes.[38]

Airways were also assessed with this software, providing the following parameters: wall area percentage (WA%=(-total airway area−airway lumen area)/(total airway area)×100), WT and the square root of the wall area of a hypothetical airway with a 10 mm internal perimeter(Pi10). The Pi10 was calculated by plotting the internal perimeters of all segmental and distal airways against the square root of their wall areas. This can overcome the problem of variable bronchus sizes and anatomical inhomogeneities.[39] As shown in figure 1, WT was quantified from the bronchi, and WA% and Pi10 were calculated from WT. The quantitative parameters of the pulmonary vessels, such as total blood volume (TBV), surface, endpoint count and number of branches, were quantified by VesselVio.[36] The aggregate vessel volume for vessels less than 5 mm2(BV5), or cross-sectional area less than 5 mm^2, was quantified based on the results.

Statistical analysis

IBM SPSS V.26.0 was used for data analysis. Count data were expressed as frequencies and percentages (n, %), and rates were compared using Fisher's exact test or χ^2 test. Continuous variables are presented as mean±SD. For continuous variables, the groups were compared using the Student's t-test for independent samples or the non-parametric Mann-Whitney U test. The Kolmogorov-Smirnov test was used to assess the normality of the continuous variables. Single-factor analysis of variance was used

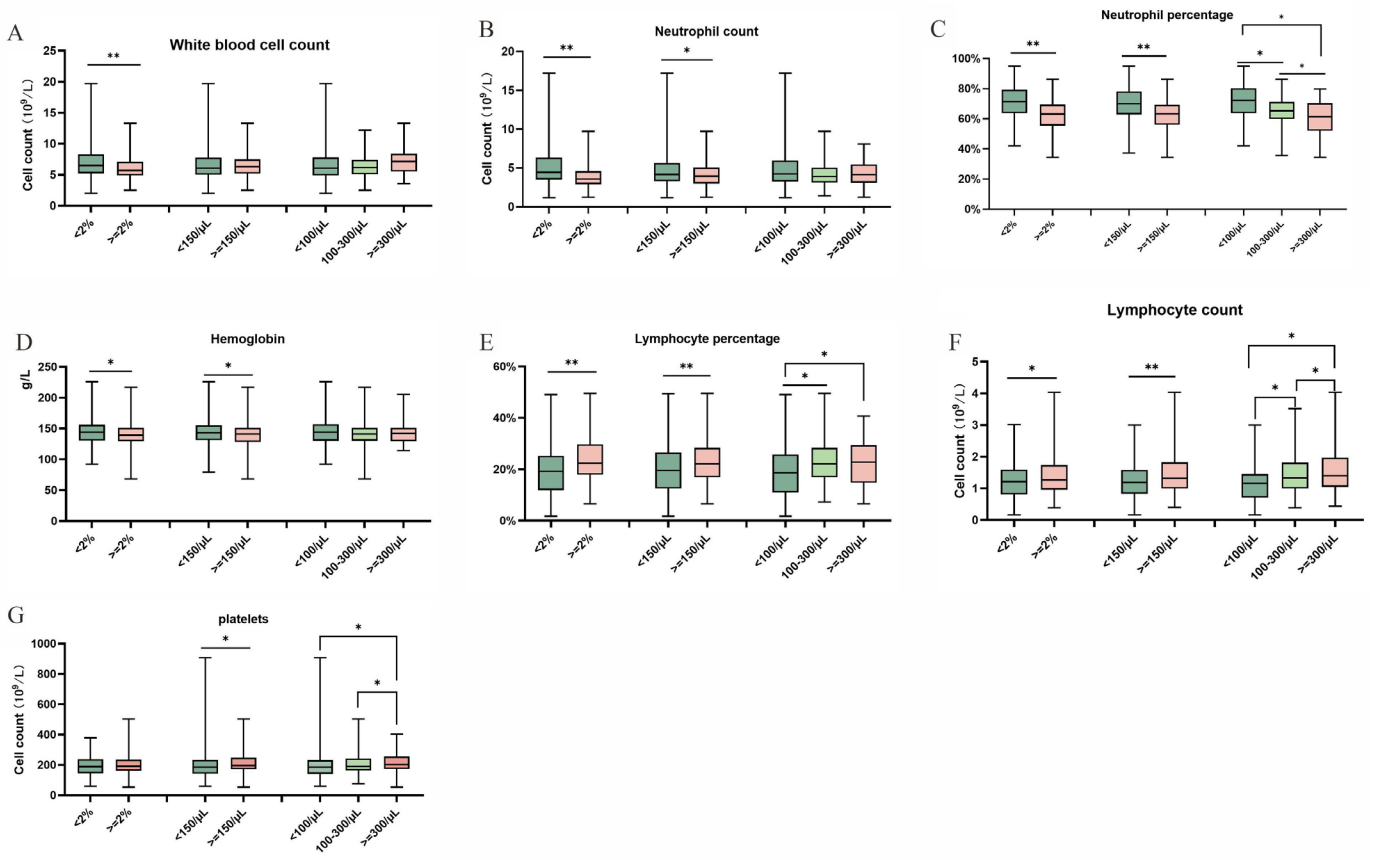

Figure 1 Laboratory data for patients with COPD based on different EOS groups. EOS is divided into different groups using three different classifications (<2%, ≥2%; <150/μL, ≥150/μL; <100/μL, 100-300/μL, ≥300/μL). (A) Comparison of white cell count in patients with COPD with different eosinophilic groups. (B) Comparison of neutrophil count in patients with COPD with different eosinophilic groups. (C) Comparison of neutrophil percentage in patients with COPD with different eosinophilic groups. (D) Comparison of haemoglobin in patients with COPD with different eosinophilic groups. (E) Comparison of lymphocyte percentage in patients with COPD with different eosinophilic groups. (F) Comparison of lymphocyte count in patients with COPD with different eosinophilic groups. (G) Comparison of platelets in patients with COPD with different eosinophilic groups. The asterisk indicates significant differences relative to other groups: *p<0.05, **p<0.01. COPD, chronic obstructive pulmonary disease; EOS, eosinophil.

