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Blood Coagulability and Inflammatory and Hematological Profiles Across Different Clinical States of Chronic Obstructive Pulmonary Disease: A Comparative Cross-Sectional Study

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) involves persistent inflammation and vascular alterations that promote a prothrombotic state. Acute exacerbations and disease progression further activate clotting pathways, elevating thrombosis risk. The associations among coagulation parameters, inflammatory markers, haematological indices, and arterial blood gas values across COPD stages remain incompletely elucidated.

Objective: To evaluate coagulation status and related inflammatory and hematological markers in patients with stable COPD, hospitalized COPD, critically ill COPD, and healthy controls.

Methodology: This prospective, comparative, cross-sectional study was conducted at Benazir Bhutto Hospital, Rawalpindi, and Muslim Youth University, Islamabad from January 2024 to September 2025. A total of 108 participants were enrolled and assigned equally to four groups: stable COPD outpatients, hospitalized COPD patients, intensive care unit (ICU) COPD patients, and healthy controls. Laboratory assessments included D-dimer, C-reactive protein (CRP), hematocrit, red cell distribution width (RDW), platelet count, mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), prothrombin time (PT), activated partial thromboplastin time (aPTT), and arterial blood gas analysis.

Results: D-dimer, CRP, MPV, PLR, and NLR differed significantly among groups ($p \leq 0.002$), with the highest levels observed in critically ill patients. PT, aPTT, hematocrit, and platelet count showed no significant variation among groups. $PaCO_2$ demonstrated positive correlations with D-dimer, CRP, RDW, and MPV.

Conclusion: Advanced stages of COPD are associated with heightened coagulation activity and inflammation. The observed relationship between D-dimer and $PaCO_2$ highlights the clinical utility of these markers for risk assessment.

Keywords: COPD; D-Dimer; Hematological Profiles; Hospitilized Patients

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disorder characterized by persistent airflow limitation and chronic respiratory symptoms. These manifestations result from structural changes in the airways and, in some cases, the alveoli.[1,2] COPD represents a significant global health burden, contributing to substantial morbidity, mortality, and frequent hospital admissions. Recent global estimates indicate that COPD affects hundreds of millions of individuals, with prevalence continuing to rise, particularly in low- and middle-income countries. Major risk factors include tobacco smoking, exposure to household and ambient air pollution, occupational hazards, and population ageing.[3,4] The current understanding of COPD extends beyond pulmonary involvement, recognizing its systemic effects, including notable cardiovascular comorbidities.

Emerging evidence increasingly associates COPD with an elevated risk of thrombotic complications. Individuals with COPD exhibit a higher propensity for blood clot formation, which is thought to result from chronic airway inflammation that promotes systemic inflammation, endothelial dysfunction, and heightened platelet activation.[3,5] During acute exacerbations of COPD, these prothrombotic mechanisms may intensify due to hypoxemia, hypercapnia, oxidative stress, and reduced mobility. Consequently, COPD is linked to an increased risk of venous thromboembolism and major cardiovascular events, including pulmonary embolism, myocardial infarction, stroke, and other vascular complications.[4,5]

Laboratory markers can provide insight into alterations in coagulation and inflammation among patients with COPD. D-dimer, a fibrin degradation product, is commonly utilized to indicate active coagulation and fibrinolysis. During acute exacerbations of COPD, D-dimer levels frequently increase, which can complicate the diagnosis of pulmonary embolism in hospitalized patients experiencing acute respiratory deterioration.6 Recent studies have also identified elevated concentrations of prothrombotic markers, such as von Willebrand factor and plasminogen activator inhibitor-1, during acute COPD exacerbations.[7] However, conventional coagulation tests, including prothrombin time (PT) and activated partial thromboplastin time (aPTT), may remain within normal ranges and do not always reflect the underlying hemostatic disturbances.[5,8]

Additional hematological and inflammatory markers provide further insight into the systemic impact of COPD. C-reactive protein (CRP), a well-established indicator of systemic inflammation, frequently increases during COPD exacerbations.[7,9,10] Other routinely available and cost-effective parameters, such as red cell distribution width (RDW), mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR), have gained attention for their roles in monitoring inflammation, platelet activation, disease severity, and the risk of adverse clinical outcomes in COPD.[9,10]

The association between respiratory dysfunction and coagulation abnormalities is clinically significant. Hypercapnia and hypoxemia induce systemic stress, whereas severe exacerbations are characterized by heightened inflammation, oxidative stress, and increased cardiovascular risk. Evidence indicates that the incidence of cardiovascular events rises during chronic obstructive pulmonary disease (COPD) exacerbations and may remain elevated subsequently, likely as a result of persistent systemic inflammation and a hypercoagulable state.[3,4] Nevertheless, the variation of these abnormalities across the spectrum of disease severity, from stable COPD to critical illness, remains insufficiently understood, particularly in resource-limited settings.

Although the systemic and prothrombotic features of COPD are well recognized, there are limited local data on coagulation and inflammatory abnormalities at different disease stages. The link between respiratory dysfunction, especially carbon dioxide retention, and blood markers of coagulation and inflammation is not well understood. This study compared coagulability in stable COPD outpatients, hospitalized patients, ICU patients, and healthy controls using D-dimer, PT, aPTT, CRP, haematological indices, PLR, NLR, and arterial blood gas results. It also examined how $PaCO_2$ relates to key coagulation and inflammatory markers to better clarify the connection between respiratory impairment, inflammation, and thrombotic risk in COPD.

