RESEARCH ARTICLE

Investigating fibrinogen levels as a biomarker for immune inflammation severity in COPD patients across GOLD stages

Hamidullah[1], Sajjad Ali[2], Ashraf[3], Imranullah[4], Ishtiaq Ahmad[5]

Abstract

Objective: To assess the association between fibrinogen levels and immune inflammation severity in patients with chronic obstructive pulmonary disease at different stages of the Global Initiative for Chronic Obstructive Lung Disease classification.

Method: The descriptive, prospective, cross-sectional study was conducted from January 2022 to November 2023 at the Pulmonology Department, Mardan Medical Complex, Khyber Pakhtunkhwa, Pakistan, and comprised chronic obstructive pulmonary disease patients of either gender aged 40-85 years. Fibrinogen levels and systemic immune-inflammatory markers were measured, and disease severity was classified based on the Global Initiative for Chronic Obstructive Lung Disease classification. Independent predictors of fibrinogen levels as well as the diagnostic accuracy of biomarkers for predicting advanced chronic obstructive pulmonary disease were identified. Data was analysed using SPSS 26.

Results: Of the 253 patients, 147(58.10%) were males and 106(41.89%) were females. Most of the patients were aged 40-50 years 72(28.45%), followed by 50-60 years 57(22.52%). A strong positive correlation was observed between fibrinogen levels and chronic obstructive pulmonary disease severity ($r=0.815$, $p<0.001$). The diagnostic accuracy of fibrinogen for predicting advanced disease stages was reliable, having an area under the curve of 0.910.

Conclusion: Fibrinogen levels could be used as a marker for immune inflammation severity in chronic obstructive pulmonary disease patients.

Key Words: Fibrinogen levels, Biomarker, Inflammation, Pulmonary disease, Chronic obstructive.

(JPMA 75: 556; 2024) **DOI: https://doi.org/10.47391/JPMA.11531**

Introduction

Chronic obstructive pulmonary disease (COPD), a common and severe respiratory condition, is characterised by a continuous restriction in airflow and a progressive loss of lung function.[1] Over three million people die from COPD each year, placing a heavy burden on healthcare systems and being a major cause of morbidity and mortality worldwide.[2] Based on their lung function, as determined by forced expiratory volume in one second (FEV1), COPD patients are divided into four phases by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification.[1] These stages (I-IV) offer important details on the severity, prognosis and available treatments for the disease.[3]

Systemic inflammation plays a significant role in the pathophysiology and development of COPD.[4] C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) are a few examples of the inflammatory mediators that are released as a result of the activation of innate and adaptive immune responses .[5] These systemic immune inflammatory markers have been linked with increased disease severity, more frequent exacerbations, and a higher risk of death in COPD patients.[6,7]

The liver produces fibrinogen (FIB), a glycoprotein that is essential for blood clotting, inflammation and tissue repair.[8] Patients with COPD frequently have high FIB levels, and a recent study has indicated that FIB may be a promising biomarker for disease severity, risk of exacerbation and death.[9] Additionally, FIB has been found to be a distinct risk factor for cardiovascular and all-cause mortality in COPD patients.[10]

Despite rising evidence of their significance in COPD, possible changes in these markers' levels across COPD stages can reveal pathophysiological processes. The data may affect risk classification, prognosis and targeted therapy. Understanding the links between these indicators and lung function can lead to new COPD treatments that reduce systemic inflammation and improve clinical outcomes.

[1,5]Department of Medicine, Mardan Medical Complex, Bacha Khan Medical College, Mardan, Pakistan.[2]Department of Pulmonology, Mardan Medical Complex, Bacha Khan Medical College, Mardan, Pakistan.[3,4]Pro-Gene Diagnostics and Research Laboratory, Mardan, Pakistan.

Correspondence: Sajjad Ali **Email:** drsajjadlrh@gmail.com

ORCID ID: 0009-0007-6396-9635

Submission complete: 28-12-2023 **First Revision received:** 26-04-2024

Acceptance: 15-01-2025 **Last Revision received:** 14-01-2025

The current study was planned to examine FIB levels and systemic immune inflammatory indicators in COPD patients at various GOLD stages.

Patients and Methods

The descriptive, prospective, cross-sectional study was conducted from January 2022 to November 2023 at the Pulmonology Department, Mardan Medical Complex (MMC), Khyber Pakhtunkhwa, Pakistan. After approval from the ethics review boards of MMC and Bacha Khan Medical College (BKMC), the sample was raised using convenience sampling technique. Those included were COPD patients of either gender aged 40-85 years meeting the GOLD criteria. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[3] Patients with other pulmonary diseases, autoimmune diseases, malignancies, a history of acute exacerbations within the preceding three months, or those receiving immunosuppressive therapy were excluded. Informed consent was obtained from all the participants.

