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Original Article

Predictive value of admission levels of IL-6 and PCT combined with the peri-treatment change in NLR (ΔNLR) for hospital length of stay in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD)

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Abstract: Background: The accurate prediction of hospital length of stay (LOS) for patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) remains a clinical challenge. While inflammatory biomarkers like Neutrophil-to-Lymphocyte Ratio (NLR), Interleukin-6 (IL-6), and Procalcitonin (PCT) are associated with severity, the predictive value of their peri-treatment dynamic changes, particularly ΔNLR, combined for LOS is not well established. Objective: This study aimed to evaluate the predictive value of ΔNLR combined with admission levels of IL-6 and PCT levels for hospital LOS in patients with AECOPD. Methods: A single-center retrospective cohort study was conducted involving 328 hospitalized AECOPD patients. Patients were divided into short-LOS (≤ 7 days, n = 186) and long-LOS (> 7 days, n = 142) groups based on the average LOS. Data on demographics, clinical characteristics, and laboratory parameters (including NLR, IL-6, and PCT before and after treatment) were collected. The predictive performance of ΔNLR, IL-6, and PCT, both individually and in combination, for long LOS was assessed using Receiver Operating Characteristic (ROC) curve analysis. Multivariate logistic regression was used to identify independent risk factors for long LOS. Results: The long-LOS group exhibited a significantly lower ΔNLR (1.2 ± 0.8 vs. 3.5 ± 1.2, P < 0.001) and higher IL-6 [45.2 (28.1, 62.3) vs. 22.5 (15.3, 30.1) pg/mL, P < 0.001] and PCT levels [0.8 (0.4, 1.5) vs. 0.3 (0.1, 0.6) ng/mL, P < 0.001]. ΔNLR was negatively correlated with LOS (r = -0.289, P < 0.001), while IL-6 (r = 0.584) and PCT (r = 0.507) were positively correlated (both P < 0.001). The combination of ΔNLR, IL-6, and PCT demonstrated the highest predictive efficacy (AUC = 0.980, 95% CI: 0.969-0.991), significantly outperforming any single indicator or the DECAF Score (all P < 0.05). At optimal cut-offs (ΔNLR ≤ 2.1, IL-6 ≥ 33.5 pg/mL, PCT ≥ 0.4 ng/mL), sensitivity was 82.3% and specificity 85.1%. Multivariate analysis confirmed ΔNLR ≤ 2.1 (OR = 3.252), IL-6 ≥ 33.5 pg/mL (OR = 2.893), PCT ≥ 0.4 ng/mL (OR = 2.561), and admission FEV_1% pred < 45% (OR = 2.183) as independent risk factors for long LOS (all P < 0.05). Conclusions: The combination of peri-treatment ΔNLR, IL-6, and PCT is a potent predictor for prolonged hospitalization in AECOPD, being superior to individual biomarkers. This model, utilizing routine clinical data, can facilitate early identification of high-risk patients and optimize resource allocation.

Keywords: AECOPD, length of hospital stay, neutrophil-to-lymphocyte ratio (NLR), interleukin-6 (IL-6), procalcitonin (PCT), predictive value

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) represents a critical phase in the course of chronic obstructive pulmonary disease (COPD), characterized by an acute worsening of respiratory symptoms such as cough, sputum production, and dyspnea [1-3]. Patients often require hospitalization due to symptom deterioration, and the duration of hospital stay is not only directly associated with treatment costs and quality of life but also

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closely linked to disease prognosis [4]. However, clinically applicable, precise, and convenient indicators for predicting hospital length of stay (LOS) in AECOPD patients remain lacking, leading to suboptimal dynamic adjustment of treatment plans and inefficient allocation of medical resources - particularly hospital beds [5-7].

The pathogenesis of AECOPD is closely associated with a marked intensification of airway and systemic inflammatory responses [8, 9]. During this pathological process, immune cells such as neutrophils and lymphocytes, along with inflammatory mediators including interleukin-6 (IL-6) and procalcitonin (PCT), play pivotal roles [10, 11]. Specifically, the neutrophil-to-lymphocyte ratio (NLR) - a simple and readily accessible biomarker reflecting systemic inflammation and immune balance - has demonstrated potential prognostic value in various infectious and respiratory diseases [12]. IL-6, a key pro-inflammatory cytokine, directly reflects the intensity of the inflammatory response, while PCT is a widely used biomarker for diagnosing bacterial infections and assessing sepsis severity [13, 14]. All three markers may be closely associated with the severity of AECOPD and therapeutic response, thereby influencing hospital LOS [15-17].

Existing studies have shown that levels of NLR, IL-6, and PCT at hospital admission are significantly elevated in AECOPD patients compared to those in stable COPD, and correlate positively with disease severity [18, 19]. Some studies have explored the predictive value of individual inflammatory markers for hospital LOS or prognosis in AECOPD, yet findings have shown heterogeneity [20, 21]. Notably, research investigating the combined predictive value of dynamic changes in NLR (i.e., ΔNLR) together with IL-6 and PCT for hospital LOS remains scarce. Current literature predominantly focuses on static measurements at admission, overlooking the potential prognostic implications of evolving inflammatory status during treatment [22]. Moreover, systematic analyses of multi-marker combinations for predicting hospital LOS in AECOPD are lacking, hindering the clinical need for precise prediction and personalized management [23].

