

Inflammatory Biomarkers as Predictors of Symptomatic Venous Thromboembolism in Hospitalized Patients with AECOPD: A Multicenter Cohort Study

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Aim: Venous thromboembolism (VTE) risk significantly increases in patients with an acute exacerbation of chronic obstructive pulmonary disease (AECOPD), which is characterized by an enhanced inflammatory response. This study aimed to evaluate the predictive value of inflammatory biomarkers for VTE in AECOPD.

Methods: A prospective, multicenter study was conducted to include patients hospitalized for AECOPD. Inflammatory biomarkers on admission were compared between the patients who developed VTE during hospitalization and the patients without VTE. A logistic regression analysis was used to identify inflammatory biomarkers with an independently predictive value.

Results: Among the 13,531 AECOPD inpatients, 405 (2.99%) developed VTE during hospitalization. Patients who developed VTE had higher levels of inflammatory biomarkers, including the white blood cell count, neutrophil percentage, systemic immune/inflammatory index, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio, C-reactive protein (CRP), procalcitonin (PCT), and lactate dehydrogenase (LDH), and lower lymphocyte and eosinophil ratios (ESOR), platelet, and albumin (p all <0.05). NLR, LDH, CRP, PCT, and ESOR were identified as independent predictors of VTE (odds ratios (ORs) were 2.22, 1.95, 1.64, 1.59, and 1.37, respectively). The incidence of VTE increased with increasing NLR, LDH, CRP, and PCT quartiles, and a decreasing ESOR quartile. Among them, NLR and LDH had predictive capabilities for VTE that were comparable to the widely used Padua and IMPROVE scores.

Conclusion: Easily available inflammatory parameters, such as NLR and LDH, can identify AECOPD patients at increased risk for VTE who may therefore be candidates for thromboprophylaxis.

Key words: Acute exacerbation of chronic obstructive pulmonary disease, Venous thromboembolism, Inflammatory biomarkers

Introduction

Methods

Chronic obstructive pulmonary disease (COPD) is the third leading cause of morbidity and mortality in the world¹. Patients may frequently experience episodes of acute exacerbations (AECOPD), which are often associated with increased local and systemic inflammation caused by airway infections, pollution, or other insults to the airways². Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a frequent and serious complication in patients hospitalized for AECOPD which poses challenges to treatment and management³. Patients admitted for AECOPD are generally considered to be at a moderate risk for the development of VTE, but the underlying mechanisms are still not well known. Several mechanisms contribute to increased thromboembolic risk in patients with AECOPD, including systemic inflammation, hypoxemia, oxidative stress, endothelial dysfunction, and a prothrombotic state⁴. Recently, increased attention has been paid to the role of the inflammatory response in VTE. The inflammatory response can be appraised by changes in (1) the complete blood count, including an increase in the white blood cell count and the neutrophil percentage (NEUT) as well as a decrease in platelets⁵ and the eosinophil ratio (ESOR)⁶; (2) biomarkers including the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin (PCT), lactate dehydrogenase (LDH)^{7, 8}, fibrinogen⁹, and albumin¹⁰; and (3) combined biomarkers including the systemic immune/inflammatory index (SII), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR)⁶. Some of these inflammatory biomarkers have been shown to be associated with the occurrence of VTE in various conditions, including lymphoma⁷, hematological malignancies¹¹ and COVID-19⁸. However, most previous studies have been single-center investigations involving only one or two indicators, with small sample sizes, and whether these inflammatory biomarkers could be potential risk indicators for VTE in patients with AECOPD remains largely unknown.

Therefore, the primary objective of this large multi-center prospective cohort study was to investigate the predictive value of inflammatory biomarkers for VTE in patients with AECOPD.

Ethical Considerations

The study was approved by the Ethics Committee on Biomedical Research, West China Hospital of Sichuan University, and the Ethics Committee of the other nine academic medical centers that participated and complied with the Declaration of Helsinki. Written informed consent was obtained from all the participants.

Study Design and Participants

Patient inclusion was based on the prospective, noninterventional, multicenter cohort study MAGNET AECOPD (MANaGement aNd advErse ouTcomes in inpatients with acute exacerbation of COPD) Registry study in China (ChiCTR2100044625). This prospective study included patients hospitalized for AECOPD in 10 large tertiary general hospitals in China between September 2017 and July 2021. The major aims of this registry study were to investigate the management and adverse outcomes (including intensive treatment usage, in-hospital venous thromboembolism, short-term and long-term mortality, and readmission) of inpatients with AECOPD and to establish and validate early warning models of these adverse outcomes, as described previously^{12, 13}. The diagnosis of AECOPD was based on the following criteria: (1) a history of COPD defined according to three items: 1) exposure to risk factors (e.g., tobacco smoking, specific environmental exposure); 2) long-term dyspnea (progressive, on exertion, or persistent), chronic cough, or sputum production; 3) postbronchodilator spirometry testing showing a forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio less than 70%; and (2) an acute worsening of respiratory symptoms resulting in additional therapy. Patients younger than 40 years and those with a length of stay less than 72 hours were excluded from the study. For the predictive efficacy assessment, a biomarker should be measured at a time when VTE is neither suspected nor diagnosed. Therefore, individuals who were diagnosed with VTE before hospitalization or within 48 hours after admission were also excluded.

Data Collection and Grouping

A standardized case report form, including baseline demographics, clinical characteristics on

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admission, laboratory and imaging findings, treatments, and in-hospital outcomes (including in-hospital venous thromboembolism, in-hospital mortality, ICU admission, mechanical ventilation, and length of stay greater than 10-days) was completed for every enrolled patient. Mechanical ventilation included invasive and noninvasive ventilation. All the data were cross-checked and centrally validated for accuracy. Demographics including age, sex, height, weight, and smoking status. Clinical characteristics including symptoms, signs, comorbidities, and some known risk factors for VTE, including long bed rest, surgery/trauma in the past month, and history of VTE, were also recorded. Laboratory results, including a complete blood count, ESR, CRP, PCT, LDH, albumin, and fibrinogen, were detected within 24 hours of admission. The SII was calculated based on the following formula: $\text{platelet} \times \text{neutrophil} / \text{lymphocyte}$, NLR was obtained from the ratio of neutrophil count to lymphocyte count, and PLR was obtained from the ratio of the platelet count to lymphocyte count. Additionally, the widely used VTE risk assessment models (RAMs) for nonsurgical patients, the Padua score¹⁴) and the IMPROVE (International Medical Prevention Registry on Venous Thromboembolism) score¹⁵) were calculated for each patient on admission. The admission, arrangement of auxiliary examinations, and the treatment of patients were carried out at the discretion of the attending physicians, and no additional direct intervention was performed.

Study Outcomes

The primary outcome of this study was symptomatic VTE, which encompassed DVT (proximal and/or distal) and PE during hospitalization. DVT was validated based on positive compression ultrasonography and/or contrast venography, while PE was confirmed based on positive computed tomography pulmonary angiography, pulmonary angiogram, or high-probability ventilation/perfusion scintigraphy. Patients were categorized into two groups: the AECOPD with VTE group and AECOPD without VTE group, according to whether VTE was diagnosed during their hospital stay.

Statistical Analysis

For continuous variables, data were presented as the mean $\pm$ standard deviation (SD) if they met normal distribution, or medians (25-75% interquartile range) if not. Normality of distribution was assessed using the Kolmogorov-Smirnov test. For categorical variables, data are presented as counts (percentages).

The study variables were compared between the AECOPD with VTE group and AECOPD without VTE group using the Mann-Whitney test or *t*-test for continuous variables and the chi-square test for categorical variables. Variables with missing data of more than 20% were included in the demographic and clinical characteristics but were excluded from univariate and multivariate logistic regression analyses. For variables with less than 20% missing data, multiple imputations were conducted using the Mice package in the R software program to impute missing data. Variables with $p < 0.05$ in univariate logistic regression and also thought to be of clinical significance were included in the multivariate logistic regression with forward LR (forward stepwise selection based on maximum likelihood estimation). For a deeper analysis, inflammatory biomarkers with independent predictive value were fitted into multivariate logistic regression models after being categorized into quartiles, and participants in the first quartile were defined as the reference group. An additional subgroup analysis considering the confounding effect of thromboprophylaxis was performed. The results were presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). The predictive accuracy of inflammatory indicators was calculated using the receiver operating characteristic (ROC) curve analysis. The area under the receiver operating characteristic curve (AUC) and Youden's index were used to identify the optimal cutoff values for these markers in terms of the best discriminative power.

All statistical analyses were conducted using the IBM SPSS software program version 27.0 (SPSS, Chicago, IL, USA) and R software 4.1.2 (R Foundation for Statistical Computing). A two-sided $p < 0.05$ was accepted as statistically significant.

