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Original Article

Combined NLR-albumin index and risk of invasive mechanical ventilation in patients with acute exacerbation of COPD complicated by type II respiratory failure: a single-center retrospective study

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Abstract: Objectives: To develop and temporally validate an admission-based neutrophil-to-lymphocyte ratio (NLR)-albumin index for estimating invasive mechanical ventilation risk in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and type II respiratory failure. Methods: We analyzed a development cohort of 155 patients (January 2023-June 2025) and a temporal validation cohort of 197 patients (July 2025-March 2026). A predicted probability (PRE) was derived from admission NLR and albumin and evaluated using logistic regression, variance inflation factors, 1,000 bootstrap resamples, receiver operating characteristic analysis, calibration, decision curve analysis, and Bonferroni correction. PRE was also combined with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. Results: Invasive ventilation was required in 43/155 (27.7%) development-cohort patients and 53/197 (26.9%) validation-cohort patients. NLR, albumin, and APACHE II were independently associated with invasive ventilation; each 0.10 increase in PRE was associated with an odds ratio of 1.620 (95% confidence interval, 1.311-2.002). Development-cohort areas under the curve were 0.794 for PRE and 0.819 for PRE plus APACHE II, with bootstrap-corrected values of 0.788 and 0.808; corresponding validation values were 0.845 and 0.881. Validation-cohort invasive ventilation rates increased from 3.3% to 24.7% and 60.4% across PRE risk groups ($P<0.001$). Exploratory 24-hour areas under the curve for PRE and ΔPRE were 0.877 and 0.890 in development and 0.919 and 0.932 in validation. Conclusions: Admission PRE, particularly when combined with APACHE II, may facilitate early risk stratification in hospitalized patients with AECOPD and type II respiratory failure; multicenter prospective validation is required.

Keywords: Acute exacerbation of chronic obstructive pulmonary disease, type II respiratory failure, neutrophil-to-lymphocyte ratio, albumin, invasive mechanical ventilation

Introduction

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major cause of hospitalization, disease progression, and mortality among patients with chronic obstructive pulmonary disease (COPD). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) characterizes exacerbations as worsening respiratory symptoms accompanied by increased airway and systemic inflammation and physiologic stress [1, 2]. In patients with advanced COPD and type II respiratory failure, carbon dioxide retention, acid-base disturbances, and respiratory muscle fatigue may rapidly compromise the effectiveness of noninvasive positive-pressure ventilation (NIPPV), necessitating escalation to endotracheal intubation or tracheostomy [3]. Decisions to escalate respiratory support currently rely primarily on blood gas findings, mental status, response to NIPPV, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score; however, these measures do not directly quantify the combined inflammatory-nutritional imbalance present at admission [4-6]. Previous studies have exam-

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ined the neutrophil-to-lymphocyte ratio (NLR), albumin, and NLR/albumin-based indices mainly in relation to mortality, readmission, or broadly defined adverse outcomes in general AECOPD or critically ill COPD populations [7-16]. The present study differs from prior work in four respects: it focuses on the narrowly defined phenotype of AECOPD complicated by type II respiratory failure; uses escalation to invasive mechanical ventilation as a clinically actionable primary endpoint; derives a transparent probability from two routine admission tests; and evaluates incremental value beyond APACHE II through bootstrap and temporal validation, calibration, decision curve analysis, and risk stratification. We therefore examined whether admission NLR, albumin, and their combined predicted probability (PRE) were associated with invasive mechanical ventilation and whether combining PRE with APACHE II could support early monitoring and respiratory support planning.

Materials and methods

Study design and patient selection

This single-center retrospective study used a prespecified temporal split-sample design. After eligibility screening, 352 patients with AECOPD complicated by type II respiratory failure were included. Patients admitted from January 2023 through June 2025 constituted the development cohort (n=155), whereas those admitted from July 2025 through March 2026 constituted the temporal validation cohort (n=197). All early-admission variables were collected during the initial assessment or within 24 hours of admission and before invasive mechanical ventilation. Variable selection, coefficient estimation, cutoff determination, and definition of risk-group thresholds were performed exclusively in the development cohort. The resulting formulas and thresholds were then applied to the temporal validation cohort without re-estimation. The study was approved by the Ethics Committee of Jianhu Clinical Medical College of Yangzhou University (Ethics Approval No.: JYLL-202605-K025-01). Because the study involved retrospective review of anonymized medical records without additional clinical intervention, the requirement for informed consent was waived.