Objective

To evaluate blood coagulability and associated inflammatory and hematological markers among patients with stable COPD, hospitalized COPD, critically ill COPD, and healthy individuals.

Methodology

This prospective, comparative, cross-sectional study was conducted at Benazir Bhutto Hospital, Rawalpindi, and Muslim Youth University, Islamabad, from January 2024 to September 2025. The study was designed to evaluate the blood coagulability state in patients with chronic obstructive pulmonary disease (COPD) across different disease severity stages compared to healthy individuals.

The sample size was calculated based on a previous study.[7] Using G Power software for analysis of variance (ANOVA) with fixed effects, omnibus, one-way design, a significance level (α) of 0.05, and statistical power (1-β) of 0.80, the minimum required sample size was calculated as 21 participants per group. To account for a 15%

potential dropout rate and to ensure adequate power for planned subgroup analyses, the sample size was adjusted to 27 participants per group. Consequently, a total of 108 participants, with 27 individuals allocated to each of the four study groups, were enrolled in this study.

Four study groups were established for this analysis. Group 1 comprised individuals with stable chronic obstructive pulmonary disease (COPD) who received outpatient treatment. Group 2 included individuals with COPD admitted to the general ward. Group 3 consisted of individuals with COPD treated in the intensive care unit. Group 4 served as the healthy control group. All COPD patients were selected according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria. For acute exacerbations of COPD (AECOPD), the indications for hospital admission were also based on the GOLD criteria. The control group included only individuals who appeared healthy, had no known health problems, were non-smokers, and demonstrated normal spirometry results.

The inclusion criteria for the study required participants to be between 40 and 75 years of age with a confirmed diagnosis of chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (post-bronchodilator $FEV_1/FVC < 0.70$). For patients with acute exacerbation of COPD (AECOPD), enrollment was limited to those presenting within 7 days of an acute exacerbation, defined by increased dyspnea, sputum volume, or sputum purulence. Stable COPD patients were defined as those without acute exacerbations in the preceding 6 weeks. All participants were required to provide informed consent. Exclusion criteria included refusal to participate, primary hematological or coagulation disorders, any malignancy, advanced hepatic or renal disease, recent surgery within the past 4 weeks, history of blood transfusion in the past 3 months, or history of blood donation or therapeutic phlebotomy within the past 3 months. Additional exclusion criteria comprised use of anticoagulant, antiplatelet, or immunosuppressant therapy; COPD with comorbid respiratory diseases such as pneumonia, asthma, bronchiectasis, interstitial lung disease, or obstructive sleep apnea; and current use of long-term anticoagulant therapy.

A detailed medical history and a comprehensive clinical examination was conducted for all enrolled patients. Demographic information, including age, sex, smoking history, and comorbidities, was recorded. Disease severity was assessed using GOLD classification criteria.

Venous blood samples were collected from study participants and analyzed in the hospital laboratory using standardized procedures and available equipment. The biomarkers assessed included coagulation markers (serum D-dimer, prothrombin time [PT], activated partial thromboplastin time [aPTT]), inflammatory markers (C-reactive protein [CRP]), hematological parameters (hematocrit [Hct], red cell distribution width [RDW], platelet count [Plt], mean platelet volume [MPV]), and derived ratios (platelet-to-lymphocyte ratio [PLR], neutrophil-to-lymphocyte ratio [NLR]) and vWF, PAI-1 and fibrinogen. Arterial blood gas analysis was conducted to measure pH, partial pressure of arterial oxygen (PaO_2), and partial pressure of arterial carbon dioxide ($PaCO_2$). All samples were collected under aseptic conditions and transported to the central clinical laboratory for analysis. PT and aPTT were measured using standard coagulation assays, while D-dimer and CRP levels were determined using validated laboratory methods.

Data analysis was conducted using SPSS version 26. The Shapiro–Wilk test assessed the normality of continuous variables. Continuous variables with normal distribution were reported as mean ± standard deviation (SD) and compared across the four study groups using one-way analysis of variance (ANOVA). When the overall ANOVA indicated statistical significance, Bonferroni post-hoc tests were applied for pairwise comparisons, with adjustments for multiple comparisons among the four groups. Categorical variables were summarized as frequencies and percentages [n (%)] and compared using the χ^2 test. Associations between continuous variables were evaluated using Pearson's correlation coefficient. All statistical tests were two-sided and performed at a 95% confidence level, with p-values <0.05 considered statistically significant.

The Institutional Research Board of MY University, Islamabad, approved the study (IRB-BS-067/24). We obtained written informed consent from all participants before enrollment. Participants received information regarding the study's purpose, the procedures involved, and their right to withdraw at any stage without repercussions. Privacy and confidentiality were ensured by withholding any identifying information from publication.

Results

This study enrolled 108 participants, with 27 individuals in each of the four groups: Group 1 (stable COPD outpatients), Group 2 (COPD inpatients), Group 3 (COPD ICU patients), and Group 4 (healthy controls). The proportion of male participants was higher than that of female participants in the COPD groups. In the healthy control group, 14 (51.9%) participants were male and 13 (48.1%) were female, indicating a relatively balanced sex distribution. Sex distribution did not differ significantly across groups ($P > 0.05$). Similarly, no significant age differences were found among the COPD subgroups ($P > 0.05$). The mean ages ranged from 48.3 ± 6.7 years in the healthy control group to 54.8 ± 8.2 years in the stable COPD outpatients group (Table 1).

