Association of thrombocytopenia with deep vein thrombosis in patients with acute exacerbations of chronic obstructive pulmonary disease: A retrospective study

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Received May 11, 2025; Accepted October 30, 2025

DOI: 10.3892/etm.2025.13052

Abstract. Acute exacerbations of chronic obstructive pulmonary disease (AE-COPD) are often accompanied by systemic inflammatory responses and can lead to coagulation disorders and thrombotic complications, thereby increasing hospitalization rates and mortality. Platelets play a critical role not only in hemostasis and thrombosis, but also in immunity and inflammation. The aim of the present study was to explore the associations among thrombocytopenia, infection severity and deep vein thrombosis (DVT) formation in patients with AE-COPD, and to develop a predictive model based on platelet-related parameters. The clinical data from 338 patients with AE-COPD who were hospitalized in the Department of Respiratory and Critical Care Medicine of The Affiliated Jiangning Hospital of Nanjing Medical University (Nanjing, China) between January 2021 and December 2023 were retrospectively evaluated. Demographic characteristics, medical history, comorbidities, laboratory test results, lower limb venous ultrasound findings, chest computed tomography scans and mechanical ventilation treatment data were collected. Statistical analyses were performed using SPSS version 26.0, GraphPad Prism version 9.0 and R version 4.1.3. Among the 338 patients with AE-COPD, 72.4% were male and the mean age was 75.60±7.42 years. The thrombocytopenia group (<150x10^9 platelets/l) had a significantly lower white blood cell count, neutrophil count, monocyte count, platelet-to-lymphocyte ratio (PLR) and plateletcrit compared with the normal platelet group (≥150 to <300x10^9 platelets/l). Among the 338 patients with AE-COPD, 5 patients in the thrombocytopenia group had DVT, while 29 patients in the normal platelet group had DVT. The incidence of DVT during hospitalization was significantly lower in the thrombocytopenia group than that in the normal platelet group (4.7 vs. 12.5%). In a specific subgroup analysis of patients who were male, >70 years old, and presented with both cardiovascular diseases and concurrent pulmonary infection, the DVT risk was found to be lower in the thrombocytopenia group. Multivariate logistic regression analysis revealed that PLR and D-dimer were independent risk factors for DVT formation during hospitalization in patients with AE-COPD. In conclusion, thrombocytopenia was associated with more severe lung infections in patients with AE-COPD. A model incorporating PLR and D-dimer showed diagnostic efficacy for predicting DVT in hospitalized patients with AE-COPD.

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Key words: chronic obstructive pulmonary disease, D-dimer, platelet-to-lymphocyte ratio, deep vein thrombosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung condition marked by ongoing respiratory symptoms and reduced airflow (1). Beyond the immediate respiratory compromise, acute exacerbations of COPD (AE-COPD) trigger a potent systemic inflammatory response, creating a prothrombotic state that markedly elevates the risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) (2,3). The concurrence of DVT in patients with AE-COPD is not a minor complication; it is a critical event associated with a notable increase in short- and long-term mortality. A study indicated that the 1-year mortality rate of AE-COPD patients with VTE was significantly higher than that of patients without VTE (12.9 vs. 4.5%) (2). In addition to acquired risk factors, underlying hereditary thrombophilias may contribute to VTE risk, as highlighted in patients with unprovoked pulmonary embolism (4), highlighting the complexity of thrombotic risk in inflammatory diseases such

as AE-COPD, thereby emphasizing the urgent need for effective risk stratification.

Platelets play a crucial role not only in hemostasis and thrombosis but also in immune and inflammatory responses; they participate in the activation of the coagulation cascade and interact with immune cells such as neutrophils, monocytes and lymphocytes, promoting cellular activation (5-7). During an AE-COPD episode, systemic inflammation leads to widespread platelet activation, which in turn amplifies the inflammatory cascade and promotes a hypercoagulable state. This dual role of platelets provides a crucial mechanistic link between the inflammatory surge of an exacerbation and the subsequent risk of thrombosis. Consequently, abnormalities in platelet counts are common in AE-COPD and serve as important prognostic indicators (8). Thrombocytosis (platelet count $>400x10^9$/l) is a well-documented phenomenon associated with the severity of exacerbations and an independent predictor of adverse outcomes (9), consistent with its established role in promoting thrombosis. However, a previous study found that a decrease in platelet count was associated with an increased risk of AE-COPD over 2 years, suggesting that platelet levels may serve as a predictive marker for COPD exacerbation risk (10). A more complex and clinically challenging scenario arises in a marked subset of patients, particularly those with severe, infection-driven exacerbations, who present with thrombocytopenia.

The development of thrombocytopenia in this context is not a passive event but rather a dynamic biomarker reflecting a dysregulated host response to severe infection, the primary trigger for most AE-COPD events. The occurrence of thrombocytopenia signifies an advanced state of systemic inflammation where accelerated platelet consumption, sequestration and impaired bone marrow production occur. This leads to a critical clinical conundrum known as the 'thrombocytopenia-thrombosis paradox' (8). While a low platelet count is traditionally viewed as a risk factor for bleeding, in pathological states of severe inflammation, such as sepsis or disseminated intravascular coagulation, it is paradoxically associated with a heightened risk of microvascular and macrovascular thrombosis (11). This occurs as the low platelet count is a direct consequence of the widespread activation and consumption of platelets in the formation of thrombi, driven by endothelial injury and systemic inflammation. This paradox presents a formidable challenge for clinicians managing patients with AE-COPD (12). The presence of infection-induced thrombocytopenia obscures the true thrombotic risk, creating a dilemma where the need to prevent potentially fatal thrombotic events must be weighed against a perceived risk of major bleeding.

Current risk assessment models for VTE are not specifically designed for this patient population and often fail to account for the complex interplay between inflammation, infection severity and platelet dysregulation. Therefore, a clear gap exists in the ability to accurately risk-stratify patients with AE-COPD, particularly those with thrombocytopenia, for the development of DVT. To address this, the aim of the current study was to explore the intricate association between thrombocytopenia, the severity of the underlying infection and the incidence of DVT in patients hospitalized with AE-COPD. It was hypothesized that a composite model that integrates biomarkers reflecting both the inflammatory state, platelet-to-lymphocyte ratio (PLR) and downstream coagulation activation (D-dimer), can more accurately predict DVT risk in this vulnerable population. The development of such a model would provide a valuable tool for clinical decision-making, enabling targeted prophylactic strategies and ultimately improving outcomes for patients with AE-COPD.