Results

Characteristics of AECOPD Patients with and without VTE

A total of 14,007 consecutive patients with AECOPD were screened for inclusion in this study. Of these patients, 476 were excluded for the following reasons: (1) age less than 40 years ($n=44$), (2) duration of stay of less than 72 hours ($n=334$), and (3) a diagnosis of VTE before hospitalization or within 48 hours after admission ($n=98$). The incidence of symptomatic VTE in patients with AECOPD was 2.99% ($n=405$). Among the AECOPD patients diagnosed with VTE, 27 had PE only (6.67%), 361 had DVT only (89.14%), and 17 had both PE and DVT (4.20%). A flowchart of the screening process is

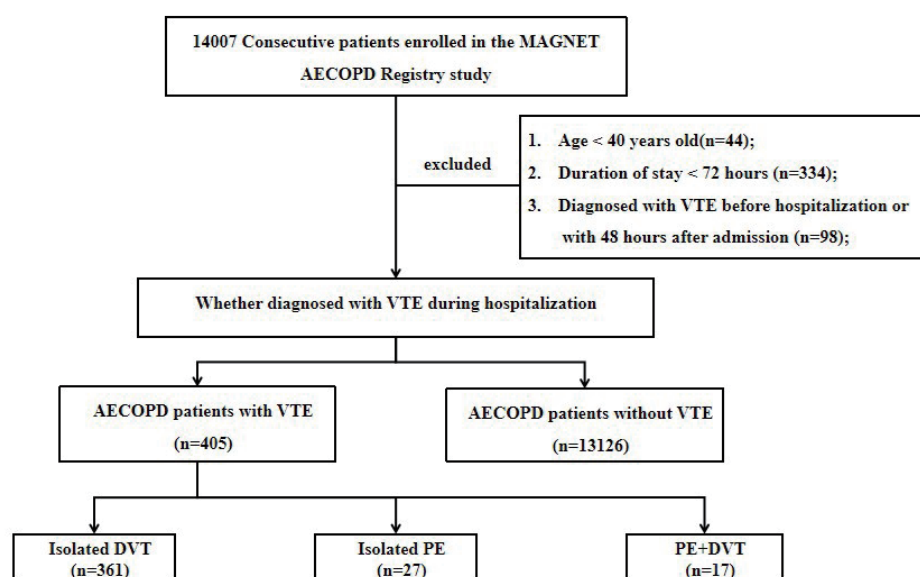


Fig. 1. Flow chart of the study

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis.

shown in **Fig. 1**. The mean age of the remaining 13531 patients was 72.47 ± 10.14 years, with 10,634 (78.6%) being males and 2,897 (21.4%) being females.

The differences in demographic and clinical characteristics between the AECOPD with VTE and AECOPD without VTE groups are described in **Table 1**. AECOPD patients with VTE were older compared to those without VTE (77.21 ± 9.34 vs 72.32 ± 10.13 years, $p < 0.05$). The VTE group also had a significantly higher proportion of female patients and patients with a body mass index (BMI) ≥ 30 kg/m² than the group without VTE (28.6% vs 21.4%, $p < 0.001$; 3.7% vs 1.9%, $p = 0.015$). Additionally, there were statistically significant differences between the two groups in terms of surgery or trauma in the past month, history of VTE, and long-term bed rest, all of which were more frequently observed in the VTE group. With respect to VTE RAMs, the Padua score and IMPROVE score of VTE group was higher than that of non-VTE group, and the difference was statistically significant ($p < 0.001$). No statistical differences were observed in the BMI and airflow limitation parameters (FEV₁/FVC and FEV₁ pred) between the two groups. Clinical symptoms and signs on admission, including fever, unconsciousness, lower limb edema, and low diastolic blood pressure, were more frequently observed in individuals with VTE ($p < 0.001$), while there were no significant differences in the common respiratory symptoms, respiratory

rate, heart rate, and systolic blood pressure between the two groups. In terms of comorbidities, patients with VTE had a higher prevalence of hypertension, heart failure, chronic pulmonary heart disease, pneumonia, diabetes, stroke, chronic hepatic insufficiency, chronic renal insufficiency, lower extremity varicose veins, osteoporosis, and anemia compared to patients without VTE ($p < 0.05$). Although the incidence of active cancer was higher in the patients with VTE, there was no statistically significant difference between the two groups. Regarding laboratory tests, it was found that patients with VTE had higher levels of D-dimer, NT-pro-BNP, and cardiac troponin T (2.04 vs 0.70 mg/L, 1149.0 vs 300.9 pg/ml, 29.20 vs 17.00 ng/L, respectively, p all < 0.001). No statistically significant differences were observed in the measured levels of hydrogen ion concentration (pH) and arterial oxygen tension (PO₂) between the two groups.

As shown in **Table 1**, the proportion of patients receiving mechanical ventilation or being admitted to the ICU was higher in the VTE group (43.2% vs 19.3% and 34.8% vs 6.5%, respectively; $p < 0.001$). Moreover, VTE was associated with worse outcomes in patients with AECOPD. Patients with VTE had a higher in-hospital mortality (9.1% vs 1.1%, $p < 0.001$) and a longer hospital stay than those without VTE (15 vs 9 days, $p < 0.001$). During the hospital stay, AECOPD patients with VTE were more likely to be prescribed antibiotics (89.6% vs 64.8%, $p < 0.001$).

Table 1. The demographic and clinical characteristics of AECOPD patients with VTE and without VTE

	Total	With VTE (n = 405)	Without VTE (n = 13126)	p-Value*
Baseline characteristics				
Age (year)	72.47 ± 10.14	77.21 ± 9.34	72.32 ± 10.13	<0.001
Age ≥ 75 years	5657 (41.8%)	258 (63.7%)	5399 (41.1%)	<0.001
Female	2897 (21.4%)	116 (28.6%)	2781 (21.4%)	<0.001
BMI (kg/m ²)	21.58 ± 4.06	22.21 ± 4.72	21.56 ± 4.03	0.111
BMI ≥ 30 (kg/m ²)	258 (1.9%)	15 (3.7%)	243 (1.9%)	0.015
Current smoking	2731 (20.3%)	53 (13.1%)	2678 (20.4%)	<0.001
Surgery/trauma in the past month	260 (1.9%)	17 (4.2%)	243 (1.9%)	<0.001
History of VTE	134 (1.0%)	55 (13.6%)	79 (0.6%)	<0.001
Long term bed rest [†]	1745 (12.9%)	118 (29.1%)	1627 (12.4%)	<0.001
FEV1/FVC (%) [†]	55.16 (44.0-62.0)	57.81 (43.13-62.75)	55.00 (43.85-61.84)	0.875
FEV1 pred (%) [†]	48.60 (35.45-65.75)	40.00 (39.50-57.35)	48.75(34.93-66.13)	0.704
Rome severity classification ^{†§}				<0.001
mild	2959 (40.9%)	102 (32.3%)	2857 (41.3%)	
moderate	2952 (40.8%)	161 (50.9%)	2791 (40.3%)	
severe	1330 (18.4%)	53 (16.8%)	1277 (18.4%)	
Padua score	1.0 (0.0-2.0)	2.0 (1.0-4.0)	1.0 (0.0-2.0)	<0.001
Padua score ≥ 4	1678 (12.4%)	127 (31.4%)	1551 (11.8%)	<0.001
IMPROVE score	1.0 (1.0-1.0)	2.0 (1.0-3.0)	1.0 (1.0-1.0)	<0.001
IMPROVE score ≥ 4	256 (1.9%)	48 (11.9%)	208 (0.4%)	<0.001
Symptoms and Vital signs				
Fever	1555 (11.5%)	77 (19.0%)	1478 (11.3%)	<0.001
Chest congestion	2995 (22.1%)	98 (24.2%)	2897 (22.1%)	0.310
Chest pain	693 (5.1%)	14 (3.5%)	679 (5.2%)	0.123
Dyspnea	8245 (60.9%)	231 (57.0%)	8014 (61.1%)	0.103
Hemoptysis	367 (2.7%)	10 (2.5%)	357 (2.7%)	0.760
Unconsciousness	429 (3.2%)	88 (21.7%)	341 (2.6%)	<0.001
Lower limb edema	1687 (12.5%)	150 (37.0%)	1537 (11.37%)	<0.001
Respiratory Rate (breath/min)	20 (20-22)	20 (20-22)	20 (20-22)	0.143
Heart Rate (bpm)	89.09 ± 16.57	89.40 ± 18.15	89.08 ± 16.52	0.721
Systolic blood pressure (mmHg)	132.12 ± 19.43	131.19 ± 23.05	132.15 ± 19.31	0.313
Diastolic blood pressure (mmHg)	78.87 ± 17.0	75.26 ± 14.78	78.98 ± 12.50	<0.001
Comorbidities				
Hypertension	4556 (33.7%)	177 (43.7%)	4379 (33.4%)	<0.001
Coronary heart disease	1509 (11.2%)	57 (14.1%)	1452 (11.1%)	0.058
Heart failure	1556 (11.6%)	109 (26.9%)	1447 (11.0%)	<0.001
Chronic pulmonary heart disease	2796 (20.7%)	166 (41.0%)	2630 (20.0%)	<0.001
OSAHS	83 (0.6%)	5 (1.2%)	78 (0.6%)	0.104
Pneumonia	3005 (22.2%)	146 (36.0%)	2859 (21.8%)	<0.001
Diabetes	1761 (13.0%)	83 (20.5%)	1678 (12.8%)	<0.001
Stroke	796 (5.9%)	53 (13.1%)	743 (5.7%)	<0.001
Chronic hepatic insufficiency	238 (1.8%)	15 (3.7%)	223 (1.7%)	0.003
Chronic renal insufficiency	502 (3.7%)	54 (13.3%)	448 (3.4%)	<0.001
Active cancer [†]	829 (6.1%)	32 (7.9%)	797 (6.1%)	0.131
Anxiety or depression	103 (0.8%)	7 (1.7%)	96 (0.7%)	0.050
GERD	129 (1.0%)	4 (1.0%)	125 (1.0%)	0.943
Varicose veins of lower extremities	79 (0.6%)	13 (3.2%)	66 (0.5%)	<0.001
Osteoporosis	340 (2.5%)	23 (5.7%)	317 (2.4%)	<0.001
Anemia [†]	4607 (34.0%)	199 (49.1%)	4408 (33.6%)	<0.001
Laboratory findings				
Red blood cell (x 10 ¹² /L) [§]	4.28 ± 0.78	4.03 ± 0.88	4.29 ± 0.78	<0.001
Hemoglobin (g/L) [§]	127.38 ± 22.47	119.90 ± 26.29	127.61 ± 22.30	<0.001
pH [§]	7.41 (7.38-7.45)	7.42 (7.38-7.46)	7.41 (7.38-7.45)	0.125
PaO ₂ (mmHg) [§]	90.33 ± 33.32	94.56 ± 42.88	90.18 ± 32.92	0.057
PaCO ₂ (mmHg) [§]	45.27 ± 14.19	48.15 ± 16.28	45.15 ± 14.09	<0.001
NT-pro-BNP (pg/ml) [§]	315.5 (101.9-1319)	1149.0 (371-3657)	300.9 (97.29-1236)	<0.001
Cardiac troponin T (ng/L) [§]	17.6 (10.6-32.5)	29.20 (17.60-57.30)	17.00 (10.30-31.28)	<0.001
D-dimer (mg/L) [§]	0.72 (0.40-1.50)	2.04 (1.08-5.25)	0.70 (0.40-1.43)	<0.001

