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Hematological and Clinical Profiling of Patients with Chronic Obstructive Pulmonary Disease

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a progressive airways disease characterized by persistent airflow limitation. Apart from airflow limitation, COPD is associated with systemic inflammation, hematological alterations, recurrent exacerbations, and the presence of multiple comorbidities, each contributing to the severity of the disease. Understanding the relation between clinical presentation, spirometric severity, and hematological indices is important for the advancement of disease evaluation.

Objective: To investigate the association of hematological and inflammatory indices with disease severity, dyspnea, and frequency of acute exacerbations.

Methodology: This was a cross-sectional observational study in 180 clinically stable COPD patients, diagnosed using the Global Initiative for COPD (GOLD) guidelines. Hematological parameters that were analyzed included hemoglobin, TLC, platelets, RDW, ESR, and CRP. Comparisons across GOLD stages were done along with analysis of factors related to disease severity.

Results: Most of the patients, 73.3%, were males aged 50 years or older, and cigarette smoking was the major identified risk factor. The patient population is largely suffering from moderate to severe disease, with a high prevalence of stages 2 (47.8%) and 3 (28.9%) according to the GOLD. The hemoglobin decreased significantly with increasing stages of GOLD ($p = 0.001$), while TLC, platelets, ESR, and CRP increased significantly ($p = 0.01$).

Conclusion: It is evident that there are serious hematological and inflammatory alterations in COPD, which tend to progress with the severity of the disease. Anemia, leukocytosis, thrombocytosis, and inflammation are highly linked with the severity of dyspnea, the number of exacerbations, and the severity of COPD stages based on the GOLD.

Keywords: Severe Chronic Obstructive Pulmonary Disease; Hematological Indexes; Systemic Inflammation; GOLD Classification; Dyspnea

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the major global public health problem that presents the persistent airflow limitation, which is usually progressive, and is associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles and gases. The disease is largely preventable and treatable, yet it remains one of the leading causes of morbidity and mortality around the world. According to the World Health Organization, COPD now ranks as the third leading cause of death globally and imposes a huge economic and healthcare burden, especially in low- and middle-income countries.[1] The rising prevalence of COPD is related to increasing tobacco consumption, biomass fuel smoke exposure, environmental pollution, and occupational hazards.

COPD is a heterogeneous disease that covers the spectrum of pathologies, including chronic bronchitis and emphysema, contributing to airflow limitation through related but distinct mechanisms. Chronic bronchitis is the presence of chronic cough with sputum production due to mucus hypersecretion and thickening of the airway wall.[2] On the other hand, in emphysema, the destruction of the alveolar walls occurs along with a loss of elastic recoil, leading to the trapping of air and subsequent hyperinflation. Chronic inflammatory cell infiltration, oxidative stress, and an imbalance between proteases and antiproteases are common in these pulmonary phenotypes, which, collectively, cause progressive impairment of lung function. Even though pulmonary aspects of COPD have been one of the main topics of discussion, the systemic nature of the disease has gained much attention over the last few decades. COPD, once thought of as a disease affecting the lungs only, is now regarded as a systemic inflammatory disorder. A growing body of evidence shows that inflammation in COPD extends beyond the respiratory system and affects multiple organ systems chronically. This systemic inflammation is associated with an increased risk of cardiovascular diseases, skeletal muscle dysfunction, osteoporosis, anemia, metabolic syndrome, and depression, which all have a great impact on patients' quality of life and survival. Several hematologic abnormalities, including anemia, polycythemia, leukocytosis, thrombocytosis, and alterations in inflammatory markers, are commonly reported among patients with COPD, particularly during acute exacerbation. The hematologic changes in COPD are thought to reflect the persistent inflammatory state, hypoxemia, and oxidative stress that characterize the disease.[3]

Hematological parameters are increasingly viewed as practical, easily available, and inexpensive biomarkers in the assessment of disease severity, prognosis, and risk stratification in COPD. Routine measures, including hemoglobin concentration, total leukocyte count, platelet count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and red cell distribution width (RDW), have been shown to correlate with the severity of the disease and the frequency of acute exacerbations. Anemia of chronic disease is related, for example, to reduced exercise capacity, increased dyspnea, poorer functional status, and increased mortality. On the other hand, secondary polycythemia may develop as a compensatory mechanism due to chronic hypoxemia and is associated with increased blood viscosity and the risk of thromboembolism. These hematological changes reflect an important part of the systemic burden in COPD and may serve as important adjuncts to clinical evaluation and spirometry.[4,5]

