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ORIGINAL RESEARCH

Prevalence and Risk Factors of Pulmonary Embolism in COPD Patients Complicated with Secondary Polycythemia

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Purpose: This study aimed to establish the prevalence of pulmonary embolism (PE) in chronic obstructive pulmonary disease (COPD) patients with secondary polycythemia (SP) and explore the risk factors for PE in COPD patients with SP.

Patients and Methods: We analyzed the prevalence of PE among COPD patients with SP who were hospitalized at Qinghai Provincial People's Hospital between January 2015 and December 2020. From January 2021 to January 2024, we enrolled patients into three groups (COPD+SP+PE, COPD+SP, and control) and performed laboratory measurements, biomarkers, echocardiography, and pulmonary function tests. Patients in the COPD+SP group received clinical treatment, and biomarkers were measured again seven days after treatment.

Results: The prevalence of PE in patients with COPD SP was 5.21%. We found that COPD+SP+PE group had significantly higher levels of erythrocyte distribution width (RDW), platelet volume distribution width (PDW), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), monocyte to large platelet ratio (MLPR), 5-hydroxytryptamine (5-HT), activated protein C (APC), urokinase-type plasminogen activator (u-PA), thrombomodulin (TM), interleukin-38 (IL-38), tissue factor (TF), and fractalkine (FKN) in contrast to COPD+SP group. Biomarkers, such as FKN, β-thromboglobulin (β-TG), APC, u-PA, TM, TF, and IL-38, were risk factors for COPD patients with SP who are complicated by PE. Clinical treatment significantly reduced the levels of β-TG, IL-38, APC, endothelin-1 (ET-1), u-PA, FKN, TM, 5-HT, and neutrophil extracellular traps (NETs) in patients with COPD+SP.

Conclusion: PE incidence was significantly higher in patients with COPD and SP. In COPD patients with SP, routine joint detection of blood and cardiac markers, blood gas analysis, and pulmonary function tests can help to identify patients with PE. APC, u-PA, TF, FKN, TM, and IL-38 are risk factors for PE in patients with COPD and SP, and clinical treatment can effectively reduce this risk.

Keywords: chronic obstructive pulmonary diseases, secondary polycythemia, pulmonary embolism, biomarker, risk factors

Introduction

Chronic obstructive pulmonary disease (COPD) is an important public health challenge and major cause of chronic morbidity and mortality throughout the world.[1] It is characterized by persistent respiratory symptoms and airflow limitation and is related to an enhanced chronic inflammatory response of the airways and lungs to noxious particles or gases.[2] Secondary polycythemia (SP) is a comorbidity of COPD due to chronic and chronic sustained hypoxia, and its prevalence in patients with COPD is approximately 2–10%,[3,4] which is closely associated with an increased risk of venous thromboembolism (VTE), pulmonary hypertension, and mortality.[5,6] Pulmonary thromboembolism is the most common type of pulmonary embolism (PE), accounting for the vast majority (> 90%) of PE cases and is often referred to as PE.[7] Studies have found that patients with COPD are four times more likely to have PE than those without COPD, and patients with COPD combined with

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PE have significantly increased mortality.[8] In addition, according to research findings, erythrocyte distribution width (RDW),[9] mean platelet volume (MPV),[10] neutrophil-to-lymphocyte ratio (NLR),[11] and D-Dimer[12] and biomarkers such as fractalkine (FKN),[13] 5-hydroxytryptamine (5-HT),[14] endothelin-1 (ET-1),[15] tissue plasminogen activator (t-PA),[16] tissue factor (TF),[17] and tissue factor pathway inhibitor (TFPI)[18] are risk factors associated with PE, which may play an important role in the pathogenesis of PE and have certain significance for clinical prognosis assessment.

COPD has been identified as an independent risk factor for PE, with a significantly increased incidence of PE observed among COPD patients.[8] However, research pertaining to the risk factors and pathogenesis of PE in COPD patients with SP is lacking. Therefore, this study sought to investigate the prevalence of PE in COPD patients with SP, evaluate the risk factors for PE in COPD patients with SP, and provide a theoretical reference for risk assessment, clinical diagnosis, and prognosis evaluation of COPD patients with S complicated with PE. To guide the clinic in taking reasonable preventive treatment measures, reducing the occurrence of PE and improving patient prognosis.

Materials and Methods

Subjects

We first analyzed the incidence of PE among COPD patients with SP who were hospitalized at Qinghai Provincial People's Hospital from January 2015 to December 2020. Then, from January 2021 to January 2024, 100 COPD patients with SP complicated with PE who were hospitalized in Qinghai Provincial People's Hospital were collected as the COPD +SP+PE group, 100 COPD patients with SP (without PE) who were hospitalized during the same period were collected as the COPD+SP group, 100 healthy subjects as the control group (Figure 1). The Baseline characteristics of the patients were collected and analyzed (Table 1).

The diagnosis of COPD was based on the Global Initiative for Chronic Obstructive Lung Disease, and the presence of a post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ≤70% confirmed the presence of persistent airflow limitation.[19] SP was redefined as hemoglobin (Hb) ≥165 g/L in males, and ≥160 g/L in females.[20,21] PE was diagnosed using multi-slice spiral CT pulmonary artery imaging.[7] The key inclusion criteria were age ≥45 years, meeting the diagnostic criteria for COPD, COPD with SP, or COPD with SP secondary PE. The exclusion criteria included malignancy, cardiovascular disease, surgical treatment within 1 year, paralysis, and immobility.

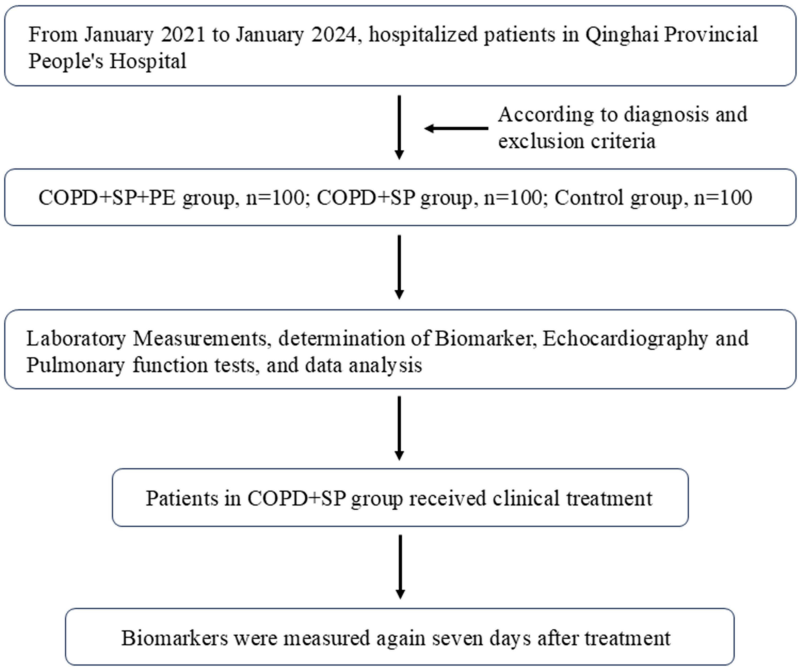

Figure 1 Flowchart of participants through the study.
Abbreviations: COPD, chronic obstructive pulmonary disease; SP, secondary polycythemia; PE, pulmonary embolism.