Against this background, this study aims to evaluate the predictive value of ΔNLR combined with IL-6 and PCT levels for hospital LOS in AECOPD patients, systematically comparing the predictive performance of individual versus combined biomarkers, to identify an optimal predictive model. From a clinical perspective, this research may provide a reliable and practical tool for predicting hospital LOS in AECOPD, facilitating early identification of high-risk patients, optimizing individualized treatment strategies, shortening hospital stays, and reducing healthcare costs. From an academic standpoint, the study will enrich the biological marker framework for AECOPD prognosis and offer new theoretical insights and practical evidence for the application of inflammatory biomarkers in outcome prediction for respiratory diseases.

Materials and methods

Patient selection

This study is a single-center retrospective cohort study. The study population consisted of adult inpatients admitted to The Nuclear Industry 417 Hospital between January 1, 2021, and June 30, 2024. Using the hospital's Electronic Medical Record (EMR) system and Laboratory Information System (LIS), we systematically retrieved and initially screened all adult patients diagnosed with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). This study has been approved by the Ethics Committee of The Nuclear Industry 417 Hospital. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

The inclusion criteria were as follows: (1) diagnosis of chronic obstructive pulmonary disease (COPD) consistent with the "Guidelines for the Diagnosis and Management of Chronic Obstructive Pulmonary Disease (2021 Revised Edition)" and currently in an acute exacerbation phase; (2) age ≥ 18 years; and (3) availability of complete clinical data during hospitalization, including neutrophil-to-lymphocyte ratio (NLR), interleukin-6 (IL-6), and procalcitonin (PCT) measurements both before and after treatment.

The exclusion criteria included: (1) coexisting severe failure of major organs such as the heart, liver, or kidneys; (2) concurrent malignant tumors, hematological disorders, or auto-

immune diseases; (3) history of severe infection (e.g., pneumonia or sepsis) or use of immunosuppressive agents within the past month; (4) pregnancy or lactation; and (5) missing critical laboratory data, rendering it impossible to calculate ΔNLR or obtain IL-6 and PCT values. A total of 328 hospitalized AECOPD patients meeting all eligibility criteria were ultimately included in the study.

Data extraction

Two researchers who had received uniform training independently extracted the required information from the electronic medical record system, using a pre-specified standardized data collection form. The extracted information included demographic and clinical characteristics such as sex, age, smoking history, and comorbidities (e.g., hypertension and diabetes); pulmonary function factors, specifically the percentage of predicted forced expiratory volume in one second (FEV_1% pred) at admission; and laboratory parameters, including complete blood count, interleukin-6 (IL-6), and procalcitonin (PCT) measured within 24 hours of admission (pre-treatment) and again within 24 hours prior to discharge or at clinical stabilization (post-treatment). The neutrophil-to-lymphocyte ratio (NLR) was calculated as the ratio of neutrophil count to lymphocyte count, and ΔNLR was defined as the difference between pre-treatment and post-treatment NLR values (ΔNLR = pre-treatment NLR - post-treatment NLR). Additionally, data on treatment regimens and total hospital length of stay (from admission to discharge) were recorded.

All laboratory tests were performed in the hospital's clinical laboratory. NLR was derived from complete blood count results obtained using an automated hematology analyzer (Sysmex XN-1000, Sysmex Corporation, Japan). Interleukin-6 (IL-6) and procalcitonin (PCT) were quantitatively measured using the i-3000 fully automated chemiluminescence immunoassay system and its corresponding reagents (Sichuan Maccura Biotechnology Co., Ltd.) based on the chemiluminescence immunoassay method. All testing procedures strictly adhered to standard operating protocols, and data accuracy was ensured through internal quality control and external quality assessment programs. In cases where the two researchers' extracted data disagreed, a third researcher reviewed and resolved the discrepancy to ensure data consistency.

Additionally, data on key treatments during hospitalization, including the use of systemic corticosteroids, antibiotics, and non-invasive ventilation (NIV), were collected to account for their potential confounding effects on both biomarker levels and length of stay.

To benchmark the performance of our biomarker model against an established clinical tool, the DECAF score was calculated for each patient where possible. The DECAF score incorporates the following components: dyspnea (eMRCD scale), eosinopenia, consolidation on chest radiograph, acidemia (pH < 7.3), and atrial fibrillation [24].

Outcome measures

The primary outcome of this study was length of hospital stay (LOS). Based on the average LOS of AECOPD patients at our hospital between 2021 and 2024 (7.2 days), patients were dichotomized into a short-stay group (≤ 7 days) and a long-stay group (> 7 days). The study aimed to evaluate the predictive value of ΔNLR, IL-6, and PCT - both individually and in combination - for the risk of prolonged hospitalization, and to identify independent risk factors associated with extended LOS in AECOPD patients.

Statistical analysis

Statistical analyses were performed using SPSS version 29.0. Continuous variables were first tested for normality using the Shapiro-Wilk test. Data that followed a normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared between groups using the independent-samples t-test. Non-normally distributed data were presented as median (interquartile range) [M (Q1, Q3)] and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as number (percentage) [n (%)] and analyzed using the chi-square (χ^2) test or Fisher's exact test when the expected cell frequency was less than 5. Pearson or Spearman correlation analyses were used to assess the relationships between ΔNLR, IL-6, PCT, and length of hospital stay (LOS), depending on data distribution. The predictive performance of each biomarker

Table 1. Comparison of baseline characteristics between AECOPD patients with short and long hospital stays

