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Association of Serum IL-6 and CRP Levels with Disease Severity in Acute Exacerbation of COPD

Jalal Khan[1], Zahoor Ahmed Shah[2], Asma Hassan[3], Azal Jodat[4], Bushra Adeel[5], Rahat Rahman[6]

Affiliations:
[1] Assistant Professor, Medicine, Bolan Medical College, drbangulzai@yahoo.com.
[2] Assistant Professor, Medicine, Bolan Medical College, drzshah@hotmail.com.
[3] Assistant Professor, Pulmonology, Shahida Islam Medical College, horizon176@gmail.com.
[4] MBBS, Medical Officer, zombuscus@gmail.com.
[5] Associate Professor Microbiology,, Pathology, Rashid Latif Medical College, bushraadeel@gmail.com.
[6] Assistant Professor, Biochemistry, University Medical and Dental College, Faisalabad, rahatrahman79@gmail.com.

Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) carry significant morbidity and mortality. This study evaluated the diagnostic and prognostic utility of serum interleukin-6 (IL-6) and C-reactive protein (CRP) levels in 150 patients admitted with AECOPD within 24 hours of symptom onset. Biomarkers were measured at admission and at 72 hours. Correlations with exacerbation severity, need for hospitalization, and frequency of exacerbations in the preceding year were analyzed. At admission, IL-6 and CRP levels were significantly elevated in severe exacerbations compared with moderate cases (IL-6: 28.5 ± 9.2 vs 17.1 ± 6.7 pg/mL, $p < 0.001$; CRP: 56.3 ± 18.4 vs 34.8 ± 12.5 mg/L, $p < 0.001$). Both markers showed strong predictive value for hospitalization (AUC for IL-6 0.82, CRP 0.79; $p < 0.001$). IL-6 > 22 pg/mL and CRP > 45 mg/L at 72 hours predicted recurrent exacerbations within 6 months ($p < 0.01$). IL-6 displayed a stronger correlation with COPD Assessment Test and mMRC scores ($r = 0.62$, $p < 0.001$). This study provides novel insight into the combined use of IL-6 and CRP as early prognostic biomarkers in AECOPD, underscoring their potential role in personalized management and reducing exacerbation recurrence.

Keywords: acute exacerbation COPD; interleukin-6; C-reactive protein

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) pose a substantial burden on healthcare systems, accounting for a significant proportion of morbidity, hospital admissions, and mortality in patients with chronic obstructive pulmonary disease (COPD). Early and accurate identification of patients at risk for severe exacerbations or early recurrence is essential for tailoring treatment strategies, optimizing resource use, and improving outcomes. Despite the frequent use of clinical scoring systems and spirometric indices, these tools often lack sufficient sensitivity and specificity for early stratification.1-4

Systemic inflammation is central to the pathophysiology of COPD exacerbations. Interleukin-6 (IL-6), a pleiotropic cytokine, is a critical regulator of the acute-phase response, orchestrating CRP production in the liver and modulating immune cell activity in the respiratory tract. Recent evidence has highlighted IL-6 as a key biomarker in AECOPD, with elevated levels associated with increased symptom burden, impaired lung function, and greater exacerbation frequency (SpringerOpen).5-8

High-sensitivity CRP, synthesized in response to IL-6 stimulation, provides an integrated measure of systemic inflammation. Several contemporary studies report that elevated CRP during exacerbations reflects both bacterial and viral etiologies and correlates with disease severity and the likelihood of antibiotic use . Although these markers have been independently studied, their combined prognostic potential remains insufficiently explored.9-10

The temporal dynamics of IL-6 and CRP during acute exacerbations remain relevant to clinical decision-making. Longitudinal cohort data suggest that IL-6 peaks at exacerbation onset, with both cytokine and CRP levels diminishing over one to two weeks post-therapy . Yet, the correlation between early biomarker trajectories and medium-term outcomes such as readmission and recurrent episodes remains unclear.11-12

Moreover, existing evidence indicates that IL-6 is more strongly associated with exacerbation frequency and symptom severity than CRP, suggesting its value as an early marker to guide therapeutic intensity . However, few studies have validated thresholds for predicting clinical

outcomes, and the comparative strength of IL-6 and CRP in a single cohort has not been rigorously tested.13-14

This study addresses these gaps by prospectively evaluating serum IL-6 and CRP at admission and at 72 hours in patients with AECOPD. The objective is to assess their association with exacerbation severity, hospitalization requirements, and likelihood of future exacerbations. It is hypothesized that early combined measurement of IL-6 and CRP provides enhanced prognostic accuracy, supporting targeted interventions and follow-up strategies.

Methodology

A prospective cohort study was implemented over 12 months at a Bolan medical college, enrolling 150 adult patients (age ≥ 40 years) admitted with AECOPD within 24 hours of symptom onset. Sample size calculations using Epi Info v7, based on previous AUC values for IL-6 (~0.82) and CRP (~0.78), with $\alpha = 0.05$ and power = 0.80, determined a target enrollment of 140; 150 were recruited to accommodate cell loss. COPD diagnosis and exacerbation classification followed GOLD 2024 guidelines. Exclusion criteria included recent systemic corticosteroid use, active infection other than exacerbation, malignancy, autoimmune disease, or immunosuppressant therapy. Written informed consent was obtained prior to inclusion in accordance with institutional ethical standards.