to compare the mean among groups. Covariance analysis was used to calculate emphysema and tracheal WT indicator differences between the different groups and adjusted for potential confounders. Values of p<0.05 were considered indicative of statistical significance.

Patient and public involvement

None.

RESULTS

Characteristics of the study population

Between 1 January 2020 and 1 January 2023, data on a total of 820 outpatients with COPD were collected. After screening according to inclusion criteria, data from 448 patients were included in the analysis, as shown in online supplemental figure 2. Online supplemental table 1 and online supplemental figure 3 summarise the main demographics of the 448 patients in this study. They were mostly men (82.6%), with a mean age of 68.79±9.04 years, blood EOS of 142.11±212.12/μL and EOS percentage of 2.28%. Of these, 26.2% had a history of smoking. A total of 161 (35.9%) subjects were diagnosed with chronic pulmonary heart disease in conjunction with COPD. A total of 415 (92.6%) patients received ICS therapy regularly. When grouped using 2% as the cut-off value, the study populations were composed of 264 patients with EOS <2% (58.9%) and 184 patients with EOS ≥2% (41.1%) (figure 3A). When the critical value is 150/μL, there were 297 cases (66.3%) in the EOS <150/μL group and 151 cases (33.7%) in the EOS ≥150/μL group (online supplemental figure 3B). When patients were classified using thresholds of 100/μL and 300/μL, the population was divided into three groups: the <100/μL group (219 cases, 48.9%), the 100-300/μL group (187 cases, 41.7%), and the ≥300/μL group (42 cases, 9.4%). (online supplemental figure 3C). According to different EOS percentages or absolute counts, the threshold, age, sex, BMI, smoking index and percentage of patients with a history of smoking did not differ (online supplemental figure 3D,E). The incidence of chronic pulmonary heart disease in the low EOS group

(EOS <2%) was higher than in the high EOS group (EOS ≥2%) (40.5% vs 29.1%, p=0.020). This difference was also observed when stratifying patients based on blood eosinophil levels < 150/µL. (39.4 vs 29.1, p=0.042). However, when the population was divided into three groups based on such groupings, there was no significant difference in the incidence of chronic pulmonary heart disease (online supplemental figure 3F).

Patients with hypereosinophilic COPD have higher neutrophil-related inflammation

Online supplemental table 2 and figure 1 show the comparison of laboratory data for different patients with eosinophilic COPD. The mean values for absolute peripheral neutrophil count, neutrophil count percentage of leucocytes, white cell count, lymphocyte percentage, lymphocyte count, haemoglobin and platelets were 4.62±2.26×10^9/L, 67.60%±11.36%, 6.67±2.48×10^9/L, 21.26%±9.59%, 1.34±0.95×10^9/L, 142.93±20.76 g/L and 219.95±388.34×10^9/L, respectively. Using 2% as the threshold to divide the population into two groups, we found that the EOS <2% group had higher white cell count (7.11 vs 6.03, p<0.001; figure 1A), neutrophil count (5.17 vs 3.82, p<0.001; figure 1B), neutrophil percentage of leucocytes (71.09 vs 62.61, p<0.001; figure 1C) and haemoglobin (144.56 vs 140.57, p=0.027; figure 1D), and lower lymphocyte percentage (19.47 vs 23.80, p<0.001; figure 1E) and lymphocyte count (1.25 vs 1.47, p=0.035; figure 1F), compared with patients with EOS ≥2%. This difference was also observed when stratifying patients based on blood eosinophil levels < 150/µL, except for white cell count and platelet. We did not observe differences in white cell count between the two groups (p=0.726; figure 1A); however, the EOS <150/µL group had lower platelets (p=0.014; figure 1G). When the blood EOS cut-off was 100/µL and 300/µL, compared with patients with EOS counts below 150/µL or between 150/µL and 300/µL, the patients with EOS counts above 300/µL had lower neutrophil percentage, higher lymphocyte count and platelet (all p<0.05; figure 1C,F,G). The EOS <100/µL group had lower lymphocyte percentage than EOS ≥300/µL (19.31 vs 22.56, p<0.001; figure 1E). In addition, the EOS <100/µL group had higher neutrophil count (figure 1B) and neutrophil percentage (figure 1C) and lower lymphocyte percentage (figure 1E) and lymphocyte count (figure 1F) than those with EOS counts between 150/µL and 300/µL (all p<0.05).