Variable	Total Sample (n = 328)	Short-Stay Group (n = 186)	Long-Stay Group (n = 142)	t/χ^2	*P* Value
Sex, male/female [n (%)]	201 (61.3%)/127 (38.7%)	112 (60.2%)/74 (39.8%)	89 (62.7%)/53 (37.3%)	0.278	0.596
Age (years, mean ± SD)	66.3 ± 8.7	65.3 ± 8.2	67.5 ± 9.1	-2.311	0.022
Smoking history [n (%)]	180 (54.9%)	98 (52.7%)	82 (57.7%)	0.890	0.346
Hypertension [n (%)]	87 (26.5%)	42 (22.6%)	45 (31.7%)	3.924	0.048
Diabetes [n (%)]	60 (18.3%)	28 (15.1%)	32 (22.5%)	3.852	0.050
FEV_1% pred at admission (%, mean ± SD)	45.3 ± 10.1	48.2 ± 10.3	41.5 ± 9.8	5.681	< 0.001
Systemic Corticosteroid Use [n (%)]	210 (64.0%)	100 (53.8%)	110 (77.5%)	23.567	< 0.001
Antibiotic Use [n (%)]	290 (88.4%)	158 (84.9%)	132 (92.9%)	6.892	0.009
Non-Invasive Ventilation Use [n (%)]	85 (25.9%)	30 (16.1%)	55 (38.7%)	24.321	< 0.001
Bronchodilator Use [n (%)]	315 (96.0%)	179 (96.2%)	136 (95.8%)	0.068	0.794

Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; FEV_1% pred, Forced Expiratory Volume in one second percentage predicted; SD, Standard Deviation.

individually and in combination for prolonged hospitalization was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), 95% confidence interval (95% CI), sensitivity, specificity, and optimal cutoff values were calculated. Differences between AUCs were compared using the DeLong Z-test. Multivariate logistic regression analysis (entry method, with entry $\alpha = 0.05$ and removal $\alpha = 0.10$) was conducted to identify independent risk factors for prolonged hospital stay in AECOPD patients. A two-sided *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

A total of 328 AECOPD patients were included, with 186 (56.7%) in the short-stay group and 142 (43.3%) in the long-stay group. Baseline characteristics and treatment use: In the short-stay group, there were 112 males (60.2%) and 74 females (39.8%), mean age 65.3 ± 8.2 years; 98 (52.7%) with smoking history, 42 (22.6%) with hypertension, 28 (15.1%) with diabetes, mean admission FEV_1% pred 48.2 ± 10.3%, 100 (53.8%) using systemic corticosteroids, 158 (84.9%) using antibiotics, 30 (16.1%) using non-invasive ventilation, and 179 (96.2%) using bronchodilators. In the long-stay group, there were 89 males (62.7%) and 53 females (37.3%), mean age 67.5 ± 9.1 years; 82 (57.7%) with smoking history, 45 (31.7%) with hypertension, 32 (22.5%) with diabetes, mean admission FEV_1% pred 41.5 ± 9.8%, 110 (77.5%) using systemic corticosteroids, 132 (92.9%) using antibiotics, 55 (38.7%) using non-invasive ventilation, and 136 (95.8%) using bronchodilators. Significant differences between groups were observed in age, hypertension, diabetes, admission FEV_1% pred, systemic corticosteroid use, antibiotic use, and non-invasive ventilation use (all $P < 0.05$; $P < 0.001$ for FEV_1% pred, systemic corticosteroid use, non-invasive ventilation use; $P = 0.009$ for antibiotics). No significant differences existed in sex, smoking history, or bronchodilator use (both $P > 0.05$, **Table 1**).

Comparison of laboratory markers between the two groups

Comparison of laboratory markers between the short-stay and long-stay groups revealed that patients in the long-stay group had significantly higher pre-treatment levels of NLR, IL-6, and PCT, significantly higher post-treatment NLR, and a significantly lower ΔNLR than those in the short-stay group, with all differences being statistically significant (all $P < 0.001$). Specifically, pre-treatment NLR was 8.2 ± 2.1 in the long-stay group versus 5.3 ± 1.5 in the short-stay group ($t = -12.363$, $P < 0.001$); post-treatment NLR was 7.0 ± 1.9 versus 1.8 ± 0.7 ($t = -28.353$, $P < 0.001$); ΔNLR was 1.2 ± 0.8 versus 3.5 ± 1.2 ($t = 18.722$, $P < 0.001$). IL-6 levels were 45.2 (28.1, 62.3) pg/mL in the long-stay group compared to 22.5 (15.3, 30.1) pg/mL in the short-stay group ($Z = -7.978$, $P < 0.001$); PCT levels were 0.8 (0.4, 1.5) ng/mL versus 0.3 (0.1, 0.6) ng/mL ($Z = -8.511$, $P < 0.001$, **Table 2**).

Table 2. Comparison of laboratory markers between the two groups of AECOPD patients

Variable	Short-Stay Group (n = 186)	Long-Stay Group (n = 142)	$t/\chi^2/Z$	*P* Value
Pre-treatment NLR (mean ± SD)	5.3 ± 1.5	8.2 ± 2.1	-12.363	< 0.001
Post-treatment NLR (mean ± SD)	1.8 ± 0.7	7.0 ± 1.9	-28.353	< 0.001
ΔNLR (mean ± SD)	3.5 ± 1.2	1.2 ± 0.8	18.722	< 0.001
IL-6 (pg/mL, median [Q1, Q3])	22.5 (15.3, 30.1)	45.2 (28.1, 62.3)	-7.978	< 0.001
PCT (ng/mL, median [Q1, Q3])	0.3 (0.1, 0.6)	0.8 (0.4, 1.5)	-8.511	< 0.001

Note: ΔNLR = Pre-treatment NLR - Post-treatment NLR. Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; NLR, Neutrophil-to-Lymphocyte Ratio; ΔNLR, Change in Neutrophil-to-Lymphocyte Ratio; IL-6, Interleukin-6; PCT, Procalcitonin.