Patients and methods

Subjects. The selection process and design of the present study are shown in Fig. 1. The medical records of patients with AE-COPD (n=945) who were hospitalized in the Department of Respiratory and Critical Care Medicine at The Affiliated Jiangning Hospital of Nanjing Medical University (Nanjing, China) between January 2021 and December 2023 were retrospectively reviewed. All enrolled patients underwent a chest computed tomography (CT) scan. The CT findings were utilized to confirm the presence and assess the severity of pulmonary infection, such as the pulmonary infiltrates of infection analyzed in the manuscript. This provided objective radiological support for the clinical diagnosis. To ensure that the present study focused specifically on the systemic response driven by pulmonary pathology, patients with definitive, active non-pulmonary infections at the time of admission were excluded. This exclusion process was based on a comprehensive review of each patient's electronic medical record, which included, but was not limited to the following: i) Reviewing the attending physician's diagnostic records to rule out infections at other sites, such as urinary tract infections, skin and soft tissue infections or intra-abdominal infections; and ii) scrutinizing relevant laboratory results (for example, urinalysis and procalcitonin) and imaging studies from other body regions (for example, abdominal ultrasound). All patients had peripheral blood drawn and underwent a systematic vascular ultrasound of both lower extremities within 24 h of admission, before starting anticoagulant therapy. Bilateral lower extremity vascular ultrasound screening is actually routinely performed for all patients with AE-COPD within The Affiliated Jiangning Hospital of Nanjing Medical University, regardless of their symptoms. COPD was diagnosed based on clinical presentations, pulmonary function tests and chest CT scans. The Padua Prediction Score (including immobility status, recent surgery, prior VTE history, history of cancer and corticosteroid use) was calculated for each patient with AE-COPD (13). The specific diagnostic criteria included: i) A previous pulmonary function test showing a post-bronchodilator forced expiratory volume in 1 sec/forced vital capacity value of <0.70, indicating irreversible airflow limitation; ii) chest CT showing signs of emphysema; and iii) AE-COPD defined as symptoms such as worsening dyspnea, increased sputum volume and yellow sputum, requiring a change in the current treatment regimen. The exclusion criteria were: i) Severe renal and liver diseases; ii) a history of malignancy undergoing radiotherapy or chemotherapy; iii) rheumatic diseases; iv) idiopathic pulmonary fibrosis; v) bronchial asthma; vi) long-term use of oral antiplatelet and anticoagulant drugs; vii) hematological diseases; viii) infections in other sites; ix) missing essential

Table I. Sociodemographics of patients with acute exacerbations of chronic obstructive pulmonary disease.

Factors	Thrombocytopenia	Normal platelets	P-value
Total patients, n	106	232	-
Age, years	73.60±7.18	76.60±7.35	0.448
Male, n (%)	83 (78.3)	162 (69.8)	0.106
Smoking history, n (%)	51 (48.1)	86 (37.1)	0.055
BMI, kg/m^2	21.32±3.51	22.24±3.92	0.039[a]
Padua prediction score	3.43±1.86	3.71±1.81	0.196

[a]P<0.05. BMI, body mass index.

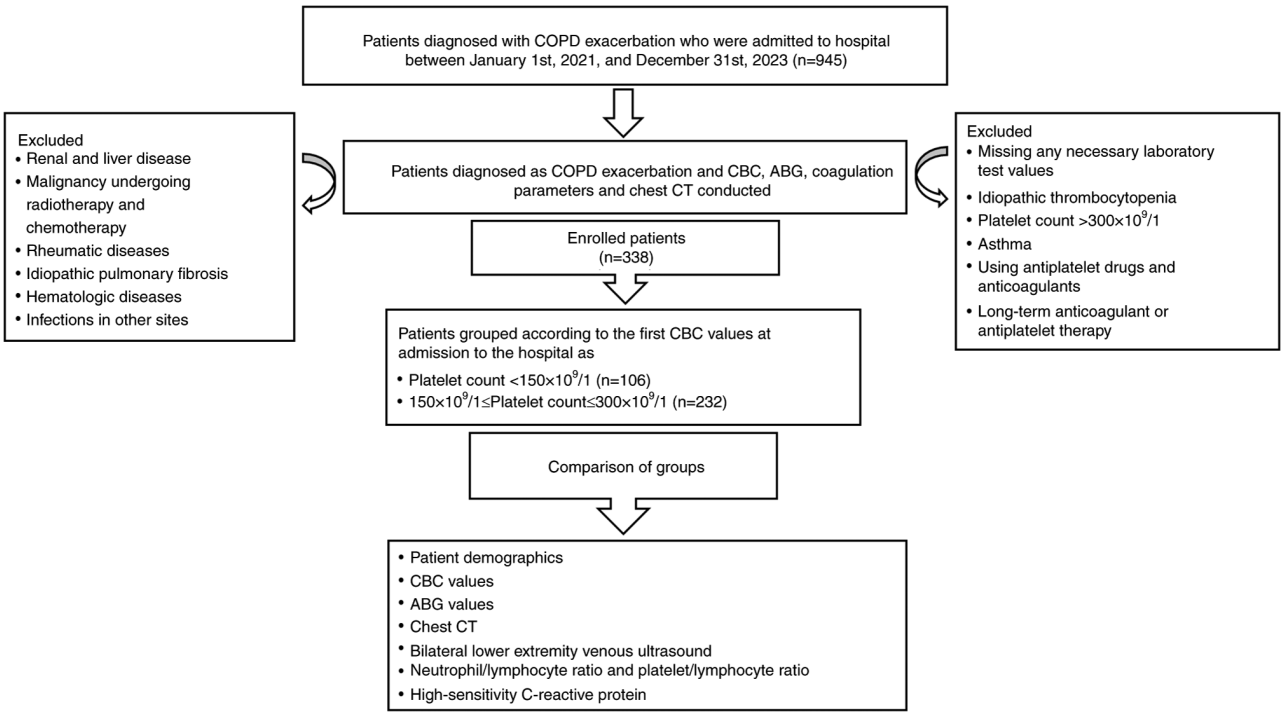

Figure 1. Flow chart of the study. COPD, chronic obstructive pulmonary disease; CBC, complete blood cell; ABG, arterial blood gas; CT, computed tomography.

laboratory test results; and x) anticoagulant therapy initiation before blood samples were obtained and a lower extremity venous ultrasound was performed. Ultimately, 338 patients with AE-COPD were included in the present study, with an age range of 57-93 years and a median age of 75 years.