Serum D-dimer values differed significantly among the groups ($P < 0.001$). The highest concentrations were

Table 1. Comparison of age and sex distribution among the study groups

Variable		Group 1	Group 2	Group 3	Group 4	P-value
Age (years)		54.8 ± 8.2	52.1 ± 9.4	51.3 ± 7.8	48.3 ± 6.7	0.06
Range		47–65	43–58	44–61	39–56	
Gender	Male	18 (66.7%)	15 (55.6%)	16 (59.3%)	14 (51.9%)	0.82
	Female	9 (33.3%)	12 (44.4%)	11 (40.7%)	13 (48.1%)	

observed in COPD ICU patients (group 3), with a mean of 4.52 ± 3.21 µg/mL, followed by COPD inpatients (group 2) at 2.34 ± 1.48 µg/mL. Stable COPD outpatients (group 1) exhibited lower values at 0.85 ± 0.49 µg/mL, while the lowest concentrations were found in healthy controls (group 4) at 0.24 ± 0.09 µg/mL. Comparisons between subgroups revealed significant differences among most groups, except between group 1 and group 4, where the difference was not statistically significant (P = 0.21) (Table 2).

C-reactive protein (CRP) levels varied significantly among the groups (P < 0.001). COPD ICU patients demonstrated the highest CRP levels (62.14 ± 8.32 mg/L), followed by COPD inpatients (46.82 ± 7.91 mg/L), stable COPD outpatients (7.42 ± 1.35 mg/L), and healthy controls (1.92 ± 1.18 mg/L). Subgroup analysis revealed significant differences between most groups. However, no significant differences were found between G1 and G4 (P = 0.48) or between G2 and G3 (P = 0.07) (Table 3).

Hematocrit (Hct) values did not differ significantly among the groups (P = 0.19), with mean values ranging from 38.45 ± 7.92% in COPD ICU patients to 44.52 ± 3.58% in healthy controls. Red cell distribution width (RDW) was significantly higher in COPD patients compared to healthy controls (P = 0.001). No significant differences in RDW were found among the COPD subgroups (G1 vs. G2, P = 0.88; G1 vs. G3, P = 0.19; G2 vs. G3, P = 0.28). Platelet counts did not show statistically significant differences across all four groups (P = 0.24). Mean platelet counts ranged from 242.18 ± 58.32 × 10^3/µL in stable COPD outpatients to 285.62 ± 74.18 × 10^3/µL in COPD inpatients (Table 4).

Mean platelet volume (MPV) differed significantly among the four study groups on one-way ANOVA (P < 0.001). Mean MPV was 9.08 ± 1.52 fL in stable COPD outpatients (G1), 10.12 ± 1.62 fL in COPD inpatients (G2), 10.82 ± 2.45 fL in COPD ICU patients (G3), and 8.12 ± 0.98 fL in healthy controls (G4). Bonferroni-adjusted post-hoc pairwise comparisons were performed to determine which groups differed significantly. The pairwise comparisons are presented in Table 5.

The platelet-to-lymphocyte ratio (PLR) was significantly elevated in chronic obstructive pulmonary disease (COPD) subgroups compared to healthy controls (P = 0.002). The mean PLR values ranged from 157.42 ± 41.28 in healthy controls to 294.56 ± 158.34 in COPD intensive care unit (ICU) patients. However, no significant differences were observed among the COPD subgroups (G1 vs. G2, P = 0.68; G1 vs. G3, P = 0.12; G2 vs. G3, P = 0.24) (Table 6).

The neutrophil-to-lymphocyte ratio (NLR) was significantly elevated in COPD subgroups compared to healthy controls (P < 0.001). Mean NLR values ranged from 2.48 ± 1.32 in healthy controls to 11.42 ± 8.62 in COPD ICU patients. However, no significant differences were detected among the COPD subgroups (G1 vs. G2, P = 0.58; G1 vs. G3, P = 0.06; G2 vs. G3, P = 0.21) (Table 7).

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) showed no statistically significant variation across the groups (P = 0.52 and P = 0.38,

Table 2. Comparison of serum D-dimer levels among the study groups

Group	Mean ± SD (µg/mL)	Range	P-value
G1 (Stable COPD outpatients)	0.85 ± 0.49	0.12–2.10	P < 0.001
G2 (COPD inpatients)	2.34 ± 1.48	0.60–6.80	
G3 (COPD ICU patients)	4.52 ± 3.21	0.90–11.20	
G4 (Healthy controls)	0.24 ± 0.09	0.10–0.45	

Table 3. Comparison of C-reactive protein levels among the study groups

Group	Mean ± SD (mg/L)	Range	Significance Level
G1 (Stable COPD outpatients)	7.42 ± 1.35	0.90–24.50	P < 0.001
G2 (COPD inpatients)	46.82 ± 7.91	2.10–135.40	
G3 (COPD ICU patients)	62.14 ± 8.32	1.90–152.30	
G4 (Healthy controls)	1.92 ± 1.18	0.10–4.80	

respectively). Mean PT values ranged from 12.48 ± 1.18 seconds in stable COPD outpatients to 12.82 ± 0.82 seconds in healthy controls. Mean aPTT values ranged from 30.52 ± 5.48 seconds in healthy controls to 33.18 ± 4.12 seconds in COPD ICU patients (Table 8).