The sample size calculation for the study was determined using the formula

$$n = \frac{z^2 \cdot \sigma^2}{d^2}$$

sample size per GOLD stage was calculated as approximately 35 patients. Considering the four GOLD stages, the total required sample size was 140 patients. To account for an anticipated dropout rate of 10%, the sample size was adjusted using the formula

$$n_{\text{adjusted}} = \frac{n_{total}}{1 - \text{dropout rate}}$$

resulting in a final adjusted sample size of approximately 156 patients. To ensure adequate representation and account for practical recruitment feasibility, the target sample size was set at 160 patients, distributed approximately equally across the four GOLD stages.[11]

For determining the GOLD stage, a spirometer was used to measure the ratio between FEV1 and forced vital capacity (FVC), according to the manufacturer's instructions by spirobank ii made in Italy. Stage I (mild) required an FEV1/FVC ratio of <0.70 and FEV1 80%. Patients could have a persistent cough and sputum production at this point, but they might not be aware of any breathing problems. Stage II (moderate) meant FEV1 50-79%, and FEV1/FVC ratio <0.70. Patients could have a persistent cough and sputum production, and experienced breathlessness during physical exertion. Stage III (severe) meant FEV1/FVC ratio 0.70, and projected FEV1 30-49%. Stage IV (very severe) meant FEV1/FVC ratio 0.70 and FEV1 30-50% plus chronic respiratory failure. Patients could have significant shortness of breath (SOB) and could experience exacerbations necessitating hospitalisation.[5]

Blood samples from all the participants were collected in vacutainer containers and centrifuged at 4°C at 3,000 rpm for 10 minutes. The separated serum was kept at -80 degrees Celsius until further examination. The Clauss method, entailing a coagulometer-based automated assay, was used tso determine FIB levels.[12] For systemic immune inflammation, a sensitive chemiluminescence immunoassay (CLIA) was used to measure CRP levels by using Roche cobas e411 automated immunoassay analyzer made in Germany. IL-6 and TNF-α levels were measured using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions by ELK biotechnology made in the united states of America. In addition, total leukocytes count (TLC), neutrophils (NEU) and lymphocytes (LYM) counts were collected as baseline testing using a haematology analyser (Horiba ABX Micros es60) made in the France.

Data was analysed using SPSS 26. Continuous variables were reported as medians with interquartile ranges (IQR), and categorical variables were presented as frequencies and percentages. For the comparison of categorical variables, chi-square test was utilised. In instances where the frequencies fell <5, Fisher's exact test was applied to maintain statistical accuracy. Given the non-parametric distribution of continuous variables, Kruskal-Wallis test was used to analyse differences in baseline parameters, systemic immune inflammation markers, and FIB levels across the GOLD stages. Correlations involving FIB levels, baseline characteristics, and systemic immune inflammation markers with GOLD stages were examined using Spearman's correlation coefficient, which is an appropriate method for non-parametric data. To assess the discriminatory ability of baseline parameters, systemic inflammation markers, and FIB levels in predicting advanced GOLD stages, a receiver operating characteristic (ROC) curve analysis was conducted, and the area under the curve (AUC) was calculated. Despite the non-normal distribution of FIB levels, simple linear regression analysis was performed to determine independent predictors of FIB. This approach was considered appropriate given that linear regression could still provide reliable results in larger datasets where violations of the normality assumption have a reduced impact. Adjustments for potential confounding variables, including age, gender, smoking status, body mass index (BMI) and COPD severity, and all other studied variables were made to improve the accuracy of the model. A 95% confidence interval (CI) was applied to all statistical tests

where applicable, and p<0.05 was considered statistically significant.

Results

Of the 253 patients, 147(58.10%) were males and 106(41.89%) were females. Most of the patients were aged 40-50 years 72(28.45%), followed by 50-60 years 57(22.52%). There were 69(27.27%) patients having GOLD stage I, 82(35.17%) stage II, 62(24.50%) stage III, and 33(13.04%) stage IV. Physical and clinical characteristics of all the patients were noted in detail (Table 1).

Table-1: Demographic, physical and clinical characteristic of chronic obstructive pulmonary disease (COPD) patients.