Data collection and assessment. Relevant clinical information was collected from the patients' hospitalization records. If multiple repeated tests were conducted during hospitalization, the results from the first test upon admission were selected. Data on the demographic characteristics, medical history, comorbidities, laboratory tests, bilateral lower limb venous ultrasound examinations, chest CT scans and mechanical ventilation treatment of patients with AE-COPD were collected. The PLR was calculated as the platelet count divided by the lymphocyte count. The neutrophil-to-lymphocyte ratio (NLR) was calculated as the neutrophil count divided by the lymphocyte count. The D-dimer-to-lymphocyte ratio (DLR) was calculated as the D-dimer level divided by the lymphocyte count. Based on the platelet count at the time of admission, patients were divided into the thrombocytopenia group (<150x10^9 cells/l) and the normal platelet count group (≥150 to <300x10^9 cells/l) (14).

Statistical analysis. All statistical analyses were conducted using SPSS (version 26.0; IBM Corp.), GraphPad Prism (version 9.0; Dotmatics) and the R (version 4.1.3; R Core Team). Normality of all continuous variables was assessed using the Shapiro-Wilk test. Quantitative data conforming to a normal distribution are presented as the mean ± standard deviation and were compared between groups using an unpaired Student's t-test. Non-normally distributed continuous variables are presented as median (interquartile range) and were compared using the Mann-Whitney U test. Categorical variables are described using frequencies (percentages) and were compared using the χ^2 test. Correlation analysis between

Table II. Laboratory data of patients with acute exacerbations of chronic obstructive pulmonary disease.

Factors	Reference range	Thrombocytopenia	Normal platelets	P-value
WBC count, $x10^9$/l	3.5-9.5	5.8 (2.9)	7.77 (4.33)	<0.001[a]
Red blood cell count, $x10^{12}$/l				
Male	4.3-5.8	4.20 (0.88)	4.36 (0.89)	0.258
Female	3.8-5.1	4.03 (0.83)	4.34 (0.68)	0.252
Neutrophil count, $x10^9$/l	1.8-6.3	4.4 (3.09)	6.5 (4.22)	<0.001[a]
Neutrophils, %	40-75	78.9 (16.35)	80.2 (15.17)	0.231
Lymphocyte count, $x10^9$/l	1.1-3.2	0.72 (0.59)	0.9 (0.64)	0.460
Lymphocytes, %	20-50	13.20 (13.4)	11.2 (9.7)	0.191
Monocyte count, $x10^9$/l	0.1-0.6	0.40 (0.22)	0.54 (0.45)	<0.001[a]
Monocytes, %	3-10	6.58±2.75	6.50±3.78	0.888
PLR	-	150.0 (116.6)	230.97 (172.6)	<0.001[a]
NLR	-	6.16 (8.00)	7.07 (7.13)	0.164
DLR	-	0.85 (1.11)	0.78 (1.44)	0.528
MPV, fl	7.4-12.5	10.92±1.41	10.78±1.49	0.534
PDW, %	12-16.5	15.2 (3.6)	14.4 (4.7)	0.120
Plateletcrit, %	0.11-0.28	0.19 (0.09)	0.21 (0.08)	0.014[b]
Hemoglobin, mmol/l				
Male	8.1-10.9	7.94±1.10	8.06±1.09	0.390
Female	7.1-9.3	7.88±1.06	7.74±1.05	0.588
Hs-CRP, mg/l	0.95-95.2	84.1 (404.2)	100.3 (583.4)	0.285
Procalcitonin, pmol/l	0.0-38.5	4.6 (10.8)	5.4 (13.1)	0.318
D-dimer, μmol/l	0.0-3.06	3.50 (3.06)	3.89 (5.78)	0.052
FBG-G, g/l	5.9-11.8	10.47 (3.59)	10.58 (5.38)	0.823
TT, sec	14-21	14.3 (2.15)	14.1 (1.9)	0.408
PT, sec	9-15	11.9 (2.0)	12 (1.7)	0.943
APTT, sec	20-40	32.3 (4.1)	31.8 (5.1)	0.132
INR, %	0.8-1.2	1.1 (0.16)	1.11 (0.16)	0.764
OI, mmHg	300-500	313.8±78.0	313.2±98.11	0.960
$PaCO_2$, mmHg	35-45	46 (17.5)	45 (19.9)	0.241
Pathogen positivity rate of sputum, n (%)	Negative	21 (19.8)	61 (26.3)	0.197

[a]P<0.001; [b]P<0.05. Data are presented as median (interquartile range) or mean ± SD unless otherwise stated. WBC, white blood cells; PLR, platelet-to-lymphocyte ratios; NLR, neutrophil-to-lymphocyte ratio; DLR, D-dimer-to-lymphocyte ratio; Hs-CRP, high sensitivity C-reactive protein; FBG-G, fibrinogen; MPV, mean platelet volume; PDW, platelet distribution width; TT, thrombin time; APTT, activated partial thromboplastin time; INR, International Normalized Ratio; PT, prothrombin time; OI, oxygenation index; $PaCO_2$, partial pressure of carbon dioxide.

two continuous variables was conducted using Spearman's correlation coefficient. Subgroup analyses were performed to assess intergroup associations and thrombosis risk within different subgroups. Univariate and multivariate analyses were conducted using binary logistic regression. Discrimination in the prediction model was assessed using the area under the receiver operating characteristic curve (AUC-ROC). Bootstrap ROC was used to evaluate the performance of the prediction model. Two-sided P<0.05 was considered to indicate a statistically significant difference.

Results

Patient demographics and clinical characteristics. As shown in Table I, 338 patients with AE-COPD were included, with 72.4% being male and with an overall mean age of 75.60±7.42 years. Among these, 106 patients had platelet counts <$150x10^9$ cells/l, and 232 patients had platelet counts of 150-$300x10^9$ cells/l. The body mass index (BMI) of patients in the thrombocytopenia group was significantly lower than that of patients in the normal platelet count group (P=0.039). There were no significant statistical differences between the two groups regarding age, smoking history sex and Padua prediction score.

