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ORIGINAL RESEARCH

Predictive Value of the Neutrophil-to-Lymphocyte Ratio/Serum Albumin for All-Cause Mortality in Critically Ill Patients Suffering from COPD

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Background: Among critically ill patients, chronic obstructive pulmonary disease (COPD) is an independent risk factor for death. Recently, biomarkers such as neutrophil-lymphocyte ratio (NLR) and albumin (ALB) have been used to predict the prognosis in patients with COPD. However, the association between NLR/ALB and all-cause mortality in critically ill COPD patients remains unclear. This study aims to explore the association between the NLR/ALB and prognosis in critically ill patients with COPD.

Methods: Data was sourced from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. Primary outcome was 28-day all-cause mortality, with secondary outcomes being in-hospital and 90-day all-cause mortality. The area under the receiver operating characteristic curve (AUROC) was calculated to compare prognostic accuracy of NLR, NLR/ALB, PLR, SII and MLR variables. After identifying the most predictive factor, KM survival curves, Cox models and subgroup analyses were used to examine NLR/ALB's relationship with mortality in critically ill COPD patients. Additionally, patients with COPD from the National Health and Nutrition Examination Survey data (1999–2018) was used with Cox regression to investigate NLR/ALB's correlation with all-cause mortality in COPD patients.

Results: 1916 critically ill COPD patients from MIMIC IV, divided into quartiles by NLR/ALB levels: Q1 (NLR/ALB<1.108), Q2 (2.095>NLR/ALB≥1.108), Q3 (4.221>NLR/ALB≥2.095), Q4 (NLR/ALB≥4.221). In multivariate Cox regression, Q4 vs Q1: 28-day mortality HR=2.27 (95% CI: 1.63–3.16); 90-day mortality HR=2.06 (95% CI: 1.56–2.71); in-hospital mortality HR=1.93 (95% CI: 1.35–2.77); P<0.001. Subgroup analyses showed that the correlation between NLR/ALB and 28-day mortality was stable Additionally, we recruited 2,003 COPD patients from the NHANES that found NLR/ALB also correlated with all-cause mortality in COPD (In multivariate Cox regression: Q4 vs Q1 hR=1.92 (95% CI: 1.45–2.55, P<0.001)).

Conclusion: Elevated NLR/ALB levels are associated with increased all-cause mortality in critically ill patients with COPD.

Keywords: critically ill patients with COPD, COPD, NLR/ALB, mortality

Introduction

Chronic obstructive pulmonary disease (COPD) ranks as the third leading cause of mortality across the globe, with a global prevalence rate documented at 10.1% in 2017.[1] Individuals experiencing acute exacerbations of COPD frequently find it necessary to be hospitalized or even admitted to the intensive care unit (ICU).[2] Research indicates that critically ill patients suffering from COPD face a heightened mortality risk when compared to their non-COPD counterparts.[3,4] Consequently, the early recognition of risk factors for critically ill patients with COPD holds paramount importance.

Systemic inflammation is a common pathophysiological feature of COPD. It has been linked to an increase in hyperresponsiveness in the airway, which can lead to worsening conditions and the development of COPD.[5–7] There is increasing evidence that the inflammatory biomarker is predictive of poor outcome in patients with COPD and is one of the effective predictors.[8–10] Some studies have reported that inflammatory biomarkers: NLR, platelet-to-lymphocyte ratio

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(PLR), systemic immune inflammatory index (SII) and monocyte-to-lymphocyte ratio (MLR) variables improve risk prediction in critically ill patients with COPD.[11–13] NLR is the ratio of neutrophil count to lymphocyte count, which reflects the body's inflammatory status and immune balance. The changes in neutrophil and lymphocyte counts constitute a dynamic, multifaceted process, influenced by the regulation of diverse immune, neuroendocrine, humoral, and biological mechanisms. In COPD patients, NLR tends to be elevated due to chronic airway inflammation and immune imbalance. Studies have shown that NLR is of great significance in predicting the risk of all-cause mortality and cardiovascular mortality in COPD patients.[14,15] ALB is a major blood plasma protein that has implications for predicting adverse outcomes in chronic respiratory disease, systemic inflammation, sepsis, postoperative and post-traumatic conditions.[16,17] And the ALB serves as an indicator of an individual's nutritional status and malnutrition is common in critical care patients with COPD. Hypoproteinemia raises the risk of acute exacerbations of COPD, increases the length of hospital stay and also effects quality of life of patients.[18,19] NLR/ALB is a relatively novel marker for assessing inflammation; however, there exists a limited number of studies investigating its prognostic significance.[20] This study explored the relationship between various inflammatory markers and the prognosis of critical care patients with COPD, highlighting the superior predictive value of the NLR/ALB. The observed significance may arise from the combined effects of inflammation-induced reduced albumin levels and increased neutrophil counts. Given their ability to predict adverse outcomes in various diseases, neutrophils, lymphocytes and ALB are likely to play a critical role in clinical practice. However, the prognostic value of the NLR/ALB in critically ill patients with COPD is not yet fully established. Therefore, this research aimed to evaluate the correlation between the NLR/ALB and prognosis in critically ill patients with COPD.

Materials and Methods

Medical Information Mart for Intensive Care-IV (MIMIC-IV-2.2) is a freely accessible database that encompasses over 50,000 ICU admissions at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2008 to 2019.

The NHANES dataset is collected by the National Center for Health Statistics (NCHS), a division of the Centers for Disease Control and Prevention (CDC). This survey is specifically designed to evaluate the health and nutritional status of both adults and children in the United States. The NHANES interview section includes demographic, socioeconomic, dietary and health-related questions. The physical examination portion includes physiological measurements and laboratory tests. The results of the survey will be used to determine the prevalence of epidemic diseases.