(Cont. Table 1)

	Total	With VTE (n = 405)	Without VTE (n = 13126)	p-Value*
Treatments and Outcomes				
In-hospital mortality	184 (1.4%)	37 (9.1%)	147 (1.1%)	<0.001
Length of stay greater than 10 days	6393 (47.2%)	341 (77.5%)	6079 (46.3%)	<0.001
Length of stay (days)	9 (7-14)	15 (10-26)	9 (7-13)	<0.001
Admission to ICU	1000 (7.4%)	141 (34.8%)	859 (6.5%)	<0.001
Mechanical ventilation	2710 (20.0%)	175 (43.2%)	2535 (19.3%)	<0.001
Hospital bills	13112.4 (8930.1-20038.5)	25321.2 (14740.9-58972.1)	12988.7 (8871.2-19692.0)	<0.001
Glucocorticoid use (I.V. or Oral)	5586 (41.3%)	176 (43.5%)	5410 (41.2%)	0.197
Anti-biotic use	8864 (65.5%)	363 (89.6%)	8501 (64.8%)	<0.001
Thromboprophylaxis	1792 (13.24%)	51 (12.59%)	1741 (13.26%)	0.824

Abbreviations: AECOPD=acute exacerbation of chronic obstructive pulmonary disease; VTE=venous thromboembolism; BMI=body mass index; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; bpm=beats per minute; OSAHS=obstructive sleep apnea-hypopnea syndrome; GERD=gastroesophageal reflux disease; pH=hydrogen ion concentration; PO2=the partial pressure of oxygen; PaCO2=the partial pressure of carbon dioxide; NT-pro-BNP= N-terminal pro-brain natriuretic peptide; ICU=intensive care unit; I.V. =intravenous.

Notes: Data are presented as mean $\pm$ SD (standard deviation), median (25-75% interquartile range) or counts (percentages).

*Those with P value <0.05 were highlighted using the bold font.

† Long term bed rest means that the patient had been in bed for greater than 14 days before admission due to illness or other reasons. FEV1/FVC, FEV1% predicted are from the stable stage of the patients. The ROME severity classification, which including six variables (dyspnea, arterial oxygen saturation, respiratory rate, heart rate, serum C-reactive protein and arterial blood gases) has been included in the GOLD (Global Initiative on Obstructive Lung Disease) report since 2023 as a severity evaluation tool for AECOPD. Active cancer was defined as solid or hematological cancer requiring chemotherapy, radiation therapy, surgery, or palliative care during the last 3 months. Anemia was judged according to the blood routine results.

§ Missing data: Rome severity classification was available in 7241 (53.51%) patients; red blood cell was available in 13351(98.67%) patients; hemoglobin was available in 13354 (98.69%) patients; pH was available in 8796 (65.01%) patients; PaO2 was available in 10320 (76.30%) patients; PaCO2 was available in 8573 (63.36%) patients; NT-pro-BNP was available in 8301(61.3%) patients; Cardiac troponin T was available in 5039 (37.2%) patients; D-dimer was available in 10553(77.99%) patients.

However, there was no difference in the use of systemic glucocorticoids between the two groups (43.5% vs 41.2%, $p=0.197$). The use of thromboprophylaxis was lower in the AECOPD with VTE group than in the AECOPD without VTE group, although the difference was not statistically significant (12.59% vs 13.26%, $p=0.824$).

Inflammatory Biomarkers and VTE

Table 2 and Supplementary Fig. 1 show the differences in inflammatory biomarkers detected on admission between patients with VTE and those without VTE. The levels of white blood cells, NEUT, LDH, CRP, and PCT on admission were significantly higher among patients who later developed VTE compared to those who did not develop VTE (8.67 vs 7.67 $\times 10^9/L$, 82.2 vs 75.0%, 236.5 vs 215.79 IU/L, 25.30 vs 11.30 mg/L, 0.14 vs 0.05 ng/ml, respectively, $p<0.05$). The median SII, NLR, and PLR in patients who developed VTE were higher than those who didn't (1308.08 vs 837.28, 8.27 vs 4.20, 206.76 vs 155.74, respectively, $p<0.001$). In contrast, the levels of lymphocytes, ESOR, platelet, fibrinogen, and albumin on admission were lower in patients with VTE than in those without (0.82 vs 1.12 $\times 10^9/L$, 0.4% vs 1.0%, 183.10 vs 205.95 $\times 10^9/L$, 3.46 vs 3.88 g/L, 34.39 vs 36.83 g/L, respectively, $p<0.05$). The

ESR levels were generally comparable between the two groups. As shown in Fig. 2, after dividing the inflammatory biomarkers into quartiles, the incidence of VTE increased significantly as the NEUT, CRP, PCT, LDH, SII, NLR, and PLR quartiles increased (NEUT:1.3% vs 2.1% vs 3.6% vs 5.1%, CRP: 1.3% vs 3.3% vs 4.8% vs 6.0%, PCT: 1.8% vs 4.1% vs 7.8%, LDH:1.7% vs 2.4% vs 3.0% vs 6.7%, SII:1.4% vs 2.2% vs 3.7% vs 4.6%, NLR:1.1% vs 1.7% vs 3.4% vs 5.7%, PLR:1.8% vs 2.5% vs 3.3% vs 4.3%, respectively, $p<0.05$). The incidence increased significantly as the lymphocyte, ESOR, platelet, and albumin quartiles decreased (lymphocyte: 4.5% vs 4.0% vs 2.1% vs 1.4%, ESOR:4.5% vs 3.6% vs 2.1% vs 1.7%, platelet:4.3% vs 2.9% vs 2.6% vs 2.2%, albumin:5.1% vs 3.3% vs 2.2% vs 1.7%). However, the prevalence of VTE from the first to the fourth quartiles did not show an increasing or decreasing trend in the white blood cell, ESR, and fibrinogen levels.

Inflammatory Biomarkers as Independent Predictors of VTE in AECOPD Patients

The univariate and multivariate logistic regression results obtained after transforming continuous variables into categorical variables are shown in Supplementary Table 1 and Table 3.