Laboratory results (Table II) showed that the thrombocytopenia group had a significantly lower white blood cell count (WBC; P<0.001), neutrophil count (P<0.001) and monocyte count (P<0.001), as well as lower PLR (P<0.001) and plateletcrit (P=0.014), compared with the normal platelet group, with no other results showing statistical significance.

Comparison of comorbidities and changes in clinical status upon admission and discharge in the two groups. As shown

Table III. Comparison of comorbidities and changes in clinical status upon admission and discharge.

Factors	Thrombocytopenia	Normal platelets	P-value
Patient number	106	232	-
Arrhythmia, n (%)	19 (17.9)	78 (33.6)	0.810
Assisted ventilation, n (%)	19 (17.9)	39 (16.8)	0.951
Respiratory failure, n (%)	62 (58.5)	129 (55.6)	0.619
Hypertension, n (%)	53 (50.0)	116 (50.0)	1.000
Diabetes, n (%)	16 (15.1)	34 (14.7)	0.916
CVD, n (%)	35 (33.0)	103 (44.4)	0.048[a]
Pulmonary infection, n (%)	86 (81.1)	170 (74.6)	0.118
Cor pulmonale, n (%)	43 (40.6)	79 (34.1)	0.247
DVT, n (%)	5 (4.7)	29 (12.5)	0.027[a]
Pulmonary infiltrates of infection, n (%)[c]			<0.001[b]
None	20 (18.9)	62 (26.7)	
Patchy infiltrates	40 (37.7)	129 (55.6)	
Confluent infiltrates	46 (43.4)	41 (17.7)	

[a]P<0.05; [b]P<0.001. [c]None vs. patchy infiltrates, P=0.198; none vs. confluent infiltrates, P<0.001; and patchy infiltrates vs. confluent infiltrates, P<0.001. CVD, cardiovascular diseases; DVT, deep vein thrombosis.

Table IV. Univariate and multivariate logistic regression analysis of deep vein thrombosis formation during hospitalization in patients with acute exacerbations of chronic obstructive pulmonary disease.

	Univariate analysis		Multivariate analysis	
Factors	OR (95% CI)	P-value	OR (95% CI)	P-value
Platelet count, x10^9/l	1.012 (1.005-1.019)	<0.001[a]	1.009 (0.997-1.020)	0.130
Normal platelets	2.886 (1.085-7.678)	0.034[b]	0.891 (0.211-3.765)	0.875
Lymphocyte count, x10^9/l	0.286 (0.109-0.747)	0.011[b]	0.845 (0.183-4.014)	0.845
Lymphocytes, %	0.934 (0.882-0.989)	0.019[b]	1.081 (0.923-1.122)	0.723
Monocytes, %	0.867 (0.776-0.967)	0.011[b]	0.945 (0.837-1.068)	0.366
NLR	1.043 (1.016-1.071)	0.032[b]	0.995 (0.944-1.049)	0.894
PLR	1.004 (1.003-1.006)	<0.001[a]	1.004 (1.001-1.007)	0.012[b]
DLR	1.212 (1.089-1.349)	<0.001[a]	0.975 (0.846-1.123)	0.720
D-dimer, mg/l	1.423 (1.203-1.683)	<0.001[a]	1.454 (1.051-2.011)	0.024[b]

[a]P<0.001; [b]P<0.05. PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; DLR, D-dimer-to-lymphocyte ratio; OR, odds ratio; CI, confidence interval.

in Table III, there were no statistically significant differences in the proportions of arrhythmias, cor pulmonale, respiratory failure, assisted ventilation, hypertension and diabetes between the thrombocytopenia group and the normal platelet group among patients with AE-COPD. However, the ratio of patients with cardiovascular diseases (CVDs) was 33.0% in the thrombocytopenia group compared with 44.4% in the normal platelet group, a difference that was statistically significant (P=0.048). The incidence of DVT during hospitalization was significantly lower in the thrombocytopenia group than in the normal platelet group (4.7 vs. 12.5%; P=0.027). While there was no significant difference in the overall pulmonary infiltrate rates between the two groups, the percentage of patients with pulmonary confluent infiltrates infections was significantly higher in the thrombocytopenia group than in the normal platelets group (43.4 vs. 17.7%; P<0.001). The analysis revealed the following results: None vs. patchy infiltrates, P=0.198; none vs. confluent infiltrates, P<0.001; and patchy infiltrates vs. confluent infiltrates, P<0.001.

Correlation between laboratory measurements in the two groups. The results of the correlation analysis between platelet parameters, coagulation markers and infection indicators in patients with AE-COPD are shown in Fig. 2. The correlations were weak, with PLR being positively correlated with high sensitivity C-reactive protein (r=0.300; P<0.001; Fig. 2A), and

Table V. ROC curve analysis for D-dimer and PLR.

Factors	AUC-ROC	95% CI	Cut-off	P-value
D-dimer, mg/l	0.802	0.733-0.971	0.520	0.012[b]
PLR	0.745	0.649-0.841	408.510	0.024[b]

[a]P<0.001; [b]P<0.05. ROC, receiver operating characteristic; AUC, area under the curve; PLR, platelet-to-lymphocyte ratio; CI, confidence interval.