Although spirometry remains the gold standard for the diagnosis and staging of COPD, lung function parameters alone do not capture the systemic and clinical complexity of the disease. Composite indices, such as the BODE index (Body mass index, Airflow obstruction, Dyspnea, and Exercise capacity), have been developed to provide a more holistic assessment of disease severity and prognosis. Likewise, the COPD Assessment Test and the modified Medical Research Council dyspnea scale are commonly used tools in current practice to assess symptom severity and impact on daily life. Integrating hematological parameters with clinical and functional assessments may therefore provide a more comprehensive understanding of disease phenotype, severity, and outcomes.[6]

Nutritional status, chronic infections, and healthcare-seeking behavior may also influence hematological and clinical patterns in different ways among COPD patients. Therefore, region-specific data are needed with a view to furthering the understanding of disease characteristics to optimize management strategies and improve patient outcomes. For this reason, the present study was aim to conduct to comprehensively characterize the hematological and clinical profiles of patients with COPD. This shall be realized by systematically analyzing routine hematological parameters in conjunction with detailed clinical characteristics to elucidate their relationship with disease severity, frequency of exacerbations, and functional status.

Objective

To investigate the association of hematological and inflammatory indices with disease severity, dyspnea, and frequency of acute exacerbations.

Methodology

This was a hospital-based, cross-sectional, observational study conducted in the Department of Pulmonology, Agha Khan University Hospital, Karachi, Pakistan from January 24 to December 2024. In the present study, 180 patients with COPD diagnosis were considered. Sample

size was determined based on the expected prevalence of hematological abnormalities in COPD patients with a confidence level of 95% and margin of error of 5%. Patients were recruited through consecutive (non-probability) samplings from both outpatient and inpatient departments during the study period.

Patients with age ≥ 40 years, clinically stable COPD patients as per GOLD guidelines of diagnosis, and Patients who can provide written informed consent were included in this study. Patients were excluded if they presented with an acute exacerbation of COPD at the time of enrolment into the study; if they had other chronic respiratory diseases such as bronchial asthma, bronchiectasis, or interstitial lung disease; if they have active pulmonary TB or a history of TB in the last 6 months; and if they have chronic liver disease, chronic kidney disease, or any autoimmune disorder.

Informed consent was followed by the administration of a pre-designed, structured questionnaire for acquiring detailed demographic and clinical data. Details regarding age, sex, smoking in pack-years, occupational exposure, biomass fuel exposure, duration of symptoms, number of exacerbations in the past year, co-morbid conditions (hypertension, diabetes, ischemic heart disease), and medications consumed were also noted. All patients underwent a thorough general physical examination where height, weight, body mass index, respiratory rate, pulse rate, and blood pressure were measured, with oxygen saturation measured on pulse oximetry. Pulmonary function was measured on a calibrated spirometer by qualified technicians using ATS/ERS guidelines. FEV_1, FVC, and the FEV_1/FVC ratio were measured postbronchodilator administration. The severity of disease was classified according to GOLD criteria as GOLD 1: $FEV_1 \geq 80\%$ predicted, GOLD 2: FEV_1 50–79% predicted, GOLD 3: FEV_1 30–49% predicted, and GOLD 4: $FEV_1 < 30\%$ predicted. A venous blood sample of 5 mL was drawn from all patients aseptically. Samples were analyzed in the hospital's central laboratory on an automated hematology analyzer. The following hematological parameters were noted: Hemoglobin concentration (g/dL), Red blood cell count, Total leukocyte count, Differential leukocyte count (neutrophils, lymphocytes, eosinophils, monocytes), and Platelet count. ESR and CRP were also measured using conventional laboratory techniques.

All collected data was entered into SPSS version 25.0 for analysis purposes. Continuous variables have been expressed as mean ± SD or median with interquartile range, as appropriate. Categorical variables are expressed as frequencies and percentages. Comparisons of hematological parameters across the GOLD stages were done by one-way ANOVA for normally distributed data and Kruskal–Wallis test for non-parametric data. Pearson or Spearman correlation coefficients were determined for assessing the relation between hematological parameters and clinical variables. A $p < 0.05$ has been considered statistically significant.