Table 1 Baseline Characteristics

Characteristic	COPD+SP+PE Group (n=100)	COPD+SP Group (n=100)	Control Group (n=100)
Age (years), mean (SD)	69.42±11.82	68.40±10.98	68.16±8.62
Sex, male, n (%)	55 (55%)	50 (50%)	50 (50%)
Current smoking*, n (%)	30 (30%)	24 (24%)	27 (27%)
Current drinking#, n (%)	20 (20%)	23 (23%)	23 (23%)
Hypertension, n (%)	49 (49%)	55 (55%)	52 (52%)
Type 2 diabetes mellitus, n (%)	13 (13%)	13 (13%)	14 (14%)
BMI (kg/m^2), mean (SD)	22.49 ± 4.09	22.78 ± 4.27	23.32±4.26
Heart rate (bpm), mean (SD)	87.94 ± 15.29	84.43 ± 15.37	84.06±12.54
SBP (mmHg), mean (SD)	125.92 ± 19.63	130.48 ± 18.87	126.26±17.28
DBP (mmHg), mean (SD)	77.78 ± 12.51	78.68 ± 14.29	75.93±10.33

Notes: Statistically no sense among the three groups. *Current smoking was defined as smoking cessation for less than 5 months and continuous or cumulative smoking for 6 months or more; #Current drinking was defined as having consumed wine at least once in the past week with a volume of alcohol exceeding 50 mL.
Abbreviations: COPD, chronic obstructive pulmonary disease; SP, secondary polycythemia; PE, pulmonary embolism; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

This study strictly complies with the Declaration of Helsinki. Ethical approval was provided by the Medical Ethics Committee of Qinghai Provincial People's Hospital (2022–89) and written informed consent was obtained from all participants.

Laboratory Measurements

Fasting blood samples were collected the morning after admission. Complete blood counts were measured using a Sysmex-XN10 automatic blood cell analyzer (Japan). Coagulation parameters, including D-dimer and fibrinogen degradation product (FDP), were measured using a CS-5100 automatic coagulation instrument. Laboratory biochemical variables were measured using an automatic biochemical analyzer (AU5831, Beckman Coulter, United). Brain natriuretic peptide (BNP) levels were measured using an automatic chemiluminescence immunoassay analyzer (DxI 800, Beckman). Interleukin-6 (IL-6) and procalcitonin (PCT) levels were measured using a Roche Cobas e 602 automatic chemiluminescence immunoassay analyzer. Arterial blood gas analysis was performed using a Denmark Ray Bio ABL800FLEX. Special needles and detection reagents for blood gas collection were provided by the manufacturer.

Determination of Biomarker

Three milliliters of fasting blood was collected from the subjects after admission, placed in clean and dry vacuum tubes without any additives, and kept stationary at room temperature for 1 h. Serum was obtained after blood centrifugation at 3000 rpm for 10 min at 4°C. All samples were aliquoted and immediately stored at −80°C. After sample collection, biomarkers were detected using ELISA kits (Jiangsu Enzyme Labeling Biotechnology Co., LTD, China) according to the manufacturer's protocols.[22]

Echocardiography and Pulmonary Function Tests

The transverse diameter of the right ventricle (RVTD), right ventricular wall thickness (RVWT), right ventricular outflow tract (RVOT), and pulmonary artery systolic pressure (PASP) were measured by experienced sonographers using a Philips EPIQ 7c color Doppler ultrasonography. Forced expiratory volume in 1s (FEV1), forced vital capacity (FVC) and FEV1/FVC were detected by Master Screen PFT pulmonary function instrument (JAEGE company, FVCvital capacity Germany). All data and diagnoses were acquired according to the standard guidelines.

Clinical Treatment

Patients in COPD+SP group received non-drug treatment according to the Guidelines for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (Revised 2021), including exercise, diet, abdominal breathing and other health education; According to the need to give sputum (ambroxol), antispasmodic asthma (aminophylline) and other drugs

treatment; Low flow oxygen therapy was given: the flow rate was (2.0–3.0) L/min, and the duration of oxygen inhalation was >10 h per day.[23] After 7 days of treatment, 3 mL of fasting blood was collected to determine the biomarkers.

Statistical Analysis

SPSS 23.0 was used for statistical analysis. Baseline characteristics were summarized as frequencies with percentages, means with standard deviations, or medians with interquartile ranges. Differences in baseline characteristics were tested using the chi-square test for binary or categorical variables. One-way analysis (of) or a two-sample *t*-test was used for normally distributed continuous variables. The correlation between laboratory measurements and D-dimer levels was assessed using Pearson's correlation test. Binary logistic regression analyses incorporated individual risk factors. Receiver Operating Characteristic Curve (ROC) analysis was employed to evaluate the sensitivity and specificity. To evaluate the diagnostic accuracy, we employed the area under the curve (AUC). Statistical significance was established for group differences at P <0.05.

Results

Prevalence of PE in COPD Patients with Secondary Polycythemia

From January 2015 to December 2020, a total of 4531 COPD patients were hospitalized in Qinghai Provincial People's Hospital, of which 80 patients had PE; the incidence of PE in COPD patients was approximately 1.73%. In 2017, 105 COPD patients with SP had PE, and the incidence of PE in COPD patients with SP was approximately 5.21% (Figure 2), 5.21% vs 1.73, $P < 0.05$.

Sample Characteristics

There were no significant differences in age, sex, current smoking, current drinking, hypertension, type 2 diabetes, body mass index (BMI), heart rate, systolic blood pressure (SBP), or diastolic blood pressure (DBP) among the three groups ($P > 0.05$, Table 1).

Comparison of Laboratory Measurements

The comparison of complete blood counts among three groups showed that red blood cell volume distribution width (RDW), platelet volume distribution width (PDW), NLR, platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and monocyte to large platelet ratio (MLPR) in the COPD+SP+PE group were significantly higher than those in the COPD+SP group, and significantly higher than those in the control group, the differences were statistically significant ($P < 0.05$, Figure 3); MPV and erythrocyte sedimentation rate (ESR) in the COPD+SP+PE group were significantly higher than those in the COPD+SP group ($P < 0.05$), but no difference between COPD+SP group and control group ($P > 0.05$, Figure 3).