Characteristic	No of patients	Values/percentages
Total Patients	253	100
Gender		
Male	147	58.10
Female	106	41.89
Age (Years)		
40-50	72	28.45
50-60	57	22.52
60-70	45	17.78
70-80	51	20.15
80-85	28	11.06
Sign Symptoms		
Shortness Of Breath	253	100
Wheezing	186	73.51
Chest Tightness	172	67.98
Chronic Cough	253	100
Mucous Production	61	24.11
Fatigue	33	13.04
Weight Loss	33	13.04
Recurrent Respiratory Infections		
Pneumonia	14	5.53
Bronchitis	31	12.25
Body Mass Index		
<18.5	49	19.36
18.5-24.9	73	28.85
25.0-29.9	67	26.48
30.0-34.9	36	14.22
>35.0	28	11.06
Smoking History		
Yes	122	48.22
No	131	51.77
Respiratory Rate	253	23(21-25)
Heart Rate	253	93(88-110)
Diastolic Pressure	253	88(79-94)
Systolic Pressure	253	136(125-149)
Body Temperature	253	36.6(36.33-37.04)
Spirometry		
Fev1 % Predicted	253	63.00(31.00-81.00)
Fev1/Fvc Ratio	253	0.65(0.62-0.71)
Arterial Blood Gases		
Ph	253	7.39(7.36-7.42)
Paco2	253	62.3(42.6-69.9)
Pao2/Fio2	253	299(258–391)
Hco3	253	29.5(27.29-32.51)
Gold Stage		
Stage 1	69	27.27
Stage 2	89	35.17
Stage 3	62	24.50
Stage 4	33	13.04

PCO2: Partial pressure of carbon dioxide, HCO3: Bicarbonate, PaO2/FiO2: Partial arterial oxygen/fractional inspired oxygen, Ph: Potential of hydrogen, FEV1: Forced expiratory volume in 1 second, FCV: Forced vital capacity.

As the severity of COPD increased, there was a notable increase in TLC, NEU, CRP, IL6, TNF-α and FIB levels, while LYM levels decreased (Table 2).

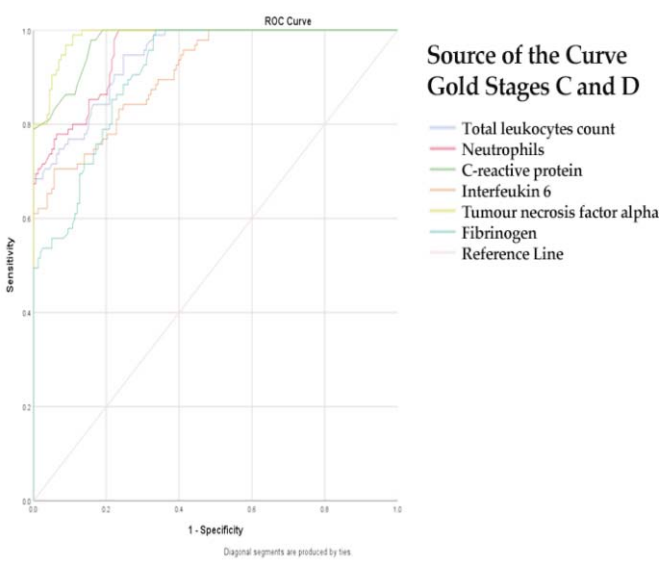
The correlation between FIB and GOLD stage (0.815, p<0.000) suggested a significant association between FIB levels and COPD severity (Table 3).

All biomarkers showed statistically significant values (p<0.05). The ROC curve analysis demonstrated that TNF-α had the highest AUC (0.987), followed by CRP (0.977) and NEU (0.955). Fibrinogen also exhibited a notable AUC value (0.910) (Table 4, Figure 1).

Table-2: Systemic immune inflammation severity based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages.

Characteristic	Stage 1	Stage 2	Stage 3	Stage 4	P-VALUE
Patients	69(27.27)	89(35.17)	62(24.50)	33(13.04)	
TLC	7.52(7.26-7.90)	7.73(7.01-8.56)	9.29(8.41-10.14)	11.37(10.57-12.22)	< 0.001
NEU	5.26(4.84-5.54)	5.67(5.12-6.58)	7.20(6.48-8.15)	9.60(8.80-10.43)	< 0.001
LYM	1.52(1.39-1.69)	1.17(1.09-1.24)	1.14(1.03-1.25)	0.94(0.84-1.10)	< 0.001
CRP	10.31(6.00-13.44)	20.01(15.33-28.91)	39.06(31.00-49.11)	55.46(46.29-59.21)	< 0.001
IL6	2.65(1.93-3.43)	6.46(4.70-8.22)	11.73(6.95-14.11)	13.91(9.14-23.55)	< 0.001
TNF-α	5.07(4.01-7.01)	10.08(6.06-14.09)	26.04(18.06-34.02)	42.07(39.03-53.05)	< 0.001
FIB	305(295-313)	365(315-419)	439(380-493)	634(572-740)	< 0.001

TLC: Total leukocyte count, NEU: Neutrophils, LYM: Lymphocytes, IL6: Interleukin 6, TNF-α: Tumour necrosis factor-alpha, CRP: C-reactive protein, FIB: Fibrinogen.