Hypereosinophilic COPD is associated with better pulmonary spirometry

The lung ventilation function parameters in our study included FEV_1%, FVC%, FEV_1/FVC%, MEF75%, MEF50% and MEF25%, with mean values of 47.60±18.85, 71.8±20.82, 50.45±11.45, 22.90±15.02, 18.05±11.34 and 22.59±11.19, respectively. Using 2% as the threshold for grouping, FEV_1% (figure 2A), FVC% (figure 2B), FEV_1/FVC% (figure 2C), MEF75% (figure 2D), MEF50% (figure 2E) and MEF25% (figure 2F) of the EOS >2% group were higher than those of the EOS <2% group, but the difference was not statistically significant (all p>0.05). When grouped by the cut-off value of 150/µL, the statistical result is similar to 2%, with the only difference being that the EOS ≥150/µL group had higher FVC% than the EOS <150/µL group (77.76 vs 69.41, p=0.024; figure 2B). When the EOS count cut-off value was 100/µL and 300/µL, the high blood EOS group (EOS ≥300/µL) had significantly higher FEV_1% (figure 2A), MEF75% (figure 2D), MEF50% (figure 2E) and MEF25% (figure 2F) compared with the middle or low EOS groups (EOS <100/µL or 100-300/µL) (all p<0.05). However, further intergroup analysis comparing EOS <100/µL and 100-300/µL did not find any difference in the above indicators (online supplemental table 3).

Hypoeosinophilic COPD is associated with higher lung volume parameters

The lung volume parameters in our study included IC%, RV%, TLC% and RV:TLC, with mean values of 68.66±24.78, 107.20±56.20, 77.89±22.65 and 53.09±11.16, respectively. Online supplemental table 3 and figure 2 present the comparisons of lung volume parameters between hypereosinophilic and hypoeosinophilic patients using the different thresholds. When 2% is used as the cut-off value, we did not find any difference in the lung volume parameters (all p>0.05) between groups with EOS <2% and EOS ≥2% (figure 2G,H). Even when the population was divided into three groups (<100/µL, 100–300/µL and ≥300/µL), there was no significant difference in terms of lung volume parameters among these three (all p>0.05; figure 2G,H). Different observations were found in the subgroup stratified according to the 150/µL blood EOS demarcation point; the EOS ≥150/µL group had lower RV:TLC (49.53 vs 54.23, p=0.003) compared with patients with low blood EOS (EOS <150/µL) (figure 2H).

Hypereosinophilic COPD is associated with better pulmonary diffusion function

The mean value of DLCO% was 52.68±22.60. Grouped according to three different classifications, the relatively high EOS group (EOS ≥2% or 150/µL or 300/µL) had higher DLCO%, and the difference was statistically significant (all p<0.05; figure 2I).

Hypoeosinophilic COPD is associated with more severe airway remodelling

The mean values of Pi10, WT and WA% were 3.42±0.90, 1.03±0.40 and 0.53±0.06. The EOS <2% group had higher Pi10 (3.56 vs 3.24, p<0.001; figure 3A), WA% (0.54 vs 0.52, p=0.005; figure 3B) and WT (1.09 vs 0.94, p=0.002; figure 3C) than the EOS ≥2% group (online supplemental table 4). When the EOS cut-off was 150/µL, the statistical results were the same as for 2%. For patients with EOS counts below 150/µL, their Pi10 (3.53 vs 3.21, p<0.001), WA% (0.54 vs 0.52, p=0.027) and WT (1.07 vs 0.94, p=0.001) were higher compared with patients with EOS counts above 150/µL (online supplemental