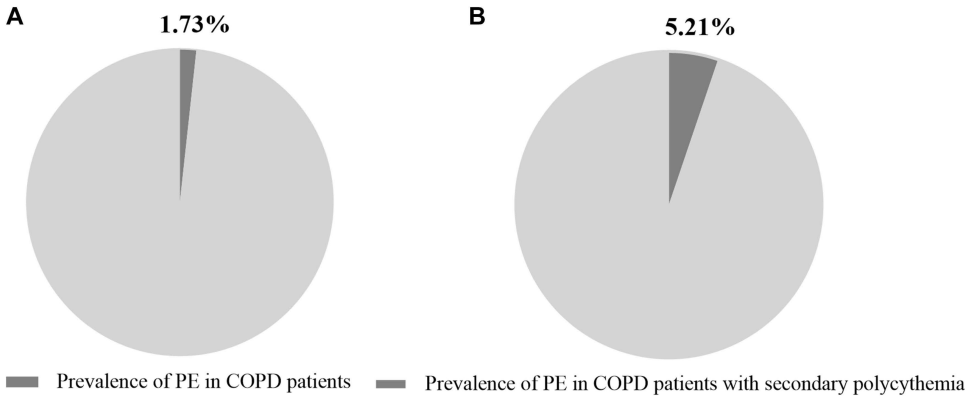

Figure 2 Prevalence of PE in COPD patients with secondary polycythemia. (**A**) represent the prevalence of PE in COPD patients. (**B**) represent the prevalence of PE in COPD patients with secondary polycythemia.
Abbreviations: PE, pulmonary embolism; COPD, chronic obstructive pulmonary disease.

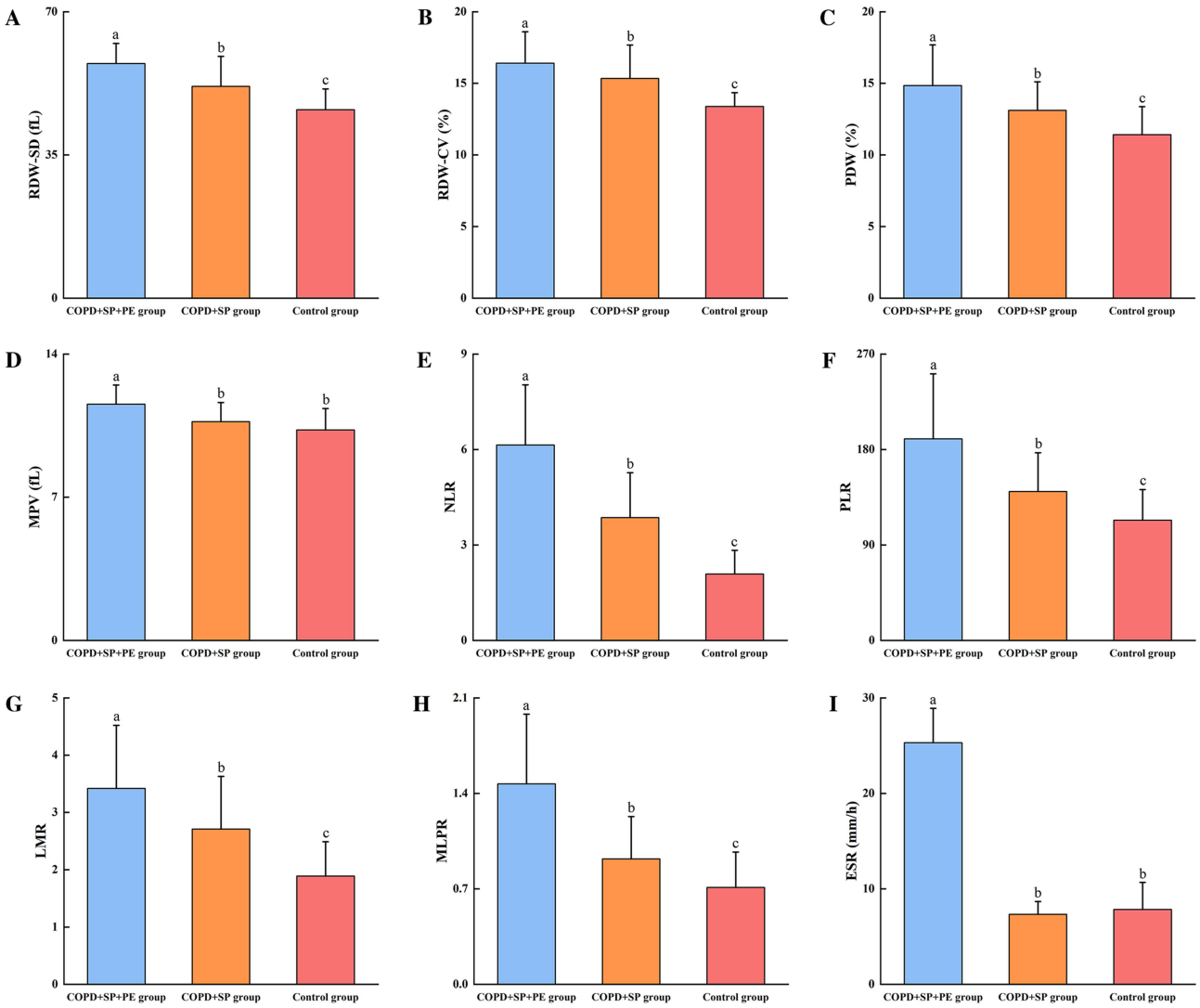

Figure 3 The complete blood counts of the three groups. (**A**) RDW, red blood cell volume distribution width; (**B**) RDW, red blood cell volume distribution width; (**C**) PDW, platelet volume distribution width; (**D**) MPV, mean platelet volume; (**E**) NLR, neutrophil to lymphocyte ratio; (**F**) PLR, platelet to lymphocyte ratio; (**G**) LMR, lymphocyte to monocyte ratio; (**H**) MLPR, monocyte to large platelet ratio; (**I**) ESR, erythrocyte sedimentation rate.
Abbreviations: COPD, chronic obstructive pulmonary disease; SP, secondary polycythemia; PE, pulmonary embolism.

The comparison of coagulation parameters, biochemical parameters, BNP, IL-6, PCT, and arterial blood gas analysis among the three groups showed that cardiac troponin I (cTnI), BNP, PCT, IL-6 in the COPD+SP+PE group were significantly higher than those in the COPD+SP group, and significantly higher than those in the control group, the differences were statistically significant ($P < 0.05$, Figure 4); D-Dimer and FDP in the COPD+SP+PE group were significantly higher than those in the COPD+SP group ($P < 0.05$), but no difference between COPD+SP group and control group ($P > 0.05$, Figure 4); Albumin (ALB) and partial pressure of oxygen (PO_2) in the COPD+SP+PE group were significantly lower than those in the COPD+SP group, and significantly lower than those in the control group, the differences were statistically significant ($P < 0.05$, Figure 4); Oxygen saturation (SO_2) in the COPD+SP+PE group was significantly lower than that in the COPD+SP group ($P < 0.05$), but no difference between COPD+SP group and control group ($P > 0.05$, Figure 4).

Analysis of Correlation Between Laboratory Measurements and D-Dimer

Pearson's correlation analysis indicated that RDW-SD, RDW-CV, PDW, NLR, PLR, LMR, MLPR, FDP, cTnI, BNP, ESR, PCT, and IL-6 were positively correlated with D-dimer levels, while PO_2 and SO_2 were negatively correlated with D-dimer levels ($P < 0.05$, Table 2).