Eligibility criteria

Patients were eligible if they (1) met the diagnostic criteria for AECOPD; (2) had type II respiratory failure on admission arterial blood gas analysis, defined as partial pressure of arterial carbon dioxide ($PaCO_2$) >50 mmHg together with hypoxemia or a need for oxygen therapy; (3) were aged ≥40 years; (4) underwent key examinations, including complete blood count, albumin measurement, and blood gas analysis, during the initial assessment or within 24 hours of admission and before initiation of invasive mechanical ventilation; and (5) had medical records that clearly documented whether invasive mechanical ventilation was used during hospitalization. Patients were excluded for (1) endotracheal intubation or tracheostomy before admission; (2) cardiopulmonary arrest; (3) concurrent active malignancy, hematologic disease, or immune system disease; (4) recent treatment likely to substantially alter leukocyte counts, including chemotherapy, radiotherapy, or long-term high-dose glucocorticoid therapy; (5) conditions likely to substantially reduce albumin levels, such as severe hepatic failure or nephrotic syndrome; or (6) missing data for essential variables.

Definition of primary outcome and review of treatment decisions

The primary outcome was invasive mechanical ventilation during hospitalization, defined as ventilatory support delivered through an artificial airway, such as an endotracheal tube or tracheostomy. To minimize bias related to treatment decisions, two investigators independently reviewed the medical records for indications for invasive ventilation [17]. These indications included NIPPV failure, worsening acidosis or respiratory failure, impaired consciousness or inability to protect the airway, severe hypercapnia/acidosis, respiratory muscle fatigue, and worsening hypoxemia. The investigators also recorded factors that could influence the decision to initiate invasive ventilation, including refusal of intubation, intensive care unit (ICU) bed limitations, and the initial NIPPV strategy. No patient was denied invasive ventilation because of explicit refusal or lack of an ICU bed; therefore, these factors were not incorporated into the early-admission prediction model. Secondary outcomes included

Table 1. Baseline characteristics stratified by invasive mechanical ventilation status

Variable	No invasive ventilation (n=112)	Invasive ventilation (n=43)	Test statistic	*P* value
Age (years)	71.01±7.59	72.65±7.96	t=-1.165	0.248
BMI (kg/m^2)	22.78±3.45	22.85±3.80	t=-0.102	0.919
COPD duration (years)	8.72±4.37	8.48±3.77	t=0.338	0.736
Respiratory rate (breaths/min)	23.46±3.41	24.88±3.38	t=-2.353	0.021
SpO_2 (%)	88.99±4.10	86.06±3.72	t=4.268	<0.001
APACHE II score	12.52±3.82	15.51±3.73	t=-4.441	<0.001
pH	7.32±0.04	7.29±0.04	t=4.523	<0.001
$PaCO_2$ (mmHg)	70.45±10.12	75.41±8.80	t=-3.010	0.003
PaO_2/FiO_2	179.27±49.87	154.47±40.45	t=3.195	0.002
Albumin (g/L)	35.81±3.47	33.13±3.17	t=4.586	<0.001
No. of exacerbations in the past year	1.00 (1.00, 2.00)	2.00 (1.00, 2.00)	U=2007.5	0.097
No. of hospitalizations in the past year	1.00 (0.00, 1.00)	0.00 (0.00, 1.00)	U=2683.0	0.235
NLR	6.41 (5.04, 9.03)	11.36 (8.59, 17.82)	U=1059.5	<0.001
CRP (mg/L)	36.00 (24.05, 53.43)	53.80 (33.85, 65.85)	U=1666.0	0.003
Male	70 (62.5)	29 (67.4)	chi-square = 0.329	0.566
Smoking history	74 (66.1)	34 (79.1)	chi-square = 2.485	0.115
Hypertension	49 (43.8)	24 (55.8)	chi-square = 1.815	0.178
Diabetes mellitus	21 (18.8)	13 (30.2)	chi-square = 2.392	0.122
Coronary heart disease	18 (16.1)	12 (27.9)	chi-square = 2.788	0.095
Chronic heart failure	15 (13.4)	8 (18.6)	chi-square = 0.668	0.414
Cor pulmonale	32 (28.6)	12 (27.9)	chi-square = 0.007	0.935
Concomitant pulmonary infection	66 (58.9)	33 (76.7)	chi-square = 4.274	0.039
Consciousness disturbance	13 (11.6)	16 (37.2)	chi-square = 13.391	<0.001

Note: Normally distributed continuous variables are presented as the mean ± standard deviation, skewed continuous variables as the median (25th percentile [P25], 75th percentile [P75]), and categorical variables as number (%). BMI, body mass index; COPD, chronic obstructive pulmonary disease; SpO_2, peripheral oxygen saturation; APACHE II, Acute Physiology and Chronic Health Evaluation II; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2/FiO_2, ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein.

Table 2. Variables retained by least absolute shrinkage and selection operator regression and their standardized coefficients

Variable	Standardized coefficient	Direction
NLR	0.524	Positive
SpO_2	-0.243	Negative
Albumin	-0.156	Negative
Consciousness disturbance	0.145	Positive
APACHE II score	0.101	Positive
pH	-0.073	Negative
No. of exacerbations in the past year	0.023	Positive

Note: LASSO, least absolute shrinkage and selection operator; NLR, neutrophil-to-lymphocyte ratio; SpO_2, peripheral oxygen saturation; APACHE II, Acute Physiology and Chronic Health Evaluation II.