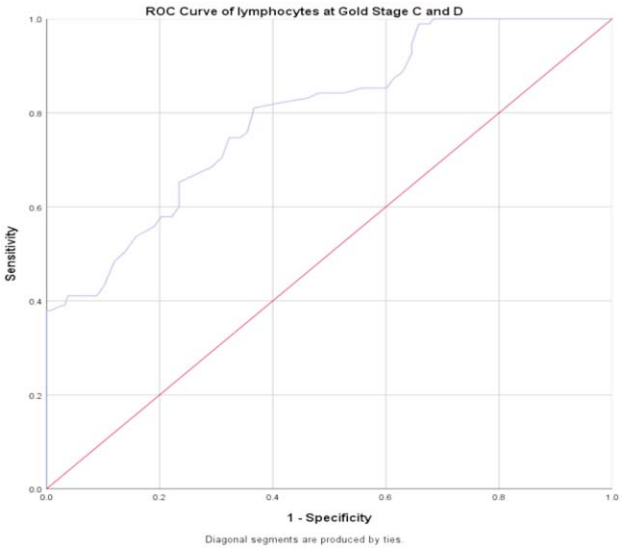


Figure-1: Arrow pointing at the right lower parathyroid gland in the picture. Stitch is retracting the right lobe of the thyroid gland medially.

Table-3: Correlation metrics of the studied diagnostic blood parameters for systemic immune inflammation severity.

Biomarkers	Correlation and significance	TLC	NEU	LYM	CRP	IL-6	TNF-α	FIB	GOLD Stages
TLC	Correlation Coefficient	1	0.991	-0.435	0.728	0.646	0.751	0.647	0.787
	P-value		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
NEU	Correlation Coefficient	0.991	1	-0.554	0.768	0.673	0.781	0.686	0.839
	P-value	< 0.001		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
LYM	Correlation Coefficient	-0.435	-0.554	1	-0.626	-0.498	-0.575	-0.575	-0.736
	P-value	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
CRP	Correlation Coefficient	0.728	0.768	-0.626	1	0.670	0.800	0.708	0.882
	P-value	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001	< 0.001
IL-6	Correlation Coefficient	0.646	0.673	-0.498	0.670	1	0.659	0.681	0.752
	P-value	< 0.001	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001	< 0.001
TNF-α	Correlation Coefficient	0.751	0.781	-0.575	0.800	0.659	1	0.770	0.876
	P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001		< 0.001	< 0.001
FIB	Correlation Coefficient	0.647	0.686	-0.575	0.708	0.681	0.770	1	0.815
	P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001		< 0.001
GOLD Stages	Correlation Coefficient	0.787	0.839	-0.736	0.882	0.752	0.876	0.815	1
	P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	

TLC: Total leukocyte count, NEU: Neutrophils, LYM: Lymphocytes, IL6: Interleukin 6, TNF-α: Tumour necrosis factor-alpha, CRP: C-reactive protein, FIB: Fibrinogen.

Table-4: MReceiver operating characteristic (ROC) curve data of different blood parameters of systemic immune inflammation severity for disease stages C and D.

Test Result Variable	AUC	Std. Error	95% CI		p-value
			Lower Bound	Upper Bound	
TLC	0.943	0.013	0.918	0.968	< 0.001
NEU	0.955	0.011	0.933	0.976	< 0.001
LYM	0.795	0.028	0.739	0.850	< 0.001
CRP	0.977	0.007	0.963	0.990	< 0.001
IL6	0.907	0.018	0.872	0.943	< 0.001
TNF-α	0.987	0.005	0.978	0.996	< 0.001
FIB	0.910	0.017	0.877	0.943	< 0.001

TLC: Total leukocyte count, NEU: Neutrophils, LYM: Lymphocytes, IL6: Interleukin 6, TNF-α: Tumour necrosis factor-alpha, CRP: C-reactive protein, FIB: Fibrinogen. AUC: Area under the curve. CI: Confidence interval.