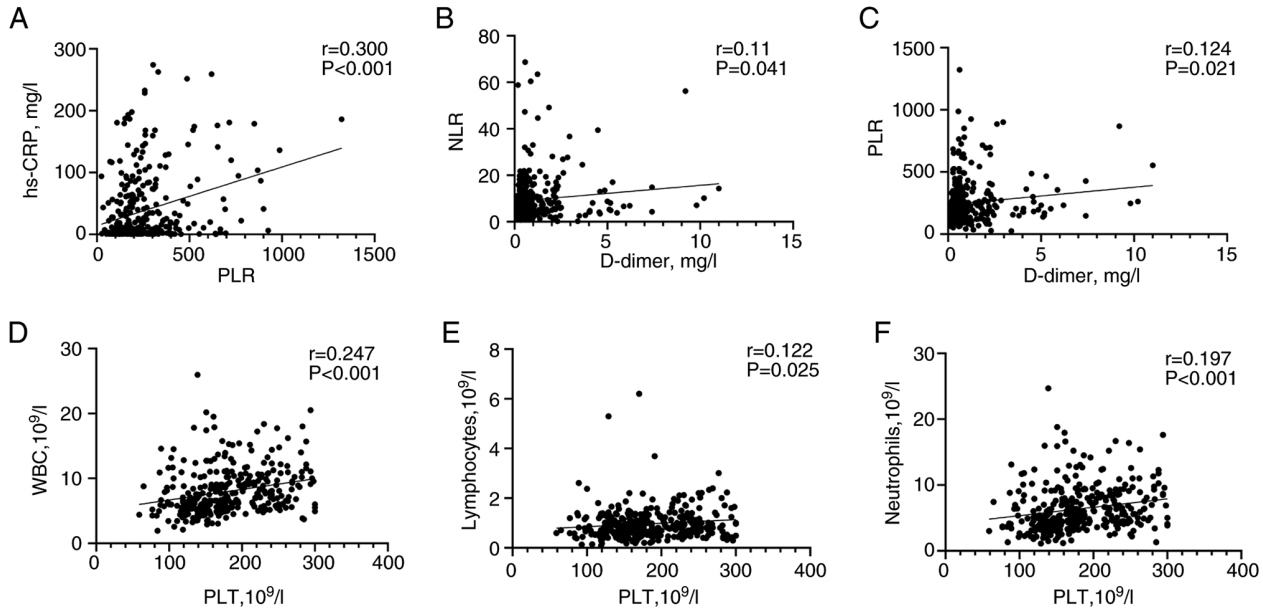

Figure 2. Correlation analysis of platelet parameters, coagulation markers and infection. (A) Correlation between PLR and hs-CRP [correlation coefficient (r)=0.300; P<0.001). (B) Correlation between D-dimer and NLR (r=0.110; P=0.041). (C) Correlation between D-dimer and PLR (r=0.124; P=0.021). (D) Correlation between PLT and WBC (r=0.247; P<0.001). (E) Correlation between PLT and lymphocytes (r=0.122; P=0.025). (F) Correlation between PLT and neutrophils (r=0.197; P<0.001). hs-CRP, high sensitivity C-reactive protein; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; WBC, white blood cell; PLT, platelet.

with D-dimer being positively correlated with NLR (r=0.110; P=0.041; Fig. 2B) and PLR (r=0.124; P=0.021; Fig. 2C), all showing statistical significance. Additionally, platelet count was positively significantly correlated with WBC (r=0.247; P<0.001; Fig. 2D), lymphocyte count (r=0.122; P<0.025; Fig. 2E) and neutrophil count (r=0.197; P<0.001; Fig. 2F).

Subgroup analysis. A forest plot was used to perform stratified analysis of DVT risk. In most subgroups, the risk of DVT was lower in the thrombocytopenia group compared with that in the normal platelet group. Notably, in the subgroup of males who were >70 years old with CVD and concurrent pulmonary infection, patients with AE-COPD in the normal platelet group had a higher risk of DVT (Fig. 3).

Risk factors associated with DVT development in patients with AE-COPD. Initially, a univariate logistic regression analysis was performed to identify the variables influencing thrombus formation during hospitalization in patients with AE-COPD. Significant indicators identified include platelet count (P=0.130), normal platelets (P=0.875), lymphocyte count (P=0.845), lymphocyte percentage (P=0.723), monocyte percentage (P=0.366), NLR (P=0.894), PLR (P=0.012), DLR (P=0.720) and D-dimer (P=0.024) (Table IV). Subsequent multivariate logistic regression analysis revealed that PLR [odds ratio (OR), 1.004; 95% confidence interval (CI), 1.001-1.007; P=0.012] and D-dimer (OR, 1.454; 95% CI, 1.051-2.011; P=0.024) were independent risk factors for thrombus formation during hospitalization of patients with AE-COPD (Table IV). The AUC-ROC values of D-dimer and PLR were 0.802 (95% CI, 0.733-0.971; cut-off, 0.520; P=0.012) and 0.745 (95% CI, 0.649-0.841; cut-off, 408.51; P=0.024), respectively (Table V). The AUC-ROC in the model of PLR and D-dimer in the present study was 0.832 (95% CI, 0.758-0.905; P<0.001; Fig. 4A). Given the small sample size, the bootstrap method was used to validate the prediction model. After 1,000 repeated samplings, the AUC-ROC was 0.821 and the optimal cut-off was 0.1 (95% CI, 0.742-0.895; P<0.001; Fig. 4B).

Discussion

The current study demonstrated that a diagnostic model combining D-dimer level and PLR exhibited excellent performance in detecting DVT in patients with AE-COPD.

Subgroups	Thromobocytopenia (n=106)	Normal platelets (n=232)	OR (95% CI)	P-value
Sex				
Male	83	163	3.268 (1.091-9.789)	0.027
Female	23	69	2.063 (0.235-18.095)	0.505
Age, years				
>70	70	181	4.949 (1.135-21.382)	0.019
≤70	36	51	1.467 (0.342-6.296)	0.650
Pulmonary infection				
Yes	20	170	3.701 (1.248-10.976)	0.012
No	86	62	0.966 (0.095-9.845)	0.997
Smoking				
Yes	55	146	4.363 (0.943-20.191)	0.043
No	51	86	2.117 (0.592-7.571)	0.239
Hypertension				
Yes	53	116	2.145 (0.047-10.290)	0.330
No	53	116	3.472 (0.984-12.250)	0.042
Cardiovascular diseases				
Yes	35	103	11.351 (1.482-86.930)	0.004
No	71	129	0.927 (0.275-3.122)	0.902
Arrhythmia				
Yes	19	39	2.194 (0.418-11.520)	0.345
No	87	193	3.419 (0.992-11.784)	0.040

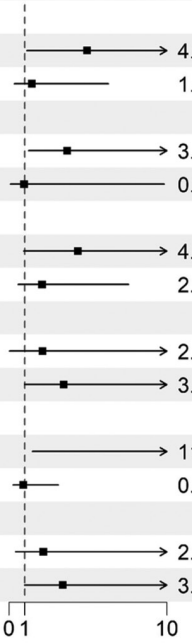

Figure 3. Subgroup analysis of different clinical factors in relation to deep vein thrombosis formation. OR, odds ratio; CI, confidence interval.