NIPPV failure, ICU admission, length of hospital stay, in-hospital mortality, and cumulative all-cause mortality within 90 days of admission. Ninety-day mortality was defined as all-cause death within 90 days after admission and included in-hospital deaths. Because vital status at 90 days was available for all patients, mortality rates were compared across the three risk groups. NIPPV failure was assessed only among patients who initially received NIPPV.

Collection of early admission variables for AECOPD and type II respiratory failure

Demographic and clinical history variables included age, sex, body mass index (BMI), smoking history, COPD duration, acute exacerbations and hospitalizations during the previous year, pulmonary infection, and major comorbidities. Indicators of the severity of type II respiratory failure within 24 hours of admission included respiratory rate, peripheral oxy-

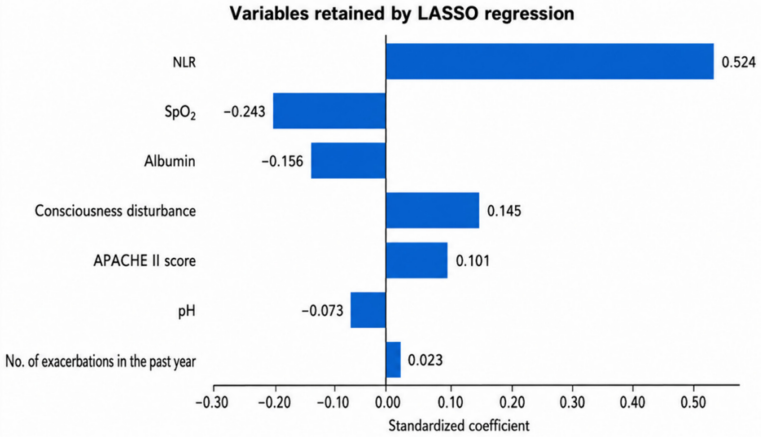


Figure 1. LASSO-selected variables and standardized coefficients. Note: LASSO, least absolute shrinkage and selection operator; NLR, neutrophil-to-lymphocyte ratio; SpO_2, peripheral oxygen saturation; APACHE II, Acute Physiology and Chronic Health Evaluation II.

gen saturation (SpO_2), disturbance of consciousness, arterial pH, partial pressure of arterial carbon dioxide ($PaCO_2$), the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2), initial NIPPV use, and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [18]. Laboratory measures of inflammatory and nutritional status included neutrophil and lymphocyte counts, NLR, C-reactive protein (CRP), and albumin. Treatment-course variables, including NIPPV failure, intensive care unit (ICU) admission, and invasive mechanical ventilation, were used only as outcomes or descriptors of the clinical course and were not included as admission predictors.

Assessment of serial NLR and albumin measurements

Neutrophil count, lymphocyte count, albumin, NLR, and PRE values measured approximately 24 and 48 hours after admission were extracted. Only measurements obtained before initiation of invasive mechanical ventilation were eligible. For patients with paired admission and follow-up measurements, changes were calculated as the follow-up value minus the admission value. Available-case landmark analyses used the Mann-Whitney U test to compare changes in NLR, albumin, and PRE between patients with and without subsequent invasive ventilation, and receiver operating characteristic analysis was used to assess discrimination. Missing serial measurements were not imputed.

Construction of the combined NLR-albumin index

NLR was calculated as the neutrophil count divided by the lymphocyte count. In the development cohort, NLR and albumin were entered into a binary logistic regression model to derive the predicted probability (PRE) of invasive mechanical ventilation: PRE = 1/[1 + exp(-(3.718 + 0.143 × NLR -0.179 × albumin))]. The NLR/albumin ratio was retained as a simplified comparator. The development formula was applied unchanged to the temporal validation cohort. The combined-model probability was calculated as 1/[1 + exp(-(-4.409 + 4.826 × PRE + 0.140 × APACHE II score))].

Model development, validation, and statistical analysis

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 26.0 and Python version 3.13. Normally distributed continuous variables were summarized as the mean ± standard deviation and compared using Welch's t test; skewed continuous variables were summarized as the median (25th percentile [P25], 75th percentile [P75]) and compared using the Mann-Whitney U test. Categorical variables were summarized as number (%) and compared using the chi-square test or Fisher's exact test, as appropriate. Twenty-three early-admission candidate predictors were standardized and screened in the development cohort using least absolute shrinkage and selection operator (LASSO) regression with fivefold cross-validation. Multivariable logistic regression was subsequently used to estimate associations with invasive mechanical ventilation. Multicollinearity was evaluated using variance inflation factors (VIFs), with VIF <5 considered acceptable. Discrimination was assessed using receiver operating characteristic (ROC) curves, area under the ROC curve (AUC), 95% confidence intervals (CIs), sensitivity, and specificity; optimal cutoffs were determined using the Youden index. Calibration and optimism-corrected AUCs were evaluated using 1,000 boot-

