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Research Article

Association of Serum C - reactive protein And Lactate Levels with Disease Severity in Patients with Stable Chronic Obstructive Pulmonary Disease: A Hospital-Based Cross-Sectional Analytical Study

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Abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation accompanied by systemic inflammation and chronic tissue hypoxia. C-reactive protein (CRP) and serum lactate have emerged as potential biomarkers reflecting these pathophysiological processes. This study evaluated the association of serum CRP and lactate levels with disease severity among patients with stable COPD.

Methods: A hospital-based cross-sectional analytical study was conducted among 100 clinically stable COPD patients attending the Department of General Medicine, Sardar Patel Medical College and P.B.M. Associated Group of Hospitals, Bikaner. Disease severity was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria using post-bronchodilator spirometry. Serum CRP was estimated by the immunoturbidimetric/high-sensitivity assay, while serum lactate was measured using the lactate oxidase method or blood gas analyzer. Biomarker levels were compared across GOLD stages, and their correlations with FEV_1% predicted, CAT score, mMRC dyspnea grade, oxygen saturation, smoking exposure, and exacerbation frequency were evaluated. Multivariable linear regression and receiver operating characteristic (ROC) curve analyses were performed.

Results: Both serum CRP and lactate levels increased significantly with advancing COPD severity ($p<0.001$). Serum CRP demonstrated significant negative correlations with FEV_1% predicted ($r = -0.712$) and oxygen saturation ($r = -0.531$), while positive correlations were observed with CAT score, mMRC dyspnea grade, smoking exposure, and exacerbation frequency (all $p<0.001$). Serum lactate showed an even stronger inverse correlation with FEV_1% predicted ($r = -0.734$) and oxygen saturation ($r = -0.648$), together with significant positive correlations with clinical severity indices (all $p<0.001$). Both biomarkers independently predicted reduced FEV_1 on multivariable analysis. ROC analysis demonstrated good diagnostic performance for identifying severe COPD, with serum lactate (AUC = 0.889) outperforming serum CRP (AUC = 0.861).

Conclusion: Serum CRP and lactate levels were significantly associated with worsening airflow limitation, symptom burden, hypoxemia, and disease severity in patients with stable COPD. Their combined assessment may provide valuable adjunctive information beyond spirometry and facilitate improved clinical evaluation and risk stratification of COPD patients.

Keywords: Chronic Obstructive Pulmonary Disease; C-reactive Protein; Serum Lactate; Biomarkers; Disease Severity; GOLD Classification; Systemic Inflammation

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable, and treatable respiratory disorder characterized by persistent respiratory symptoms and progressive airflow limitation resulting from chronic airway and alveolar abnormalities caused by prolonged exposure to noxious particles and gases [1]. It is a major cause of morbidity and mortality worldwide, imposing a substantial socioeconomic and healthcare burden. According to the World Health Organization, COPD ranks among the leading causes of death globally, with the greatest burden occurring in low- and middle-income countries where tobacco smoking, biomass fuel exposure, environmental pollution, and occupational hazards remain highly prevalent [2,3]. India contributes significantly to the global burden of COPD, with prevalence estimates ranging from 4% to 10%, particularly among smokers and individuals exposed to biomass smoke [4,5].

COPD is now recognized as a multisystem disease extending beyond airflow limitation. Persistent inflammation within the airways triggers systemic inflammatory responses, oxidative stress, endothelial dysfunction, and chronic hypoxemia, all of which contribute to disease progression and extrapulmonary manifestations [6-8]. Although spirometry remains the gold standard for diagnosing and grading COPD severity, it primarily reflects airflow obstruction and provides limited information regarding systemic inflammation, tissue hypoxia, and metabolic disturbances that influence prognosis and clinical outcomes [1]. Consequently, considerable attention has been directed toward identifying easily measurable biomarkers that complement spirometric assessment and improve evaluation of disease severity.