Table 3. Multivariate logistic regression analysis for prolonged hospital stay in AECOPD patients

Independent Variable	Regression Coefficient (β)	Standard Error (SE)	Wald χ^2	OR	95% CI
ΔNLR ≤ 2.1 (Yes = 1, No = 0)	1.18	0.32	13.564	3.252	1.82-5.81
IL-6 ≥ 33.5 pg/mL (Yes = 1, No = 0)	1.06	0.34	9.783	2.893	1.56-5.35
PCT ≥ 0.4 ng/mL (Yes = 1, No = 0)	0.94	0.35	7.452	2.561	1.38-4.75
FEV_1% pred at admission < 45% (Yes = 1, No = 0)	0.78	0.36	4.716	2.183	1.15-4.13
Systemic Corticosteroid Use (Yes = 1, No = 0)	0.12	0.35	0.117	1.127	0.56-2.27
Antibiotic Use (Yes = 1, No = 0)	0.08	0.38	0.045	1.083	0.52-2.26
Non-Invasive Ventilation Use (Yes = 1, No = 0)	0.15	0.36	0.174	1.162	0.59-2.29
Bronchodilator Use (Yes = 1, No = 0)	0.03	0.41	0.005	1.031	0.45-2.37
Constant	-1.31	0.45	8.412	0.270	-

Note: Model goodness-of-fit assessed by Hosmer-Lemeshow test: $\chi^2 = 6.15$, P = 0.551. Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; ΔNLR, Change in Neutrophil-to-Lymphocyte Ratio; IL-6, Interleukin-6; PCT, Procalcitonin; FEV_1% pred, Forced Expiratory Volume in one second percentage predicted; OR, Odds Ratio; CI, Confidence Interval.

Multivariate logistic regression analysis of prolonged hospital stay in AECOPD patients

Using prolonged hospital stay (yes = 1, no = 0) as the dependent variable, multivariate logistic regression was performed with variables showing significant univariate differences (age, hypertension, diabetes, FEV_1% pred at admission, ΔNLR, IL-6, PCT). Results indicated that ΔNLR ≤ 2.1 (OR = 3.252, 95% CI: 1.82-5.81, P < 0.001), IL-6 ≥ 33.5 pg/mL (OR = 2.893, 95% CI: 1.56-5.35, P = 0.001), PCT ≥ 0.4 ng/mL (OR = 2.561, 95% CI: 1.38-4.75, P = 0.003), and FEV_1% pred at admission < 45% (OR = 2.183, 95% CI: 1.15-4.13, P = 0.017) were independent risk factors for prolonged hospital stay in AECOPD patients (**Table 3**).

Predictive performance and clinical utility of the combined biomarker model

ROC curve analysis showed that the combination of ΔNLR, IL-6, and PCT achieved the highest predictive performance for prolonged hospitalization in AECOPD patients, with an AUC of 0.980 (95% CI: 0.969-0.991) - significantly superior to any individual biomarker or the DECAF Score (all P < 0.05). At the optimal cutoff (ΔNLR ≤ 2.1, IL-6 ≥ 33.5 pg/mL, PCT ≥ 0.4 ng/mL), the model yielded a sensitivity of 82.3%, specificity of 85.1%, positive predictive value (PPV) of 81.2%, and negative predictive value (NPV) of 85.9% (**Figure 1**; **Table 4**).

Analysis of the clinical prediction nomogram revealed the relative contribution of each biomarker within the combined model (**Figure 2**). Procalcitonin (PCT) was the most influential predictor (229.3 points), followed by ΔNLR (64.5 points) and interleukin-6 (IL-6, 24.0 points), highlighting their differential weighting in the risk stratification model.

Decision curve analysis (DCA) revealed that across a wide range of risk thresholds (0.0-1.0), the combined model provided a higher

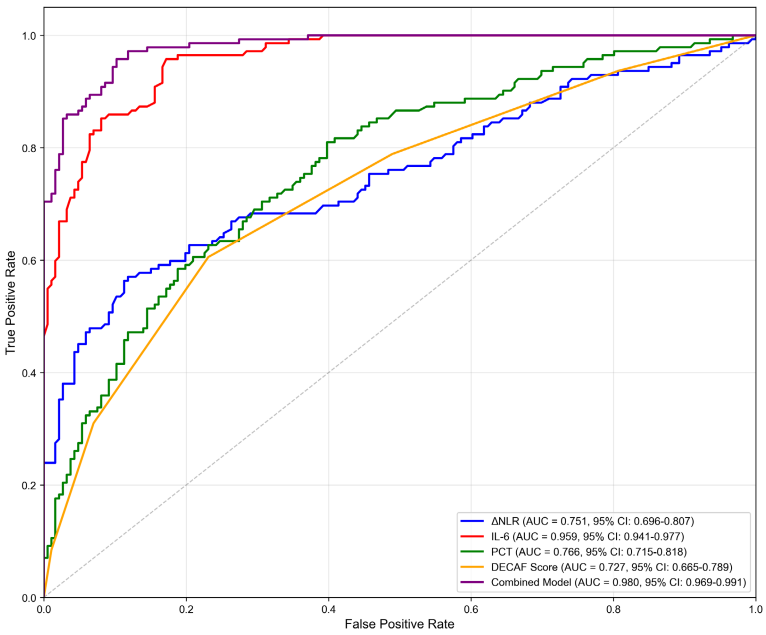

Figure 1. ROC curves for predicting prolonged hospital stay in AECOPD patients using ΔNLR, IL-6, and PCT - individually and in combination. Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; ΔNLR, Change in Neutrophil-to-Lymphocyte Ratio; IL-6, Interleukin-6; PCT, Procalcitonin; ROC, Receiver Operating Characteristic.

net benefit than both the "treat all" and "treat none" strategies. It maintained positive net benefits within the threshold range of approximately 0.0 to 0.9, supporting its utility in clinical decision-making (**Figure 3**).