GOLD stage, wheezing, mucous production, FEV1% predicted, bicarbonate (HCO3), , PaO2/FiO2: Partial arterial carbon dioxide (PaCO2), and the ration between partial arterial oxygen (PaO2) and fractional inspired oxygen (FiO2) were significant predictors of FIB levels ($p<0.05$). Other variables, like age, body mass index (BMI) and vital signs, were not significant predictors of FIB levels (Table 5).

There was a positive linear relationship of TLC, NEU, IL-6, TNF-α, CRP and FIB levels with GOLD stage, while there was a negative linear relationship between LYM count and GOLD stage (Figure 2).

Table-5: Assessment of needs in Health Professions Education according to faculty track.

CHARACTERISTIC	UN Standardised	Standardised	95.0% CI		t-VLAUE	P VALUE
			Lower Bound	Upper Bound		
Age (1 year)	-0.143	-0.16	-1.252	0.965	-0.225	0.799
Gender (male)	-18.43	-0.075	-49.01	12.14	-1.18	0.236
BMI (1 kg/m^2)	3.32	0.174	0.99	5.66	2.80	< 0.001
Body Temperature (1 ℃)	28.38	0.100	-18.847	22.379	0.169	0.866
Respiratory Rate (1 breaths/min)	9.01	0.53	4.29	12.56	9.86	< 0.001
Heart Rate (1 beats/min)	-0.182	-0.014	-1.107	0.742	-0.389	0.698
Systolic Pressure (1 mmHg)	0.605	0.038	-0.554	1.763	1.028	0.305
Diastolic Pressure (1 mmHg)	-0.267	-0.013	-1.706	1.173	-0.365	0.715
Smoking (yes)	5.243	0.022	-25.029	35.163	0.341	0.732
Gold Stage (1-4)	99.94	0.815	91.11	108.77	22.28	< 0.001
Fev1 % Predicted 1 Percent)	-4.34	-0.77	-4.79	-3.89	-19.13	< 0.001
HCO3 (1 mEq/L)	18.87	0.56	15.47	22.26	10.93	< 0.001
PCO2 (1 mmHg)	7.89	0.65	6.79	9.03	13.69	< 0.001
PAO2/FIO2 (1 mmHg)	-5.33	-0.49	-3.91	-7.89	-9.45	< 0.001
Ph (1 unit)	88.61	0.026	-339.40	516.63	0.408	0.71
SOB (yes)	39.01	0.59	34.29	52.56	10.11	< 0.001
Wheezing (yes)	67.94	0.49	53.01	82.86	8.96	< 0.001
Chest Tightness (yes)	65.51	0.50	51.49	79.53	9.20	< 0.001
Fatigue (yes)	121.95	0.71	107.11	136.69	16.23	< 0.001
Weight Loss (yes)	137.89	0.76	123.35	152.39	18.70	< 0.001
Recurrent Respiratory Infections (yes)	18.48	0.10	3.81	40.79	1.69	0.009
Mucous Production (yes)	43.29	0.46	26.34	60.24	5.03	< 0.001
TLC (1000 cells/µL)	52.50	0.647	44.82	60.19	13.45	< 0.001
NEU (1 Percent)	51.43	0.686	44.64	58.22	14.92	< 0.001
LYM (1 Percent)	-84	-0.571	-235.18	-34.33	-11.12	< 0.001
CRP (1 mg/L)	4.97	0.70	4.35	5.59	15.86	< 0.001
IL6 (1 pg/mL)	14.06	0.68	12.19	15.94	14.75	< 0.001
TNF (1 pg/mL)	6.49	0.77	5.80	7.13	19.12	< 0.001

PCO2: Partial pressure of carbon dioxide, HCO3: Bicarbonate, PaO2/FiO2: Partial arterial oxygen/fractional inspired oxygen, Ph: Potential of hydrogen, FEV1: Forced expiratory volume in 1 second, FCV. Forced vital capacity, SOB: Shortness of breath, TLC: Total leukocyte count, NEU: Neutrophils, LYM: Lymphocytes, IL6: Interleukin 6, TNF-α: Tumour necrosis factor-alpha, CRP: C-reactive protein, FIB: Fibrinogen.

Discussion

In the current study, the demographic distribution of patients aligned with global trends, with a slightly higher proportion of male participants (58.10%) compared to females (41.89%).[13] The current age range of 40-85 years accurately represented the adult demographic most commonly affected by COPD[14], strengthening the external validity of the findings and their applicability to the broader patient population.