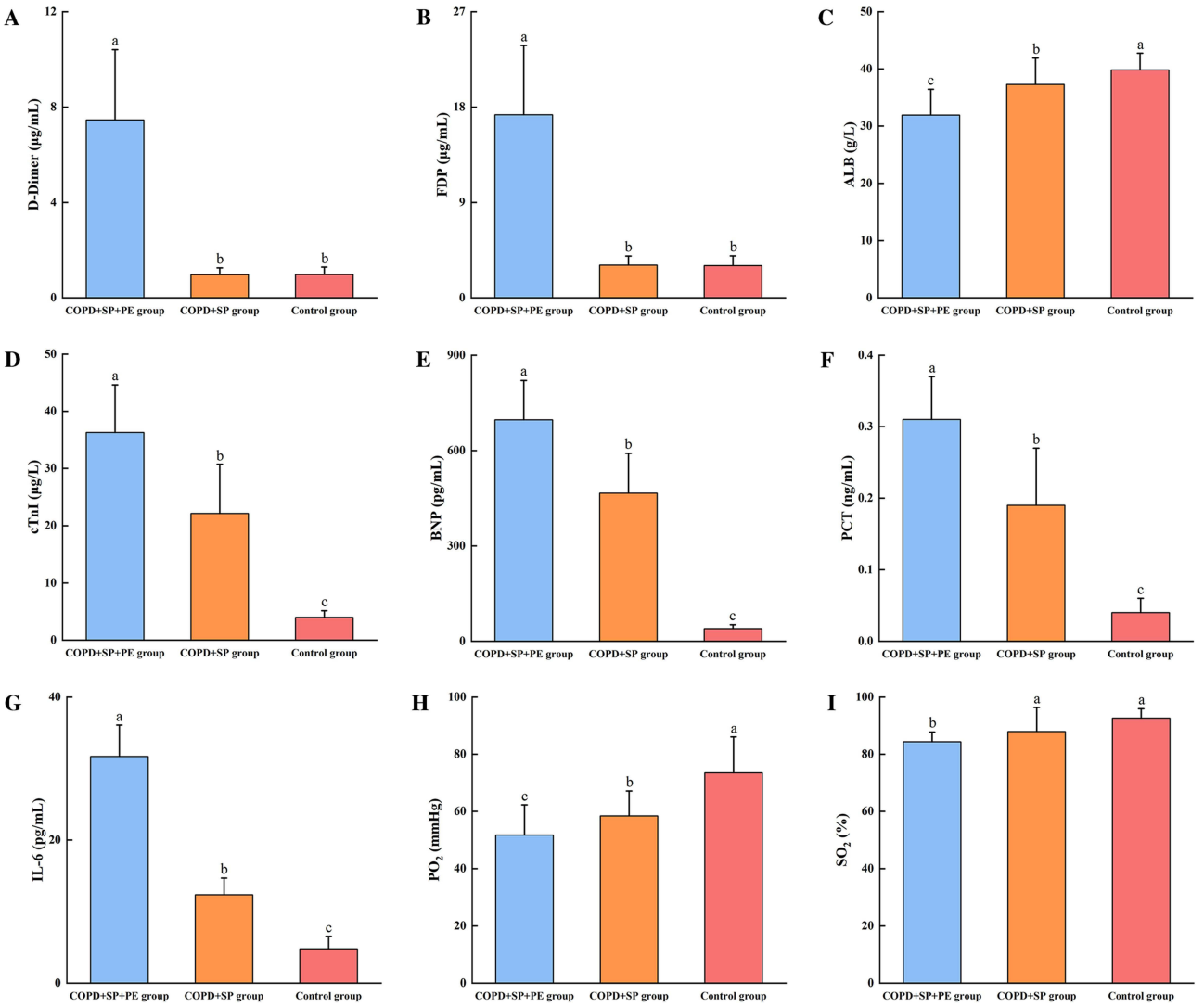

Figure 4 The coagulation parameters, biochemical parameters, BNP, IL-6, PCT, and blood gas analysis among the three groups. (**A**) D-Dimer. (**B**) FDP, fibrinogen degradation product; (**C**) ALB, Albumin; (**D**) cTnI, cardiac troponin I; (**E**) BNP, brain natriuretic peptide; (**F**) PCT, procalcitonin; (**G**) IL-6, interleukin-6; (**H**) PO_2, partial pressure of oxygen; (**I**) SO_2, oxygen saturation.
Abbreviations: COPD, chronic obstructive pulmonary disease; SP, secondary polycythemia; PE, pulmonary embolism.

The results of Echocardiography and Pulmonary Function

Echocardiography showed that RVTD, RVOT, and PASP in the control group was significantly lower than those in the COPD +SP+PE group ($P < 0.05$), but there was no difference between the COPD+SP+PE and COPD+SP groups ($P > 0.05$, Figure 5); RVWT did not differ among the three groups ($P > 0.05$; Figure 5). FEV1 in the COPD+SP+PE group were significantly lower than that in the COPD+SP group and significantly lower than that in the control group; the differences were statistically significant ($P < 0.05$, Figure 5); FEV1/FVC was significantly lower in COPD+SP+PE group and COPD+SP group than that in control group, but no difference between COPD+SP+PE group and COPD+SP group ($P > 0.05$, Figure 5).

Biomarker

The levels of activated protein C (APC), urokinase-type plasminogen activator (u-PA), TF and FKN in the COPD+SP+PE group were significantly higher than those in the COPD+SP group, and significantly higher than those in the control group ($P < 0.05$, Figure 6); 5-HT, thrombomodulin (TM), and interleukin-38 (IL-38) in the COPD+SP+PE group were significantly higher than those in the COPD+SP group ($P < 0.05$), but no difference between COPD+SP group and control group ($P > 0.05$, Figure 6); β-thromboglobulin (β- TG), ET-1, t-PA, TFPI and neutrophil extracellular traps (NETs) in COPD+SP+PE group and COPD+SP

Table 2 The Correlation Between Laboratory Measurements and D-Dimer

Indicators	*r* Value	*P* value
RDW-SD (fl)	0.308	0.000*
RDW-CV (%)	0.378	0.000*
PDW (%)	0.304	0.008*
MPV (fl)	0.066	0.623
NLR	0.597	0.000*
PLR	0.412	0.001*
LMR	0.328	0.011*
MLPR	0.539	0.000*
FDP (ug/mL)	0.955	0.000*
cTnI (μg/L)	0.672	0.000*
BNP (pg/mL)	0.462	0.000*
ESR (mm/h)	0.456	0.000*
PCT (ng/mL)	0.365	0.002*
IL-6 (pg/mL)	0.791	0.000*
pH	0.272	0.080
PO_2 (mmHg)	−0.286	0.009*
SO_2 (%)	−0.212	0.038*

Note: *$P < 0.05$ was considered statistically significant.

Abbreviations: RDW, erythrocyte distribution width; PDW, platelet volume distribution width; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte to monocyte ratio; MLPR, monocyte-to-large platelet ratio; FDP, fibrinogen degradation product; cTnI, cardiac troponin I; BNP, Brain natriuretic peptide; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; IL-6, interleukin-6; PO_2, partial pressure of oxygen; SO_2, oxygen saturation.

group were significantly higher than those in control group ($P<0.05$, Figure 6), but no difference between COPD+SP+PE group and COPD+SP group ($P > 0.05$, Figure 6).