The calibration curve indicated excellent agreement between predicted probabilities and actual outcomes for the combined model, with the curve closely aligning with the ideal line. The Brier score was 0.0536, confirming high calibration accuracy (**Figure 4**).

The clinical impact curve further illustrated that as patients were ranked by predicted risk, a substantial proportion of true positives were concentrated among those identified as high-risk, highlighting the model's effectiveness in risk stratification and potential for targeting interventions (**Figure 5**).

Additionally, the precision-recall curve showed that the combined model achieved an average precision (AP) of 0.975, maintaining a precision above 0.9 across most recall thresholds, which further validates its robust performance in identifying patients with prolonged hospitalization (**Figure 6**).

Correlation analysis between each biomarker and length of hospital stay

Spearman correlation analysis showed that ΔNLR was negatively correlated with length of hospital stay ($r = -0.289$, $P < 0.001$), indicating that a smaller ΔNLR was associated with a longer hospital stay. In contrast, both IL-6 ($r = 0.584$, $P < 0.001$) and PCT ($r = 0.507$, $P < 0.001$) were positively correlated with length of hospital stay, suggesting that higher levels of these biomarkers were associated with prolonged hospitalization (**Figure 7**; **Table 5**).

Discussion

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is one of the leading causes of disability and mortality from respiratory diseases worldwide [25]. The length of hospital stay (LOS) for AECOPD not only directly impacts patients' financial burden - according to Guidelines for the diagnosis and management of chronic obstructive pulmonary disease (revised version 2021), the average cost per AECOPD hospitalization is as high as RMB 18,000 - but is also closely associated with the long-term risk of recurrent exacerbations and irreversible lung function decline [26]. However, current clinical practice still relies heavily on subjective, experience-based assessment tools for predicting LOS, such as the modified Medical Research Council (mMRC) dyspnea scale or the percentage of predicted forced expiratory volume in one second (FEV_1% pred). There remains a critical lack of convenient, objective, and precise biological predictors - a gap that constitutes the central clinical challenge this study aims to address [27].

From a pathophysiological perspective, AECOPD is characterized by a cascade amplification of localized airway inflammation into a systemic inflammatory state [28]. Neutrophil infiltration, lymphocyte functional suppression, and the aberrant release of multiple pro-inflam-

Table 4. Performance of individual and combined biomarkers in predicting prolonged hospital stay in AECOPD patients

Testing Method	AUC	95% CI	Optimal Cutoff Value	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
ΔNLR alone	0.751	0.696-0.807	≤ 2.1	57.0	88.2	78.6	72.9
IL-6 alone	0.959	0.941-0.977	≥ 33.5 pg/mL	95.8	82.8	81.0	96.2
PCT alone	0.766	0.715-0.818	≥ 0.4 ng/mL	81.0	60.2	60.8	80.6
DECAF Score	0.727	0.665-0.789	≥ 3 points	60.6	76.9	66.7	71.9
Combined ΔNLR + IL-6 + PCT	0.980	0.969-0.991	ΔNLR ≤ 2.1 + IL-6 ≥ 33.5 pg/mL + PCT ≥ 0.4 ng/mL	82.3	85.1	81.2	85.9

Note: The AUC of the combined model was significantly higher than that of each individual biomarker (all $P < 0.05$). Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; ΔNLR, Change in Neutrophil-to-Lymphocyte Ratio; IL-6, Interleukin-6; PCT, Procalcitonin; DECAF Score; AUC, Area Under the Curve; CI, Confidence Interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value.

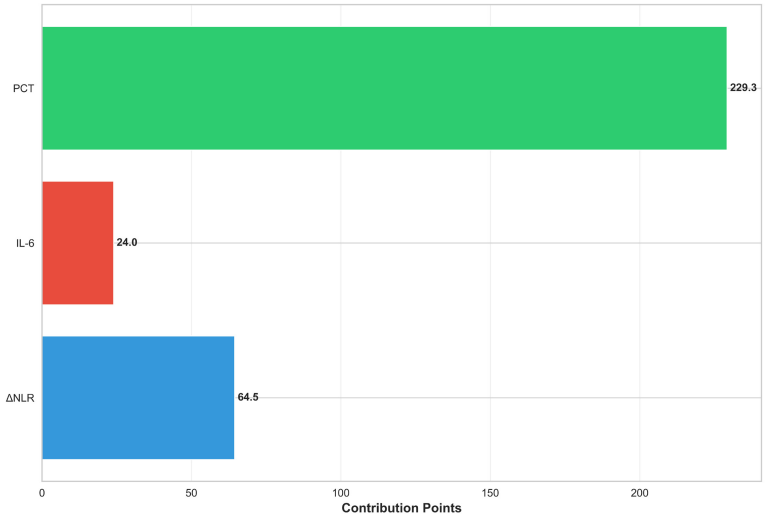

Figure 2. Clinical prediction nomogram - feature contribution. Abbreviations: PCT, Procalcitonin; ΔNLR, Change in Neutrophil-to-Lymphocyte Ratio; IL-6, Interleukin-6.

matory cytokines, collectively form a key driver axis of disease progression. Existing studies have confirmed that levels of inflammatory biomarkers at admission - such as the neutrophil-to-lymphocyte ratio (NLR), interleukin-6 (IL-6), and procalcitonin (PCT) - are significantly associated with the severity of AECOPD [29]. Nevertheless, current research exhibits three notable limitations: First, most studies focus on static measurements (e.g., single-timepoint values at admission) and overlook the potential prognostic value of dynamic changes in NLR during treatment (ΔNLR) for assessing therapeutic response and outcomes [30]. Many studies have limited sample sizes (typically fewer than 300 patients) and rarely consider the clinical feasibility and cost-effectiveness of biomarker testing; some proposed markers require additional assays that may increase healthcare expenditures, thereby limiting their adoption in routine clinical practice [25].