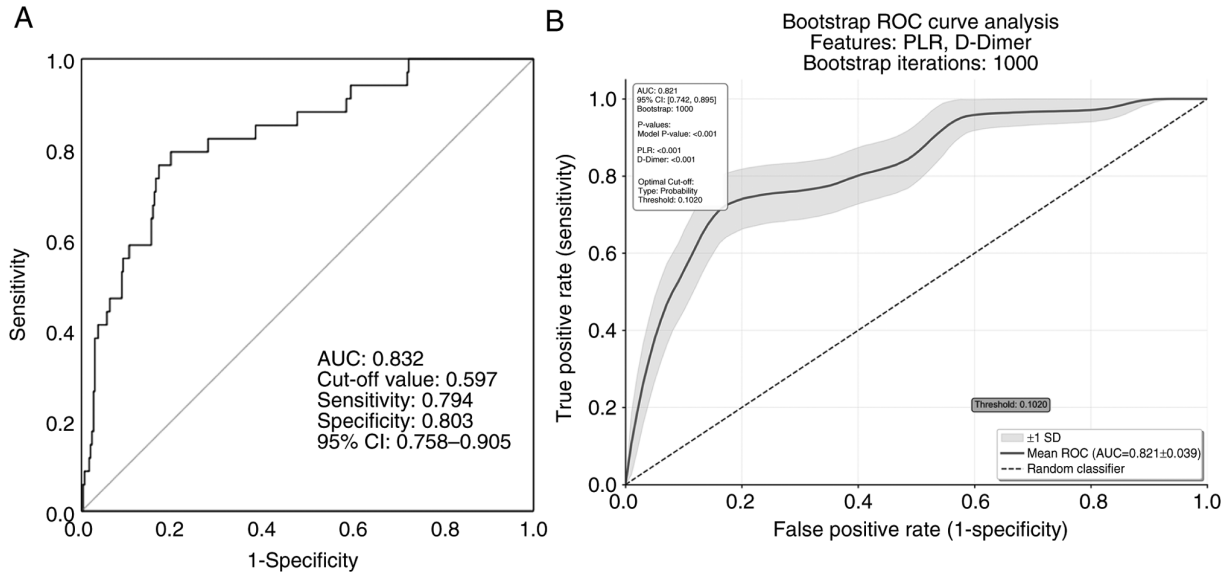

Figure 4. ROC and bootstrap ROC curve analysis of the prediction model for DVT of patients with acute exacerbations of chronic obstructive pulmonary disease. (A) ROC curve for PLR and D-dimer, with an AUC value of 0.832. The optimal cut-off value for the model was 0.597, with a specificity of 79.4% and corresponding sensitivity of 50.0% (P<0.001). (B) Bootstrap ROC curve for PLR and D-dimer, with an AUC value of 0.821 (P<0.001). AUC, area under the curve; ROC, receiver operating characteristic; CI, confidence interval; PLR, platelet-to-lymphocyte ratio.

Additionally, it was shown that males >70 years old with pulmonary infections and CVDs are at higher risk of DVT. Furthermore, thrombocytopenia may be associated with more severe pulmonary infections, as the results confirmed that patients with AE-COPD and thrombocytopenia were more likely to develop extensive infiltrative infections. These findings can assist clinicians in risk-stratifying patients upon admission to rapidly identify those at high risk for developing thrombocytopenia.

The interplay between inflammation, platelet activation and coagulation function has been extensively studied (15,16). The present study found that the incidence of DVT was significantly lower in the thrombocytopenia group compared with that in patients with normal platelet counts (4.7 vs. 12.5%). We

speculate that this phenomenon may be related to consumptive thrombocytopenia (17). A previous study found that 20% of patients with AE-COPD experience thrombocytopenia, which is closely associated with systemic infections (18). In the context of infection and inflammation, platelets may be excessively consumed or destroyed. Infection can cause abnormal aggregation and consumption of platelets within the body, especially at sites of pulmonary inflammation, further exacerbating thrombocytopenia (19). The severe inflammatory response and infection in AE-COPD can activate the coagulation system, leading to the formation of microthrombi within the pulmonary and systemic microvasculature (20). This process consumes a large number of platelets, resulting in a decreased peripheral platelet count.

D-dimer level and PLR reflect different yet related pathological processes. While the continuous OR from the current regression analysis quantified the statistical risk associated with rising D-dimer levels, a more clinically actionable insight arose from the ROC curve analysis. This analysis identified an optimal D-dimer cut-off of 0.520 for predicting DVT. This finding reinforces the utility of using a standard D-dimer threshold to identify patients with high-risk AE-COPD who may require further diagnostic evaluation, such as lower limb venous ultrasound, even when other traditional risk factors are not prominent. PLR represents the inflammation-platelet activation state (an upstream event), whereas D-dimer reflects the ultimate outcome of fibrin formation and degradation (a downstream event) (21). The weak correlation suggests that PLR and D-dimer may provide complementary, rather than redundant, risk information. For instance, a high PLR might indicate that a patient is in an intense inflammatory storm with high thrombotic potential, even while their D-dimer level has not yet become significantly elevated (22). Combining these two markers may therefore offer a more comprehensive assessment of a patient's thrombosis risk than using either one alone. After internal validation, the optimal cut-off value for the combined prediction model was determined to be 0.10. In clinical practice, this model can be developed into a tool where clinicians input a patient's D-dimer and PLR values to calculate a predictive score. A score >0.10 would indicate a higher risk for DVT, thereby prompting the early initiation of pharmacological and mechanical anticoagulant therapies.

A key finding of the current study is the discordance between absolute platelet count and thrombotic risk. Logistic regression analysis identified D-dimer level and PLR as independent prognostic factors for in-hospital thrombosis in patients with AE-COPD, but it did not confirm platelet count as an independent factor influencing DVT. In acute inflammatory diseases such as AE-COPD, the risk of thrombosis depends not only on the quantity of procoagulant cells but, more importantly, on the complex interplay between the systemic inflammatory state and the coagulation system, a concept known as immuno-thrombosis (23). The PLR, as a composite biomarker, aptly captures the essence of this interaction; it reflects platelet-driven prothrombotic activity (the numerator) occurring within the context of severe systemic inflammation and immunosuppression (the denominator). By contrast, a simple platelet count fails to capture this critical inflammatory background, thus limiting its predictive power. Therefore, in the context of AE-COPD, the driving force behind DVT risk is not the absolute number of platelets, but rather their activation state and the host's inflammatory microenvironment, as reflected by lymphocytopenia (24).