The diverse array of symptoms experienced by the current patients unveiled a complex clinical landscape. SOB and chronic cough emerged as the most prevalent and universally experienced symptoms.[15] wheezing and chest tightness were also reported by a substantial proportion of patients, highlighting their importance in COPD symptomatology.[16,17] In contrast, mucus production, fatigue and weight-loss were less frequent, suggesting variability in COPD manifestations.[18] Furthermore, the study revealed the presence of recurrent respiratory infections, such as pneumonia and bronchitis, in a small percentage of patients, underlining the potential complications associated with COPD.

The BMI distribution and smoking history of the current patients mirrored patterns observed in previous studies, providing a foundation for comparison.[19,20] The current findings related to spirometry and arterial blood gas values were consistent with the existing literature, further substantiating the relevance of the current patient population.[21] The distribution of GOLD stages among the patients aligned with other studies, indicating that milder stages (I and II) were more common than severe stages (III and IV).[22]

The current study noted that COPD patients at various GOLD stages exhibited FIB levels exceeding 400mg/dl. This intriguing finding was linked to a more potent and vigorous immune-inflammatory reaction. As a major acute-phase reactant, FIB is integral to the body's

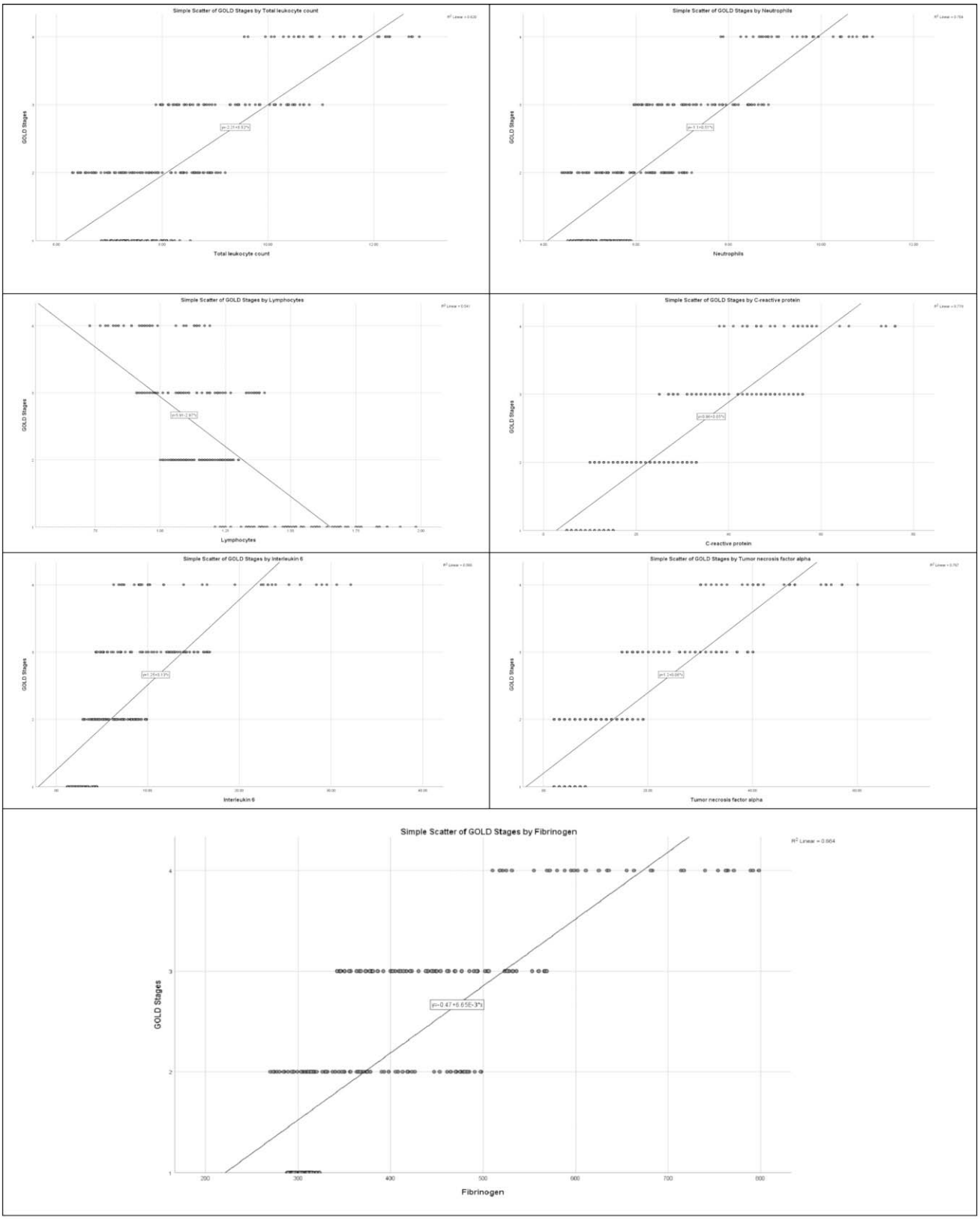


Figure-2: Scatter plots showing the relationship between different blood parameters of systemic immune inflammation severity with disease severity.