This study retrospectively analyzed 328 hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) to systematically investigate the associations between three inflammation-related biomarkers - ΔNLR (change in neutrophil-to-lymphocyte ratio), IL-6 (interleukin-6), and PCT (procalcitonin) - and length of hospital stay (LOS), and further evaluated the clinical utility of their combined use in predicting prolonged hospitalization.

ΔNLR, as a composite indicator integrating neutrophil-mediated inflammation and lymphocyte-mediated immune function, dynamically reflects the inflammatory-immune balance during AECOPD exacerbations. During acute exacerbation, airway mucosal injury triggers massive neutrophil infiltration and the release of inflammatory mediators such as elastase, while lymphocyte counts decrease due to increased apoptosis and functional suppression, leading to a marked elevation in NLR. With standardized treatment, inflammation gradually subsides, neutrophil counts decline,

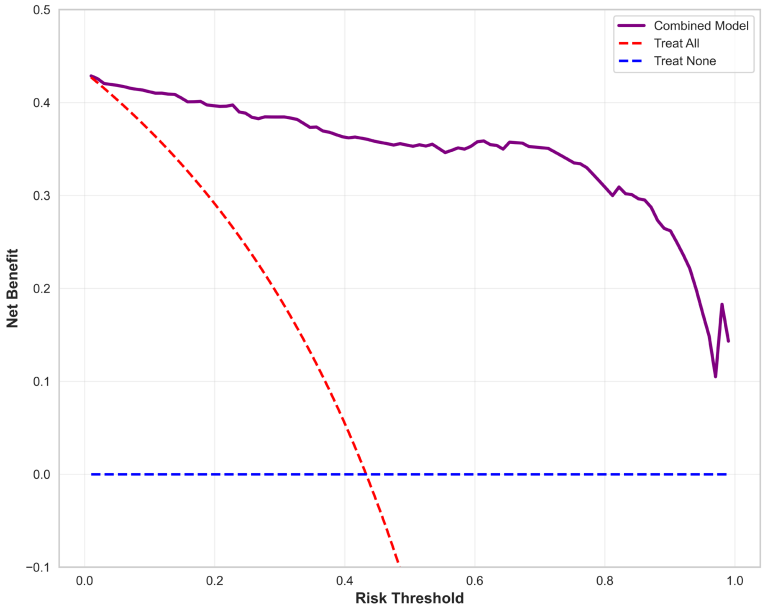

Figure 3. Decision curve analysis for AECOPD hospital stay prediction. Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

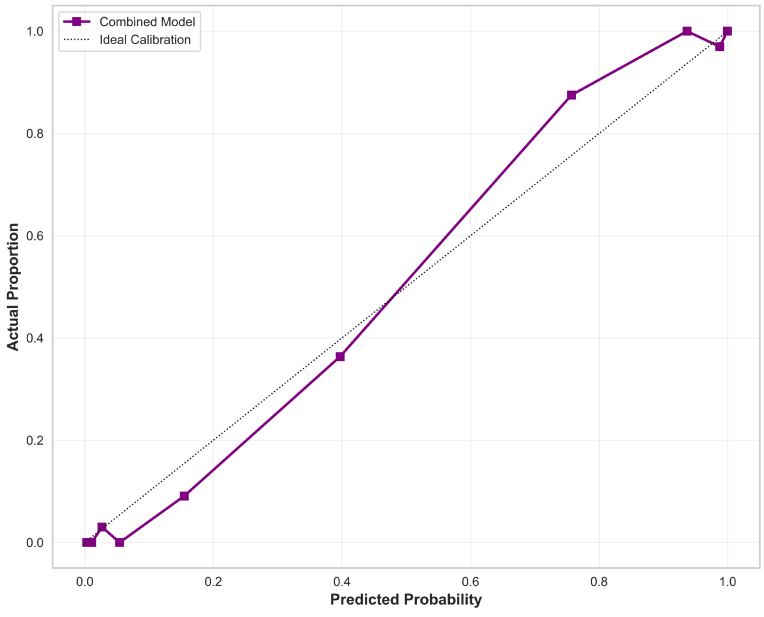

Figure 4. Calibration curve for AECOPD hospital stay prediction. Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

and lymphocyte function recovers, resulting in a reduction in NLR. Thus, ΔNLR serves as an effective dynamic marker for assessing treatment response. Our study found that ΔNLR was significantly lower in the long-stay group than in the short-stay group and was negatively correlated with LOS, suggesting that a smaller ΔNLR reflects a weaker anti-inflammatory response to therapy, more protracted disease course, and consequently longer hospitalization. Compared with a single NLR measurement at admission, ΔNLR better captures dynamic changes following therapeutic intervention, offering real-time prognostic insights - a finding consistent with Zhang et al.'s study of 287 AECOPD patients.