The highest levels of vWF (148.7%) were observed in patients in group 3, followed by those in group 2. PAI-1 concentrations were also elevated (48.9 ng/mL) in group 3. D-Dimer levels were higher (0.96) in group 3, and fibrinogen concentrations (512.4 mg/dL) were also increased in this group. Prothrombin time (PT) was elevated (13.6 seconds) in group 3, as was activated partial thromboplastin time (aPTT) (35.9 seconds). In contrast, platelet count was highest in group 4 (265.6 $\times 10^3/\mu L$). Comparisons were conducted using one-way ANOVA with a post-hoc Bonferroni test. Statistically significant differences were found among groups for all biomarkers ($p < 0.05$) (Figure 1).

Partial pressure of carbon dioxide in arterial blood ($PaCO_2$) demonstrated a positive correlation with several coagulation and inflammatory markers. Statistically significant positive correlations were observed between $PaCO_2$ and D-dimer ($r = 0.48$, $P < 0.001$), CRP ($r = 0.41$, $P < 0.001$), RDW ($r = 0.38$, $P < 0.001$), and MPV ($r = 0.34$, $P = 0.008$). These findings suggest potential links between respiratory dysfunction and systemic changes in COPD patients, consistent with studies from Pakistani settings demonstrating that coagulation dysfunction is significantly associated with hypercapnia in COPD patients . The correlations between $PaCO_2$ and PLR ($r = 0.18$, $P = 0.07$) and NLR ($r = 0.24$, $P = 0.12$) were not statistically significant (Table 9).

$PaCO_2$ showed a moderate positive correlation with D-dimer ($r = 0.48$, $P < 0.001$), indicating that higher $PaCO_2$ levels were associated with higher D-dimer concentrations. Similarly, $PaCO_2$ was positively correlated with CRP ($r = 0.41$, $P < 0.001$) (Figure 2).

Discussion

This study showed that COPD is associated with measurable increases in blood clotting and inflammation, which intensify as disease severity progresses. By comparing individuals with stable COPD, hospitalized patients, intensive care unit (ICU) patients, and healthy controls, this research offers a comprehensive perspective beyond studies limited to stable or acute cases. The principal findings include consistent elevations in D-dimer and C-reactive protein (CRP) levels across groups, as well as increased red cell distribution width (RDW),

Table 4. Hematological Parameters Among the Study Groups

Parameter		Group 1	Group 2	Group 3	Group 4	P-value
Hematocrit (%)	Mean ± SD (%)	40.82 ± 4.52	39.14 ± 5.38	38.45 ± 7.92	44.52 ± 3.58	0.19
	Range	33.80–52.00	30.50–52.00	20.80–52.50	40.00–51.00	
Red Cell distribution (%)	Mean ± SD (%)	16.12 ± 1.45	16.05 ± 1.72	16.72 ± 2.48	14.18 ± 0.82	0.001
	Range	12.80–21.00	12.90–20.10	11.80–22.40	11.20–15.30	
Platelet counts ($\times 10^3/\mu L$)	Mean ± SD ($\times 10^3/\mu L$)	242.18 ± 58.32	285.62 ± 74.18	264.85 ± 108.42	252.48 ± 72.85	0.24
	Range	138–378	152–468	155–745	142–448	

Table 5. Comparison of mean platelet volume among the study groups

Group	Mean ± SD (fL)	Range	P-value
G1 (Stable COPD outpatients)	9.08 ± 1.52	6.80–12.40	P < 0.001
G2 (COPD inpatients)	10.12 ± 1.62	7.50–15.20	
G3 (COPD ICU patients)	10.82 ± 2.45	7.00–16.80	
G4 (Healthy controls)	8.12 ± 0.98	5.80–10.40	

mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) in COPD patients relative to healthy individuals. Platelet count, hematocrit, prothrombin time (PT), and activated partial thromboplastin time (aPTT) did not differ significantly between groups. Elevated arterial carbon dioxide ($PaCO_2$) was also correlated with D-dimer, CRP, RDW, and MPV. Collectively, these findings indicate a strong interrelationship among respiratory impairment, inflammation, and coagulation in COPD.

The primary hemostatic finding in this study was a substantial elevation of D-dimer levels among patients with chronic obstructive pulmonary disease (COPD), particularly those requiring intensive care unit (ICU) admission. Mean D-dimer concentrations increased from 0.85 ± 0.49 µg/mL in stable COPD to 2.34 ± 1.48 µg/mL in hospitalized patients and 4.52 ± 3.21 µg/mL in ICU patients, compared with 0.24 ± 0.09 µg/mL in healthy controls. Although the difference between stable COPD and controls was not statistically significant, the overall integral reached statistical significance. This suggests that activity and fibrin deposition are more pronounced with clinical deterioration, rather than being uniformly present in all patients with stable COPD.

These findings align with results from Husebø et al., whose study showed that D-dimer and other coagulation markers increased substantially during acute exacerbations compared with the stable state. Notably, higher baseline D-dimer was also associated with subsequent mortality, underscoring the clinical relevance of D-dimer beyond its role as an isolated laboratory abnormality.[8] Similarly, Chen et al. reported significantly higher D-dimer concentrations in acute exacerbations of COPD (AECOPD) compared with stable COPD and healthy individuals. They found that D-dimer increased with worsening airflow limitation.[11] The particularly high D-dimer concentration observed in the intensive care unit (ICU) group in the present study may therefore reflect the cumulative effects of severe systemic inflammation, tissue injury, hypoxemia, hypercapnia, immobility, and endothelial activation.