response to inflammation. Its synthesis is significantly upregulated during inflammatory events, underscoring its importance in the immune system's defence mechanism.[23] A study found a distinct difference in FIB levels during various stages of COPD, reporting that during acute COPD exacerbations, FIB concentrations were markedly higher, averaging 455.38±159.71mg/dL. Meanwhile, FIB levels were considerably lower in the control group, with an average of 255.50±7.98mg/dl.[24]

The current study's comprehensive examination of systemic inflammation in COPD patients yielded fascinating insights. As the severity of COPD advanced from stage I to stage IV, a marked elevation was noted in inflammatory markers, which included TLC, NEU, TNF-α, IL-6, CRP, and FIB levels. In contrast, a reduction in LYM levels was noted, suggesting a complex interplay between the immune system and the progression of the disease. The study, in conjunction with existing literature [9,25,26], emphasised the intricate relationship between systemic inflammation and COPD severity, furthering our understanding of the pathophysiology underlying this chronic condition.

A significant finding of the current was related to the identification of FIB as a promising biomarker for evaluating immune inflammation severity in COPD patients. Another significant aspect of the study was the identification of key factors predicting FIB levels.

The current study has its limitations. The cross-sectional design allowed for the identification of associations, but precluded the establishment of causality. Further, the study was conducted at a single centre, which affected the generalisability of the findings. Also, the study had a limited sample size. A larger sample might have yielded a more comprehensive understanding of COPD symptomatology and systemic inflammation. Finally, the study did not compare the FIB level with immune inflammatory severity.

Future studies should address these limitations, and investigate each co-morbid condition separately in greater depth to better understand their individual contribution to COPD outcomes.

Conclusion

FIB, a major acute-phase reactant, was found to play a crucial role in the body's response to inflammation. In COPD patients across the GOLD stages, FIB levels demonstrated a significant, non-linear association with immune inflammation severity. The observed patterns implied that FIB might be a more informative marker for specific stages or patient subgroups, rather than uniformly for all patients. To further understand the factors influencing this relationship, future research should concentrate on exploring the underlying mechanisms and connections. Additionally, the development of a more comprehensive panel of biomarkers should be prioritised in order to improve the assessment and management of COPD patients, enabling a more accurate evaluation of disease severity and progression.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: Pro-Gene Diagnostics and Research Laboratory, Mardan, Pakistan.

References

1. Agarwal AK, Raja A, Brown BD. Chronic Obstructive Pulmonary Disease. Treasure Island, FL: StatPearls Publishing; 2025.
2. GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 2020;8:585-96. doi: 10.1016/S2213-2600(20)30105-3
3. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. Eur Respir J 2019;53:1900164. doi: 10.1183/13993003.00164-2019
4. Mehta M, Dhanjal DS, Paudel KR, Singh B, Gupta G, Rajeshkumar S, et al. Cellular signalling pathways mediating the pathogenesis of chronic inflammatory respiratory diseases: an update. Inflammopharmacology 2020;28:795-817. doi: 10.1007/s10787-020-00698-3
5. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347-65. doi: 10.1164/rccm.201204-0596PP
6. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax 2004;59:574-80. doi: 10.1136/thx.2003.019588
7. Man SF, Connett JE, Anthonisen NR, Wise RA, Tashkin DP, Sin DD. C-reactive protein and mortality in mild to moderate chronic obstructive pulmonary disease. Thorax 2006;61:849-53. doi: 10.1136/thx.2006.059808
8. Vilar R, Fish RJ, Casini A, Neerman-Arbez M. Fibrin(ogen) in human disease: both friend and foe. Haematologica 2020;105:284-96. doi: 10.3324/haematol.2019.236901
9. Sun W, Cao Z, Ma Y, Wang J, Zhang L, Luo Z. Fibrinogen, a Promising Marker to Evaluate Severity and Prognosis of Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Retrospective Observational Study. Int J Chron Obstruct Pulmon Dis 2022;17:1299-310. doi: 10.2147/COPD.S361929
10. Singh D, Criner GJ, Dransfield MT, Halpin DMG, Han MK, Lange P, et al. InforMing the PAthway of COPD Treatment (IMPACT) trial: fibrinogen levels predict risk of moderate or severe exacerbations. Respir Res 2021;22:130. doi: 10.1186/s12931-021-01706-y.
11. Lenth RV. Some practical guidelines for effective sample size determination. Am Stat 2001;55:187-93. doi: 10.1198/000313001317098149