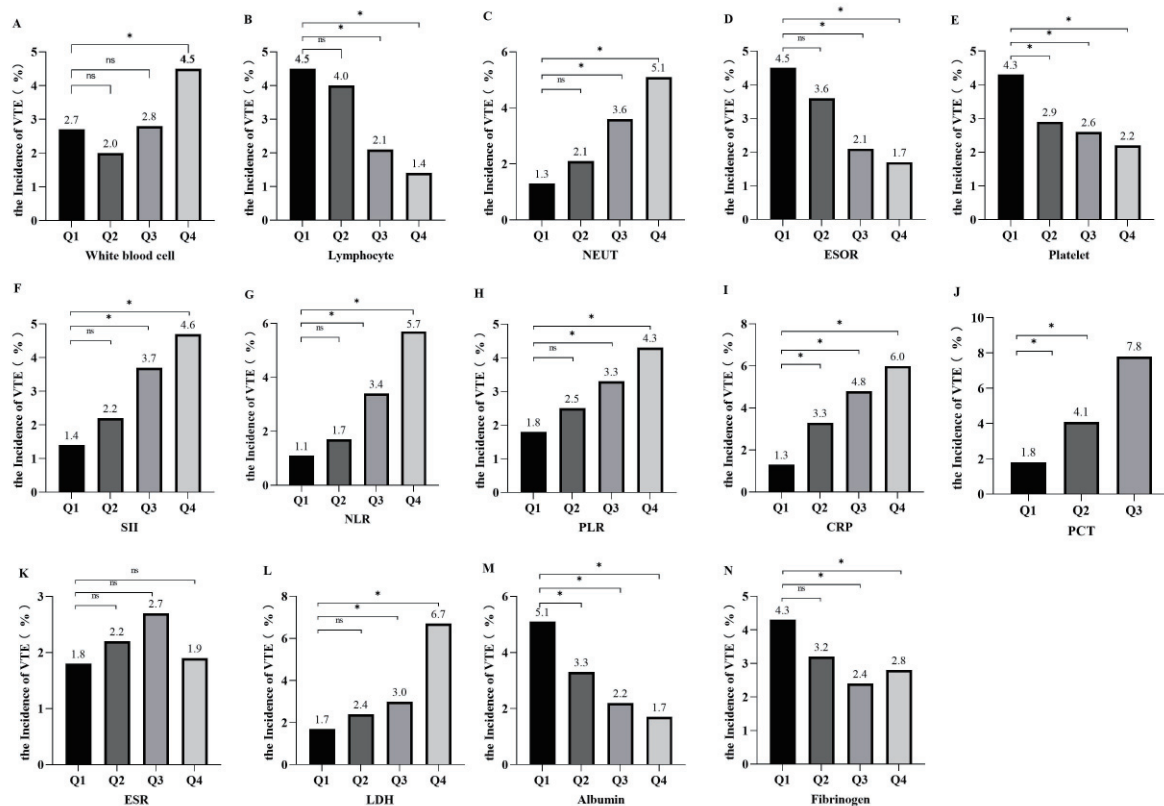
Table 2. Comparison of inflammatory biomarkers on admission between AECOPD patients with and without VTE

	AECOPD With VTE (n = 405)	AECOPD without VTE (n = 13126)	p-Value*
White blood cell (x 10 ⁹ /L)	8.67 (6.17-12.06)	7.67 (5.88-10.10)	<0.001
Lymphocyte (x 10 ⁹ /L)	0.82 (0.50-1.19)	1.12 (0.66-1.65)	<0.001
NEUT (%)	82.20 (74.48-89.30)	75.00 (65.50-90.20)	<0.001
EOSR (%)	0.40 (0.00-1.40)	1.00 (0.10-2.60)	<0.001
Platelet (x 10 ⁹ /L)	183.10 ± 89.20	205.95 ± 94.57	<0.001
SII	1308.08 (746.54-3002.88)	837.28 (433.03-1778.96)	<0.001
NLR	8.27 (4.59-16.49)	4.40 (2.50-8.74)	<0.001
PLR	206.76 (135.87-314.83)	155.74 (101.07-257.99)	<0.001
CRP (mg/L)	25.30 (9.75-82.30)	11.30 (3.65-43.74)	<0.001
PCT (ng/ml)	0.14 (0.06-0.42)	0.05 (0.05-0.13)	<0.001
ESR (mm/h)	34.00 (15.50-57.50)	31.00 (13.00-60.00)	0.765
LDH (IU/L)	236.50 (185.00-299.00)	215.79 (161.00-238.00)	<0.001
Albumin (g/L)	34.39 ± 5.33	36.83 ± 5.50	<0.001
Fibrinogen (g/L)	3.46 (2.69-4.78)	3.88 (2.98-5.09)	<0.001

Abbreviations: AECOPD=acute exacerbation of chronic obstructive pulmonary disease; VTE=venous thromboembolism; NEUT=neutrophil percentage; ESOR=eosinophil ratio; SII=systemic immune/inflammatory index; NLR=neutrophil to lymphocyte ratio; PLR=platelet to lymphocyte ratio; CRP=C-reactive protein; ESR=Erythrocyte Sedimentation Rate; PCT=procalcitonin; LDH=lactate dehydrogenase.

Notes: Data are presented as mean ± SD (standard deviation), median (25-75% interquartile range) or counts (percentages).

*Those with *p* value <0.05 were highlighted using the bold font.

**Fig. 2.** Incidence of VTE in the different quartile groups of the inflammatory biomarkers

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; VTE, venous thromboembolism; NEUT, Neutrophil ratio; ESOR, eosinophil ratio; SII, systemic immune/inflammatory index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; PCT, procalcitonin; ESR=Erythrocyte Sedimentation Rate; LDH, lactate dehydrogenase.

Notes: * Those with a *p* value <0.05.

Table 3. Multivariate logistic regression analysis for predictors of VTE in AECOPD patients

Variables [†]	OR	95% CI	<i>p</i> -Value*
Age ≥ 75 (years)	1.61	(1.28–2.02)	<0.001
Long term bed rest	2.24	(1.76–2.87)	<0.001
History of VTE	16.96	(11.38–25.27)	<0.001
Lower limb edema	2.32	(1.84–2.94)	<0.001
Varicose veins of lower extremities	6.42	(3.21–12.85)	<0.001
Arrhythmia	1.35	(1.02–1.78)	0.036
Chronic pulmonary heart disease	1.83	(1.45–2.29)	<0.001
Pneumonia	1.28	(1.02–1.61)	0.035
Stroke	1.57	(1.13–2.19)	0.008
Osteoporosis	1.76	(1.10–2.83)	0.019
Chronic renal insufficiency	1.67	(1.19–2.36)	0.003
Anemia	1.36	(1.09–1.69)	0.006
NLR > 4.38	2.22	(1.72–2.85)	<0.001
LDH > 250 (IU/L)	1.95	(1.56–2.45)	<0.001
CRP ≥ 5 (mg/L)	1.64	(1.30–2.08)	<0.001
PCT ≥ 0.5 (ng/ml)	1.59	(1.19–2.13)	0.002
ESOR < 2 (%)	1.37	(1.05–1.79)	0.022

Abbreviations: VTE= venous thromboembolism; AECOPD=acute exacerbation of chronic obstructive pulmonary disease; CPHD=chronic pulmonary heart disease; NLR=neutrophil to lymphocyte ratio; LDH=lactate dehydrogenase; CRP=C-reactive protein; PCT=procalcitonin; ESOR=eosinophil ratio.

Notes: *Those with *p* value <0.05 were highlighted using the bold font.

[†] Covariates adjusted in multivariate logistic regression analysis: age ≥ 75 years, female, BMI ≥ 30 kg/m², history of surgery or trauma in 1 month, long term bed rest, history of VTE, lower limb edema, comorbidities including hypertension, heart failure, arrhythmia, chronic pulmonary heart disease, pneumonia, diabetes, stroke, chronic hepatic insufficiency, chronic renal failure, lower extremity varicose vein, osteoporosis, anemia, white blood cell > ×10⁹/L, lymphocyte < 1×10⁹/L, NEUT > 75%, EOSR < 2%, platelet < 100 ×10⁹/L, NLR > 4.38, PLR > 196.39, CRP ≥ 5mg/L, PCT ≥ 0.5ng/ml, LDH > 250 IU/L, albumin < 35g/L, fibrinogen < 2 g/L.

Inflammatory biomarkers that demonstrated statistically and clinically significant differences in univariate logistic analyses were included in the multivariate logistic regression analysis. After adjusting for potential confounders, five inflammatory markers were identified as independent predictors for the development of VTE in patients with AECOPD, including NLR > 4.39 (OR=2.22; 95%CI: 1.72–2.85), LDH > 250 IU/L (OR=1.95; 95%CI: 1.56–2.45), CRP ≥ 5 mg/L (OR=1.64; 95%CI: 1.30–2.08), PCT ≥ 0.5 ng/ml (OR=1.59; 95%CI: 1.19–2.13), ESOR < 2% (OR=1.37; 95%CI: 1.05–1.79). Age ≥ 75 years, long-term bed rest, history of VTE, lower limb edema, comorbidities including varicose veins of the lower extremities, arrhythmia, chronic pulmonary heart disease, pneumonia, stroke, osteoporosis, chronic renal insufficiency, and anemia were found to be independent risk factors for VTE in patients with AECOPD. Furthermore, according to the findings shown in [Table 4](#), the risk of VTE (ORs) increased with increasing NLR, LDH, CRP, and PCT quartiles and decreasing ESOR quartile after adjusting for confounding factors.

ROC curves were constructed for the inflammatory

markers identified as independent predictors of VTE by a multivariate analysis. As shown in [Fig. 3 and Table 5](#), NLR had the highest AUC of 0.677 (95%CI: 0.652–0.702) with an optimal cutoff value of 4.38. LDH showed an AUC of 0.662 (95%CI: 0.634–0.690), with a cut-off of 239 IU/L. The AUCs for PCT, CRP, and ESOR for predicting VTE were 0.644, 0.640, and 0.609, respectively. Of the five, the prediction accuracies of NLR and LDH were comparable to the Padua score (AUC=0.620, 95%CI: 0.682–0.734 with a cut-off value of 4 points, AUC=0.708, 95%CI: 0.682–0.734 with a cut-off value of 2 points) and the IMPROVE score (AUC=0.678, 95%CI: 0.649–0.707 with cut-off value of 2, AUC=0.551, 95%CI: 0.521–0.582 with cut-off value of 4 points). As shown in [Supplementary Fig. 2](#), the incorporation of NLR and LDH into the Padua and IMPROVE scores could improve the VTE risk discrimination of VTE RAMs (ΔAUC: 0.027, 95%CI: 0.021–0.034, *p*<0.001 for NLR and LDH to Padua; ΔAUC: 0.057, 95%CI: 0.043–0.071 for NLR and LDH to IMPROVE).