The magnitude of D-dimer elevation observed in the present study exceeded that reported in some previous cohorts. This discrepancy may be attributable to the inclusion of critically ill patients, whereas several prior investigations primarily compared stable COPD with AECOPD without specifically distinguishing ICU patients. Variations in assay methodology, patient age, comorbidities, infection status, thromboprophylaxis, and exclusion of clinically overt thromboembolism may also influence D-dimer concentrations. It is important to note that D-dimer elevation should not be interpreted as definitive evidence of venous thromboembolism in every COPD patient, as D-dimer reflects activation of coagulation and fibrinolysis and can increase in the context of infection and systemic inflammation.

Li et al. supported the clinical significance of this observation, demonstrating that the D-dimer-to-albumin

Table 6. Comparison of platelet-to-lymphocyte ratio among the study groups

Group	Mean ± SD	Range	P-value
G1 (Stable COPD outpatients)	241.52 ± 118.46	92 – 645	P = 0.002
G2 (COPD inpatients)	254.18 ± 155.72	72 – 725	
G3 (COPD ICU patients)	294.56 ± 158.34	68 – 632	
G4 (Healthy controls)	157.42 ± 41.28	78 – 215	

Table 7. Comparison of neutrophil-to-lymphocyte ratio among the study groups

Group	Mean ± SD	Range	P-value
G1 (Stable COPD outpatients)	8.42 ± 6.14	1.20 – 24.80	P < 0.001
G2 (COPD inpatients)	9.28 ± 5.72	0.15 – 21.40	
G3 (COPD ICU patients)	11.42 ± 8.62	1.80 – 32.40	
G4 (Healthy controls)	2.48 ± 1.32	1.00 – 4.80	

ratio was associated with hospital readmission among patients with AECOPD.[12] More recently, Zhao et al. reported that combining D-dimer with a systemic immune-inflammatory index could improve the prediction of pulmonary thromboembolism in patients with AECOPD.[13] Collectively, these findings indicate that D-dimer may have greater clinical utility when interpreted alongside inflammatory and clinical parameters rather than as an isolated marker.

CRP demonstrated a pronounced severity-related pattern in this study. Mean CRP values increased from 1.92 ± 1.18 mg/L in healthy controls to 7.42 ± 1.35 mg/L in stable COPD, 46.82 ± 7.91 mg/L in hospitalized COPD patients, and 62.14 ± 8.32 mg/L in ICU patients. Although the difference between the ward and ICU groups was not statistically significant, the overall increase across the four groups was highly significant. These results reinforce the established concept that systemic inflammation is present in COPD and becomes markedly amplified during acute clinical deterioration. These findings are consistent with those of Hassan and Jabbar, who studied COPD patients at a tertiary-care hospital in Islamabad and found that elevated CRP was associated with greater COPD severity.[14] The concordance between the present study and this Pakistani cohort suggests that CRP behaves similarly across diverse clinical populations, despite differences in study design. Additionally, Hsu et al. demonstrated that CRP was associated with pneumonia.[15]

Liu et al. further supported the link between inflammation and coagulation, finding that patients with AECOPD showed abnormalities in several coagulation parameters and that PT, aPTT, and fibrinogen were related to neutrophil and CRP concentrations. In the present study, we also observed a relationship between PT and $PaCO_2$, suggesting that infection, inflammation, and hypercapnia may jointly influence hemostatic abnormalities.[16] Therefore, the simultaneous elevation of CRP and D-dimer in the hospitalized and ICU groups may reflect interconnected inflammatory and coagulation pathways rather than two independent abnormalities.

The absence of a significant difference in CRP levels between the ward and ICU groups should not be interpreted as evidence that inflammation does not increase with severity. The relatively small number of participants in each subgroup (27 per group), substantial biological variability in CRP, differences in underlying infection and treatment, and the cross-sectional study design may have limited the ability to detect differences between adjacent severity categories.

RDW was significantly elevated in all COPD groups compared to healthy controls; however, no significant differences were detected among stable, hospitalized, and ICU COPD patients. These findings indicate that RDW may serve more effectively as a marker of the

Table 8. Comparison of prothrombin time and activated partial thromboplastin time among the study groups

Group	PT (seconds) Mean ± SD	Range	aPTT (seconds) Mean ± SD	Range
G1 (Stable COPD outpatients)	12.48 ± 1.18	10.20–14.40	31.02 ± 5.52	21.40–36.20
G2 (COPD inpatients)	12.72 ± 1.12	10.40–14.20	31.68 ± 4.92	23.80–38.40
G3 (COPD ICU patients)	12.78 ± 0.92	10.20–14.00	33.18 ± 4.12	26.20–37.40
G4 (Healthy controls)	12.82 ± 0.82	11.80–14.00	30.52 ± 5.48	29.20–36.40
Significance	P = 0.52		P = 0.38	

Table 9. Correlation of arterial carbon dioxide pressure ($PaCO_2$) with coagulation and inflammatory markers

Variable	Correlation coefficient (r)	P value
D-dimer	0.48	< 0.001
CRP	0.41	< 0.001
RDW	0.38	< 0.001
MPV	0.34	0.008
PLR	0.18	0.07
NLR	0.24	0.12

systemic effects of COPD rather than as a direct indicator of varying degrees of acute clinical severity.