Analysis of Correlation Between Biomarker and D-Dimer

The Pearson correlation analysis between Biomarker and D-dimer in COPD+SP+PE group showed that 5-HT, β-TG, APC, ET-1, u-PA, FKN, TF, and TFPI were positively correlated with D-dimer ($P < 0.05$), while IL-38, TM, tPA, and NETs were not correlated with D-dimer ($P > 0.05$, Table 3).

Risk Factors for the COPD Patients with SP Complicated by PE

Multivariate Logistic regression analysis was done for COPD patients with SP complicated by PE. The results showed that β-TG (OR value was 1.098, 95% CI: 1.020–1.182, $P < 0.05$), APC (OR value 1.006, 95% CI: 1.002–1.010, $P < 0.05$), u-PA (OR value 1.006, 95% CI: 1.003–1.009, $P < 0.05$), TM (OR value 1.684, 95% CI: 1.186–2.393, $P < 0.05$), TF (OR value 1.034, 95% CI: 1.001–1.005, $P < 0.05$), IL-38 (OR value 1.001, 95% CI: 1.000–1.001, $P < 0.05$), and FKN (OR value 1.004, 95% CI: 1.001–1.008, $P < 0.05$) were risk factors for COPD patients with SP complicated by PE (Table 4).

Diagnostic Accuracy of Biomarker

Figure 7 displays the ROC curve analysis results for β-TG, APC, u-PA, TM, TF, IL-38, and FKN. The evaluation of COPD patients with SP complicated by PE using β-TG resulted in a sensitivity of 94.10% and a specificity of 51.40% at

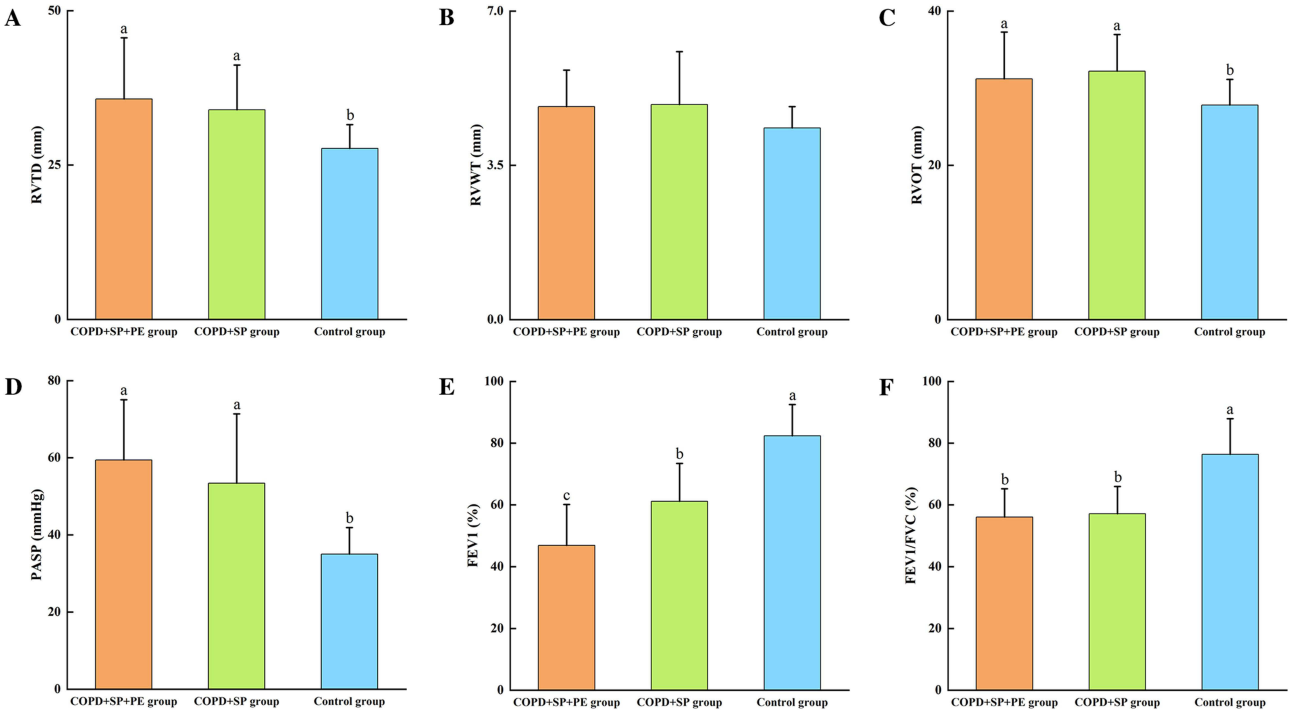

Figure 5 The results of echocardiography and pulmonary function tests among the three groups. (**A**) RVTD, right ventricle transverse diameter; (**B**) RVWT, right ventricular wall thickness; (**C**) RVOT, right ventricular outflow tract; (**D**) PASP, pulmonary artery systolic pressure; (**E**) FEV1, forced expiratory volume in 1 second; (**F**) FEV1/FVC, forced expiratory volume in 1 second /forced vital capacity.
Abbreviations: COPD, chronic obstructive pulmonary disease; SP, secondary polycythemia; PE, pulmonary embolism.

a cut-off value of 44.515. The AUC for β-TG was calculated to be 0.736. When APC was used to assess COPD patients with SP complicated by PE, the optimal cut-off APC was determined to be 1113.025, with an AUC of 0.787. The sensitivity and specificity for APC were 52.90% and 95.40%, respectively. Similarly, u-PA exhibited a sensitivity of 70.60% and a specificity of 81.70% at a cut-off value of 1047.465, resulting in an AUC of 0.818. TM showed a sensitivity of 47.10% and a specificity of 89.00% at a cut-off value of 7.090, resulting in an AUC of 0.643. The cut-off of TF was 184.100, the AUC was 0.794, the sensitivity was 58.80%, the specificity was 89.90%. The optimal cut-off of IL-38 was 5886.020, the AUC was 0.678, the sensitivity was 70.60%, and the specificity was 62.40%. FKN exhibited a sensitivity of 100.00% and a specificity of 62.40% at optimal cut-off value of 1145.375, resulting in an AUC of 0.826. In this study, we found that FKN and β-TG had the highest diagnostic accuracy in COPD patients with SP complicated by PE, whereas APC, u-PA, TM, TF, and IL-38 show a better diagnostic specificity. The diagnostic accuracy of the biomarker is listed in Table 5.

Effect of Clinical Treatment on Biomarker in COPD Patients with Secondary Polycythemia

Compared with before treatment, 5-HT, β-TG, IL-38, APC, ET-1, u-PA, FKN, TM and NETs in COPD patients were significantly decreased after treatment ($P < 0.05$, Table 6); However, t-PA, TF and TFPI had no statistical significance before and after treatment ($P > 0.05$, Table 6).