IL-6, a pivotal cytokine linking local and systemic inflammatory responses, plays a central role in the pathogenesis of AECOPD. It exacerbates airway remodeling and lung function impairment by activating the JAK/STAT signaling pathway and promoting the release of other pro-inflammatory cytokines such as TNF-α and IL-1β. Our results showed that IL-6 levels were significantly positively correlated with LOS and identified IL-6 as an independent risk factor for prolonged hospitalization, indicating that higher IL-6 levels reflect more intense systemic inflammation, greater disease severity, and a longer required treatment duration. Notably, in this retrospective setting, IL-6 data were readily extracted from the hospital's Laboratory Information System (LIS) without additional testing, offering advantages of low cost and easy accessibility, making it suitable as a routine prognostic marker - a conclusion also supported by Wang et al.'s findings.

PCT, a specific biomarker for bacterial infection, is present at very low serum concentrations (< 0.1 ng/mL) in healthy individuals but rises significantly during bacterial infections. Given that bacterial infection is the leading trigger of AECOPD exacerbations, our study found that PCT levels were significantly higher in the

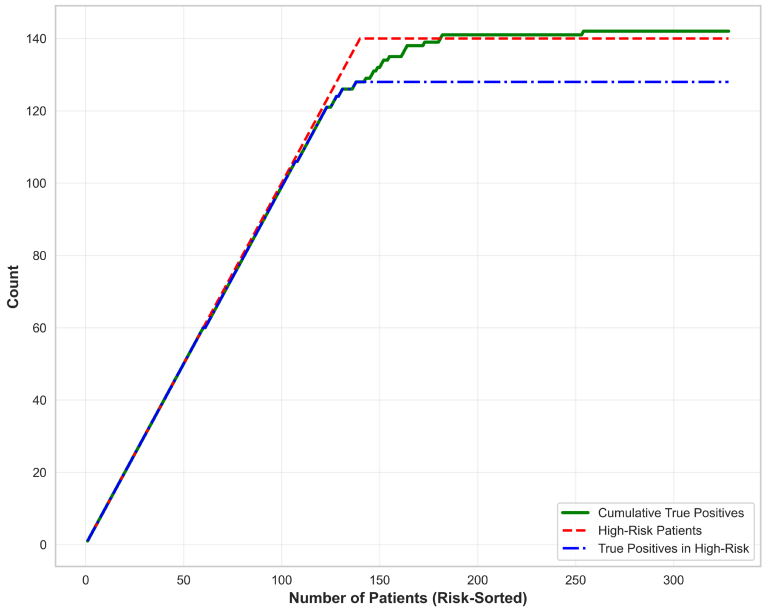

Figure 5. Clinical impact curve for AECOPD hospital stay prediction. Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

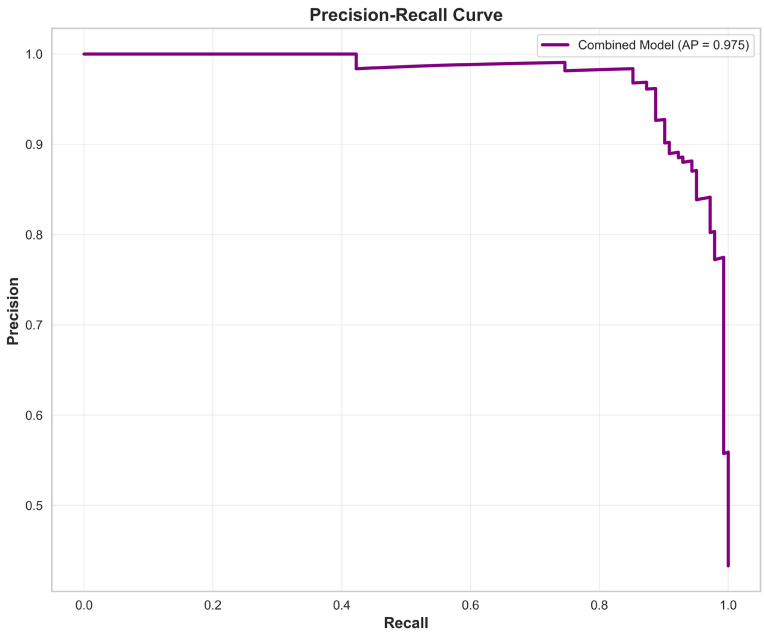

Figure 6. Precision-recall curve for AECOPD hospital stay prediction. Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

long-stay group than in the short-stay group and positively correlated with LOS, suggesting that elevated PCT may indicate uncontrolled bacterial infection or antimicrobial resistance, leading to recurrent symptoms and prolonged hospitalization. In clinical practice, PCT-guided antibiotic therapy - such as discontinuing antibiotics when PCT < 0.25 ng/mL - has been recommended by the GOLD guidelines to optimize antimicrobial strategies, reduce unnecessary antibiotic exposure, and potentially shorten hospital stays.