Recent studies corroborate this interpretation. Marvisi et al. reported elevated RDW in COPD patients and identified associations between RDW, CRP, COPD Assessment Test score, exacerbation frequency, and GOLD severity.[17] Similarly, He et al. demonstrated that increased RDW was independently associated with poor prognosis in patients with AECOPD.[18] Zhu et al. further showed that dynamic changes in RDW correlated with an increased 30-day readmission risk following AECOPD.[19] Collectively, these findings suggest that RDW reflects a combination of inflammation, oxidative stress, nutritional abnormalities, altered erythropoiesis, and other systemic effects of chronic disease.

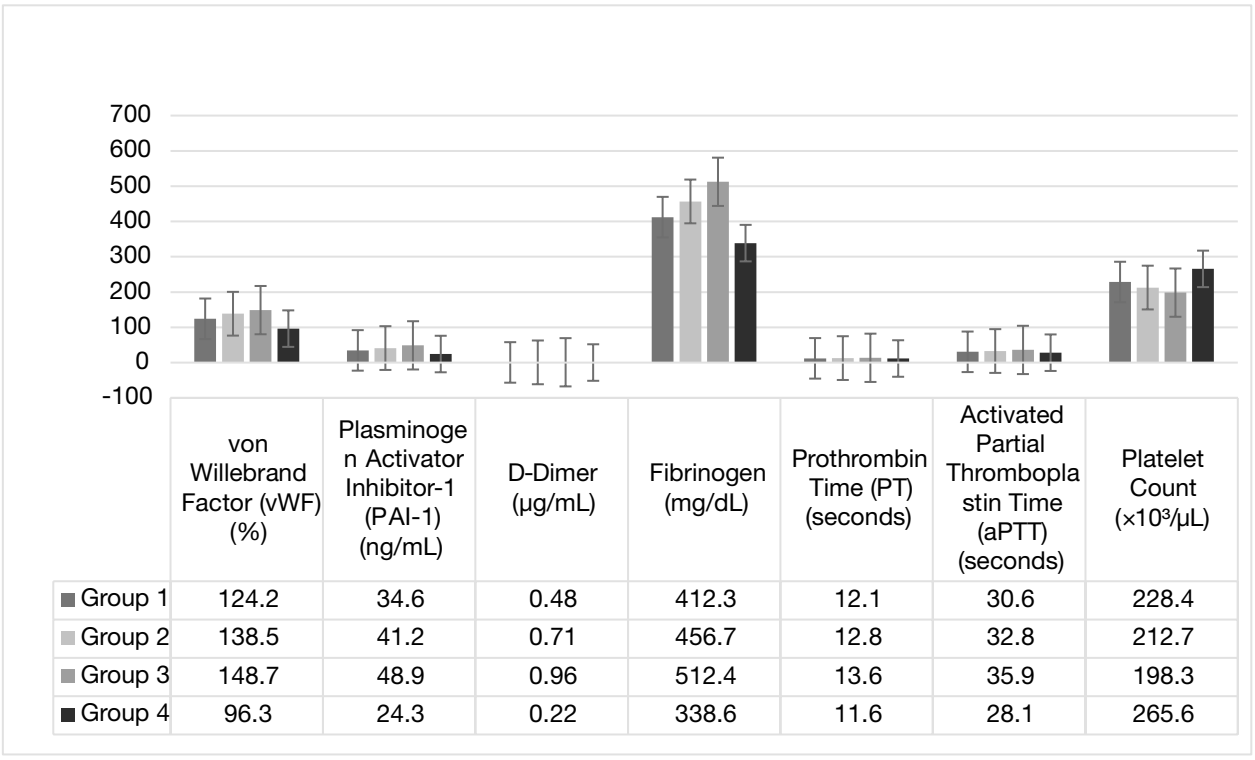
The present finding of elevated RDW in COPD, without significant differences among COPD severity groups, contrasts with studies that identified RDW as a marker of exacerbation severity. For instance, Alparslan Bekir et al. examined a large AECOPD cohort and reported significant differences in RDW based on treatment location.[20] This discrepancy may be attributable to differences in study populations and design. Furthermore, this study compared stable disease with hospitalized and ICU cases, while their analysis focused exclusively on exacerbation severity. Therefore, these findings support RDW as a marker of COPD-associated systemic disturbance but indicate that its discriminatory capacity between adjacent severity categories may be limited in small cross-sectional samples.

Platelet count did not differ significantly among the four groups in the present study, although hospitalized COPD patients exhibited a numerically higher mean platelet count. This observation aligns with existing evidence indicating that platelet number alone may not sufficiently represent platelet activation in COPD. A systematic review and meta-analysis by Zinellu et al. demonstrated that platelet indices are altered in COPD, but the direction and magnitude of platelet-count changes vary between stable and exacerbated disease.[21] The absence of a significant platelet-count difference in this study may therefore indicate that platelet activation can occur without substantial changes in circulating platelet numbers.

Mean platelet volume (MPV) increases progressively from healthy controls to stable, hospitalized, and intensive care unit (ICU) patients with chronic obstructive pulmonary disease (COPD), indicating increased platelet activation with advancing disease severity. MPV may provide clinically relevant information that is not captured by platelet count alone. Studies by Chen et al. and Gómez-Rosero et al. demonstrate that MPV serves as a valuable marker of inflammation and coagulation in COPD, alongside C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR). Recent findings from the MESA COPD cohort further associate platelet activation with both clinical and imaging characteristics of COPD, underscoring the significant role of platelets in disease progression.[11,22,23]

However, not all studies have reported increased MPV during exacerbations. Variability in MPV findings may result from factors such as platelet consumption, release of larger immature platelets, effects of inflammatory cytokines, smoking status, medication exposure, and timing of blood collection. Consequently, MPV should be considered a surrogate marker rather than a direct measurement of platelet activation.