C-reactive protein (CRP) is one of the most extensively studied inflammatory biomarkers in COPD. It is an acute-phase reactant synthesized predominantly by hepatocytes in response to pro-inflammatory cytokines, particularly interleukin-6, and serves as a sensitive indicator of systemic inflammation [9]. Elevated CRP levels have consistently been reported in both stable COPD and acute exacerbations and have been associated with worsening lung function, increased symptom burden, reduced exercise tolerance, frequent exacerbations, cardiovascular complications, and increased mortality [10-14]. Persistent elevation of CRP reflects the chronic low-grade systemic inflammatory state that characterizes COPD and contributes to its progression.

Serum lactate is another important biomarker that reflects tissue hypoxia and metabolic dysfunction. Lactate is generated during anaerobic glycolysis when oxygen delivery is insufficient to meet metabolic demands. In patients with COPD, chronic hypoxemia, ventilation-perfusion mismatch, increased respiratory muscle workload, and impaired oxidative metabolism contribute to elevated lactate production [15-17]. Previous studies have demonstrated that increased lactate levels are associated with severe airflow limitation, prolonged hospitalization, increased need for ventilatory support, and poor clinical outcomes in COPD patients [18,19]. As lactate directly reflects impaired tissue oxygen utilization, it may provide valuable information regarding disease severity and physiological compromise.

Although CRP and lactate represent distinct pathophysiological pathways—systemic inflammation and tissue hypoxia—they are closely interconnected in the progression of COPD. Simultaneous assessment of these biomarkers may therefore provide a more

comprehensive evaluation of disease severity than spirometry alone [20]. However, studies evaluating their combined association with stable COPD severity, particularly in the Indian population, remain limited. Therefore, the present study was undertaken to evaluate the association of serum C-reactive protein and lactate levels with disease severity in patients with stable COPD and to determine their potential role as adjunctive biomarkers for clinical assessment and risk stratification.

Materials and Methods

This hospital-based cross-sectional analytical study was conducted in the Department of General Medicine, Sardar Patel Medical College and P.B.M. Associated Group of Hospitals, Bikaner, Rajasthan, over a period of six months after obtaining approval from the Institutional Ethics Committee. The study enrolled clinically stable patients aged ≥40 years with a confirmed diagnosis of Chronic Obstructive Pulmonary Disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, defined by a post-bronchodilator forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) ratio of <0.70. Patients with acute exacerbation of COPD within the preceding four weeks, active respiratory infection, significant cardiac failure (New York Heart Association class III–IV), chronic liver disease, advanced chronic kidney disease (estimated glomerular filtration rate <30 mL/min/1.73 m^2), active malignancy, systemic inflammatory disorders, recent major surgery or trauma, pregnancy, or those receiving medications likely to interfere with inflammatory or metabolic biomarker estimation were excluded from the study.

The sample size was estimated using Fisher's Z transformation formula for correlation studies, assuming an expected correlation coefficient (r) of 0.30, a 95% confidence level, and 80% statistical power. The minimum calculated sample size was 85 participants. To improve statistical precision and compensate for possible incomplete investigations, 100 consecutive eligible patients fulfilling the inclusion and exclusion criteria were recruited after obtaining written informed consent.

A detailed clinical evaluation was performed for all participants, including demographic characteristics, smoking status and smoking exposure (pack-years), duration of COPD, history of exacerbations during the previous 12 months, hospitalization history, associated comorbidities, and maintenance treatment. Anthropometric measurements were recorded using standard techniques, and body mass index (BMI) was calculated. Symptom severity was assessed using the Modified Medical Research Council (mMRC) dyspnea scale and the COPD Assessment Test (CAT). Spirometry was performed before and after bronchodilator administration according to standard recommendations, and post-bronchodilator FEV_1 percentage predicted values were used to classify disease severity into GOLD stages I–IV.

Venous blood samples were collected under aseptic precautions, preferably in the fasting state, and processed according to standard laboratory protocols. Serum C-reactive protein (CRP) levels were estimated using the immunoturbidimetric/high-sensitivity CRP assay, while serum lactate levels were measured using the lactate oxidase method or a blood gas analyzer as per institutional laboratory availability. Particular care was taken to minimize pre-analytical errors during lactate estimation by ensuring prompt sample transport and immediate processing. Routine laboratory investigations, including complete blood count, serum creatinine, and fasting blood glucose, were performed as clinically indicated.

Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0. Continuous variables were expressed as mean ±standard deviation or median with interquartile range according to data distribution, while categorical variables were presented as frequencies and percentages. Normality of data was assessed using the Shapiro–Wilk test. Serum CRP and lactate levels were compared across GOLD stages using the Kruskal–Wallis test and one-way analysis of variance (ANOVA),

respectively. Correlations between biomarker levels and FEV_1% predicted, CAT score, mMRC dyspnea grade, oxygen saturation, smoking exposure, and exacerbation frequency were assessed using Spearman's rank correlation coefficient for CRP and Pearson's correlation coefficient for lactate, as appropriate. Multivariable linear regression analysis was performed to identify independent predictors of reduced FEV_1% predicted after adjusting for age, body mass index, and smoking exposure. Receiver operating characteristic (ROC) curve analysis was carried out to evaluate the diagnostic performance of serum CRP and lactate in identifying severe COPD (GOLD stage III–IV). A p-value of <0.05 was considered statistically significant.

The study was approved by the Institutional Ethics Committee of Sardar Patel Medical College, Bikaner. Written informed consent was obtained from all participants before enrollment, and confidentiality and anonymity of participant information were maintained throughout the study.

Results

A total of 100 clinically stable patients with COPD were enrolled in the study. The baseline demographic and clinical characteristics of the study population are summarized in Table 1. The majority of participants were males (74%), with a mean age of 63.48 ±9.12 years. Most patients belonged to the GOLD II (39%) and GOLD III (34%) categories. The mean smoking exposure among ever-smokers was 13.05 ±7.95 pack-years, while the mean post-bronchodilator FEV_1 was 48.62 ±18.94% predicted.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Participants (n = 100)

Variable	Value
Age (years), Mean ± SD	63.48 ± 9.12
Male sex, n (%)	74 (74.0)
Rural residence, n (%)	78 (78.0)
Current/Former smokers, n (%)	82 (82.0)
Smoking exposure (pack-years), Mean ± SD	13.05 ± 7.95
BMI (kg/m²), Mean ± SD	21.84 ± 3.76
SpO_2 on room air (%), Mean ± SD	91.62 ± 4.18
Duration of COPD (years), Mean ± SD	8.36 ± 4.72
CAT score, Mean ± SD	18.94 ± 6.48
mMRC dyspnea grade, Mean ± SD	2.71 ± 0.91
FEV_1 (% predicted), Mean ± SD	48.62 ± 18.94
GOLD I, n (%)	12 (12.0)
GOLD II, n (%)	39 (39.0)
GOLD III, n (%)	34 (34.0)
GOLD IV, n (%)	15 (15.0)

Both serum C-reactive protein (CRP) and serum lactate levels increased significantly with advancing COPD severity. Patients with GOLD IV disease exhibited the highest concentrations of both biomarkers, and the differences across GOLD stages were statistically significant (**Table 2**).

Table 2. Comparison of Serum C-Reactive Protein and Serum Lactate Levels Across GOLD Stages

GOLD Stage	CRP (mg/dL) Mean ± SD	Lactate (mmol/L) Mean ± SD
GOLD I (n=12)	3.18 ± 1.26	1.34 ± 0.32
GOLD II (n=39)	5.42 ± 1.84	1.82 ± 0.48
GOLD III (n=34)	8.64 ± 2.71	2.48 ± 0.56
GOLD IV (n=15)	12.16 ± 3.82	3.36 ± 0.72

Biomarker	Statistical Test	Test Value	p-value
Serum CRP	Kruskal–Wallis	H = 41.72	<0.001
Serum Lactate	One-way ANOVA	F = 39.14	<0.001

Significant associations were observed between both biomarkers and all evaluated clinical severity parameters (**Table 3**). Serum lactate demonstrated a stronger inverse correlation with FEV_1% predicted and oxygen saturation than serum CRP.