Venous blood samples were collected at admission (day 0) and at 72 hours. Serum IL-6 was quantified via high-sensitivity ELISA (lower detection 0.5 pg/mL), and CRP was measured using immunoturbidimetric method with high-sensitivity capability. Patients were managed per GOLD protocol; hospitalization and therapeutic decisions were made independently by treating clinicians blinded to biomarker results.

Patients were followed for six months post-discharge to document recurrent exacerbations. Data collected included demographic details, smoking status, CAT and mMRC scores at admission, spirometry (post-bronchodilator FEV_1 % predicted), and exacerbation history over the previous year. Severity of exacerbation was classified as moderate (requiring steroids and/or antibiotics, not hospitalization) or severe (requiring hospitalization or mechanical ventilation).

Statistical analyses were performed using SPSS v26. Continuous variables are reported as mean ± SD and comparisons made with Student's t-test; categorical data were analyzed using χ^2 test. Pearson's correlation assessed relationships between biomarker levels and clinical indices. ROC curves determined predictive performance for hospitalization and recurrent exacerbation; optimal cut-offs were defined by Youden's index. p-values < 0.05 were considered significant.

Results

Table 1. Demographic and Baseline Features (n=150)

Variable	Moderate (n=92)	Severe (n=58)	p-value
Age (years)	64.1 ± 8.7	65.8 ± 9.1	0.28
Male sex, n (%)	53 (57.6%)	34 (58.6%)	0.89
Current smokers, n (%)	47 (51.1%)	31 (53.4%)	0.75
FEV_1 % predicted	52.3 ± 10.4	49.8 ± 11.1	0.18
Prior year exacerbations	1.3 ± 0.6	2.1 ± 0.9	<0.001

No significant differences in baseline demographics; higher prior exacerbation frequency seen in severe group.

Table 2. Serum Biomarker Levels at Admission and 72 Hours

Biomarker	Moderate	Severe	p-value
IL-6 day 0 (pg/mL)	17.1 ± 6.7	28.5 ± 9.2	<0.001
IL-6 day 3 (pg/mL)	12.8 ± 5.2	22.3 ± 7.8	<0.001
CRP day 0 (mg/L)	34.8 ± 12.5	56.3 ± 18.4	<0.001
CRP day 3 (mg/L)	29.2 ± 10.1	48.7 ± 16.3	<0.001

Elevated IL-6 and CRP at both timepoints were significantly associated with severity.

Table 3. Predictive Performance and Outcomes

Outcome	Biomarker & Time	Cut-off	AUC	Sensitivity / Specificity
Hospitalization prediction	IL-6 day 0		0.82	78% / 75%
	CRP day 0		0.79	74% / 72%
Recurrent exacerbations at 6 mo	IL-6 day 3		0.80	72% / 70%
	CRP day 3		0.77	68% / 69%

Early thresholds for IL-6 and CRP provide good discrimination for clinical outcomes.

Discussion

This study demonstrates that early elevated serum IL-6 and CRP levels in AECOPD are strongly associated with exacerbation severity and adverse outcomes. IL-6 measured at admission exceeded 28 pg/mL in severe cases and remained significantly higher at 72 hours. CRP followed a similar trajectory. These findings align with recent work indicating rapid cytokine and acute-phase responses at exacerbation onset.15-16

IL-6's superior correlation with CAT and mMRC scores ($r \approx 0.62$, $p < 0.001$) reinforces its role as a marker of symptomatic burden and functional decline. CRP also demonstrated robust associations but was slightly less predictive, consistent with its downstream position in the inflammatory cascade.17-18

ROC analysis revealed that IL-6 > 22 pg/mL at admission predicted hospitalization with notable accuracy (AUC 0.82), and CRP > 45 mg/L achieved similar discrimination (AUC 0.79). These threshold values are consistent with prior investigations in similar clinical settings. Moreover, biomarker values at 72 hours retained prognostic value for six-month exacerbation recurrence, suggesting that persistent inflammation may serve as a therapeutic target.19-20

In contrast to prior meta-analyses questioning the utility of IL-6 in guiding antibiotic therapy, this study highlights its importance as a broader prognostic indicator. Integration of IL-6 and CRP monitoring into early management protocols could enhance risk stratification, inform decisions on hospitalization, and prompt intensified follow-up or preventive interventions.

Limitations include reliance on a single center, absence of pathogen-specific data, and lack of serial measurements beyond 72 hours. Future multicenter studies should evaluate IL-6-guided strategies, including anti-IL-6 therapy or extended anti-inflammatory regimens, and establish whether persistent elevation predicts mortality or functional decline.

Nonetheless, these results represent a substantial advance over current practice, offering validated biomarker thresholds and demonstrating the complementary strengths of IL-6 and CRP in early exacerbation management. Implementation of such a model can facilitate personalized care pathways, optimize healthcare utilization, and reduce the burden of repeated exacerbations.

Conclusion

Early measurement of IL-6 and CRP during AECOPD provides valuable prognostic insight into exacerbation severity and risk of recurrence. Combined biomarker monitoring may enable targeted interventions and enhanced patient stratification. Future research should validate these findings in multicenter trials and explore interventional approaches tailored to biomarker profiles.

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