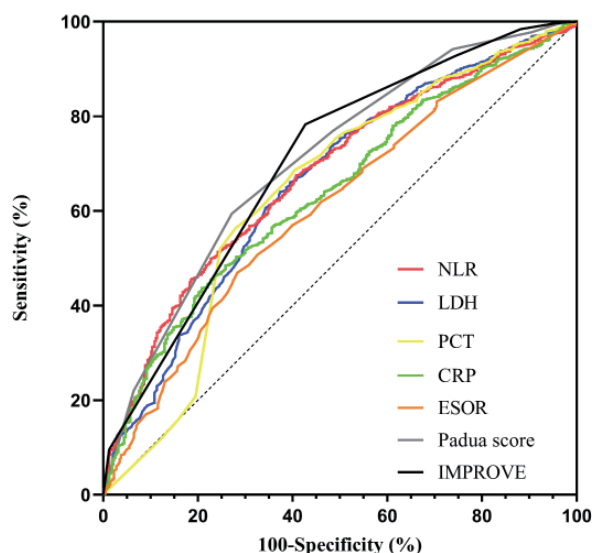
Table 4. Multivariate logistic regression analysis for NLR, LDH, CRP, PCT, and ESOR in the quartiles

Variables [†]	OR	95%CI	<i>p</i> -Value*
NLR			
Q1 (≤ 2.53)	1	[Reference]	
Q2 (2.54-4.48)	1.61	(1.25, 2.08)	<0.001
Q3 (4.49-8.94)	2.74	(2.01, 3.76)	<0.001
Q4 (≥ 8.95)	3.62	(2.51, 5.24)	<0.001
LDH			
Q1 (≤ 162 IU/L)	1	[Reference]	
Q2 (163-193 IU/L)	1.86	(1.40, 2.46)	<0.001
Q3 (194-239 IU/L)	2.00	(1.48, 2.71)	<0.001
Q4 (≥ 240 IU/L)	2.69	(1.92, 3.77)	<0.001
CRP			
Q1 (≤ 3.80 mg/L)	1	[Reference]	
Q2 (3.81-11.76 mg/L)	1.33	(0.99, 1.78)	0.056
Q3 (11.77-45.34 mg/L)	1.67	(1.20, 2.33)	0.002
Q4 (≥ 45.35 mg/L)	2.90	(1.86, 4.50)	<0.001
PCT			
Q1 (≤ 0.05 ng/ml)	1	[Reference]	
Q2 (0.06-0.14 ng/ml)	1.72	(1.30, 2.28)	<0.001
Q3 (11.77-45.34 ng/ml)	2.62	(1.95, 3.53)	<0.001
ESOR			
Q4 ($\geq 2.61\%$)	1	[Reference]	
Q3 (1.01-2.60%)	1.16	(0.90, 1.50)	0.265
Q2 (0.11-1.00%)	1.98	(1.44, 2.70)	<0.001
Q1 ($\leq 0.1\%$)	2.17	(1.56, 3.02)	<0.001

Abbreviations: AECOPD=acute exacerbation of chronic obstructive pulmonary disease; VTE=venous thromboembolism; NLR=neutrophil to lymphocyte ratio; LDH=lactate dehydrogenase; CRP=C-reactive protein; PCT=Procalcitonin; ESOR=eosinophil ratio.

Notes: * Those with *p* value <0.05 were highlighted using the bold font.

[†] Covariates adjusted in multivariate logistic regression analysis: age ≥ 75 years, female, BMI ≥ 30 kg/m², history of surgery or trauma in 1 month, long term bed rest, history of VTE, lower limb edema, comorbidities including hypertension, heart failure, arrhythmia, Chronic pulmonary heart disease, pneumonia, diabetes, stroke, chronic hepatic insufficiency, chronic renal failure, lower extremity varicose vein, osteoporosis, anemia.

**Fig. 3.** ROC curve of inflammatory biomarkers and VTE RAMs for the prediction of VTE in patients with AECOPD

Abbreviations: ROC, receiver operating characteristic; VTE, venous thromboembolism; RAMs, risk assessment models; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; CRP, C-reactive protein; PCT, procalcitonin; ESOR, eosinophil ratio.

Table 5. The AUC value of inflammatory biomarkers to predict VTE during hospitalization

Variables	Cut-off	AUC	95%CI	Sensitivity	Specificity	p-Value*
NLR	4.38	0.677	(0.652, 0.702)	80.07%	45.71%	<0.001
LDH (IU/L)	239	0.662	(0.634, 0.690)	51.22%	73.20%	<0.001
PCT (ng/ml)	0.11	0.644	(0.611, 0.677)	62.37%	65.24%	<0.001
CRP (mg/L)	8.66	0.640	(0.611, 0.669)	80.14%	42.60%	<0.001
ESOR (%)	1.13	0.609	(0.582, 0.637)	60.00%	56.66%	<0.001
IMPROVE [†]	4	0.551	(0.521, 0.582)	11.85%	98.41%	<0.001
IMPROVE [§]	2	0.678	(0.649, 0.707)	57.28%	78.30%	<0.001
Padua score [†]	4	0.620	(0.589, 0.650)	38.50%	85.4%	<0.001
Padua score [‡]	2	0.708	(0.682, 0.734)	59.43%	72.84%	<0.001

Abbreviations: AUC=area under the ROC curve; VTE=venous thromboembolism; NLR=neutrophil to lymphocyte ratio; LDH=lactate dehydrogenase; CRP=C-reactive protein; PCT=procalcitonin; ESOR=eosinophil ratio.

Notes: *Those with *p* value <0.05 were highlighted using the bold font.

[†] According to the IMPROVE score, a high risk means a cumulative risk score of ≥ 4 ; according to the Padua score, a high risk means a cumulative risk score of ≥ 4 .

[§] According to the IMPROVE score, a moderate-high risk means a cumulative risk score of ≥ 2 .

[‡] For Padua RAM, a score of 2 points is the optimal cut-off value found in this study.

Subgroup Analysis Based on Thromboprophylaxis

A subgroup analysis (Supplementary Table 2) based on thromboprophylaxis was performed. It turns out that $\text{NLR} > 4.39$, $\text{CRP} \geq 5 \text{ mg/L}$, $\text{PCT} \geq 0.5 \text{ ng/ml}$ and $\text{LDH} > 250 \text{ IU/L}$ were still independent predictors for VTE in the subgroup without thromboprophylaxis according to a multivariate logistic regression analysis, which is consistent with the results obtained from the overall cohort. Interestingly, no inflammatory biomarkers were independently correlated with an increased risk of VTE in the subgroup that received thromboprophylaxis during hospitalization.

Discussion

In this large multicenter study, inflammatory biomarkers, including NLR, LDH, CRP, PCT, and ESOR, were found to be independent predictors for the development of VTE. Furthermore, the incidence and risk of VTE increased with rising levels of NLR, LDH, CRP, and PCT and with decreasing levels of ESOR. Among these inflammatory biomarkers, NLR and LDH had predictive capabilities for VTE to those of the widely used Padua and IMPROVE scores.

Despite being recommended by the guidelines, thromboprophylaxis is largely underused in medical inpatients (including AECOPD), with an increased risk of VTE in clinical practice in the real world, especially in China, as indicated by the extremely low proportion of patients who received thromboprophylaxis in this study (1792/13531, 13.24%). This was in accordance with the findings of a large multicenter investigation conducted in China, which reported that

the overall rate of prophylaxis was 12.9% among medical inpatients¹⁶. Thromboprophylaxis is more often administered in Western countries, but still less than half of high-risk medical inpatients received appropriate thromboprophylaxis¹⁷⁻¹⁹. An overall VTE incidence of 2.99% was observed in inpatients with AECOPD during hospitalization in this study. The incidence was relatively low compared to the prevalence reported in previous studies mainly conducted in non-Asian populations, which ranged from 2.1% to 29.1%²⁰⁻²⁷. The relatively low incidence of VTE in this study may be attributed to the following reasons: 1) Whites and African Americans have proven to show a significantly higher prevalence of PE and DVT than Asian people^{28, 29}; 2) the screening of inpatients with AECOPD for asymptomatic VTE was not routinely performed in this study; and 3) we strictly excluded VTE events acquired before hospitalization (a total of 99 patients diagnosed with VTE before admission or within 48 hours after admission were excluded). Nevertheless, the prevalence of VTE is still higher than that in general medical inpatients, which was reported to be 0.25–1.1%^{16, 30-32}. AECOPD patients who developed VTE during hospitalization demonstrated worse in-hospital outcomes, which was in line with previous studies^{3, 33}, and this highlighted the importance of exploring effective and easily available predictors of VTE in this population to guide thromboprophylaxis and improve prognosis.

The historical understanding of venous thrombus formation is centered on the mechanisms now well described as Virchow's triad, which includes vessel wall damage, venous stasis, and hypercoagulability.