Table 3. Multivariable logistic regression analysis of factors associated with invasive mechanical ventilation

Model	Variable	beta	SE	OR (95% CI)	VIF	*P* value
Model 1	NLR	0.135	0.038	1.145 (1.063-1.233)	1.184	<0.001
	Albumin (g/L)	-0.146	0.064	0.864 (0.762-0.979)	1.174	0.022
	APACHE II score	0.138	0.059	1.148 (1.022-1.288)	1.178	0.020
Model 2	PRE (per 0.10 increase)	0.483	0.108	1.620 (1.311-2.002)	1.157	<0.001
	APACHE II score	0.140	0.058	1.150 (1.026-1.290)	1.157	0.016

Note: beta, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; VIF, variance inflation factor; PRE, predicted probability derived from NLR and albumin; NLR, neutrophil-to-lymphocyte ratio; APACHE II, Acute Physiology and Chronic Health Evaluation II. Model 1 included NLR, albumin, and APACHE II; Model 2 included PRE and APACHE II. PRE was not entered in the same model as NLR and albumin.

Table 4. Receiver operating characteristic analysis of indicators for predicting invasive mechanical ventilation

Indicator	AUC (95% CI)	Bootstrap-corrected AUC	Cutoff value	Sensitivity	Specificity
NLR	0.780 (0.698-0.857)	-	≥8.570	0.767	0.705
Decreased albumin	0.723 (0.627-0.808)	-	≤36.200	0.884	0.527
NLR/ALB	0.792 (0.708-0.864)	-	≥0.280	0.698	0.795
PRE	0.794 (0.709-0.873)	0.788	≥0.247	0.791	0.705
PRE + APACHE II	0.819 (0.737-0.887)	0.808	≥0.247	0.814	0.732

Note: ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; ALB, albumin; PRE, predicted probability; APACHE II, Acute Physiology and Chronic Health Evaluation II.

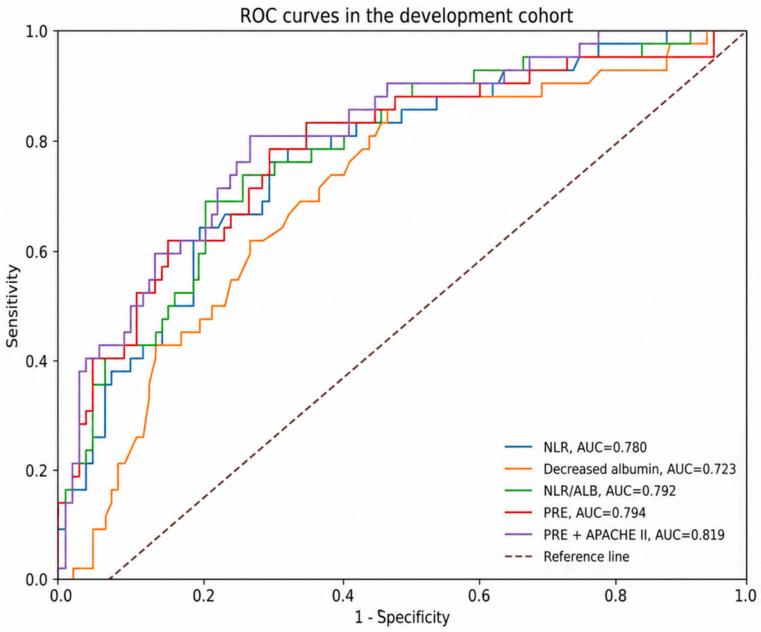


Figure 2. Receiver operating characteristic curves for invasive mechanical ventilation in the development cohort. Note: AUC, area under the receiver operating characteristic curve; NLR, neutrophil-to-lymphocyte ratio; ALB, albumin; PRE, predicted probability; APACHE II, Acute Physiology and Chronic Health Evaluation II.

strap resamples. Four prespecified ROC comparisons were conducted using the DeLong test with Bonferroni-adjusted *P* values. PRE tertiles derived from the development cohort were used to define low-, medium-, and high-risk groups. Six clinical outcomes were compared across risk strata using Bonferroni-adjusted *P* values, with adjusted pairwise comparisons performed only when the overall comparison remained significant. Decision curve analysis (DCA) was used to evaluate net benefit across threshold probabilities of 0.05-0.70. All formulas and cutoffs were applied unchanged in the temporal validation cohort. Except for the prespecified multiplicity-adjusted analyses, a two-sided P<0.05 was considered statistically significant. Before finalization, all descriptive statistics, regression coefficients, VIF values, ROC indices, bootstrap estimates, Bonferroni-adjusted *P* values, risk-group counts, and tem-