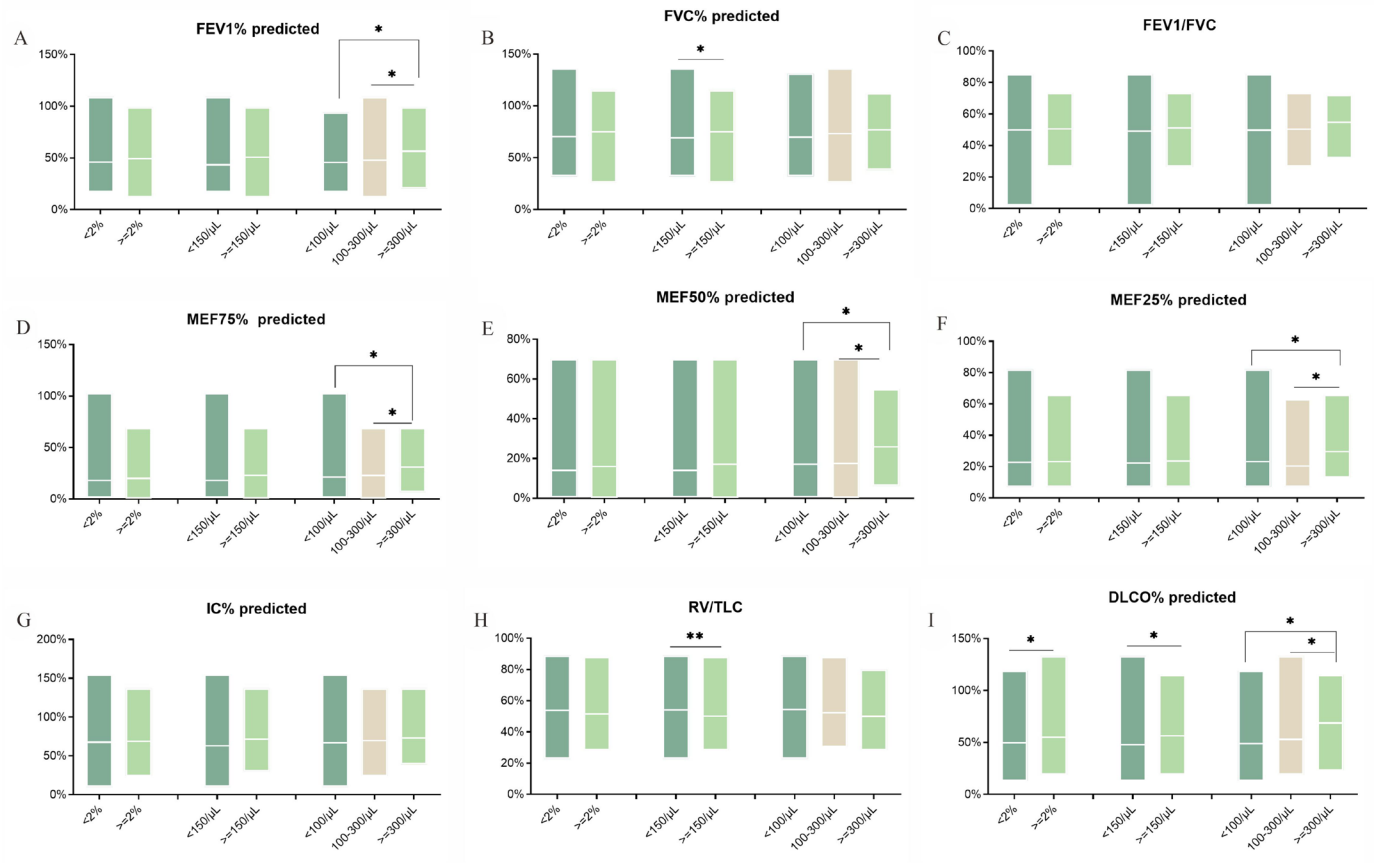

Figure 2 Pulmonary function of patients with COPD based on different EOS groups. The white line in the box plot represents the median (Q2), which is the middle value in the data set. EOS is divided into different groups using three different classifications (<2%, ≥2%; <150/μL, ≥150/μL; <100/μL, 100-300/μL, ≥300/μL). (A) Comparison of FEV_1% predicted in patients with COPD with different eosinophilic groups. (B) Comparison of FVC% predicted in patients with COPD with different eosinophilic groups. (C) Comparison of FEV_1/FVC in patients with COPD with different eosinophilic groups. (D) Comparison of MEF75% predicted in patients with COPD with different eosinophilic groups. (E) Comparison of MEF50% predicted in patients with COPD with different eosinophilic groups. (F) Comparison of MEF25% predicted in patients with COPD with different eosinophilic groups. (G) Comparison of IC% predicted in patients with COPD with different eosinophilic groups. (H) Comparison of RV:TLC in patients with COPD with different eosinophilic groups. (I) Comparison of DLCO% predicted in patients with COPD with different eosinophilic groups. The asterisk indicates significant differences relative to other groups: *p<0.05, **p<0.01. COPD, chronic obstructive pulmonary disease; DLCO%, per cent predicted diffusing lung capacity for carbon monoxide; EOS, eosinophil; FEV_1%, per cent predicted forced expiratory volume in 1 s; FVC%, per cent predicted forced vital capacity; IC%, inspiratory capacity; MEF25%、MEF50%、MEF75%, Maximal Expiratory Flow at 25%/50%/75% of lung volume; RV, residual volume; TLC, total lung capacity.

table 5 and figure 3). Testing of differences in subgroups between EOS counts below 100/μL, 100–300/μL and above 300/μL, respectively, showed that there was a significant difference in Pi10, WT and WA% among the three groups (p<0.001). On further analysis within the group, we found that the middle group (100–300/μL) had lower Pi10, WT and WA% than the lower group (EOS <100/μL) (all p<0.05). In addition, Pi10 was lower in the EOS ≥300/μL group compared with the EOS <100/μL group (3.30 vs 3.61, p<0.05; online supplemental table 6 and figure 3).

There is no clear relationship between EOS and emphysema

Online supplemental tables 4–6 show the lung volumes and proportional areas of emphysema with different cut-off values, respectively. We found that EOS did not appear to be associated with emphysema as measured by QCT. Whether the threshold is at 2% or 150/μL, the whole lung volume (figure 4A) and EI (figure 4B), the volume and EI of the right lung, the volume and EI of the upper (figure 4C,D), middle and lower lobe of the right lung, the volume and EI of the left lung, the volume and EI of the upper and lower lobe of the left lung, and the HI (figure 4E) were not significantly different (all p>0.05; online supplemental tables 4 and 5). Similar observations were found among subgroups stratified by 100/μL and 300/μL blood EOS cut-off points; the only exception is that the EI of the EOS ≥300/μL group was lower than the 100≤EOS<300/μL group (0.32 vs 0.37, p<0.05; online supplemental table 6 and figure 4C).