Results

A total of 180 participants were enrolled in this study. Participants aged 60–69 years formed the largest age group, accounting for 35.6% (n = 64) of the sample. Among the study cases, 132 (73.3%) were males. Current smokers constituted the largest proportion, with 78 (43.3%) participants were actively smoking at the time of data collection. Ex-smokers accounted for 35.6%. Among study cases, 69 (38.3%) participants had a history of biomass exposure, while 111 (61.7%) reported no such exposure (Table 1).

In relation to the prevalence of disease, it was observed that 116 (64.4%) patients experienced two or more exacerbations in the previous year. Data from the hospitalization history showed that 92 (51.1%) participants had at least one admission in the previous year. Hypertension was found in 72 (40%) participants, followed by Diabetes Mellitus (32.2%), and Ischemic Heart Disease (18.9%). Assessment of dyspnea by mMRC scale identified that overall patients had moderate symptoms of dyspnea, with 45% (n=81) belonging to Grade 2. Moreover, 31.7% (n=57) patients had severe dyspnea, representing Grades 3-4, whereas 23.3% (n=42) patients had mild dyspnea, belonging to grades 0-1. Regarding disease duration, nearly half of the participants (46.1%) had been living with COPD for 5–10 years, making this the most common duration group. (Table 2).

Among study participants, 86 (47.8%) experienced Moderate COPD stage. The severe form of COPD (GOLD3) was the second most common stage in the population, contributing to 28.9% of patients with a considerable level of functional impairment. There was relative equality in the proportion of patients with either GOLD stage 1 (Mild) or GOLD stage 4 (Very Severe) COPD; both contributed to around 11.7% (n=21) or 11.6% (n=21) of patients, respectively (Table 3).

The average hemoglobin level was 12.1 ± 2.1 g/dL. The average RBC was $4.3 \pm 0.7 \times 10^6$/µL. The level of leukocytes was $9.8 \pm 2.9 \times 10^3$/µL, which was in the upper-normal limit and may represent the presence of systemic inflammatory processes. The relative differential leukocyte counts revealed that the neutrophils were moderately increased at 69.2 ± 9.4%, nearing the upper margin of the value in the normal limit. However, the relative number of lymphocytes was slightly low at 21.8 ± 7.1%, in the lower margin of the value in the normal limit. The average relative number of platelets was in the normal limit at $284 \pm 78 \times 10^3$/µL. The Red Cell Distribution Width (RDW) was slightly raised among the study subject at 14.8 ± 2.3%. The mean value of ESR was 32.4 ± 15.1 mm/hr. Also, the value of the CRP level was high with a mean

value of 6.9 ± 3.4 mg/L (Table 4).

Anemia was found to be evident in 78 (43.3%) cases. Leukocytosis was found in 69 (38.3%) individuals. Thrombocytosis was found in 34 (18.9%) participants. Elevated values were obtained in 68.9% (n = 124) individuals. Similarly, CRP values were high in 56.1% (n = 101) patients (Table 5).

Hemoglobin levels presented a significant downward trend ($p < 0.001$), with the highest mean values in GOLD 1 (13.6 ± 1.4 g/dL) and lowest in GOLD 4 (10.9 ± 2.2 g/dL). The Total Leukocyte Count (TLC) also escalated with increasing levels of disease severity ($p < 0.001$), from 7.9 ± 2.1 × 10^3/μL in GOLD 1 to 11.8 ± 3.1 × 10^3/μL in GOLD 4. Platelet count followed an increasing pattern ($p = 0.002$), from 241 ± 66 × 10^3/μL in GOLD 1 to 326 ± 88 × 10^3/μL in GOLD 4. Inflammatory indices escalated significantly with increasing levels of disease staging. The ESR values increased from 18.2 ± 8.5 mm/hr in GOLD 1 to 45.3 ± 16.2 mm/hr in GOLD 4 ($p < 0.001$), while CRP levels escalated from 3.1 ± 1.8 mg/L in GOLD 1 to 10.4 ± 4.0 mg/L in GOLD 4 ($p < 0.001$) (Table 6).