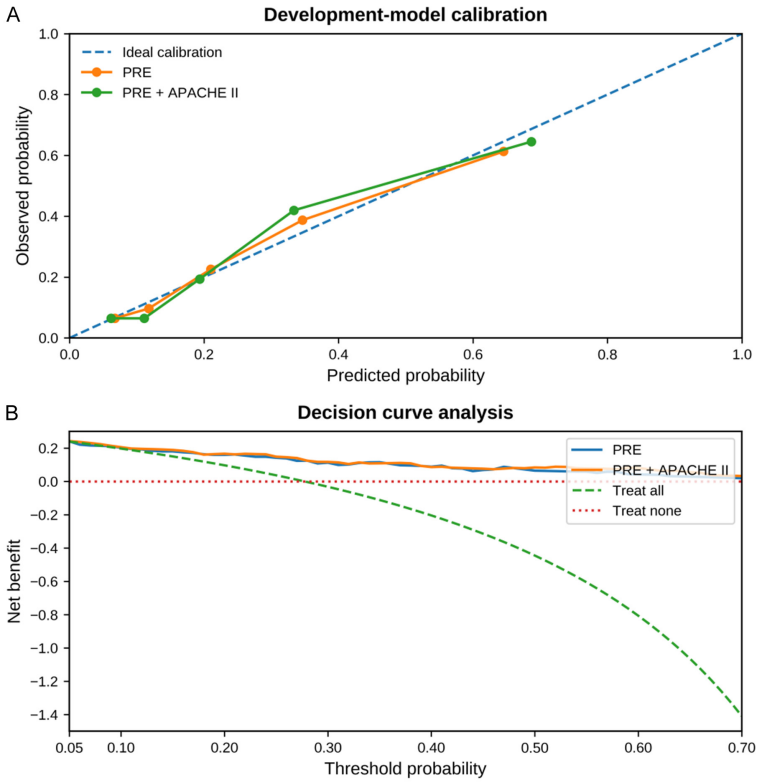


Figure 3. Calibration plots and decision curve analysis in the development cohort. Note: PRE, predicted probability derived from the neutrophil-to-lymphocyte ratio (NLR) and albumin; APACHE II, Acute Physiology and Chronic Health Evaluation II.

poral validation metrics were independently recalculated from the patient-level dataset and cross-checked against the tables and figures.

Results

Baseline characteristics by invasive mechanical ventilation status

The development cohort included 155 patients, of whom 43 (27.7%) received invasive mechanical ventilation and 112 did not. Compared with patients who did not receive invasive ventilation, those who received it had higher respiratory rate, $PaCO_2$, NLR, CRP, and APACHE II scores; lower SpO_2, pH, PaO_2/FiO_2, and albumin levels; and higher frequencies of pulmonary infection and disturbance of consciousness at admission. These findings are summarized in **Table 1**.

Candidate variables for invasive mechanical ventilation selected by LASSO

Twenty-three early-admission candidate variables were entered into the LASSO model in the development cohort. Seven retained nonzero standardized coefficients were: NLR, SpO_2, albumin, disturbance of consciousness, APACHE II score, pH, and the number of acute exacerbations during the previous year. The results are presented in **Table 2** and **Figure 1**.

Association of the combined NLR-albumin index with invasive mechanical ventilation

In Model 1, higher NLR and APACHE II scores and lower albumin levels were independently associated with invasive mechanical ventilation. In Model 2, each 0.10 increase in PRE was associated with an odds ratio of 1.620 (95% CI, 1.311-2.002) after adjustment for APACHE II. VIFs ranged from 1.174 to 1.184 in Model 1 and were 1.157 in Model 2, indicating no meaningful multicollinearity. The results are presented in **Table 3**.

Discrimination, calibration, and internal validation of the prediction models

In the development cohort, the apparent AUC was 0.794 (95% CI, 0.709-0.873) for PRE and 0.819 (95% CI, 0.737-0.887) for PRE plus APACHE II; the corresponding bootstrap-corrected AUCs were 0.788 and 0.808. Both models showed acceptable calibration and a positive net benefit across clinically relevant thresholds, with the combined model generally providing the greatest net benefit. After Bonferroni correction, none of the four prespecified DeLong comparisons remained significant; adjusted *P* values were 1.000 for NLR versus PRE, 0.050 for low albumin versus PRE, 1.000 for the NLR/albumin ratio versus PRE, and 0.894 for PRE versus PRE plus APACHE II. The results are presented in **Table 4** and **Figures 2**, **3**.