Pulmonary vascular parameters do not differ between hypereosinophilic COPD and hypoeosinophilic COPD

In terms of pulmonary vascular parameters, according to our three different classification methods, there

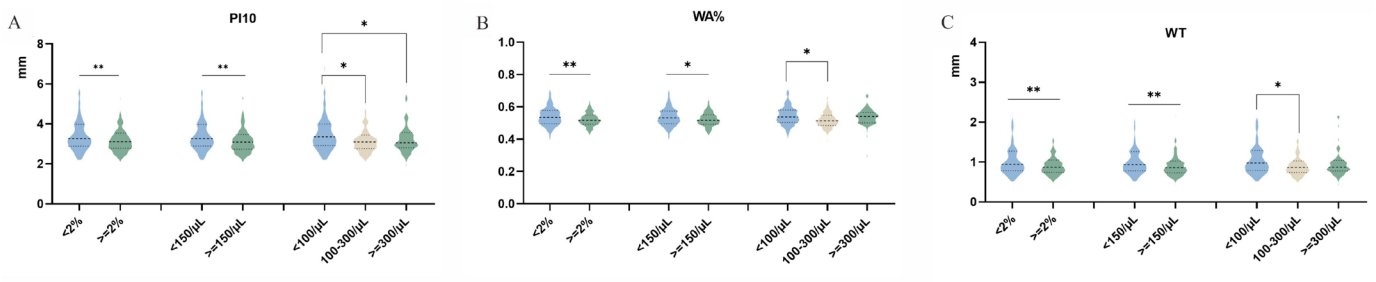

Figure 3 Bronchial wall parameters of patients with COPD based on different EOS groups. EOS is divided into different groups using three different classifications (<2%, ≥2%; <150/μL, ≥150/μL; <100/μL, 100–300/μL, ≥300/μL). (A) Comparison of Pi10 in patients with COPD with different eosinophilic groups. (B) Comparison of WA% in patients with COPD with different eosinophilic groups. (C) Comparison of WT in patients with COPD with different eosinophilic groups. The asterisk indicates significant differences relative to other groups: *p<0.05, **p<0.01. COPD, chronic obstructive pulmonary disease; EOS, eosinophil; Pi10, the square root of the wall area of a hypothetical airway with a 10 mm internal perimeter; WA%, wall area percentage; WT, wall thickness.

were no statistical differences in BV5, TBV, BV5/TBV, network length, branchpoints and endpoints (all p>0.05; figure 5A–F).

Results for QCT parameters remain consistent after controlling for confounding variables

Adjusted for potential confounding factors, like age, sex, BMI, smoking index, complication and ICS therapy, patients with hypereosinophilic COPD demonstrated lower bronchial wall parameters compared with those with low EOS, regardless of the specific cut-off group selected (online supplemental tables 7–9). In terms of emphysema parameters, we got a similar conclusion after excluding the potential confounding factors, with lower EI in the right upper lobe of patients with COPD in the EOS ≥300/L group (p=0.042; online supplemental table 9). There was no significant difference in pulmonary vascular parameters among all groups (p>0.05).

DISCUSSION

COPD is a complex and heterogeneous disease. Eosinophilic COPD has garnered significant attention in recent years, but the imaging features of hypereosinophilic COPD remain controversial. In this study, we comprehensively evaluated the CT imaging characteristics associated with different EOS levels in patients with COPD and identified several clinically relevant findings. First, hypoeosinophilic COPD (<2% or <150/μL or <100/μL) was associated with more severe bronchial remodelling. Second, we observed that the EI of patients with high EOS did not seem to be