However, mounting evidence has highlighted the impact of inflammation on the pathophysiology of thrombosis. The infiltration of inflammatory cells and aggregation of inflammatory factors can activate the complement system and enhance the oxidative stress response, directly or indirectly damaging vascular endothelial cells, causing the aggregation and adhesion of platelets, and further activating the body's coagulation system, making the body appear to be in a hypercoagulable state³⁴). Another plausible mechanism is that proinflammatory cytokines such as interleukin not only play a central role in the hepatic production of CRP, fibrinogen, and other acute-phase proteins involved in the inflammatory process but also play a role in the activation of coagulation³⁵). Some systemic inflammatory diseases, such as inflammatory bowel disease and COVID-19, have been associated with a thrombotic tendency and increased risk of VTE^{8, 36}). Similar to COVID-19, inflammation contributes to the pathogenesis of AECOPD and an increase in inflammatory biomarkers may alter the coagulation profile. However, to our knowledge, no previous study has investigated the role of inflammatory biomarkers in the development of VTE in AECOPD. Through this large multicenter study, we confirmed for the first time that inflammatory biomarkers, including NLR, LDH, CRP, PCT, and ESOR, were independent predictors of VTE development. NLR, which represents the relationship between neutrophils and lymphocytes in inflammation, provides important information about the systemic inflammation status. The increase in neutrophil count represents a systemic inflammatory process, while the decrease in lymphocytes indicates ongoing stress inflicted by the disease³⁷). Previous studies have revealed that NLR is significantly associated with the onset of PE and NLR could predict the occurrence of VTE in surgical patients³⁸). Our study confirmed the promising predictive capability of NLR for the development of VTE in AECOPD patients. To date, a correlation between elevated LDH and a higher risk of VTE has been observed in lymphoma⁷) and COVID-19 patients³⁹). Consistent with the results reported in the two conditions, the LDH level on admission was significantly higher in patients with AECOPD who later developed VTE than in those who did not develop VTE. LDH mainly exists in human tissue cells, and its increase is related to intravascular erythrocyte hemolysis and tissue cell damage. When hypercoagulability occurs, local tissue ischemia, hypoxia, edema, and degeneration tend to occur due to blood circulation disorders. LDH in tissue cells is then released into the blood, resulting in increased LDH levels⁴⁰). This may be the underlying mechanism

linking the increased LDH level and the increased risk of VTE. A significant body of work has demonstrated that destabilized isoforms of CRP possess important pro-inflammatory and pro-thrombotic properties⁴¹), but the direct causal role of CRP in VTE pathogenesis has not yet been thoroughly investigated. Research has focused on whether CRP is associated with VTE in limited clinical contexts, including inflammatory bowel disease and COVID-19⁸). Our study validated the predictive value of CRP for VTE in AECOPD patients for the first time, thus providing further insights into the potential pathogenic role of CRP in VTE development in AECOPD patients. Our study found that the level of admission PCT was significant higher in patients who later acquired VTE and PCT ≥ 0.5 ng/ml was an independent risk factor of VTE in AECOPD inpatients. This may be explained by the higher likelihood of patients suffering from more severe infections, as PCT often rises in response to inflammatory stimuli caused by bacterial infections. Few studies have so far explored the predictive role of PCT in VTE. Heerink *et al.* explored the added value (beyond D-dimer) of PCT for the prediction of VTE and found no statistically significant difference between VTE and non-VTE populations⁴²). Therefore, whether PCT is a reliable predictor of VTE occurrence needs to be studied. Similarly, whether eosinophil activation markers can predict VTE in patients and how eosinophil levels correlate with the incidence of VTE remain controversial. Liu *et al.* discovered that a high eosinophil count has a predictive capability for VTE in 63 patients with eosinophilia⁴³). However, Wypasek *et al.* identified no significant increase in the eosinophil count among 70 patients with VTE compared to the controls⁴⁴). Importantly, the subjects of previous studies on the predictive value of eosinophils for VTE were mainly patients with eosinophil-related diseases in the acute phase⁴⁵), whereas this study was mainly aimed at patients with AECOPD. The mechanisms of thrombus formation are not identical because of the heterogeneity of different diseases. Our research team previously discovered that non-eosinophilic (ESOR $<2\%$) AECOPD patients tend to have increased levels of inflammatory biomarkers such as leukocytes, neutrophils, PCT, and CRP⁴⁶). Therefore, the link between low ESOR and VTE development may be attributed to mechanisms similar to those of other inflammatory biomarkers studied here. In summary, it is reasonable to speculate that AECOPD patients with increased systemic inflammation, as indicated by high NLR, LDH, CRP, PCT, and low ESOR, present an increased risk of developing VTE because of the close relationship between inflammation and thrombosis.

Further studies are needed to validate the underlying mechanisms that explain these associations.

Interestingly, no inflammatory biomarkers were independently correlated with an increased risk of VTE in the subgroup that received thromboprophylaxis in multivariate analysis. This result suggests that the administration of prophylactic anticoagulation can dilute the association between inflammatory biomarkers and VTE development and may even reduce the increased risk of VTE caused by systemic inflammation, although our research did not reach such a conclusion. However, some studies showed that low molecular weight heparin (LMWH), the main prophylactic anticoagulant used during hospitalization in this cohort study, demonstrated good anti-inflammatory effects and it has become a promising treatment option for various inflammatory disorders, such as COVID-19^{47, 48}). In addition, enoxaparin has been reported as an effective add-on therapy in patients with stable COPD, thus leading to improvements in blood gas tension, dyspnea, and reduced salbutamol dosage²⁰). However, most of these data are from pilot studies with small sample sizes and have not found their way into mainstream clinical use. Thus, it is still unknown whether anticoagulant drugs used for thromboprophylaxis can reduce the risk of VTE through anti-inflammatory effects in AECOPD and other diseases. However, this issue is worth studying.

As is well known, the Padua score and the IMPROVE score, which are recommended by the American College of Chest Physicians Guidelines for Antithrombotic Therapy and Prevention of Thrombosis 9th edition (ACCP-9)⁴⁹), are widely used VTE RAMs in hospitalized medical inpatients. The study verified that the predictive accuracy of NLR and LDH was comparable to that of the two VTE RAMs, and the incorporation of elevated NLR and LDH did improve discrimination compared with the Padua score or IMPROVE score alone. Inflammatory biomarkers may have several advantages related to VTE RAMs. First, inflammatory biomarkers may directly reflect coagulation activity, whereas RAMs mainly consist of comorbidities that cannot promptly and effectively predict VTE occurrence alone. Furthermore, inflammatory biomarkers, such as neutrophils, the lymphocyte count, and LDH, can be easily and objectively obtained as almost every patient with AECOPD receives a blood test on admission, and the simple value is more convenient and objective than scoring. While with complexity and difficulty in taking the time to question patients, VTE RAMs could be easily influenced by low compliance or information collection bias. The score-derived VTE

risk categorization has significant variability in the cutoff points used to define the risk categories, which limits implementation across different centers²¹). Taking the Padua score as an example, our results demonstrated that a cut-off score of 2 points was superior to the widely recommended cut-off score of 4 points in AECOPD patients studied here. But how inflammatory biomarkers could improve VTE RAMs in predicting VTE in AECOPD patients and thereby help to achieve more accurate risk prediction strategies still needs to be further validated in large prospective studies and clinical practice.

Our study has several strengths. Primarily, the prospective and consecutive inclusion of inpatients with AECOPD from multiple centers and comprehensive data collection ensured high data quality and should reflect true associations in a real-world setting. To our knowledge, this is the first large-scale multicenter study to reveal the association between inflammatory biomarkers and VTE risk in patients with AECOPD. Simultaneously, our findings should be interpreted in the context of certain limitations. First, the problem of missing data might be a concern; however, during the analytical process of the study, multiple imputation, a widely accepted and accurate method of data processing, was conducted to impute missing data if the missing values were less than 20%. Variables with a missing rate of more than 20% were excluded from multivariate logistic regression analyses, such as D-dimer level, which is a known indicator of VTE. However, the results (see [Supplementary Table 3](#)) of a multivariate logistic regression analysis including D-dimer as an additional confounding factor indicated that NLR, LDH, CRP, PCT, and ESOR remained independent predictors for the development of VTE in AECOPD patients, thus suggesting that these inflammatory biomarkers could be new predictors of VTE in AECOPD patients beyond D-dimer. Interestingly, new perspectives suggest that D-dimer is an emerging inflammatory marker⁵⁰). Second, we only recorded the results of inflammation biomarkers tested on admission, without recording the subsequent changes of these indicators, nor could we study the relationship between these changes and the occurrence of VTE. Third, VTE screening was not routinely carried out in inpatients with AECOPD in this study, which may have resulted in the absence of mild or asymptomatic VTE. However, we defined symptomatic VTE as the main outcome, and the clinical implications and need for treatment of asymptomatic VTE remain controversial³⁴). Finally, because of the observational and non-interventional design of this study, our findings of inflammatory biomarkers related to an

elevated risk of VTE in AECOPD patients do not imply causality, and we can only speculate about the underlying mechanisms that explain these associations.