It is well known that PLR reflects the inflammatory and immune status of the body, and research has shown that PLR is a good predictor of VTE incidence, poor prognosis and mortality (25,26). The NLR is a recognized indicator of subclinical inflammation, with a high NLR suggesting increased systemic inflammation and being considered a negative prognostic factor for various arterial diseases (27,28). Elevated NLR is markedly linked to mesenteric artery embolism and venous thrombosis in patients with coronary artery disease (29,30). The results of the present study align with the findings of the study by Selvaggio *et al* (31), which observed that patients with concurrent DVT show a heightened inflammatory-immune response, exhibiting higher NLR and PLR levels compared with those without DVT. After adjusting for confounding factors, PLR, but not NLR, remained notably associated with DVT (OR, 3.379). This suggests that in acute inpatient settings, the interplay between platelets and the immune response, captured by PLR, is a robust indicator of thrombotic events. This conclusion somewhat contradicts the results in the study by Artoni *et al* (32), which determined that high PLR and NLR were not generally linked to an increased risk of VTE or cerebral venous thrombosis (CVT). However, this discrepancy is likely attributable to fundamental differences in the study populations. The study by Artoni *et al* (32) included non-acute outpatients referred for thrombophilia screening after their first objectively confirmed VTE or CVT episode. These patients were in a stable, non-acute phase, whereas the current study focused exclusively on patients during an active, inflammatory state of AE-COPD. It is likely that the predictive value of inflammatory markers such as PLR is most prominent during acute systemic inflammation, which acts as a potent trigger for thrombosis. Therefore, the differing results are not necessarily conflicting but rather highlight that the utility of these biomarkers is context-dependent, being particularly relevant in acutely ill, hospitalized patients. Further research is still needed to fully elucidate these associations.

Additionally, in the present study, it was observed that the patients in the thrombocytopenia group had a significantly lower BMI compared with the patients in the normal platelet count group. COPD, being a chronic disease, is often accompanied by malnutrition, which can result in a deficiency of key hematopoietic nutrients, such as vitamin B12 and folic acid (33), potentially impairing bone marrow function and resulting in reduced platelet production. This may, in turn, lead to relatively lower D-dimer levels upon hospital admission, which might explain the observations in the present study. While the present study did not include specific nutritional markers, such as serum albumin, the lower BMI in the thrombocytopenia group suggests that poor nutritional status may be a contributing factor, potentially leading to reduced platelet production and relatively lower D-dimer levels upon hospital admission. Future studies should incorporate these nutritional assessments to further clarify their role.

However, as the present study is a retrospective analysis, the results primarily reveal associations rather than causal

relationships. Future research should focus on validating these findings through large-scale, prospective cohort studies and further investigate the underlying pathophysiological mechanisms by which these risk factors lead to thrombocytopenia, in order to provide a scientific basis for more precise clinical interventions. Limitations of the study include the fact that the number of DVT cases in the thrombocytopenia group was small, which could lead to increased variance in the statistical analysis. Additionally, the potential influence of various hematological parameters should be recognized. For example, protein-energy malnutrition and specific micronutrient deficiencies, such as vitamin B12 or folate, are known factors that can cause or exacerbate thrombocytopenia and anemia (34). However, specific nutritional markers other than hemoglobin were not systematically gathered or recorded. Subsequent studies should build upon the current results by incorporating protocols that include distinct groups with and without the use of anticoagulants, intravenous corticosteroids and other agents; these will allow for a more detailed investigation into how these variables affect the association between platelets and DVT incidence.

Acknowledgements

Not applicable.

Funding

This study was supported by grants from the Nanjing Science and Technology Project (grant no. ZKX22062) and the Affiliated Jiangning Hospital of Nanjing Medical University Youth Innovation Scientific Research Project (grant nos. JNY YZXKY202305 and JNYYZXKY202205).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YG and LW were responsible for data collection and the writing of the draft manuscript. ZW, YW and QL were responsible for statistical analysis and editing the presentation of data and figures. XZ analyzed the data. LW and BW were responsible for designing and planning the entire research project, as well as reviewing and revising the manuscript. LW and BW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of The Affiliated Jiangning Hospital of Nanjing Medical University (Nanjing, China; approval no. 2024-03-037-K01). Informed consent was not required for this study, as it is a retrospective analysis utilizing de-identified clinical data without active patient recruitment. The study adheres to the principles outlined in The Helsinki Declaration.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Kim V and Aaron SD: What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement. Eur Respir J 52: 1801261, 2018.
2. Liu X, Jiao X, Gong X, Nie Q, Li Y, Zhen G, Cheng M, He J, Yuan Y and Yang Y: Prevalence, risk factor and clinical characteristics of venous thrombus embolism in patients with acute exacerbation of COPD: A prospective multicenter study. Int J Chron Obstruct Pulmon Dis 18: 907-917, 2023.
3. Song YJ, Zhou ZH, Liu YK, Rao SM and Huang YJ: Prothrombotic state in senile patients with acute exacerbations of chronic obstructive pulmonary disease combined with respiratory failure. Exp Ther Med 5: 1184-1188, 2013.
4. Gegin S, Karakaya T, Aksu EA, Özdemir B, Özdemir L and Pazarlı AC: The distribution of hereditary risk factors in patients with pulmonary thromboembolism without identifiable acquired risk factors. Duzce Med J 27: 69-74, 2025.
5. Yan C, Wu H, Fang X, He J and Zhu F: Platelet, a key regulator of innate and adaptive immunity. Front Med (Lausanne) 10: 1074878, 2023.
6. Bakogiannis C, Sachse M, Stamatelopoulos K and Stellos K: Platelet-derived chemokines in inflammation and atherosclerosis. Cytokine 122: 154157, 2019.
7. Rawish E, Nording H, Münte T and Langer HF: Platelets as mediators of neuroinflammation and thrombosis. Front Immunol 11: 548631, 2020.
8. van der Vorm LN, Li L, Huskens D, Hulstein JJJ, Roest M, de Groot PG, Ten Cate H, de Laat B, Remijn JA and Simons SO: Acute exacerbations of COPD are associated with a prothrombotic state through platelet-monocyte complexes, endothelial activation and increased thrombin generation. Respir Med 171: 106094, 2020.
9. Harrison MT, Short P, Williamson PA, Singanayagam A, Chalmers JD and Schembri S: Thrombocytosis is associated with increased short and long term mortality after exacerbation of chronic obstructive pulmonary disease: A role for antiplatelet therapy? Thorax 69: 609-615, 2014.
10. Nieri D, Morani C, De Francesco M, Gaeta R, Niceforo M, De Santis M, Giusti I, Dolo V, Daniele M, Papi A, *et al*: Enhanced prothrombotic and proinflammatory activity of circulating extracellular vesicles in acute exacerbations of chronic obstructive pulmonary disease. Respir Med 223: 107563, 2024.
11. Jiménez-Zarazúa O, González-Carrillo PL, Vélez-Ramírez LN, Vélez-Ramírez LN, Alcocer-León M, Salceda-Muñoz PAT, Palomares-Anda P, Nava-Quirino OA, Escalante-Martínez N, Sánchez-Guzmán S and Mondragón JD: Survival in septic shock associated with thrombocytopenia. Heart Lung 50: 268-276, 2021.
12. Xiang M, Wu X, Jing H, Liu L, Wang C, Wang Y, Novakovic VA and Shi J: The impact of platelets on pulmonary microcirculation throughout COVID-19 and its persistent activating factors. Front Immunol 13: 955654, 2022.
13. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, De Bon E, Tormene D, Pagnan A and Prandoni P: A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: The Padua Prediction Score. J Thromb Haemost 8: 2450-2457, 2010.
14. Fawzy A, Anderson JA, Cowans NJ, Crim C, Wise R, Yates JC and Hansel NN: Association of platelet count with all-cause mortality and risk of cardiovascular and respiratory morbidity in stable COPD. Respir Res 20: 86, 2019.
15. Semple JW, Italiano JE Jr and Freedman J: Platelets and the immune continuum. Nat Rev Immunol 11: 264-274, 2011.
16. Nicolai L and Massberg S: Platelets as key players in inflammation and infection. Curr Opin Hematol 27: 34-40, 2020.