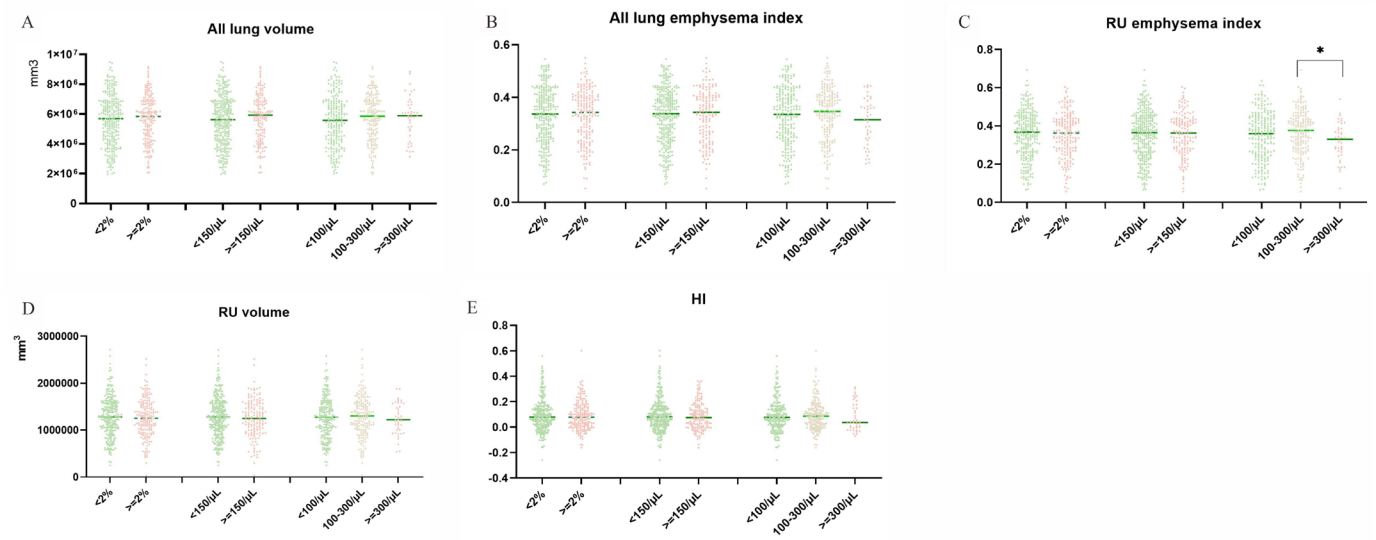

Figure 4 Emphysema among patients with COPD based on different EOS groups. EOS is divided into different groups using three different classifications (<2%, ≥2%; <150/μL, ≥150/μL; <100/μL, 100-300/μL, ≥300/μL). (A) Comparison of all lung volume in patients with COPD with different eosinophilic groups. (B) Comparison of all lung volume index in patients with COPD with different eosinophilic groups. (C) Comparison of RU emphysema index in patients with COPD with different eosinophilic groups. (D) Comparison of RU volume in patients with COPD with different eosinophilic groups. (E) Comparison of HI in patients with COPD with different eosinophilic groups. The asterisk indicates significant differences relative to other groups : *p<0.05. COPD, chronic obstructive pulmonary disease; EOS, eosinophil; RU, Upper lobe of the right lung,HI, heterogeneity index.

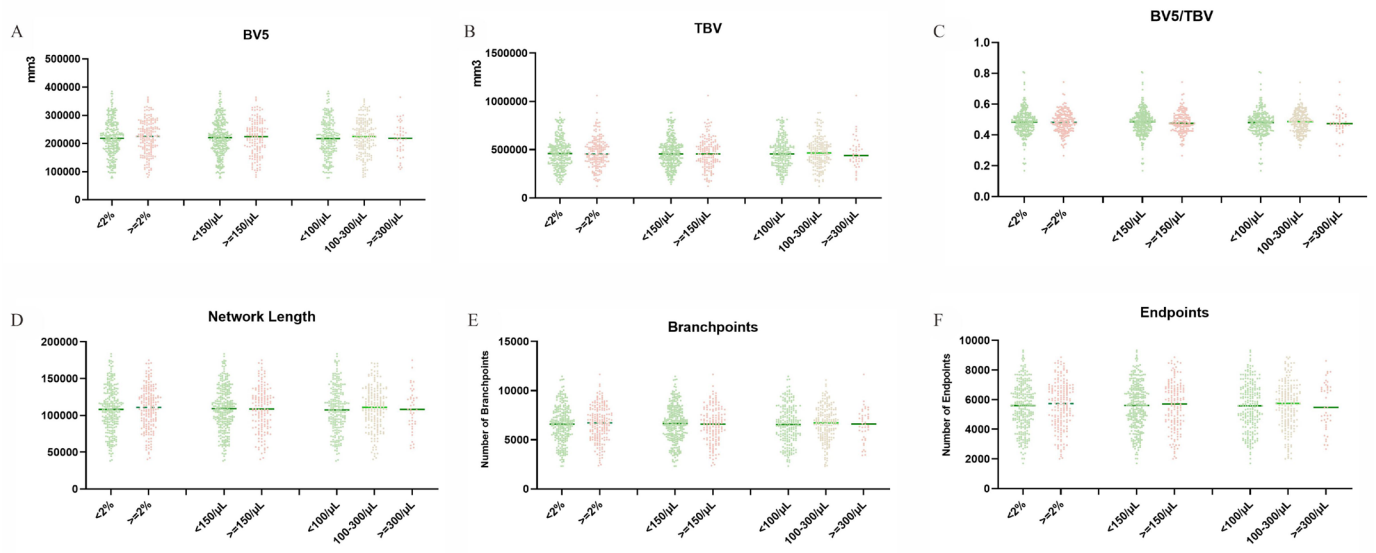

Figure 5 Pulmonary vascular parameters of patients with COPD based on different EOS groups. EOS is divided into different groups using three different classifications (<2%, ≥2%; <150/μL, ≥150/μL; <100/μL, 100-300/μL, ≥300/μL). (A) Comparison of BV5 in patients with COPD with different eosinophilic groups. (B) Comparison of TBV in patients with COPD with different eosinophilic groups. (C) Comparison of BV5/TBV in patients with COPD with different eosinophilic groups. (D) Comparison of network length in patients with COPD with different eosinophilic groups. (E) Comparison of branchpoints in patients with COPD with different eosinophilic groups. (F) Comparison of endpoints in patients with COPD with different eosinophilic groups. BV5, cross-sectional area less than 5 mm^2; COPD, chronic obstructive pulmonary disease; EOS, eosinophil; TBV, total blood volume.