Discussion

Clinical studies have found that the incidence of PE in COPD is 2–4 times higher than that in non-COPD patients.[24] The results of this study showed that the incidence of PE in COPD patients was approximately 1.73% and the incidence of PE in COPD patients with SP was approximately 5.21% (Figure 2). The incidence of PE in patients with COPD and SP was significantly higher than that in patients with COPD alone ($P < 0.05$). The hypercoagulable state, inflammatory state, and

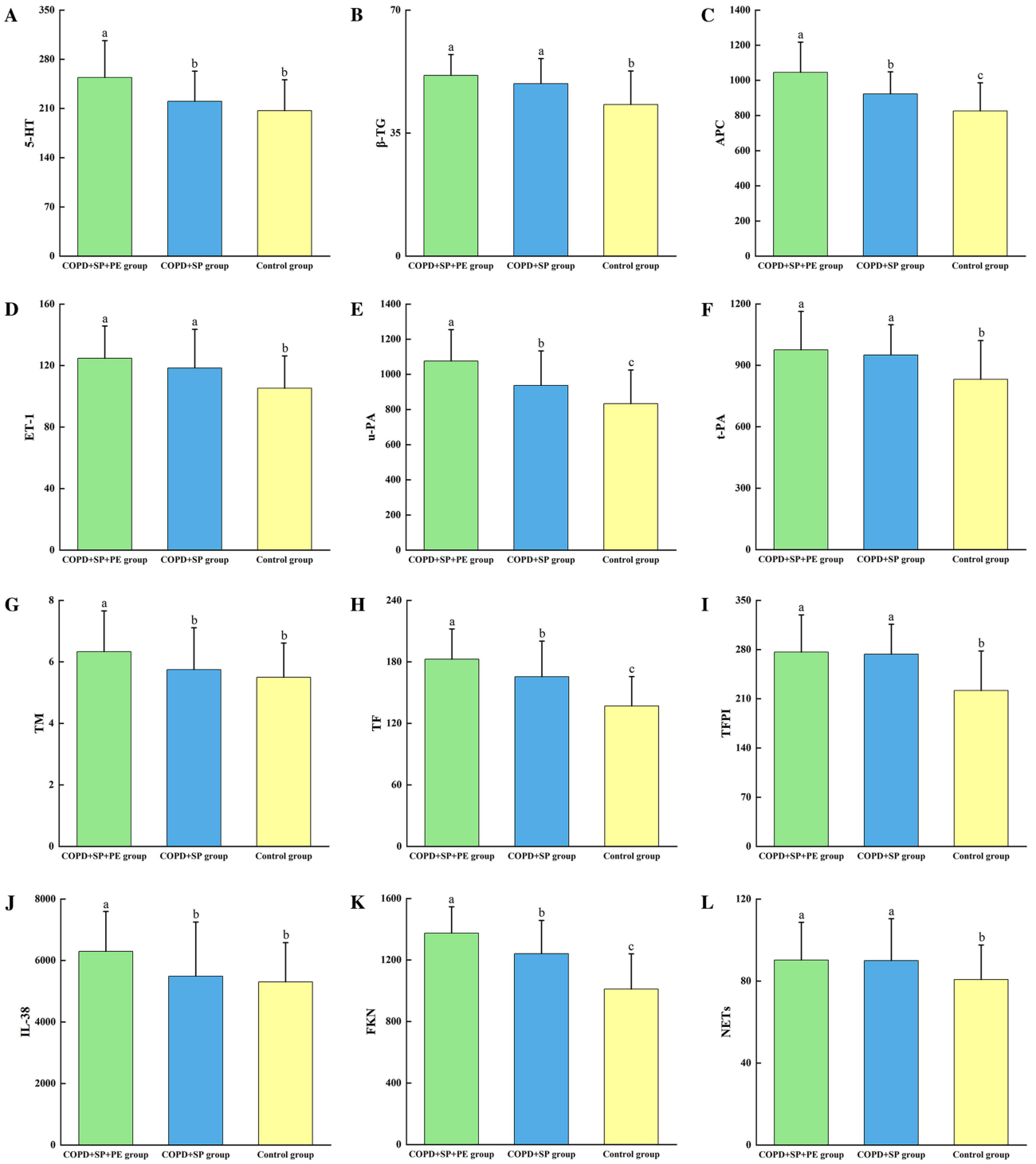

Figure 6 The results of serum cytokines level among the three groups. (**A**) 5-HT, 5-hydroxytryptamine; (**B**) β-TG, β-thromboglobulin; (**C**) APC, activated protein C; (**D**) ET-1, endothelin-1; (**E**) u-PA, urokinase-type plasminogen activator; (**F**) t-PA, tissue plasminogen activator; (**G**) TM, thrombomodulin; (**H**) TF, tissue factor; (**I**) TFPI, tissue factor pathway inhibitor; (**J**) IL-38, interleukin-38; (**K**) FKN, fractalkine; (**L**) NETs, neutrophil extracellular traps.
Abbreviations: COPD, chronic obstructive pulmonary disease; SP, secondary polycythemia; PE, pulmonary embolism.

vascular endothelial injury in COPD patients with SP are considered to be in a pre-thrombotic state, which further leads to PE.

Patients with COPD have decreased lung function and limited activity, and some are bedridden for a long time. In addition, COPD patients are in a state of chronic hypoxia, secondary erythrocytosis, venous blood stasis, venous

Table 3 The Correlation Between Biomarker and D-Dimer

Indicators	r Value	P value
5-HT	0.157	0.022*
β-TG	0.144	0.039*
APC	0.260	0.000*
ET-1	0.380	0.005*
u-PA	0.200	0.003*
tPA	0.121	0.076
TM	0.130	0.067
TF	0.199	0.010*
TFPI	0.155	0.026*
IL-38	0.087	0.193
FKN	0.226	0.001*
NETs	10.026	0.714

Note: *$P < 0.05$ was considered statistically significant.

Abbreviations: 5-HT, 5-hydroxytryptamine; β-TG, β-thromboglobulin; APC, activated protein C; ET-1, endothelin-1; u-PA, urokinase-type plasminogen activator; t-PA, tissue plasminogen activator; TM, thrombomodulin; TF, tissue factor; TFPI, tissue factor pathway inhibitor; IL-38, interleukin-38; FKN, fractalkine; NETs, neutrophil extracellular traps.

Table 4 Binary Logistic Regression Analysis of Risk Factors for COPD Patients with SP Complicated by PE

Indicators	OR	P value	95% CI
5-HT	1.011	0.132	0.997–1.026
β-TG	1.098	0.013*	1.020–1.182
APC	1.006	0.002*	1.002–1.010
ET-1	1.013	0.301	0.988–1.038
u-PA	1.006	0.000*	1.003–1.009
tPA	1.003	0.060	1.000–1.006
TM	1.684	0.004*	1.186–2.393
TF	1.034	0.000*	1.001–1.005
TFPI	1.009	0.191	0.966–1.022
IL-38	1.001	0.001*	1.000–1.001
FKN	1.004	0.020*	1.001–1.008
NETs	1.033	0.104	0.993–1.073

Note: *$P < 0.05$ was considered statistically significant.