Results showed that Hemoglobin correlated negatively with dyspnea grade (r = -0.41) and exacerbations (r = -0.38). Also, total leucocyte count (TLC) correlated positively with dyspnea grade (r = 0.45) and exacerbations (r = 0.49). Moreover, platelet counts correlated moderately with dyspnea grade (r = 0.36) and exacerbations (r = 0.40). However, correlations with the markers of inflammation were more prominent. Indeed, both ESR and CRP correlate) with dyspnea grade (r = 0.52) and exacerbations (r = 0.57), and CRP showed the highest correlation with both parameters, with r = 0.55 and r = 0.61, respectively for dyspnea grade and exacerbation frequency. Moreover, the combined p value remains highly significant (<0.001) (Table 7).

Table 1. Demographic Characteristics of Study Participants

Variable	Category	Frequency (n)	Percentage (%)
Age (years)	40–49	28	15.6
	50–59	51	28.3
	60–69	64	35.6
	≥ 70	37	20.5
Gender	Male	132	73.3
	Female	48	26.7
Smoking Status	Current smoker	78	43.3
	Ex-smoker	64	35.6
	Never smoker	38	21.1
Biomass Fuel Exposure	Yes	69	38.3
	No	111	61.7

Discussion

COPD is a multifactorial and progressive respiratory disease, including not only persistent airflow limitation but also significant systemic manifestations. Besides pulmonary involvement, COPD is now increasingly appreciated as a multisystem disease characterized by systemic inflammation, hematological changes, and a high burden of comorbid diseases. Interaction among clinical severity, inflammatory status, and hematological impairment plays a key role in shaping disease progression, symptom burden, exacerbation frequency, and overall prognosis.[3]

The demographic profile of the study population provides important information on the epidemiological patterns and risk factors of COPD. It is generally regarded that COPD is a disease of older adults, males, and those who are exposed to tobacco smoke or environmental pollutants over a long period of time. In the present study, most participants belonged to the 60–69 age category (35.6%), followed by the 50–59 category (28.3%). Hence, more than half the patients had attained an age of above

Table 2. Clinical Characteristics of COPD Patients

Clinical Variable	Category	Frequency (n)	Percentage (%)
Duration of Disease	< 5 years	46	25.6
	5–10 years	83	46.1
	> 10 years	51	28.3
Dyspnea (mMRC)	Grade 0–1	42	23.3
	Grade 2	81	45.0
	Grade 3–4	57	31.7
Exacerbations (past 1 year)	0–1	64	35.6
	≥ 2	116	64.4
Hospitalization (past year)	Yes	92	51.1
	No	88	48.9
Comorbidities	Hypertension	72	40.0
	Diabetes Mellitus	58	32.2
	Ischemic Heart Disease	34	18.9

50 years. This verifies the observation found in the BOLD study by Buist et al. (2007)[7] that COPD prevalence rises significantly with advanced age. Similarly, Mannino and Braman (2007)[8] stated that age-related decline in lung function, along with cumulative exposure to risk factors, contributes greatly to the development of COPD in an aging population. A considerable proportion of patients aged ≥70 years (20.5%) in this study supports the concept that COPD is largely a disease of the elderly, reflecting delayed diagnosis and progressive disease course. A strong male preponderance was evident with 73.3% being males and 26.7% females. Salvi and Barnes (2009)[9] reported that COPD prevalence is higher among men in regions where smoking rates are substantially greater in males. Similarly, Jindal et al. (2012),[10] in an Indian population-based study, found a significantly higher COPD prevalence among men and attributed the difference to occupational exposure and higher tobacco consumption among them. Smoking remains the most significant risk factor for COPD, and this was eminently reflected in the current results. As many as 79% of participants were either current smokers (43.3%) or ex-smokers (35.6%). Lee et al. (2018)[11] reported that ex-smokers continue to harbor a significant COPD burden due to irreversible airway damage, which explains the high proportion of ex-smokers in clinical cohorts. Biomass fuel exposure was reported by 38.3% of participants, thereby highlighting it as an important non-smoking-related risk factor for COPD. This finding is concordant with those of the studies of Kurmi et al. (2010)[12] and Po et al. (2011),[13] who identified a strong biomass smoke exposure-COPD association, particularly in women and the rural population. Salvi et al. (2009)[9] suggested that chronic indoor air pollution through biomass fuels can produce inflammatory and structural lung changes similar to those produced by tobacco smoke. Although a higher proportion in this study reported no biomass exposure, it highlighted again the public health relevance of the exposed group due to household air pollution in COPD pathogenesis.