Table 3. Correlation of Serum C-Reactive Protein and Serum Lactate with Clinical Severity Parameters

Parameter	CRP (r)	Lactate (r)	p-value
FEV_1 (% predicted)	-0.712	-0.734	<0.001
CAT score	0.641	0.628	<0.001
mMRC dyspnea grade	0.604	0.586	<0.001
SpO_2 (%)	-0.531	-0.648	<0.001
Exacerbation frequency	0.516	0.554	<0.001
Smoking pack-years	0.382	0.401	<0.001

Multivariable linear regression analysis identified both serum CRP and serum lactate as independent predictors of reduced FEV_1 after adjustment for age, body mass index, and smoking exposure (**Table 4**). Among the evaluated biomarkers, serum lactate demonstrated the strongest independent association with airflow limitation.

Table 4. Multivariable Linear Regression Analysis for Predictors of Reduced FEV_1 (% Predicted)

Variable	β Coefficient	Standard Error	t-value	p-value
Serum CRP	-1.86	0.64	-2.91	0.005
Serum Lactate	-5.42	1.38	-3.93	<0.001
Age	-0.38	0.14	-2.71	0.008
BMI	0.72	0.29	2.48	0.015
Smoking pack-years	-0.46	0.11	-4.18	<0.001

Model Performance: $R^2 = 0.684$; Adjusted $R^2 = 0.661$; Overall model $p < 0.001$.

Receiver operating characteristic analysis demonstrated that both biomarkers showed good discriminatory ability for identifying severe COPD (GOLD III–IV), with serum lactate exhibiting superior diagnostic performance compared with serum CRP (**Table 5**).

Table 5. Receiver Operating Characteristic Analysis of Serum C-Reactive Protein and Serum Lactate for Predicting Severe COPD

Biomarker	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)	p-value
Serum CRP	>7.4 mg/dL	0.861 (0.789–0.932)	83.7	80.4	<0.001
Serum Lactate	>2.3 mmol/L	0.889 (0.824–0.955)	87.8	82.4	<0.001

Serum lactate demonstrated the highest area under the receiver operating characteristic curve, indicating superior accuracy for identifying patients with severe COPD compared with serum C-reactive protein.

Discussion

The present hospital-based cross-sectional analytical study evaluated the association of serum C-reactive protein (CRP) and serum lactate levels with disease severity among patients with stable Chronic Obstructive Pulmonary Disease (COPD). The study demonstrated that both biomarkers increased progressively with advancing GOLD stage and showed significant correlations with airflow limitation, symptom burden, hypoxemia, smoking exposure, and exacerbation frequency.

Furthermore, serum CRP and lactate emerged as independent predictors of reduced lung function, while receiver operating characteristic (ROC) analysis demonstrated good diagnostic performance for identifying severe COPD. These findings reinforce the concept that systemic inflammation and tissue hypoxia play central roles in COPD progression and that both biomarkers may serve as valuable adjuncts in assessing disease severity.

The mean serum CRP level in the present study was 7.26 ±3.94 mg/dL, and nearly half of the participants had CRP levels exceeding 6 mg/dL. Serum CRP levels increased significantly from 3.18 ±1.26 mg/dL in patients with GOLD I disease to 12.16 ±3.82 mg/dL among those with GOLD IV disease. Similar findings have been reported by Gan et al. [10], whose systematic review demonstrated significantly higher CRP levels in patients with COPD than in healthy controls, supporting the presence of persistent systemic inflammation. Zhang et al. [12], in a meta-analysis, also reported significantly elevated CRP concentrations among patients with severe COPD compared with those having mild disease. Karadag et al. [21] further demonstrated a positive association between CRP levels and disease severity, while the ECLIPSE study by Agustí et al. [14] identified persistent systemic inflammation, characterized by elevated CRP, as an important predictor of poor clinical outcomes. Collectively, these studies support the findings of the present study and emphasize the role of CRP as a reliable marker of systemic inflammatory activity in COPD. Serum CRP demonstrated a significant negative correlation with FEV_1% predicted and oxygen saturation, while showing positive correlations with CAT score, mMRC dyspnea grade, smoking exposure, and exacerbation frequency. These observations indicate that increasing systemic inflammation is closely associated with worsening pulmonary function, greater symptom burden, and increased clinical instability. Similar findings have been reported by Leuzzi et al. [13], who demonstrated that elevated baseline CRP levels were associated with increased mortality among COPD patients. Agustí et al. [11] also observed that patients with persistent systemic inflammation experienced more frequent exacerbations and poorer long-term outcomes despite comparable spirometric impairment. These findings suggest that CRP reflects not only inflammatory burden but also the overall clinical severity of COPD.