Abbreviations: 5-HT, 5-hydroxytryptamine; β-TG, β-thromboglobulin; APC, activated protein C; ET-1, endothelin-1; u-PA, urokinase-type plasminogen activator; t-PA, tissue plasminogen activator; TM, thrombomodulin; TF, tissue factor; TFPI, tissue factor pathway inhibitor; IL-38, interleukin-38; FKN, fractalkine; NETs, neutrophil extracellular traps.

endothelial injury, and hypercoagulable blood, which make COPD patients with secondary erythrocytosis are at high-risk of PE.[5] Moreover, the clinical manifestations of COPD and PE are similar, with increased missed and misdiagnosed rates of PE, thereby delaying patient treatment and increasing patient mortality rate. The early identification of PE in patients with COPD is of great significance for improving prognosis. The results of this study showed that laboratory

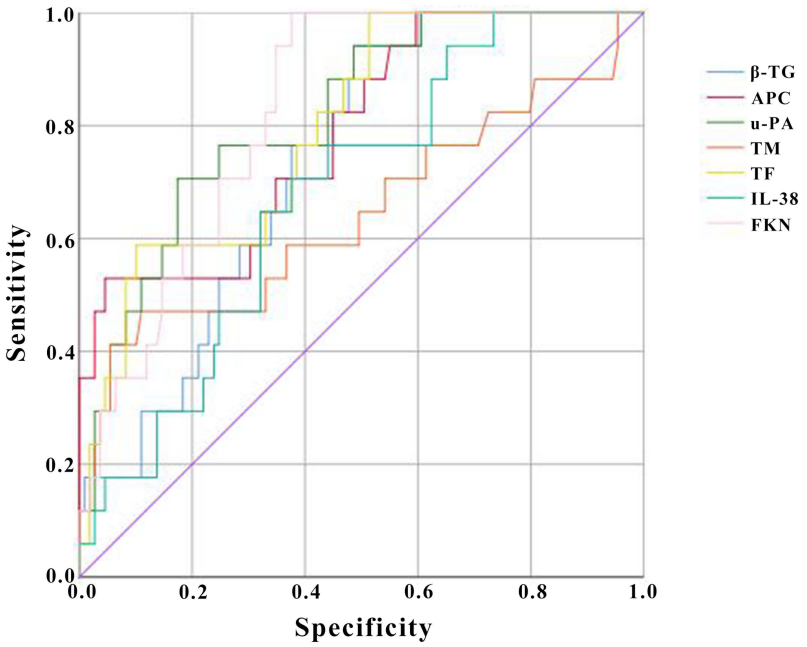

Figure 7 The receiver operating characteristic (ROC) curves of biomarkers to evaluate diagnostic accuracy.
Abbreviations: β-TG, β-thromboglobulin; APC, activated protein C; u-PA, urokinase-type plasminogen activator; TM, thrombomodulin; TF, tissue factor; IL-38, interleukin-38; FKN, fractalkine.

measurements, such as RDW, PDW, NLR, PLR, LMR, and MLPR, were significantly increased in COPD patients with SP complicated with PE and showed a gradual increase in the control, COPD SP, and COPD SP complicated with PE groups (Figure 3). Studies have shown that RDW is a predictor of acute PE (APE) and an independent predictor of PE.[25] Wang et al[26] found that the RDW of COPD patients with PE increased significantly; therefore, the RDW may help predict the occurrence of PE in COPD patients. The MPV is a marker that reflects the size and activity of platelets.[27] PDW is an index that reflects the degree of difference in the platelet volume. The increase in PDW also indicated the presence of many large platelets. With the increase of PDW, platelets are prone to morphological changes and form pseudopodia, and the formation of pseudopodia enhances the adhesion of platelets and the cohesion between platelets, which is prone to thrombosis.[28] Therefore, researchers believe that the larger the MPV and PDW in COPD patients, the more likely they are to develop thrombosis. The study found that NLR has a good predictive ability for the occurrence and prognosis of venous thromboembolism, and an increase in NLR is closely related to all-cause mortality of APE.[29] The PLR is a novel marker of inflammation and thrombosis. In the acute phase of inflammation, the vascular endothelium is damaged by inflammatory reactants such as IL-1, IL-6, tumor necrosis factor, and high-sensitivity C-reactive protein. TF is released after vascular endothelial injury and activates the platelets. After platelet activation, more platelets adhere to the platelet

Table 5 Development of PE in COPD Patients with SP and Construction of Prediction Model

Indicators	AUC	95% CI	*P* value	Cut-off	Sensitivity	Specificity	Jorden Index
β-TG	0.736	0.633–0.839	0.002*	44.515	94.10	51.40	0.455
APC	0.787	0.672–0.902	0.000*	1113.025	52.90	95.40	0.483
u-PA	0.818	0.719–0.917	0.000*	1047.465	70.60	81.70	0.532
TM	0.643	0.476–0.810	0.043*	7.090	47.10	89.00	0.361
TF	0.794	0.691–0.898	0.000*	184.100	58.80	89.90	0.487
IL-38	0.678	0.558–0.799	0.018*	5886.020	70.60	62.40	0.330
FKN	0.826	0.746–0.907	0.000*	1145.375	100.00	62.40	0.624

Note: *$P < 0.05$ was considered statistically significant.
Abbreviations: β-TG, β-thromboglobulin; APC, activated protein C; u-PA, urokinase-type plasminogen activator; TM, thrombomodulin; TF, tissue factor; IL-38, interleukin-38; FKN, fractalkine.

Table 6 Comparison of Serum Cytokines Before and After Clinical Treatment

Serum Cytokines	Before Treatment (n=100)	After Treatment (n=100)	*P* value
5-HT	242.36 ± 49.42	217.02 ± 43.32	0.01*
β-TG	47.34 ± 10.63	41.67 ± 10.74	0.02*
APC	867.72 ± 181.69	751.10 ± 170.95	0.00*
ET-1	116.02 ± 31.62	101.27 ± 22.90	0.03*
u-PA	870.27 ± 214.51	741.83 ± 209.34	0.01*
t-PA	972.01 ± 209.02	939.32 ± 247.40	0.53
TM	5.52 ± 1.19	4.86 ± 1.21	0.01*
TF	166.42 ± 40.85	165.76 ± 37.74	0.94
TFPI	301.07 ± 66.75	297.90 ± 82.78	0.85
IL-38	6041.62 ± 1228.63	4669.30 ± 1221.36	0.04*
FKN	1246.97 ± 250.23	1123.43 ± 254.74	0.03*
NETs	81.76 ± 14.51	71.17 ± 19.42	0.02*

Note: *$P < 0.05$ was considered statistically significant.
Abbreviations: 5-HT, 5-hydroxytryptamine; β-TG, β-thromboglobulin; APC, activated protein C; ET-1, endothelin-1; u-PA, urokinase-type plasminogen activator; t-PA, tissue plasminogen activator; TM, thrombomodulin; TF, tissue factor; TFPI, tissue factor pathway inhibitor; IL-38, interleukin-38; FKN, fractalkine; NETs, neutrophil extracellular traps.

clusters through adhesion, release, and aggregation. When the exogenous coagulation pathway is activated, thrombin binds to the platelet surface antibody, which further enlarges and retracts platelet aggregates, forming irreversible platelet masses that become the starting point for thrombosis. After thrombosis, lymphocytes undergo rapid apoptosis under oxidative stress, and the PLR increases.[30] Therefore, PLR can predict the occurrence of thromboembolism and serves as a predictor of mortality in APE.[30–32] The results of this study suggest that indicators such as RDW, PDW, NLR, PLR, LMR, and MLPR can serve as risk factors for secondary PE in patients with COPD and SP.