Nearly half the population studied had a disease duration of 5–10 years, and 28.3% had COPD for more than a decade, denoting long-standing illness in a substantial proportion of patients. Similar patterns were recorded by few other studies also.[14,15] Dyspnea assessment using the mMRC scale showed most patients to have moderate to severe breathlessness, with 45% belonging to Grade 2 and 31.7% to Grades 3–4. This is very much in line with Celli et al., (2004),[6] where it was said that increasing the grades of mMRC scales as per the progression of the

Table 3. Spirometry-Based COPD Severity (GOLD Staging)

GOLD Stage	FEV_1 (% Predicted)	Number of Patients	Percentage (%)
GOLD 1 (Mild)	≥ 80%	21	11.7
GOLD 2 (Moderate)	50–79%	86	47.8
GOLD 3 (Severe)	30–49%	52	28.9
GOLD 4 (Very Severe)	< 30%	21	11.6

disease are strong predictors of functional limitation and mortality. Again, according to Nishimura et al., (2002),[16] dyspnea grades correlating with reduced exercise tolerance and poorer health-related quality of life support the high dyspnea burden found in this cohort. The frequency of exacerbations was high, with as many as 64.4% of the patients were in two or more than two exacerbations in the preceding year. For Hurst et al. (2010),[17] COPD patients had identified a "frequent exacerbator phenotype" that is stable over time and is associated with increased inflammation, faster lung function decline, and worse clinical outcomes. Comparable exacerbation rates were documented by Wedzicha and Seemungal et al., (2007)[18] to support the important role of exacerbations as one of the major determinants of disease progression and healthcare utilization. Correspondingly, more than half of the patients, 51.1%, needed hospitalization in the past year. This percentage agrees with that of Soler-Catelluna et al. (2005),[19] who defined one of the main factors that determine hospitalization and mortality in COPD as the presence of frequent exacerbations. The burden of comorbidities in the present study underscores the systemic nature of COPD. Hypertension, 40%, was the most common comorbidity, while diabetes mellitus appeared as the second, 32.2%, and ischemic heart disease as the third, 18.9%. These results agree with large cohort studies such as Barnes (2009)[10] and Celli et al. (2004),[6] reporting a high prevalence of cardiovascular and metabolic comorbidities among COPD patients due to common risk factors and systemic inflammation. Similarly, the study by Mannino et al. (2007)[8] demonstrated that independently of airflow limitation, the presence of cardiovascular disease and diabetes contributes greatly to morbidity and mortality in COPD. The coexistence of these comorbid conditions underlines the need for comprehensive clinical evaluation and integrated management approaches.

The current study shows the distribution of COPD severity according to spirometric GOLD staging, with moderate to

Table 4. Hematological Parameters of Study Participants (n = 180)

Parameter	Mean ± SD	Normal Range
Hemoglobin (g/dL)	12.1 ± 2.1	13–17 (M), 12–15 (F)
RBC count ($\times 10^6$/μL)	4.3 ± 0.7	4.5–5.9
Total Leukocyte Count ($\times 10^3$/μL)	9.8 ± 2.9	4.0–11.0
Neutrophils (%)	69.2 ± 9.4	40–70
Lymphocytes (%)	21.8 ± 7.1	20–40
Platelet count ($\times 10^3$/μL)	284 ± 78	150–450
RDW (%)	14.8 ± 2.3	11.5–14.5
ESR (mm/hr)	32.4 ± 15.1	< 20
CRP (mg/L)	6.9 ± 3.4	< 5