PRE-based risk stratification and clinical outcomes

Development-cohort PRE tertiles defined the low-risk (PRE <0.128; n=52), medium-risk (PRE

Table 5. Clinical outcomes across predicted probability risk strata

Outcome indicator	Low risk (n=52)	Medium risk (n=51)	High risk (n=52)	Test statistic	Adjusted *P* value
Invasive mechanical ventilation	5 (9.6)	11 (21.6)	27 (51.9)	chi-square = 24.661	<0.001
ICU admission	9 (17.3)	13 (25.5)	27 (51.9)	chi-square = 15.728	0.002
NIPPV failure	3/26 (11.5)	5/32 (15.6)	19/33 (57.6)	chi-square = 19.436	<0.001
Length of hospital stay	9.50 (7.72, 12.30)	11.40 (9.10, 13.00)	12.15 (9.10, 13.83)	H=9.213	0.060
In-hospital mortality	3 (5.8)	1 (2.0)	4 (7.7)	chi-square = 1.787	1.000
90-day cumulative mortality	3 (5.8)	7 (13.7)	10 (19.2)	chi-square = 4.238	0.721

Note: ICU, intensive care unit; NIPPV, non-invasive positive pressure ventilation. NIPPV failure was evaluated only among patients who initially received NIPPV. *P* values were Bonferroni-adjusted for six outcome comparisons. Pairwise comparisons were interpreted only when the adjusted overall comparison remained significant.

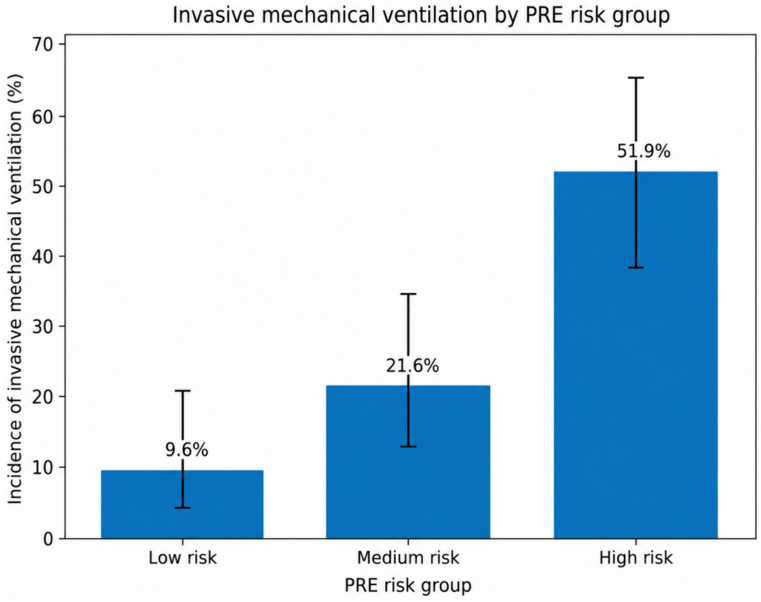


Figure 4. Incidence of invasive mechanical ventilation across PRE risk strata in the development cohort.

0.128-0.317; n=51), and high-risk (PRE >0.317; n=52) groups. After Bonferroni correction for six outcomes, invasive mechanical ventilation, ICU admission, and NIPPV failure remained significantly different across risk strata, whereas length of hospital stay, in-hospital mortality, and 90-day cumulative mortality did not. Adjusted pairwise comparisons showed higher rates of invasive mechanical ventilation, ICU admission, and NIPPV failure in the high-risk group than in both the low- and medium-risk groups (all Bonferroni-adjusted P<0.05). The results are presented in **Table 5** and **Figures 4**, **5**.

Temporal validation of the prediction models

The temporal validation cohort included 197 patients, of whom 53 (26.9%) received invasive mechanical ventilation. Application of the fixed development formulas and cutoffs yielded an AUC of 0.845 (95% CI, 0.784-0.900) and a Brier score of 0.143 for PRE, compared with an AUC of 0.881 (95% CI, 0.822-0.927) and a Brier score of 0.129 for PRE plus APACHE II. Invasive ventilation rates increased stepwise from 3.3% in the low-risk group to 24.7% in the medium-risk group and 60.4% in the high-risk group (chi-square = 44.580, P<0.001). The results are presented in **Tables 6**, **7**.

Availability of serial NLR and albumin measurements

Paired 24-hour measurements were available for 130 patients in the development cohort, including 32 who subsequently received invasive ventilation, and for 170 patients in the temporal validation cohort, including 37 invasive-ventilation events. Corresponding 48-hour measurements were available for 94 patients with 11 events and 114 patients with 17 events, respectively. In the development cohort, patients who subsequently received invasive ventilation had greater 24-hour increases in NLR [median ΔNLR, 1.67 (0.64, 3.41) vs -1.13 (-1.75, -0.55)], greater decreases in albumin [-0.90 (-1.30, -0.40) vs -0.20 (-0.70, 0.20)], and higher ΔPRE [0.069 (0.018, 0.110) vs -0.014 (-0.039, 0.000); all P<0.001]. At 48 hours, these patients also had greater increases in NLR [3.34 (1.36, 6.28) vs -1.83 (-2.74, -1.36)] and greater decreases in albumin [-1.80