12. Solomon C, Baryshnikova E, Tripodi A, Schlimp CJ, Schöchl H, Cadamuro J, et al. Fibrinogen measurement in cardiac surgery with cardiopulmonary bypass: analysis of repeatability and agreement of Clauss method within and between six different laboratories. Thromb Haemost 2014;112:109-17. doi: 10.1160/TH13-12-0997
13. Lisspers K, Larsson K, Janson C, Ställberg B, Tsiligianni I, Gutzwiller FS, et al. Gender differences among Swedish COPD patients: results from the ARCTIC, a real-world retrospective cohort study. NPJ Prim Care Respir Med 2019;29:45. doi: 10.1038/s41533-019-0157-3
14. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017;5:691-706. doi: 10.1016/S2213-2600(17)30293-X
15. Cazzola M, Hanania NA, MacNee W, Rüdell K, Hackford C, Tamimi N. A review of the most common patient-reported outcomes in COPD--revisiting current knowledge and estimating future challenges. Int J Chron Obstruct Pulmon Dis 2015;10:725-38. doi: 10.2147/COPD.S77368
16. Tsiligianni I, Kampouraki M, Ierodiakonou D, Poulonirakis I, Papadokostakis P. COPD patients' characteristics, usual care, and adherence to guidelines: the Greek UNLOCK study. Int J Chron Obstruct Pulmon Dis 2019;14:547-56. doi: 10.2147/COPD.S185362
17. Buttery SC, Zysman M, Vikjord SAA, Hopkinson NS, Jenkins C, Vanfleteren LEGW. Contemporary perspectives in COPD: Patient burden, the role of gender and trajectories of multimorbidity. Respirology 2021;26:419-41. doi: 10.1111/resp.14032
18. Scoditti E, Massaro M, Garbarino S, Toraldo DM. Role of Diet in Chronic Obstructive Pulmonary Disease Prevention and Treatment. Nutrients 2019;11:1357. doi: 10.3390/nu11061357
19. Wu Z, Yang D, Ge Z, Yan M, Wu N, Liu Y. Body mass index of patients with chronic obstructive pulmonary disease is associated with pulmonary function and exacerbations: a retrospective real world research. J Thorac Dis 2018;10:5086-99. doi: 10.21037/jtd.2018.08.67
20. Wheaton AG, Liu Y, Croft JB, VanFrank B, Croxton TL, Punturieri A, et al. Chronic Obstructive Pulmonary Disease and Smoking Status - United States, 2017. MMWR Morb Mortal Wkly Rep 2019;68:533-8. doi: 10.15585/mmwr.mm6824a1
21. Storgaard LH, Hockey HU, Laursen BS, Weinreich UM. Long-term effects of oxygen-enriched high-flow nasal cannula treatment in COPD patients with chronic hypoxemic respiratory failure. Int J Chron Obstruct Pulmon Dis 2018;13:1195-20. doi: 10.2147/COPD.S159666
22. Mannino DM, Valvi D, Mullerova H, Tal-Singer R. Fibrinogen, COPD and mortality in a nationally representative U.S. cohort. COPD 2012;9:359-66. doi: 10.3109/15412555.2012.668249.
23. Vilar R, Fish RJ, Casini A, Neerman-Arbez M. Fibrin(ogen) in human disease: both friend and foe. Haematologica 2020;105:284-96. doi: 10.3324/haematol.2019.236901
24. Agale SA. Serum fibrinogen level in COPD patients - A comparative study. J Med Sci Clin Res 2018;6:701-3.
25. Wei J, Xiong XF, Lin YH, Zheng BX, Cheng DY. Association between serum interleukin-6 concentrations and chronic obstructive pulmonary disease: a systematic review and meta-analysis. PeerJ 2015;3:e1199. doi: 10.7717/peerj.1199
26. Garcia-Rio F, Miravitlles M, Soriano JB, Muñoz L, Duran-Tauleria E, Sánchez G, et al. Systemic inflammation in chronic obstructive pulmonary disease: a population-based study. Respir Res 2010;11:63. doi: 10.1186/1465-9921-11-63.

Authors Contribution:
H: Data Collection, analysis, interpretation, study design, critical revision, drafting.
SA: Data Collection, analysis, interpretation, study design, critical revision, drafting, final approval.
A: Data Collection, analysis, interpretation, study design, drafting.
I & IA: Data Collection, critical revision, drafting.