Table 5. Distribution of Hematological Abnormalities

Parameter	Category	Frequency (n)	Percentage (%)
Hemoglobin	Anemia	78	43.3
	Normal	80	44.4
	Polycythemia	22	12.3
WBC Count	Leukocytosis	69	38.3
	Normal	111	61.7
Platelet Count	Thrombocytosis	34	18.9
	Normal	146	81.1
Inflammatory Markers	Raised ESR	124	68.9
	Raised CRP	101	56.1

severe airflow limitation predominating, as evidenced by the composition of GOLD 2 making up 47.8%, GOLD 3 making up 28.9%, cumulatively accounting for more than three-quarters of the subjects. The pattern suggests that most patients tend to come to seek medical care during a stage of the disease beyond the mild one. The same observation was seen in the BOLD study conducted by Buist et al. (2007)[7] where moderate COPD represented the greatest proportion of diagnosed cases across several countries, while Mannino et al. (2007)[8] similarly reported the most commonly encountered stage in clinical settings to be GOLD 2, which mirrored underdiagnosis of early stages and delayed health-seeking behavior. The small proportion of patients classified as GOLD 1, comprising 11.7% in this study, is consistent with Lamprecht et al. (2011),[20] where it was demonstrated that mild COPD is often under-recognized due to minimal symptoms and lack of routine spirometry in primary care, and these early-stage patients may remain undiagnosed for several years until symptoms worsen, which may explain their lower representation in hospital-based studies like the present one. In contrast, the remarkable proportion of GOLD 4 patients, 11.6%, indicates the inclusion of patients with advanced disease, likely a result of referral bias toward tertiary care. Vestbo et al. (2013)[15] have shown similar proportions of very severe COPD in the ECLIPSE study, which included a wide range of disease severity and demonstrated the heavy clinical burden of advanced airflow limitation. The high prevalence of severe and very severe COPD amounting to 40.5% observed in this study points to the progressive nature of the illness and the cumulative effect of longstanding exposure to risk factors like smoking and biomass fuel. Celli et al. (2004)[6] and Wedzicha (2007)[18] pointed out that GOLD 3 and GOLD 4 patients are more prone to frequent exacerbations and systemic inflammation with co-morbidities, which agree with the clinical and haematological abnormalities in the present study. Recently, Agustí et al. (2022)[14] reported that an increasing GOLD stage strongly relates not only to worsening symptom burden and reduced exercise capacity but also to increased mortality risk, further supporting the clinical relevance of spirometric grading.

The hematological profile presented in this study delineates the systemic inflammatory and hematopoietic changes associated with COPD. COPD is increasingly considered a systemic disease, and abnormalities in circulating blood elements have been reported, reflecting not only the severity of the disease but also chronic hypoxia and persistent inflammation. In the present study, the mean hemoglobin level was 12.1 ± 2.1 g/dL, which is below the normal range for both males and females, thus revealing a highly anemic tendency among the participants. John et al. (2005)[21] showed that anemia is a common and under-recognized comorbidity in COPD patients, especially those with reduced exercise intolerance and increased mortality. Similarly, Cote et al. (2007)[22] found that lower hemoglobin levels were independently associated with poor functional status and high dyspnea scores. The moderately decreased RBC count, as obtained in the current study, that is, 4.3 ± 0.7 $\times 10^6$/μL, is supportive evidence for chronic anemia attributed to inflammation induced suppression of erythropoiesis. The mean leukocyte count, which was 9.8 ± 2.9 $\times 10^3$/μL, falls within the upper limits of the normal range and thereby indicates the persistence of systemic inflammation. Elevated or high normal counts of

Table 6. Comparison of Hematological Parameters Across GOLD Stages

Parameter	GOLD 1 (n=21)	GOLD 2 (n=86)	GOLD 3 (n=52)	GOLD 4 (n=21)	p-value
Hemoglobin (g/dL)	13.6 ± 1.4	12.4 ± 1.8	11.6 ± 2.0	10.9 ± 2.2	<0.001
TLC (×10³/µL)	7.9 ± 2.1	9.2 ± 2.4	10.6 ± 2.8	11.8 ± 3.1	<0.001
Platelets (×10³/µL)	241 ± 66	268 ± 72	298 ± 81	326 ± 88	0.002
ESR (mm/hr)	18.2 ± 8.5	28.5 ± 12.1	36.9 ± 14.6	45.3 ± 16.2	<0.001
CRP (mg/L)	3.1 ± 1.8	5.6 ± 2.9	7.8 ± 3.2	10.4 ± 4.0	<0.001