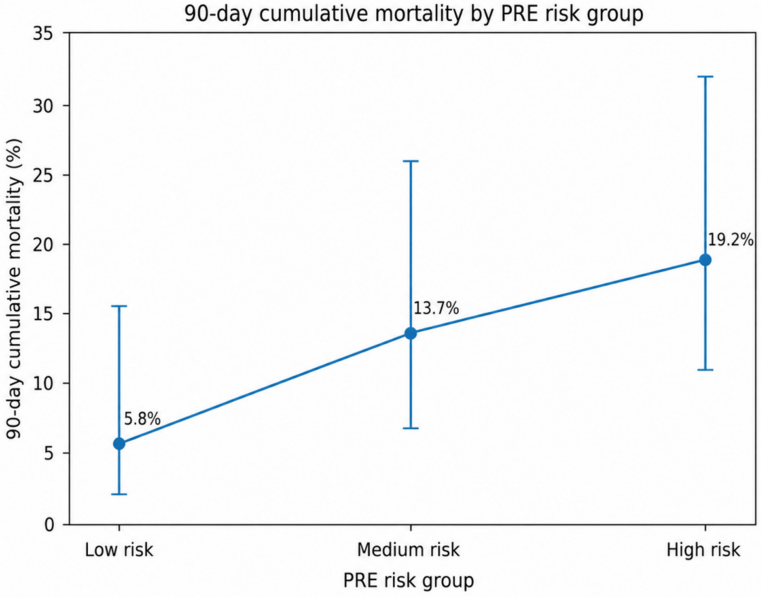


Figure 5. Ninety-day cumulative mortality across PRE risk strata in the development cohort.

(-2.50, -1.25) vs 0.00 (-0.60, 0.50); both P<0.001]. The AUCs for 24-hour PRE and ΔPRE were 0.877 and 0.890 in the development cohort and 0.919 and 0.932 in the temporal validation cohort. At 48 hours, the corresponding AUCs were 0.922 and 1.000 in the development cohort and 0.982 and 0.975 in the temporal validation cohort. Because of the smaller number of events, the 48-hour findings were considered exploratory. The results are presented in **Table 8**.

Discussion

AECOPD complicated by type II respiratory failure cannot be explained by an isolated blood gas abnormality; rather, it reflects the interaction of airway obstruction, dynamic lung hyperinflation, ventilation-perfusion mismatch, increased work of breathing due to respiratory muscle loading, infection-related inflammation, and systemic metabolic impairment [19]. Assessment of acute hypercapnia should therefore integrate $PaCO_2$ with oxygenation, mental status, severity of acidosis, respiratory muscle fatigue, and response to NIPPV [20]. O'Brien and colleagues reported an association between the mode of respiratory support used during acute hypercapnic episodes and the subsequent clinical course in patients with COPD [21]. In the present study, patients who required invasive ventilation had more severe ventilatory dysfunction, impaired oxygenation, acid-base disturbances, altered consciousness, and inflammatory-nutritional imbalance at admission. Rates of ICU admission, NIPPV failure, and invasive ventilation also increased across progressively higher risk strata. A simple, reproducible, and interpretable admission risk indicator may therefore help identify patients at high risk of intubation before overt decompensation, prompting timely repeat blood gas analysis, closer assessment of NIPPV effectiveness, and consideration of ICU transfer.

The association between the combined inflammation-nutrition burden and invasive mechanical ventilation was biologically and clinically plausible. Patients requiring invasive ventilation had greater inflammatory stress, more severe impairment of oxygenation and acid-base balance, and lower albumin levels at admission. LASSO retained NLR, SpO_2, albumin, disturbance of consciousness, APACHE II score, pH, and the number of acute exacerbations during the previous year, capturing complementary dimensions of systemic inflammation, nutritional and physiologic reserve, and acute respiratory failure. Previous studies have linked NLR and other inflammation-nutrition indices primarily to disease severity, mortality, or broadly defined adverse outcomes in AECOPD [8-16]. In contrast, the present study specifically examined escalation to invasive mechanical ventilation in patients who already met the narrow phenotype of AECOPD complicated by type II respiratory failure. Its principal contribution is not the creation of a new laboratory analyte, but the conversion of two routinely available admission measurements into a transparent probability, followed by evaluation of incremental value beyond APACHE II, clinical net benefit, risk stratification, and temporal transportability. Higher NLR, lower albumin, and higher APACHE II scores remained independently associated with invasive ventilation, and each 0.10 increase in PRE corresponded to a 62.0% increase in the odds of this out-

Table 6. Temporal validation performance of the prediction models

Indicator	AUC (95% CI)	Brier score	Cutoff value	Sensitivity	Specificity
PRE	0.845 (0.784-0.900)	0.143	≥0.247	0.698	0.785
PRE + APACHE II	0.881 (0.822-0.927)	0.129	≥0.247	0.736	0.833

Note: AUC, area under the receiver operating characteristic curve; CI, confidence interval; PRE, predicted probability; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table 7. PRE-based risk stratification in the temporal validation cohort

Risk stratification	Total cases	Invasive mechanical ventilation	Incidence rate
Low risk	60	2	3.3%
Medium risk	89	22	24.7%
High risk	48	29	60.4%