Conclusion

In conclusion, AECOPD patients who developed VTE during hospitalization experienced worse clinical outcomes. Inflammatory biomarkers, including NLR, LDH, PCT, CRP, and ESOR, could serve as independent predictors for VTE in AECOPD, and among them, NLR and LDH showed comparable predictive values when compared to the current VTE RAMs. The simple and easily available inflammatory biomarkers, especially NLR and LDH, might help identify AECOPD patients who are at increased risk of VTE and tailor thromboprophylaxis management. Further studies are warranted to explore the underlying mechanisms that explain the association between inflammatory markers and VTE in patients with AECOPD.

Acknowledgements

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Conflicts of Interest

The authors declare that the research had no conflicts of interest.

Abbreviation

COPD, chronic obstructive pulmonary disease; AECOPD, Acute exacerbations of chronic obstructive pulmonary disease; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; NEUT, neutrophil percentage; ESOR, Eosinophil ratio; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; PCT, Procalcitonin; LDH, lactate dehydrogenase; SII, systemic immune/inflammatory index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MAGNET AECOPD, MAnagement aNd advErse ouTcomes in inpatients with acute exacerbation of COPD) Registry; FEV1, the first second of expiration; FVC, forced vital capacity; RAMs, risk assessment models; IMPROVE, International Medical Prevention Registry on Venous Thromboembolism SD, standard

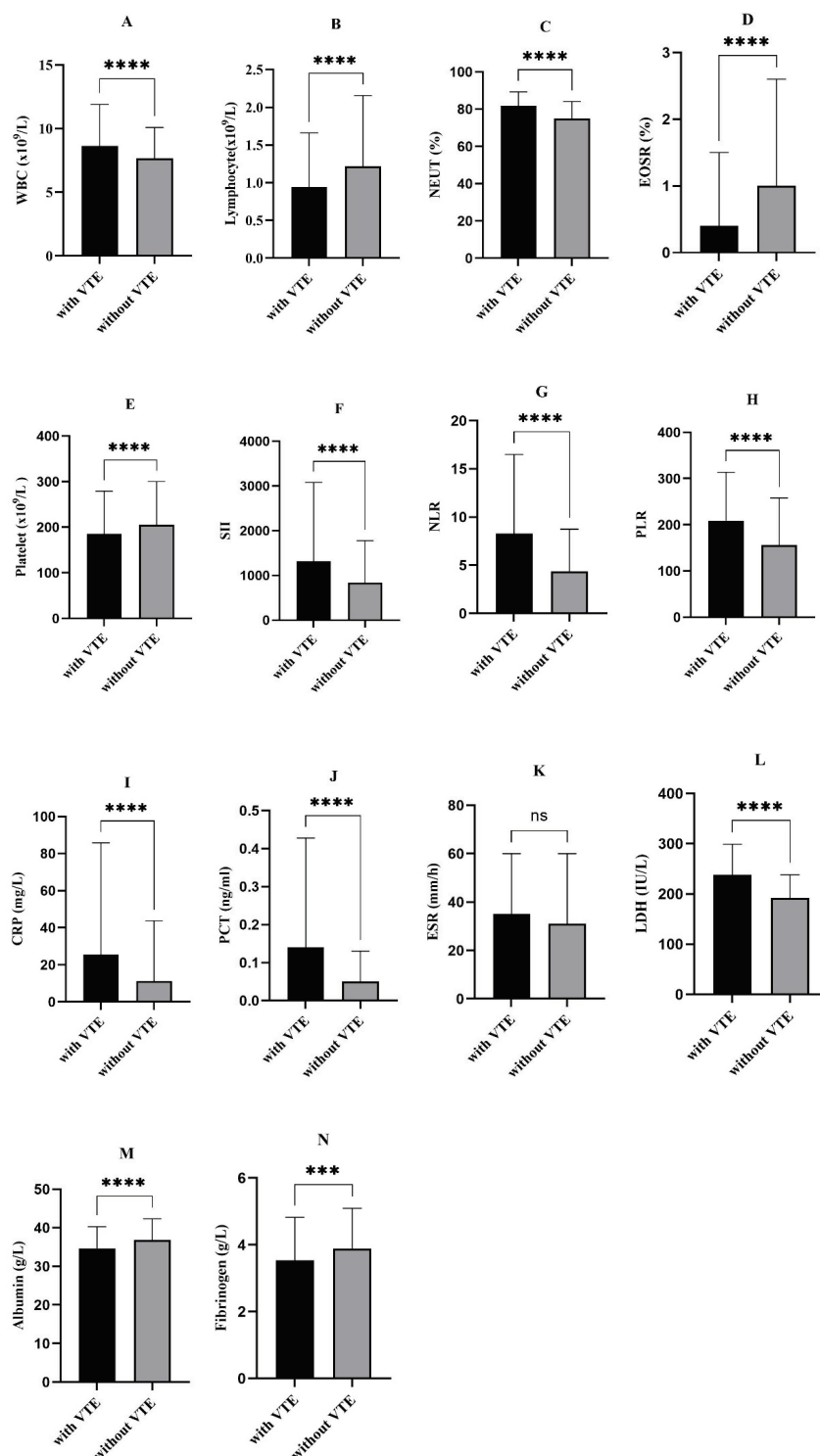
deviation; LR, forward stepwise selection based on maximum likelihood estimation; ORs, odds ratios; CIs, confidence intervals; ROC, receiver operating characteristic; AUC, area under the ROC curve; SPSS, Statistic Package for Social Science; BMI, body mass index; PaCO₂, arterial carbon dioxide tension; NT-pro-BNP, N-terminal pro-brain natriuretic peptide; pH, hydrogen ion concentration; PO₂, arterial oxygen tension; ICU, intensive care unit; LMWH, low molecular weight heparin;

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Supplementary Fig. 1. Differences of inflammatory biomarkers on admission between AECOPD with VTE and without VTE

Abbreviations: AECOPD=acute exacerbation of chronic obstructive pulmonary disease; VTE=venous thromboembolism; WBC=white blood cell counts; NEUT=neutrophil ratio; EOSR=eosinophil ratio; SII=systemic immune/inflammatory index; NLR=neutrophil to lymphocyte ratio; PLR=platelet to lymphocyte ratio; CRP=C-reactive protein; PCT=procalcitonin; ESR=Erythrocyte Sedimentation Rate; LDH=lactate dehydrogenase;

Notes: * Those with p value < 0.05 .

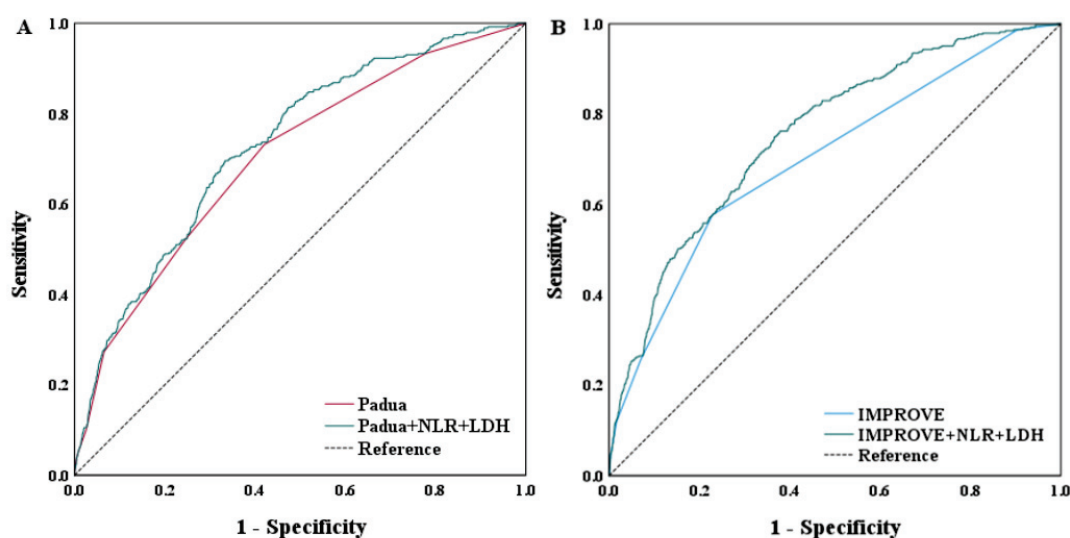
† For D) Platelet, L) Albumin, data are shown as mean and standard; For A) WBC, B) NEUT, C) EOSR, E) SII, F) NLR, G) PLR, H) CRP, I) PCT, J) ESR, K) LDH, M) Fibrinogen, data are shown as medians and interquartile ranges.