leukocytes have also been consistently reported in studies by Gan et al. (2004)[23] and Agustí et al. (2022),[14] who have related leukocytosis to systemic inflammation, frequent exacerbation, and increased cardiovascular risk. Differential counting of WBC in the present study has shown neutrophil predominance, that is, 69.2 ± 9.4%, which is suggestive of COPD-related inflammation. It further corroborates the observations made by Barnes (2009),[9] who emphasized the pivotal role of neutrophils in COPD pathogenesis, airway remodeling, and during exacerbations. Lymphocyte counts, on the other hand, were at the lower limit of normal, that is, 21.8 ± 7.1%, which indicated relative lymphopenia. The latter finding has also been discussed in some other studies which stated to associate with disease severity and even poorer outcomes.[24,25] Platelet counts were within the normal limits; however, the mean value was inclined toward the higher side of the normal range, that is, of note, however, is the slightly raised RDW observed in this study (14.8 ± 2.3%), as increasing RDW has recently emerged as a new inflammatory marker. Patel et al. (2016)[26] showed that high RDW is associated with disease severity and increased hospitalization and mortality in COPD patients. Since it presumably reflects ineffective erythropoiesis and oxidative stress. Systemic inflammation markers in the present cohort were grossly elevated. Mean ESR for this cohort was much higher than the normal limit (32.4 ± 15.1 mm/hr), which is in agreement with the findings of Karadag et al. (2008)[27] showed that ESR was significantly raised in stable and exacerbated COPD patients. Similarly, CRP levels were elevated (6.9 ± 3.4 mg/L) consistent with the presence of chronic low-grade systemic inflammation. High CRP in COPD subjects is a consistent finding as reported by much literature. de Torres et al. (2006)[28] also found strong associations between CRP levels and exacerbation frequency as well as with mortality risk.

In this present study, anemia was found in 43.3% of participants, and 12.3% showed polycythemia. This dual pattern shows the heterogeneous effects of COPD on erythropoiesis. Similar prevalence of anemia was found by John et al. 2005,[21] who also reported about one-third of the patients with COPD as having anemia and presenting as an independent cause of mortality. Cote et al. (2007)[22] also showed anemia prevalence ranging between 20–40% and associated it with greater dyspnea and reduced exercise tolerance. The polycythemia in a small subset of patients in the present study is, however, consistent with the results presented by Kent et al. (2011),[29] who discussed polycythemia as a compensatory response to sustained hypoxemia, particularly in advanced-stage patients with chronic smoking history. These findings indicate that both inflammation-induced anemia and hypoxia-induced erythrocytosis co-exist in COPD populations.

Abnormalities of platelets were less frequent, yet clinically important with thrombocytosis in 18.9% of the participants in this study. One consistency is the study Harrison et al. (2014),[25] showing that platelet count and platelet activation were increased in COPD, especially in periods of heightened inflammation or during exacerbation. There is an increasing awareness of platelets as contributors to the inflammatory and thrombotic pathways in COPD that could be an explanation for high cardiovascular risk among these patients. Inflammatory markers were very high in the present cohort, as manifested by raised ESR in 68.9% and raised CRP in 56.1% of the patients. These findings are in close agreement with the studies by Karadag et al. (2008)[27] and de Torres et al. (2006),[28] both of which demonstrated the highly raised ESR and CRP levels in stable and exacerbated COPD. More recently, Kent et al. (2007)[29] confirmed that chronic low-grade systemic inflammation, defined by permanently raised CRP, is strongly associated with frequent exacerbations and increased mortality.

The comparison of hematological parameters among the GOLD stages in the present study shows a linear and statistically significant relationship between increasing severity of COPD and worsening hematological and inflammatory profiles. A progressive decline in hemoglobin was seen from GOLD 1 (13.6 ± 1.4 g/dL) to GOLD 4 (10.9 ± 2.2 g/dL) with a highly significant p-value (<0.001). This trend indicates that anemia prevalence and