higher than that of patients with low EOS; when 100/μL and 300/μL were selected as the cut-off group, the EI of the right upper lobe of the group with EOS ≥300/μL even decreased significantly. Third, hypereosinophilic COPD has better lung function, higher MEF%, FVC%, FEV_1% and DLCO%, and lower RV:TLC. Fourth, there may be no relationship between peripheral EOS and pulmonary vascular remodelling as quantitatively assessed by chest CT. Airflow restriction in patients with COPD is mostly caused by airway remodelling. Under continuous stimulation of inflammation, the airway wall will be thickened and the lumen area will increase at the same time, thus restricting the airway airflow.[40 41] Bronchial wall measurements are considered indicators of inflammatory changes and/or airway remodelling. Several significant CT imaging parameters related to small airway diseases have been reported, including WT, WA%, Pi10 and so on.[21 42] Our findings demonstrated that patients with hypereosinophilic COPD (EOS ≥2% or ≥150/μL or ≥300/μL) exhibited milder bronchial remodelling. Additionally, clinical pulmonary function tests revealed that FEV_1%, FVC% and MEF% were significantly higher in patients with hypereosinophilic COPD (EOS ≥300/μL or EOS ≥150/μL) compared with those with hypoeosinophilic COPD. These results are consistent with observations from a previous SPIROMICS COPD cohort study, which found that, in patients with GOLD D COPD, airway WT was greater in subjects with blood EOS ≤100/μL (3.91 vs 3.86, p=0.033).[17] Furthermore, in our study, the results of QCT bronchial parameters were consistent with the results of pulmonary function, further indicating that patients with hypoeosinophilic COPD had more pronounced airway wall thickening and more severe airflow restriction. QCT measurements also seem to provide a possible structural explanation for the relationship between EOS and pulmonary ventilation function. It is well known that the high EOS group responds better to ICS therapy[2]; the beneficial effect of ICS in the high EOS group appears to explain the milder bronchial remodelling observed in this group indirectly. These findings are biologically plausible, as the inflammation in hypoeosinophilic COPD is predominantly neutrophilic.[13] Studies have shown that neutrophils may accelerate airway wall remodelling by releasing active matrix metalloproteinase-9 (MMP-9) and that the level of active MMP-9 in the sputum of patients with neutrophilic subtype COPD is significantly higher than that of eosinophilic phenotypes.[43] At the same time, our results also show that the percentage and absolute count of neutrophils in patients with hypoeosinophilic COPD (EOS <2%,EOS <150/μL, EOS <300/μL) are significantly increased, which further supports our above explanation. Therefore, this study suggests that, to some extent, the elastase released by neutrophils may have a more significant impact on tracheal structural changes and accelerate airway remodelling compared with eosinophilic inflammation. Moreover, this finding underscores the importance of effectively controlling neutrophil-dominated airway inflammation in patients with COPD, which may delay the progression of bronchial remodelling. However, our results are inconsistent with some literature reports. Tan *et al*[28] found that the EOS ≥300/μL subgroup had significantly increased Pi10 (p<0.05) and decreased total airway count (p<0.05) compared with the EOS <150/μL subgroup; Pi10 was also increased in

the 150–300/µL EOS subgroup compared with the EOS <150/µL subgroup. There was a small, 0.02 mm increase in average airway WT at RB1 (prespecified pathway in the apical segment of the right upper lobe) for hyper-eosinophilic COPD (EOS ≥200/µL).[29] The above studies suggest that those with elevated EOS counts have thickened central airway walls. Discrepancies between study results may be attributable to the heterogeneity of COPD patient populations. In addition, as the day is approaching when quantitative data from computer image analysis can serve as reliable 'imaging biomarkers', it must be acknowledged that differences may influence variations in research results in image analysis software, CT equipment and image quality. Last but not least, it is well known that EOS levels fluctuate and are susceptible to multiple factors, and therefore it is necessary to follow up with patients in the future to evaluate the relationship between EOS and bronchial remodelling dynamically.

Emphysema is a common phenotype of COPD. The exact pathological mechanism of EOS leading to the development of COPD and emphysema is not completely clear. It has been found that EOS may indirectly drive the development of emphysema by stimulating the production of MMP-12 and cathepsin L in alveolar macrophages.[44 45] The SPIROMICS cohort analysis revealed a significant increase in EI when the percentage of sputum EOS exceeded 1.25%.[29] Wen *et al*[46] found that the degree of emphysema and gas capture was more pronounced in the high-sputum EOS group (sputum EOS ≥3%). However, our findings do not seem to be consistent with the above studies. We observed that patients with COPD in the high EOS group did not appear to have higher EI compared with patients with low EOS, even when the thresholds of 100/µL and 300/µL were selected as the cut-off values; the EI of the upper lobe of the right lung decreased significantly when EOS is ≥300/µL, and our conclusion seems to favour that lower EOS is associated with severe emphysema. However, as sputum EOS data were not collected in our study, we are unable to conduct a direct comparison of the results. This represents a limitation of our study. Papaioannou *et al*[30] have reported that patients with significant emphysema on High-resolution computed tomography (HRCT) present lower levels of blood EOS. At the same time, the study of Singh *et al*[15] showed that the progression in emphysematous lesions was enhanced in subjects with persistent EOS counts <2%. Salvi *et al*[47] reported that smoking subjects with COPD with more severe emphysema appear to have lower levels of circulating EOS. Oh *et al*'s study[48] showed that patients with COPD with EOS ≥5% had lower EI, but there was no statistical difference. Further multivariate stepwise linear regression analysis showed that the severity of radiological emphysema had an independent and inverse association with BEC (B=−0.034, p=0.008). Our results are consistent with these studies to some extent. The inflammation in the lower EOS group was dominated by neutrophils, which are known to cause emphysema,[40 49] and the damage to lung parenchyma caused by elastase released from these neutrophils is equally serious, if not more so. RV:TLC represents the degree of static hyperinflation of the lungs. Our pulmonary function analysis results showed that the residual volume to total lung capacity ratio (RV/TLC) was lower in the group with blood eosinophil count (EOS) ≥150/µL compared to the group with blood EOS <150/µL. The results of this study confirmed that the RV index in pulmonary function is consistent with the manifestation of emphysema on imaging examination. Both further suggested that low EOS was more associated with severe emphysema. Furthermore, the emphysematous phenotype is usually characterised by poor outcomes in COPD; our study observed that higher EI was associated with lower EOS levels in patients with COPD, which is consistent with increasing evidence that blood EOS might have beneficial rather than detrimental effects on COPD.[31] As for the lack of a significant relationship between EOS and emphysema at thresholds of 2% or 150/µL in our study, this cannot be excluded because the lower threshold may have diluted the uniqueness of the eosinophilic phenotype in COPD. Another notable limitation lies in the relatively modest sample size of the EOS ≥300/µL cohort within our study, encompassing a mere 42 cases (9.2%), a figure markedly lower than those documented in prior studies.[50] In addition, the EI of the population included in our study is generally high, which may be due to the unique population characteristics of patients with COPD in Shanxi Province, with incidence closely associated with smoking, environmental pollution and a large amount of coal burning. There is another point that cannot be ignored where the patients in the group were generally older; the existence of senile emphysema may also have a certain impact on the experimental results. Therefore, it is necessary to conduct large-scale, multicentre COPD clinical studies in the future to further explore the relationship between EOS level and emphysema.