The results of this study showed that cTnI, BNP, PCT, and IL-6 levels were significantly increased in COPD patients with SP complicated by PE, whereas ALB, PO_2, and SO_2 levels were significantly reduced (Figure 4). There was no significant difference in RVTD, RVOT, or PASP between COPD patients with SP combined with PE and COPD patients with SP; however, it was significantly higher than that in healthy subjects. The FEV1 of COPD patients with SP combined with PE was significantly lower than that of COPD patients with SP and healthy subjects; however, there was no statistically significant difference in FEV1/FVC between COPD patients with SP complicated by PE and COPD patients with SP (Figure 5). Studies have shown that an increase in cTnI levels is associated with a 1–10% increase in short-term mortality risk in PE.[33] Multiple studies have shown that BNP levels are associated with the disease risk and prognosis in patients with COPD and PE. The higher the BNP level, the higher the risk stratification and the worse the prognosis.[34,35] Patients with COPD and PE are more prone to pulmonary arterial hypertension and right-sided heart dysfunction. The synthesis and secretion of BNP by ventricular cardiomyocytes increases when the ventricular load and/or ventricular wall tension increases. Elevated levels of active BNP and BNP precursor NT-proBNP can indicate ventricular overload.[35,36] Ventilation dysfunction caused by COPD can lead to pulmonary edema, imbalance in the ventilation blood flow ratio, and reduction in lung compliance, resulting in the reduction of PO_2 and SO_2.[7] A decrease in FEV1% indicates that patients have an obstructive ventilation disorder, which is one of the commonly used lung function evaluation indicators in the clinic. The greater the decrease in FEV1% in patients with COPD, the higher the risk of PE.[7,37] These conclusions are consistent with those of this study.

D-dimer is a specific marker of the fibrinolysis process. D-dimer, as an important screening method for evaluating pulmonary embolism in clinical practice, has good sensitivity and specificity in diagnosing PE, and a concentration <500 ug/L can be used as a criterion for excluding PE. In the general population, the sensitivity and specificity of predicting PE are 92–100% and 30–40%, respectively. In AECOPD, the sensitivity and specificity of predicting PE are 88.57% and 26.67%, respectively. However, there are many factors that affect D-dimer, such as age, infection, surgery, etc. Research

has found that raising the D-dimer threshold to 950 ug/L can increase the predictive power of PE.[38] The results of this study showed that D-dimer and FDP were significantly increased in the COPD with SP complicated with PE group; compared with the control group, D-dimer and FDP had no significant difference in COPD secondary polycythemia group (Figure 4). Therefore, although COPD patients with SP have high blood viscosity and hypercoagulability, D-D remains at a normal level, suggesting that it can still be used as a screening tool for PE. In addition, RDW, PDW, NLR, PLR, LMR, MLPR, FDP, cTnI, BNP, ESR, PCT, and IL-6 were positively correlated with D-dimer levels, whereas PO_2 and SO_2 were negatively correlated with D-dimer levels (Table 2). These results suggest that laboratory measurements can guide the clinical assessment of PE risk in COPD patients with SP.

The results of this study showed that 5-HT, APC, u-PA, TM, TF, IL-38, and FKN levels in patients with COPD with SP complicated by PE were significantly higher than those in patients with COPD with SP without PE, and significantly higher than those in healthy controls. β-TG, ET-1, t-PA, TFPI, and NETs were not significantly different between COPD patients with SP complicated with PE and COPD secondary polycythemia patients without PE, but were significantly higher than those in healthy controls (Figure 6). 5-HT, β-TG, APC, ET-1, u-PA, FKN, TF, and TFPI were positively correlated with D-dimer (Table 3). Binary logistic regression analysis results showed that β-TG, APC, u-PA, TM, TF, IL-38, and FKN, were risk factors for COPD patients with SP complicated by PE (Table 4). Further analysis found that FKN and β-TG had the highest diagnostic accuracy in COPD patients with SP complicated by PE, whereas APC, u-PA, TM, TF, and IL-38 show a better diagnostic specificity (Figure 7, Table 5). Under normal circumstances, 5-HT is stored by binding to specific receptors on the surface of platelets via a specific uptake mechanism. When platelets are destroyed or platelet uptake and storage function are abnormal, the concentration of 5-HT in the plasma increases, which can cause strong pulmonary vasoconstriction and pulmonary hypertension.[39] Studies have shown that 5-HT levels are significantly increased in the serum of patients with AECOPD and patients with PE.[14] FKN not only functions as a chemotactic protein and a cell adhesion molecule but also acts as a growth factor that promotes smooth muscle cell proliferation. Studies have shown that FKN expression in the lung tissue of rats with APE is significantly higher than that in the control group.[13] The t-PA content in the blood can reflect the function of the fibrinolytic system and risk of thrombosis. The study found that the level of t-PA in patients with AECOPD complicated by PE in the high-risk group was significantly higher than that in the low- and moderate-risk groups. The reason for this result is that the vascular endothelium is damaged during PE, which activates the endogenous fibrinolytic system, resulting in a large amount of t-PA being produced by endothelial cells and released into the blood, thus increasing plasma t-PA is increased.[16] ET-1 can promote vasoconstriction and bronchoconstriction and has a strong ability to contract pulmonary vessels. Abnormal pulmonary vascular endothelial function can be accompanied by changes in ET-1 level. Clinical studies have reported that serum ET-1 levels in AECOPD patients with PE are significantly higher than those in patients without PE.[15] A net is a fibrous network structure formed by depolymerized DNA and modified by a variety of granule proteins after stimulated neutrophil activation, which can capture pathogens. This is a new mechanism by which neutrophils capture and kill pathogens. In recent years, studies have confirmed that NETs are involved in the occurrence and development of venous thromboembolism and that NETs exist in the thrombi of patients with VTE. The concentration of NETs in the serum of patients is significantly higher than that of healthy people.[40] The results of this study showed that the levels of 5-HT, β-TG, IL-38, APC, ET-1, u-PA, FKN, TM, and NETs were significantly lower after treatment than before treatment in patients with COPD secondary erythrocytosis (Table 6). This suggests that active clinical treatment can effectively reduce the risk of PE in patients with COPD secondary polycythemia.

Conclusion

In conclusion, the incidence of PE was significantly higher in COPD patients with SP. The concurrent assessment of blood indicators, blood gas analysis, and pulmonary function is instrumental in identifying PE in COPD patients with SP. Biomarkers, such as FKN, β-TG, APC, u-PA, TM, TF, and IL-38, were the risk factors for COPD patients with SP complicated by PE. Clinical treatment has been shown to significantly reduce the levels of these biomarkers in COPD patients with SP, thereby diminishing the risk of PE.

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Disclosure

The authors report no conflicts of interest in this work.

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