Table 7. Correlation of Hematological Parameters with Clinical Severity

Parameter	mMRC Dyspnea Score (r)	Number of Exacerbations (r)	p-value
Hemoglobin	-0.41	-0.38	<0.001
TLC	0.45	0.49	<0.001
Platelet Count	0.36	0.40	<0.001
ESR	0.52	0.57	<0.001
CRP	0.55	0.61	<0.001

severity increase with the advancement of airflow limitation. John et al. (2005)[22] presented similar findings that hemoglobin levels fell significantly with increasing severity of COPD and that it is independently associated with poor survival. Cote et al. (2007)[23] further confirmed that anemia is more common and correlates with higher dyspnea scores and reduced exercise capacity in advanced GOLD stages. More recently, Ferrari et al. (2015)[30] pointed out chronic systemic inflammation and impaired erythropoietin response as contributing factors for anemia in severe grades of COPD, which support the observations in the present study. The TLC has shown a stepwise increase across the GOLD stages, which rises from 7.9 ± 2.1 ×10³/µL in GOLD 1 to 11.8 ± 3.1 ×10³/µL in GOLD 4, p<0.001. This pattern shows intensification of systemic inflammation with the progression of the disease. Comparable results were reported by Gan et al. (2004)[24] and Agustí et al. (2022)[15], who found that elevated leukocyte counts were associated with more severe obstruction of airflow, frequent exacerbations, and increased cardiovascular risk. Vestbo et al. (2013)[16] further demonstrated that leukocytosis is significantly more common in GOLD 3 and GOLD 4 patients, reinforcing its role as a marker of disease severity. Platelet counts have also increased significantly across the GOLD stages, from 241 ± 66 ×10³/µL in GOLD 1 to 326 ± 88 ×10³/µL in GOLD 4, p = 0.002. The finding is concordant with the study by Harrison et al. (2014),[26] who reported higher platelet count and platelet activation in patients with severe and very severe COPD. Platelets are increasingly recognized as active participants in inflammatory pathways, and their elevation in advanced disease may contribute to the heightened thrombotic and Markers of systemic inflammation revealed the highest stage-wise rise. ESR was significantly higher from 18.2 ± 8.5 mm/hr in GOLD 1 to 45.3 ± 16.2 mm/hr in GOLD 4, p <0.001. Similarly, CRP increased progressively from 3.1 ± 1.8 mg/L in GOLD 1 to 10.4 ± 4.0 mg/L in GOLD 4, p <0.001. In strong agreement with studies by de Torres et al. (2006)[28] showing that both ESR and CRP increase in proportion with the severity of COPD.

In the current study, hemoglobin levels had a moderate negative correlation with both mMRC dyspnea score (r = –0.41) and exacerbation frequency (r = –0.38), reflecting that the lowest levels of hemoglobin are associated with increased breathlessness and higher frequency of disease exacerbations. The results of the present study are supported by the findings of Cote et al. (2007)[23], where anemia in COPD was found to be strongly associated with increased dyspnea, decreased exercise capacity, and poor quality of life. John et al. (2005)[22] also found that lower hemoglobin levels are associated with higher rates of hospitalization and mortality, thus reinforcing the clinical relevance of anemia observed in the current study. TLC has shown significant positive correlation with dyspnea severity (r = 0.45) and exacerbation frequency (r = 0.49), thus it may reflect the role of systemic inflammation in driving symptom burden and disease instability. The data in the current study are supported by the finding of Gan et al. (2004)[24] and Agustí et al. (2022)[15] of the association between elevated leukocyte counts and more severe airflow limitation, frequent exacerbations, and increased cardiovascular risk. More recently, Cote et al. (2007)[23] reported a strong association between leukocytosis and frequent exacerbator phenotype, further validating the results of the current study. Platelet count also showed a moderate positive correlation with both dyspnea (r = 0.36) and exacerbation frequency (r = 0.40). This observation is supported by the findings of Harrison et al. (2014),[26] who demonstrated an association between high platelet count and platelet activation and increased inflammation and exacerbation risk in COPD. Systemic inflammatory markers have demonstrated the strongest correlations with clinical severity. ESR has shown a strong positive correlation with dyspnea (r = 0.52) and exacerbations (r = 0.57); whereas CRP has shown the highest values of correlation coefficients, with r = 0.55 for dyspnea and r = 0.61 for exacerbation frequency.

Conclusion

COPD in this study was found to be associated with significant hematological and inflammatory abnormalities that further deteriorate with increasing severity. Severe

anemia, leukocytosis, thrombocytosis, and high levels of ESR and CRP are strongly correlated with severe dyspnea, frequent exacerbation, and advanced GOLD stages. These findings point out the systemic nature of COPD beyond airflow limitation.

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