Further ROC curve analysis revealed that the predictive model combining ΔNLR, IL-6, and PCT achieved an AUC of 0.980, significantly outperforming any individual biomarker or the DECAF Score (all $P < 0.05$), with both sensitivity and specificity exceeding 80%, demonstrating excellent predictive performance. From a pathophysiological perspective, ΔNLR reflects the dynamic balance between inflammation and immunity, IL-6 indicates the intensity of systemic inflammation, and PCT signals the presence of bacterial infection. Together, these three markers capture distinct dimensions of disease severity, and their integration enables complementary strengths, effectively mitigating the predictive bias inherent in single biomarkers due to inter-individual variability or timing of measurement. Importantly, this combined model is constructed entirely from routinely collected clinical laboratory data, imposing no additional burden on patients, yet substantially enhancing early identification of those at high risk for prolonged hospitalization - highlighting its strong potential for clinical translation. Our correlation analysis identified that, in addition to the three inflammatory markers of primary interest, both age and baseline lung function (FEV_1% pred) were significantly associ-

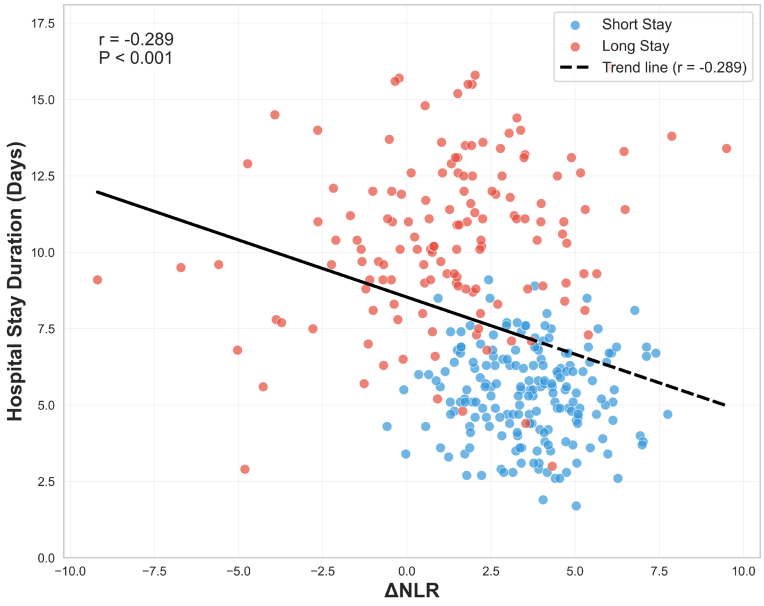

Figure 7. Scatter plot showing the correlation between ΔNLR and length of hospital stay in AECOPD patients. Abbreviations: ΔNLR, Change in Neutrophil-to-Lymphocyte Ratio; AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease.

Table 5. Correlation analysis between biomarkers and length of hospital stay in AECOPD patients

Variable	Correlation Coefficient (r)	*P* Value	Direction of Correlation
ΔNLR	-0.289	< 0.001	Negative
IL-6	0.584	< 0.001	Positive
PCT	0.507	< 0.001	Positive
Age	0.208	< 0.001	Positive
FEV_1% pred at admission	-0.347	< 0.001	Negative

Abbreviations: AECOPD, Acute Exacerbation of Chronic Obstructive Pulmonary Disease; ΔNLR, Change in Neutrophil-to-Lymphocyte Ratio; IL-6, Interleukin-6; PCT, Procalcitonin; FEV_1% pred, Forced Expiratory Volume in one second percentage predicted.

ated with LOS. However, the ROC analysis focused specifically on evaluating the predictive performance of the inflammatory markers ΔNLR, IL-6, and PCT, both individually and in combination, as this constituted the novel contribution of our study. The fact that these markers remained independent predictors in a multivariate model that adjusted for FEV_1% pred further underscores their unique value. Importantly, our combined ΔNLR, IL-6, and PCT model demonstrated significantly superior discriminative ability compared to the DECAF score (AUC 0.980 vs. 0.727, P < 0.05), a validated clinical prognostic tool for AECOPD. This suggests that our biomarker-based model may provide added value for predicting LOS beyond what is achievable with currently available clinical scores.

Nevertheless, this study has several limitations. First, its single-center retrospective design inherently carries the risk of selection bias. All participants were recruited from a secondary hospital, which typically manages more severe and complex cases. This is reflected in our cohort's mean FEV_1% pred of approximately 45%, indicating a population with moderately severe impairment. The generalizability of the conclusions of this study to hospitals of other tiers may be limited. Second, due to limitations in the completeness of electronic medical records, certain potential confounders - such as nutritional status, serum albumin levels, and treatment adherence - were not included in the analysis. Additionally, the specific types, durations, and dosages of antibiotics administered, which may influence LOS, were not detailed, potentially confounding the results. Moreover, NLR values were only collected at two time points - on admission and before discharge - lacking serial measurements during treatment, which precluded further exploration of the association between the rate of NLR change and LOS.

In light of these findings and limitations, future research should prioritize large-scale, multicenter prospective cohort studies to further validate the robustness and generalizability of the ΔNLR-IL-6-PCT combined model in predicting LOS among AECOPD patients. It is also recommended to incorporate additional clinical variables - such as nutritional markers, dynamic changes in lung function, and comorbidity

burden - to develop a more comprehensive predictive model. Furthermore, a simple, practical clinical risk scoring system could be developed based on the optimal cutoff values identified in this study, enabling rapid identification of high-risk patients through quantifiable scores, thereby improving clinical decision-making efficiency and facilitating personalized management.

Conclusion

This study found that the change in neutrophil-to-lymphocyte ratio during treatment (ΔNLR), in combination with IL-6 and PCT levels, effectively predicts length of hospital stay in patients with AECOPD. ΔNLR ≤ 2.1, IL-6 ≥ 33.5 pg/mL, and PCT ≥ 0.4 ng/mL were identified as independent risk factors for prolonged hospitalization, and the combined predictive model demonstrated significantly superior performance compared to any single biomarker (AUC = 0.979). This model is based entirely on routinely collected clinical laboratory data and incurs no additional cost, offering a practical tool for early identification of high-risk patients, optimization of treatment strategies, and rational allocation of healthcare resources.

Disclosure of conflict of interest

None.

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