The present study also demonstrated that serum lactate levels increased progressively with disease severity, with mean values rising from 1.34 ±0.32 mmol/L in GOLD I patients to 3.36 ±0.72 mmol/L in GOLD IV patients. Serum lactate showed the strongest inverse correlation with FEV_1% predicted ($r = –0.734$) and oxygen saturation, indicating a close relationship between tissue hypoxia and progressive airflow limitation. Similar observations have been reported by MacDonald et al. [18], who demonstrated that elevated blood lactate levels were associated with respiratory failure, prolonged hospitalization, and adverse outcomes in patients with acute exacerbations of COPD. Maltais et al. [17] reported exaggerated lactate accumulation during exercise among patients with severe COPD, reflecting impaired oxidative metabolism and skeletal muscle dysfunction. Likewise, Engelen et al. [22] highlighted the contribution of respiratory muscle fatigue to increased lactate production in COPD, while Xie et al. [19] demonstrated that elevated lactate-based indices independently predicted mortality among critically ill COPD patients. These findings collectively support the role of serum lactate as an objective marker of tissue hypoxia and metabolic stress in COPD.

Multivariable regression analysis in the present study identified both serum CRP and serum lactate as independent predictors of reduced FEV_1 after adjustment for age, body mass index, and smoking exposure. Receiver operating characteristic analysis further demonstrated that both biomarkers had good diagnostic performance for identifying severe COPD, with serum lactate showing superior discriminatory ability compared with CRP. This finding is biologically plausible because lactate directly reflects impaired tissue oxygen utilization and increasing metabolic stress associated with

advanced disease. The combined assessment of CRP and lactate therefore provides complementary information by simultaneously evaluating systemic inflammation and tissue hypoxia, two fundamental mechanisms underlying COPD progression.

The present study has certain limitations. Its cross-sectional design precludes assessment of temporal or causal relationships, and the single-center setting with a relatively modest sample size may limit the generalizability of the findings. Nevertheless, the study provides important evidence regarding the association of serum CRP and lactate with COPD severity in an Indian population. Future large-scale multicentric prospective studies are warranted to validate these findings and determine the prognostic value of these biomarkers in predicting exacerbations, hospitalization, and long-term clinical outcomes.

Conclusion

The present study demonstrated that serum C-reactive protein and serum lactate levels increased significantly with advancing severity of Chronic Obstructive Pulmonary Disease and were closely associated with worsening airflow limitation, greater symptom burden, hypoxemia, smoking exposure, and frequent exacerbations. Both biomarkers independently predicted reduced FEV_1 after adjustment for relevant clinical variables, highlighting their value in assessing disease severity. Receiver operating characteristic analysis further demonstrated good diagnostic performance of both biomarkers for identifying severe COPD, with serum lactate showing superior discriminatory ability. These findings suggest that CRP and lactate reflect the underlying systemic inflammation and tissue hypoxia that contribute to COPD progression. As both biomarkers are readily available and relatively inexpensive laboratory investigations, they may serve as useful adjuncts to spirometry for disease assessment and risk stratification. Further multicentric prospective studies with larger sample sizes are recommended to validate their prognostic utility and clinical applicability in routine COPD management.

Declarations

Funding: Nil.

Conflicts of Interest: The authors declare no conflicts of interest.

Ethical Approval: The study was approved by the Institutional Ethics Committee of Sardar Patel Medical College, Bikaner, Rajasthan.

Informed Consent: Written informed consent was obtained from all study participants before enrollment.

Author Contributions: All authors contributed to the study conception, data collection, analysis, manuscript preparation, and approved the final manuscript.

Data Availability: The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Use of Artificial Intelligence: The authors declare that no artificial intelligence tools were used in the conduct, analysis, or preparation of this research.

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