Pulmonary vessels constitute a significant yet often overlooked component of the COPD pathology.[51] Pulmonary vascular volume can objectively reflect the morphological changes of pulmonary vessels, and non-invasive quantification of pulmonary vascular pruning by CT imaging can reflect the degree of vascular wall remodelling at the histological level.[52 53] In recent years, there has been increasing attention to the quantitative evaluation of pulmonary small vessels in COPD using postprocessing software following chest CT imaging. Therefore, we used small vessel volume fraction (BV5/TBV) as a CT-based pruning index (lower BV5/TBV represents larger pruning) to further analyse the relationship between different EOS levels and vascular parameters of histological vascular remodelling measured by QCT. Unfortunately, no differences were observed between these groups. However, we found that hypereosinophilic COPD (EOS ≥2% or EOS ≥150/µL) was less likely to be complicated with chronic pulmonary heart disease, and DLCO% was higher, which also confirms previous research.[13 48 54] Moreover, this study seems to indicate that DLCO% captures extra

information beyond the pulmonary vascular parameters quantified by CT. It has been found that EOS may prevent pulmonary hypertension by inhibiting perivascular inflammation and maintaining pulmonary smooth muscle cell homeostasis through 14/17 hydroxy docosahexaenoic acid.[55] Although we did not observe a relationship between EOS and pulmonary vascular remodelling on quantitative chest CT, combined with the results of pulmonary function and previous literature, we considered that EOS may play a protective role in pulmonary vascular remodelling. Follow-up studies should also aim to expand the sample size as much as possible to investigate further the relationship between EOS and pulmonary vascular parameters assessed by QCT.

This study has several limitations. First, it is a single-centre retrospective study with a limited sample size, which may introduce selection bias. Future research should include larger, multicentre studies to validate further and generalise our findings. Second, in our study, we were not able to collect sputum eosinophilic counts. Although BEC has been reported to predict sputum EOS counts in patients with asthma and the results have been encouraging. Due to ease of measurement and good stability, BEC has become an important biomarker for COPD treatment. They are recommended by the GOLD initiative for COPD treatment. Blood and sputum eosinophilic counts each has their advantages and limitations in the evaluation of COPD, and the correlation between the two remains controversial in patients with COPD[29 56–59]; we will continue to collect sputum samples from patients with COPD to further study the relationship between sputum EOS and chest CT phenotypes in COPD in the future. Third, we only used the initial blood cell count on admission and did not dynamically monitor patients' blood EOS levels over time. However, it is well established that EOS counts can fluctuate between measurements; therefore, a single BEC may not be sufficient to determine the EOS phenotype accurately. In the future, it will be essential to investigate the optimal timing for BEC to accurately reflect eosinophilic airway inflammation in patients with COPD through long-term follow-up studies. Fourth, in fact, we are aware that CT attenuation is influenced by lung volume, leading to inaccuracies in the measurement of pulmonary emphysema progression in studies. Our study used LAA −950 as the sole index for pulmonary emphysema. Our goal is to address this limitation in future research by further correcting for volume to explore the relationship between EOS and pulmonary EI. Fifth, due to the limited clinical application of expiratory CT, this study was unable to incorporate the parameter response mapping derived from biphasic respiratory CT.

CONCLUSION

We highlight that the relatively high EOS levels (≥2% or ≥150/μL or ≥300/μL) were associated with mild airflow restriction, mild diffusion function limitation and less bronchial thickening. Besides, when the EOS was ≥300/μL, the EI decreased significantly, especially in the right upper lobe, which indicates that QCT is useful in addressing the heterogeneity of eosinophilic COPD. Further QCT studies are essential to better understand the disease progression of COPD.

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Patient and public involvement Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

Patient consent for publication Obtained.

Ethics approval This study involves human participants and was approved by the Ethics Committee of the Shanxi Bethune Hospital (SBQLL-2020-006). Participants gave informed consent to participate in the study before taking part.

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