Both PLR and NLR were significantly higher in patients with COPD compared to healthy controls. PLR increased from 157.42 ± 41.28 in controls to 241.52 ± 118.46 in stable COPD, 254.18 ± 155.72 in hospitalized patients, and 294.56 ± 158.34 in ICU patients. Similarly, NLR increased from 2.48 ± 1.32 in controls to 8.42 ± 6.14, 9.28 ± 5.72, and 11.42 ± 8.62 in stable, hospitalized, and ICU COPD patients, respectively. However, neither marker demonstrated statistically significant differences among the three COPD subgroups. These results indicate that PLR and NLR are sensitive indicators of systemic



	von Willebrand Factor (vWF) (%)	Plasminogen Activator Inhibitor-1 (PAI-1) (ng/mL)	D-Dimer (µg/mL)	Fibrinogen (mg/dL)	Prothrombin Time (PT) (seconds)	Activated Partial Thromboplastin Time (aPTT) (seconds)	Platelet Count (×10³/µL)
Group 1	124.2	34.6	0.48	412.3	12.1	30.6	228.4
Group 2	138.5	41.2	0.71	456.7	12.8	32.8	212.7
Group 3	148.7	48.9	0.96	512.4	13.6	35.9	198.3
Group 4	96.3	24.3	0.22	338.6	11.6	28.1	265.6

Figure 1. Comparison of coagulation biomarkers among the four study groups

inflammatory burden in COPD, but may have limited utility in distinguishing between closely related clinical severity categories within a relatively small sample.

These findings align with a 2022 systematic review and meta-analysis, which showed that higher NLR is associated with adverse outcomes in AECOPD, including mortality, mechanical ventilation, and ICU admission.[24] Similarly, Fayiad and Amer reported significantly increased NLR and PLR during COPD exacerbations compared to the stable state, with both indices correlating with CRP levels and the need for hospitalization or mechanical ventilation.[25]

The observed numerical increase in PLR and NLR, despite non-significant differences among COPD subgroups, may have clinical relevance. The inflammatory burden may increase progressively, but the study may have lacked sufficient statistical power to detect modest differences between stable and hospitalized disease or between hospitalized and ICU disease. Additionally, NLR and PLR are influenced by various factors, such as infection, corticosteroid therapy, smoking, nutritional status, and other comorbidities. These factors may reduce the specificity of these markers for assessing COPD severity.

A key finding of this study was the absence of significant differences in PT and aPTT among the four groups. Mean PT values ranged from 12.48 to 12.82 seconds, while aPTT ranged from 30.52 to 33.18 seconds. This result highlights the distinction between conventional coagulation testing and more sensitive markers of coagulation activation. Routine PT and aPTT assess selected components of the coagulation cascade, but may remain within normal limits even in the presence of coagulation activation, endothelial dysfunction, or increased fibrin turnover.

These findings align with Jin et al., who reported no significant difference in aPTT between AECOPD and control groups, despite significant abnormalities in other hemostatic biomarkers, including vWF and PAI-1.[7] The same study observed increased PT and fibrinogen in AECOPD, indicating that conventional tests may yield variable responses depending on patient population and disease state. Similarly, Rastoder et al. examined conventional coagulation parameters alongside thrombelastography and emphasized the importance of assessing coagulation beyond routine laboratory tests in COPD exacerbation.[26]

In contrast, Zheng et al. reported significant differences in PT and other coagulation parameters in AECOPD. They found that coagulation abnormalities were associated with infection and hypercapnia, although D-dimer and aPTT did not differ significantly.[27] The concordance between their findings for D-dimer/aPTT and the present results for routine coagulation parameters suggests that

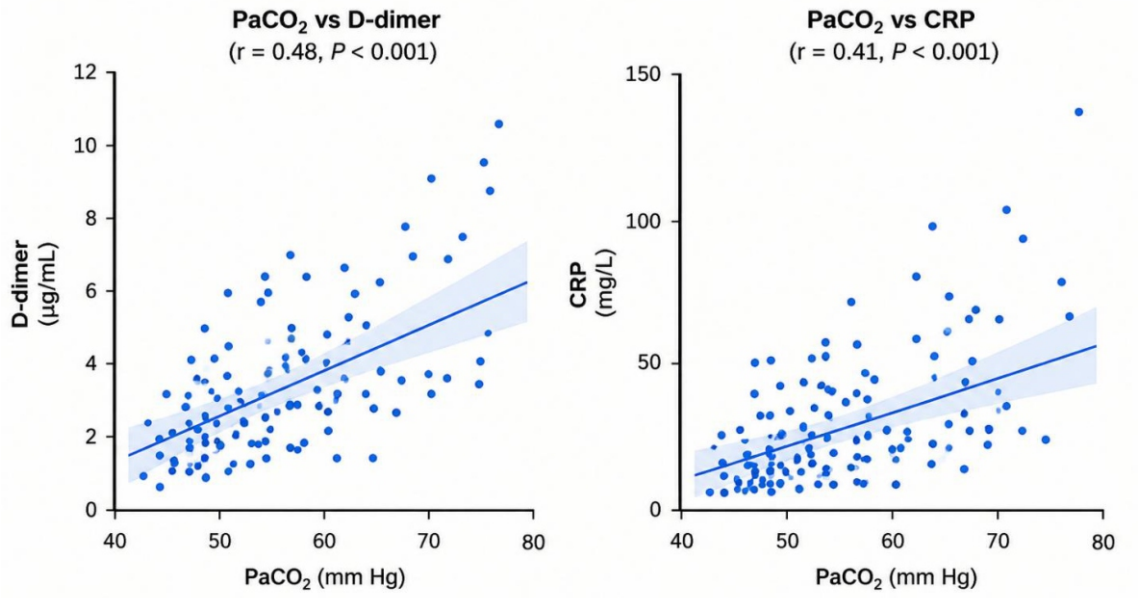


Figure 2. Scatter plots showing significant correlations between $PaCO_2$ and selected markers

COPD-related hypercoagulability may not always be detected by conventional clotting times. Variations in sampling timing, treatment status, disease severity, and inclusion criteria may account for differences in PT findings across studies.