17. Yamada S and Asakura H: How we interpret thrombosis with thrombocytopenia syndrome? Int J Mol Sci 25: 4956, 2024.
18. Rahimi-Rad MH, Soltani S, Rabieepour M and Rahimirad S: Thrombocytopenia as a marker of outcome in patients with acute exacerbation of chronic obstructive pulmonary disease. Pneumonol Alergol Pol 83: 348-351, 2015.
19. Thomas MR and Storey RF: The role of platelets in inflammation. Thromb Haemost 114: 449-458, 2015.
20. Iba T, Umemura Y, Wada H and Levy JH: Roles of coagulation abnormalities and microthrombosis in sepsis: Pathophysiology, diagnosis, and treatment. Arch Med Res 52: 788-797, 2021.
21. Mandel J, Casari M, Stepanyan M, Martyanov A and Deppermann C: Beyond hemostasis: Platelet Innate immune interactions and thromboinflammation. Int J Mol Sci 23: 3868, 2022.
22. Wen H and Chen Y: The predictive value of platelet to lymphocyte ratio and D-dimer to fibrinogen ratio combined with WELLS score on lower extremity deep vein thrombosis in young patients with cerebral hemorrhage. Neurol Sci 42: 3715-3721, 2021.
23. Zaid Y and Merhi Y: Implication of platelets in immuno-thrombosis and thrombo-inflammation. Front Cardiovasc Med 9: 863846, 2022.
24. Gasparyan AY, Ayvazyan L, Mukanova U, Yessirkepov M and Kitas GD: The platelet-to-lymphocyte ratio as an inflammatory marker in rheumatic diseases. Ann Lab Med 39: 345-357, 2019.
25. Xue J, Ma D, Jiang J and Liu Y: Diagnostic and prognostic value of immune/inflammation biomarkers for venous thromboembolism: Is it reliable for clinical practice? J Inflamm Res 14: 5059-5077, 2021.
26. Yao C, Zhang Z, Yao Y, Xu X, Jiang Q and Shi D: Predictive value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio for acute deep vein thrombosis after total joint arthroplasty: A retrospective study. J Orthop Surg Res 13: 40, 2018.
27. Kim NY, Chun DH, Kim SY, Kim NK, Baik SH, Hong JH, Kim KS and Shin CS: Prognostic value of systemic inflammatory indices, NLR, PLR, and MPV, for predicting 1-year survival of patients undergoing cytoreductive surgery with HIPEC. J Clin Med 8: 589, 2019.
28. Yüksel M, Yıldız A, Oylumlu M, Akyüz A, Aydın M, Kaya H, Acet H, Polat N, Bilik MZ and Alan S: The association between platelet/lymphocyte ratio and coronary artery disease severity. Anatol J Cardiol 15: 640-647, 2015.
29. Wang S, Liu H, Wang Q, Cheng Z, Sun S, Zhang Y, Sun X, Wang Z and Ren L: Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are effective predictors of prognosis in patients with acute mesenteric arterial embolism and thrombosis. Ann Vasc Surg 49: 115-122, 2018.
30. Luo Q, Li X, Zhao Z, Zhao Q, Liu Z and Yang W: Nomogram for hospital-acquired venous thromboembolism among patients with cardiovascular diseases. Thromb J 22: 15, 2024.
31. Selvaggio S, Brugaletta G, Abate A, Musso C, Romano M, Di Raimondo D, Pirera E, Dattilo G and Signorelli SS: Platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and monocyte-to-HDL cholesterol ratio as helpful biomarkers for patients hospitalized for deep vein thrombosis. Int J Mol Med 51: 52, 2023.
32. Artoni A, Abbattista M, Bucciarelli P, Gianniello F, Scalambrino E, Pappalardo E, Peyvandi F and Martinelli I: Platelet to lymphocyte ratio and neutrophil to lymphocyte ratio as risk factors for venous thrombosis. Clin Appl Thromb Hemost 24: 808-814, 2018.
33. Robalo Nunes A and Tátá M: The impact of anaemia and iron deficiency in chronic obstructive pulmonary disease: A clinical overview. Rev Port Pneumol (2006) 23: 146-155, 2017.
34. Lederer AK, Maul-Pavicic A, Hannibal L, Hettich M, Steinborn C, Gründemann C, Zimmermann-Klemd AM, Müller A, Sehnert B, Salzer U, *et al*: Vegan diet reduces neutrophils, monocytes and platelets related to branched-chain amino acids-A randomized, controlled trial. Clin Nutr 39: 3241-3250, 2020.