Table 8. Exploratory landmark analyses of serial NLR, albumin, and PRE

Cohort/landmark	n/ events	ΔNLR, no IMV/IMV	ΔAlbumin (g/L), no IMV/IMV	ΔPRE, no IMV/IMV	AUC, follow-up PRE/ΔPRE
Development/24 h	130/32	-1.13 (-1.75, -0.55)/ 1.67 (0.64, 3.41)	-0.20 (-0.70, 0.20)/ -0.90 (-1.30, -0.40)	-0.014 (-0.039, 0.000)/ 0.069 (0.018, 0.110)	0.877/0.890
Development/48 h	94/11	-1.83 (-2.74, -1.36)/ 3.34 (1.36, 6.28)	0.00 (-0.60, 0.50)/ -1.80 (-2.50, -1.25)	-0.026 (-0.069, -0.013)/ 0.163 (0.105, 0.230)	0.922/1.000
Temporal validation/24 h	170/37	-1.11 (-1.63, -0.42)/ 2.54 (1.10, 4.04)	-0.20 (-0.60, 0.20)/ -0.80 (-1.20, -0.30)	-0.013 (-0.028, 0.001)/ 0.118 (0.050, 0.151)	0.919/0.932
Temporal validation/48 h	114/17	-1.87 (-3.06, -1.19)/ 3.64 (1.16, 4.63)	-0.10 (-0.80, 0.30)/ -1.20 (-2.10, -1.00)	-0.028 (-0.053, -0.008)/ 0.160 (0.093, 0.284)	0.982/0.975

Note: Changes in NLR (ΔNLR), albumin (Δalbumin), and PRE (ΔPRE) are presented as the median (25th percentile [P25], 75th percentile [P75]) for patients without versus with invasive mechanical ventilation. All between-group comparisons were significant (P<0.001). AUC, area under the receiver operating characteristic curve; IMV, invasive mechanical ventilation; NLR, neutrophil-to-lymphocyte ratio; PRE, predicted probability.

come. PRE should therefore complement, rather than replace, assessment of blood gases, mental status, respiratory muscle function, and response to NIPPV.

The model achieved moderate-to-good discrimination and clinically interpretable risk stratification. In the development cohort, AUCs were 0.794 for PRE and 0.819 for PRE plus APACHE II, with bootstrap-corrected values of 0.788 and 0.808. Both models provided a net benefit over treat-all and treat-none strategies across clinically relevant threshold probabilities. However, the DeLong comparisons were not significant after Bonferroni correction; therefore, the numerical increase in AUC after adding APACHE II should not be interpreted as definitive evidence of superiority. Temporal validation nevertheless yielded AUCs of 0.845 and 0.881, Brier scores of 0.143 and 0.129, and a stepwise increase in invasive ventilation from 3.3% to 24.7% and 60.4% across PRE strata. The high-risk group also had higher rates of ICU admission and NIPPV failure after multiplicity correction, supporting the use of PRE to prompt more intensive blood gas reassessment, evaluation of the response to NIPPV, and preparation for escalation when clinically indicated. Nevertheless, PRE should serve only as an early-warning adjunct, not as an automatic indication for intubation, which must remain guided by the overall clinical course and established respiratory support criteria [22-24].

Several limitations merit consideration. First, this was a single-center retrospective study; although the temporally separated validation cohort included 197 patients, multicenter prospective validation is required before clinical implementation. Second, decisions regarding invasive ventilation may be influenced by clinician judgment, the NIPPV strategy, ICU resources, and patient preferences; therefore, residual treatment-selection bias cannot be excluded. Third, the model was developed exclusively in hospitalized adults with AECOPD complicated by type II respiratory failure and should not

be extrapolated to stable COPD, AECOPD without type II respiratory failure, or respiratory failure of other causes. Fourth, serial biomarkers were unavailable for some patients, and fewer events were available at the 48-hour landmark. Nevertheless, exploratory analyses showed that persistent increases in NLR, decreases in albumin, and increases in PRE at 24 and 48 hours were associated with subsequent invasive ventilation and provided greater discrimination than admission PRE. Because serial testing was not protocolized and its availability may have depended on the clinical course, these findings remain susceptible to selection bias and require prospective validation with fixed sampling times.

Conclusion

Among hospitalized adults with AECOPD complicated by type II respiratory failure, higher admission NLR, lower albumin, and the PRE derived from these markers were associated with invasive mechanical ventilation. PRE plus APACHE II provided numerically greater discrimination and clinically useful risk stratification, although multiplicity-adjusted ROC comparisons did not demonstrate statistical superiority. The model applies only to the narrowly defined population studied and should complement dynamic clinical assessment rather than serve as an automatic indication for invasive ventilation. Multicenter prospective validation incorporating serial NLR and albumin measurements is required before routine clinical use.

Disclosure of conflict of interest

None.

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