Hematocrit did not differ significantly among the study groups. While COPD has traditionally been linked to secondary erythrocytosis due to chronic hypoxemia, recent COPD cohorts may not consistently exhibit pronounced polycythemia. The lack of significant difference observed in this study may be attributable to relatively preserved oxygenation in stable patients, the use of oxygen therapy in some cases, and the complex, multifactorial regulation of hematocrit.

Similarly, platelet counts were statistically comparable across all groups. These results support the observation that the prothrombotic phenotype of COPD does not necessarily involve an increased number of circulating platelets or substantial changes in hematocrit. Instead, functional platelet activation, endothelial activation, and enhanced coagulation or fibrinolysis may play more significant roles in thrombotic risk. This interpretation is supported by the platelet meta-analysis conducted by Zinellu et al. and recent evidence of platelet activation in COPD [12,14].

A clinically significant finding of this study was the positive correlation between $PaCO_2$ and D-dimer (r = 0.48), CRP (r = 0.41), RDW (r = 0.38), and MPV (r = 0.34). These associations indicate that increased carbon dioxide retention is linked to heightened systemic inflammation and activation of coagulation and platelet-related pathways. The strongest correlation was observed with D-dimer, suggesting a potentially important relationship between respiratory failure and fibrin turnover.

This observation aligns with the findings of Liu et al., who specifically investigated coagulation dysfunction in acute exacerbations of COPD (AECOPD) and reported a positive correlation between PT and $PaCO_2$. Their results led to the conclusion that hypercapnia and infection may contribute to coagulation dysfunction and increased thrombosis risk [7]. Similarly, Zheng et al. reported comparable associations between coagulation abnormalities, infection, and hypercapnia in AECOPD [20]. The consistency of these findings enhances the biological plausibility of the present study's results.

Several mechanisms may underlie this relationship. Hypercapnia typically indicates more severe ventilatory impairment and may coexist with hypoxemia, systemic inflammation, endothelial dysfunction, and oxidative stress. Severe respiratory failure is often accompanied by reduced physical activity and venous stasis, especially in hospitalized or critically ill patients. The association between $PaCO_2$ and MPV may further suggest a link between respiratory dysfunction and platelet activation. However, given the cross-sectional design of this study, these correlations should not be interpreted as evidence that hypercapnia directly causes coagulation activation. Instead, $PaCO_2$ may serve as a marker of overall disease severity associated with multiple systemic pathophysiological processes.

Strengths

A major strength of this study is the four-group design,

which allowed comparison across stable COPD, hospitalized COPD, ICU-level disease, and healthy individuals rather than a simple case-control comparison. The simultaneous evaluation of coagulation, inflammatory, hematological, and arterial blood gas parameters also allowed assessment of relationships among respiratory parameters.

Limitations

Several limitations should be acknowledged. First, the sample size was relatively small, with only 27 participants per group, which may have reduced statistical power for subgroup analyses. Second, the cross-sectional design precludes determination of temporal or causal relationships between respiratory deterioration and coagulation abnormalities. Third, more specific hemostatic biomarkers, such as fibrinogen, thrombin-antithrombin complexes, hemostatic vWF, PAI-1, and thrombin-generation parameters, were not assessed. Fourth, D-dimer elevation is nonspecific and may be affected by age, inflammation, and other comorbidities. Differences in age and sex distribution between the study groups may have contributed to some of the observed differences in inflammatory and coagulation-related biomarkers. Because the present analysis did not include multivariable adjustment for potential confounders such as age and sex, residual confounding cannot be excluded. Finally, the single-center setting may limit the generalizability of these findings to other populations.

Conclusion

In summary, the findings indicate that chronic obstructive pulmonary disease (COPD) is associated with systemic inflammatory and hemostatic alterations, which are especially pronounced in hospitalized and critically ill patients. D-dimer and C-reactive protein (CRP) exhibited the most substantial increases across the clinical spectrum, whereas red cell distribution width (RDW), mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) were significantly elevated in individuals with COPD compared to healthy controls. Conversely, platelet count, hematocrit, prothrombin time (PT), and activated partial thromboplastin time (aPTT) did not differ significantly, indicating that conventional coagulation tests may not adequately reflect the broader prothrombotic phenotype observed in COPD. The significant positive correlations between arterial partial pressure of carbon dioxide ($PaCO_2$) and D-dimer, CRP, RDW, and MPV further underscore the association between respiratory dysfunction, systemic inflammation, and coagulation activation. Larger prospective multicenter studies utilizing specific endothelial, platelet, and coagulation biomarkers are needed to determine whether these accessible parameters can enhance risk stratification for thrombotic and adverse clinical outcomes in COPD.

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