Supplementary Table 1. Univariate logistic regression analysis for predictors of VTE in AECOPD patients

Variable	OR	95% CI	<i>p</i> -Value*
Age ≥ 75 (years)	2.51	(2.05, 3.09)	<0.001
Female	1.49	(1.20, 1.86)	<0.001
BMI ≥ 30 (kg/m ²)	1.95	(1.14, 3.34)	0.015
Surgery/trauma in the past month	2.32	(1.41, 3.84)	<0.001
History of previous VTE	25.95	(18.10, 37.21)	<0.001
Long term bed rest	2.91	(2.33, 3.62)	<0.001
Padua score ≥ 4	2.80	(2.26, 3.45)	<0.001
IMPROVE ≥ 4	8.35	(5.99-11.63)	<0.001
Lower limb edema	4.44	(3.60, 5.46)	<0.001
Hypertension	1.55	(1.27, 1.89)	<0.001
Coronary heart disease	1.32	(0.99, 1.75)	0.059
Heart failure	2.97	(2.37, 3.73)	<0.001
Arrhythmia	3.09	(2.42, 3.94)	<0.001
Chronic pulmonary heart disease	2.77	(2.26, 3.39)	<0.001
OSAHS	2.09	(0.84, 5.19)	0.112
Pneumonia	2.02	(1.65, 2.49)	<0.001
Diabetes	1.76	(1.37, 2.25)	<0.001
Stroke	2.51	(1.86, 3.38)	<0.001
Chronic hepatic insufficiency	2.23	(1.31, 3.79)	<0.001
Chronic renal insufficiency	4.35	(3.22, 5.89)	<0.001
Septicemia	8.91	(4.55, 17.47)	<0.001
Active cancer	1.33	(0.92, 1.92)	0.132
Anxiety or depression	2.39	(1.10, 5.18)	0.028
GERD	1.04	(0.38, 2.82)	0.943
Varicose veins of lower extremities	6.56	(3.59, 12.00)	<0.001
Osteoporosis	2.43	(1.57, 3.76)	<0.001
Anemia	1.91	(1.57, 2.33)	<0.001
White blood cell > 10 ($\times 10^9/L$)	1.85	(1.51, 2.27)	<0.001
Lymphocyte < 1 ($\times 10^9/L$)	2.39	(1.94, 2.94)	<0.001
NEUT > 75 (%)	2.66	(2.13, 3.32)	<0.001
ESOR < 2 (%)	2.19	(1.70, 2.82)	<0.001
Platelet < 100 ($\times 10^9/L$)	2.31	(1.75, 3.04)	<0.001
SII > 748.43	2.53	(2.01-3.17)	<0.001
NLR > 4.38	3.07	(2.42-3.88)	<0.001
PLR > 196.39	1.90	(1.55-2.32)	<0.001
CRP ≥ 5 (mg/L)	2.94	(2.13, 4.07)	<0.001
PCT ≥ 0.5 (ng/L)	2.45	(1.88, 3.19)	<0.001
Fibrinogen < 2 (g/L)	1.79	(1.25, 2.57)	<0.001
Albumin < 35 (g/L)	2.08	(1.70, 2.54)	<0.001
LDH > 250 (IU/L)	2.95	(2.40, 3.63)	<0.001
Thromboprophylaxis	0.96	(0.72, 1.30)	0.807

Abbreviations: AECOPD=acute exacerbation of chronic obstructive pulmonary disease; VTE=venous thromboembolism; BMI=body mass index; OSAHS=obstructive sleep apnea-hypopnea syndrome; GERD=gastroesophageal reflux disease; NEUT=neutrophil percentage; ESOR=eosinophil ratio; SII=systemic immune/inflammatory index; NLR=neutrophil to lymphocyte ratio; PLR=platelet to lymphocyte ratio; CRP=C-reactive protein; PCT=procalcitonin; LDH=lactate dehydrogenase.

Notes: *Those with *P* value < 0.05 were highlighted using the bold font.



VTE RAMs	Δ AUC (95%CI)	<i>p</i> -Value
Padua score	0.027(0.021-0.034)	<0.001
IMPROVE score	0.057(0.043-0.071)	<0.001

Supplementary Fig. 2. ROC curves for incorporation of NLR and LDH into the Padua and IMPROVE score in predicting symptomatic VTE

Abbreviations: ROC=receiver operating characteristic; NLR= neutrophil to lymphocyte ratio; LDH=lactate dehydrogenase; VTE=venous thromboembolism;

Supplementary Table 2. Subgroup multivariate logistic regression analysis of VTE based on thromboprophylaxis

Variables	the thromboprophylaxis subgroup			the non-thromboprophylaxis subgroup		
	OR	95% CI	<i>p</i> -Value*	OR	95% CI	<i>p</i> -Value*
Age75 ≥ (years)	1.45	(0.81, 2.61)	0.216	1.79	(1.41, 2.27)	<0.001
Female	1.64	(0.89, 3.04)	0.115	1.36	(1.05-1.76)	0.019
Long term bed rest	1.97	(1.04, 3.76)	0.038	2.24	(1.72, 2.92)	<0.001
Surgery/trauma in the past month	1.30	(0.34, 4.94)	0.700	1.84	(1.00, 3.42)	0.052
History of previous VTE	3.22	(1.08, 9.55)	0.035	8.30	(4.99, 13.79)	<0.001
Lower limb edema	0.83	(0.41, 1.66)	0.592	2.33	(1.81, 3.00)	<0.001
Varicose Veins of Lower Extremities	4.24	(0.43, 41.79)	0.215	4.96	(2.24, 11.01)	0.042
Arrhythmia	1.04	(0.52, 2.09)	0.910	1.39	(1.02, 1.90)	<0.001
Pneumonia	1.84	(1.05, 3.20)	0.033	1.30	(1.02, 1.67)	0.035
Chronic pulmonary heart disease	1.27	(0.69, 2.35)	0.442	1.79	(1.40, 2.28)	<0.001
Stroke	1.06	(0.45, 2.49)	0.895	1.57	(1.09, 2.26)	0.015
Chronic renal insufficiency	2.12	(0.94, 4.83)	0.072	1.65	(1.13, 2.39)	0.009
Osteoporosis	0.52	(0.11, 2.49)	0.413	1.79	(1.08, 2.97)	0.025
NLR > 4.38	1.34	(0.56, 3.24)	0.513	2.25	(1.72, 2.94)	<0.001
LDH > 250 (IU/L)	1.62	(0.91, 2.87)	0.100	2.22	(1.75, 2.83)	<0.001
CRP ≥ 5 (mg/L)	1.14	(0.64, 2.03)	0.667	1.63	(1.27, 2.10)	<0.001
PCT ≥ 0.5 (ng/ml)	1.38	(0.65, 2.95)	0.407	1.53	(1.11, 2.10)	0.010
ESOR < 2 (%)	1.01	(0.47, 2, 16)	0.982	1.08	(0.80, 1.47)	0.616

Abbreviations: NLR=neutrophil to lymphocyte ratio; LDH=lactate dehydrogenase; CRP=C-reactive protein; PCT=Procalcitonin; ESOR=eosinophil ratio;

Notes: *Those with *p* value <0.05 were highlighted using the bold font.

Supplementary Table 3. The results of multivariate logistic regression analysis after additionally adjusting severity evaluated by ROME classification

Variables [†]	OR	95% CI	<i>p</i> -Value*
Age ≥ 75 (years)	1.55	(1.24–1.94)	< 0.001
Long term bed rest	2.14	(1.68–2.74)	< 0.001
History of VTE	16.87	(11.29– 25.21)	< 0.001
Lower limb edema	2.32	(1.83–2.93)	< 0.001
Varicose veins of lower extremities	6.57	(3.25–13.29)	< 0.001
Chronic pulmonary heart disease	1.78	(1.42–2.23)	< 0.001
Pneumonia	1.26	(1.01–1.59)	0.044
Stroke	1.59	(1.14–2.21)	0.006
Osteoporosis	1.78	(1.11– 2.86)	0.017
Chronic renal insufficiency	1.71	(1.22–2.405)	0.002
Anemia	1.27	(1.01–1.58)	0.037
NLR > 4.38	2.19	(1.70–2.81)	< 0.001
LDH > 250 (IU/L)	1.77	(1.41–2.22)	< 0.001
CRP ≥ 5 (mg/L)	1.53	(1.21–1.94)	< 0.001
PCT ≥ 0.5 (ng/ml)	1.51	(1.13–2.02)	0.002
ESOR < 2 (%)	1.35	(1.03–1.76)	0.030
D-dimer ≥ 0.5(mg/L)	2.67	(1.96–3.63)	< 0.001

Abbreviations: VTE=venous thromboembolism; AECOPD=acute exacerbation of chronic obstructive pulmonary disease; CPHD=chronic pulmonary heart disease; NLR=neutrophil to lymphocyte ratio; LDH=lactate dehydrogenase; CRP=C-reactive protein; PCT=Procalcitonin; ESOR=eosinophil ratio.

Notes: * Those with *P* value < 0.05 were highlighted using the bold font.

[†] Covariates adjusted in multivariate logistic regression analysis: age ≥ 75 years, female, BMI ≥ 30 kg/m², history of surgery or trauma in 1 month, long term bed rest, history of VTE, lower limb edema, comorbidities including hypertension, heart failure, arrhythmia, chronic pulmonary heart disease, pneumonia, diabetes, stroke, chronic hepatic insufficiency, chronic renal failure, lower extremity varicose vein, osteoporosis, anemia, white blood cell > ×10⁹/L, lymphocyte < 1×10⁹/L, NEUT > 75%, EOSR < 2%, platelet < 100 ×10⁹/L, NLR > 4.38, PLR > 196.39, CRP ≥ 5mg/L, PCT ≥ 0.5ng/ml, LDH > 250 IU/L, albumin < 35g/L, fibrinogen < 2 g/L, D-dimer ≥ 0.5 mg/L.