Population

Identification of patients with COPD was based on the International Classification of Diseases, Ninth and Ten Revision (ICD-9, ICD-10) codes (ICD-9:49,121, ICD-10: J441). The enrolled patients underwent haematological tests on admission. NLR/ALB was calculated as neutrophils/lymphocytes (10^9/L)/albumin (g/L). NLR was computed as neutrophils/lymphocytes (10^9/L) and SII was counted as platelets × neutrophils/lymphocytes (10^9/L). PLR was reckoned as platelets/lymphocytes (10^9/L).When patients were admitted to the ICU, they were excluded: (1) they had multiple ICU admissions or duplicate values; (2) they were younger than 18 years of age; (3) NLR/ALB, SII, and PLR data were incomplete or unavailable within 24 hours of ICU admission; (4) more than 20% of the individual data on their records were missing.

In the NHANES database, COPD was identified based on affirmative responses recorded in the NHANES Questionnaire (Medical Condition Dataset). Individuals were classified as having COPD if they answered "yes"to any of the following questions: "Has a physician ever diagnosed you with COPD?" "Has a doctor ever told you that you have chronic bronchitis?" or "Have you ever been informed by a doctor that you have emphysema?" This approach for identifying COPD patients has been effectively utilized in numerous previous studies using NHANES data. Consequently, participants who answered affirmatively to any of these questions were categorized as having COPD.

Statistical Analysis

To assess the ability of NLR, NLR/ALB, SII and PLR to anticipate 28-predict mortality at 28 days, hospitalization and 90 days, ROC curves and scales with specificity and sensitivity were plotted and the AUC of the various parametric models were compared, thus comparing the prognostic and diagnostic accuracy of the NLR, NLR/ALB, PLR and SII variables.

Then the NLR/ALB with the highest diagnostic accuracy was selected for analysis of the association between its level and all-cause mortality. We employed KM analysis to estimate survival probabilities and visualize the data. Additionally, the Cox proportional hazards regression model was used to identify potential risk factors associated with mortality. Furthermore, subgroup analyses were conducted to investigate the impact across different populations, aiming to fully understand the significance of this association in disease prevention and treatment. The NLR/ALB were divided into quartiles based on NLR/ALB values and the first quartile was selected as the reference. Classification variables were expressed as frequencies (percentages) and sequential ones as mean ± standard deviation (SD). The Kruskal–Wallis test (for non-normal distributions), one-way ANOVA (for normal distributions), and chi-square test (for categorical variables) were used to compare different NLR/ALB quartile groups. Cox regression analysis was employed to assess the independent effect of NLR/ALB levels on mortality. To enhance the accuracy of the analysis, we adjusted for factors such as age, sex, race, respiratory rate, mean blood pressure, urea nitrogen, hemoglobin, hematocrit, albumin, platelet count, red blood cell distribution width, heart failure, chronic kidney disease, chronic liver disease, diabetes mellitus and hypertension.

Three models were developed based on these influencing factors:

Model I: unadjusted.

Model II: adjusted for race, age and gender.

Model III: further adjusted for the variables in Model II plus additional factors identified through univariate and multivariate regression ($P<0.05$), including NLR/ALB, age, red blood cell distribution width (RDW), albumin, glucose, BUN, and comorbidities such as liver disease and malignant cancer.

Finally, subgroup analyses were conducted according to Models I and III, examining the interactions of NLR/ALB levels within different subgroups categorized by gender, age (<70 and ≥70), race, MBP (<75 and ≥75 mmHg), malignant cancers, liver disease, kidney disease, congestive heart failure, diabetes and hypertension.

The MIMIC-IV dataset was divided into training and validation sets, preserving a 7:3 ratio.The training set was modeled using both univariate and multivariate COX regression analyses, succeeded by applying the eight screened variables to the validation set. Findings from the validation collection were extended to include differentiation (C index), calibration, and decision curve analysis (DCA). This research utilized a variety of imputation techniques to calculate the absent values in continuous variables. Additionally, COPD patients were recruited from the NHANES database for supplementary data, and ROC curves along with forest plots were employed to confirm the link between NLR/ALB and mortality rates in COPD patients. Statistical evaluations were conducted using the SPSS 25.0 and R4.2.3 statistical programs. Each test conducted was bi-directional, with a statistical significance threshold established at $P<0.05$.

Results

Baseline Characteristics of the Included Participants

A total of 1,916 patients diagnosed with COPD were identified from the MIMIC-IV database according to predefined selection criteria. Figure 1 illustrates the flowchart detailing the process of selecting these study participants from the database. The AUC of the different parametric models was compared using the ROC curves to compare the prognostic accuracy of the NLR, NLR/ALB, PLR, and SII variables (Figure 2). After comparing the optimal metrics, all patients were equally divided into four categories based on NLR/ALB values, and the comparison of their baseline characteristics is summarized in Table 1. The majority of patients (71.35%) were white. The mean age of the patients was 71.56 ± 11.39 years and 54.12% were male. Overall mean NLR/ALB was 3.78±5.36 and mean albumin was 3.23±0.62. Patients with high NLR/ALB values were older, with increased heart rate, respiratory rate, erythrocyte distribution width, hematocrit, platelet count, urea nitrogen values, and creatinine, while their haematocrit, hemoglobin, albumin, and blood glucose all decreased. The length of ICU stay was also positively correlated with NLR/ALB. In addition, patients with higher NLR/ALB had higher SAPII and SOFA scores.

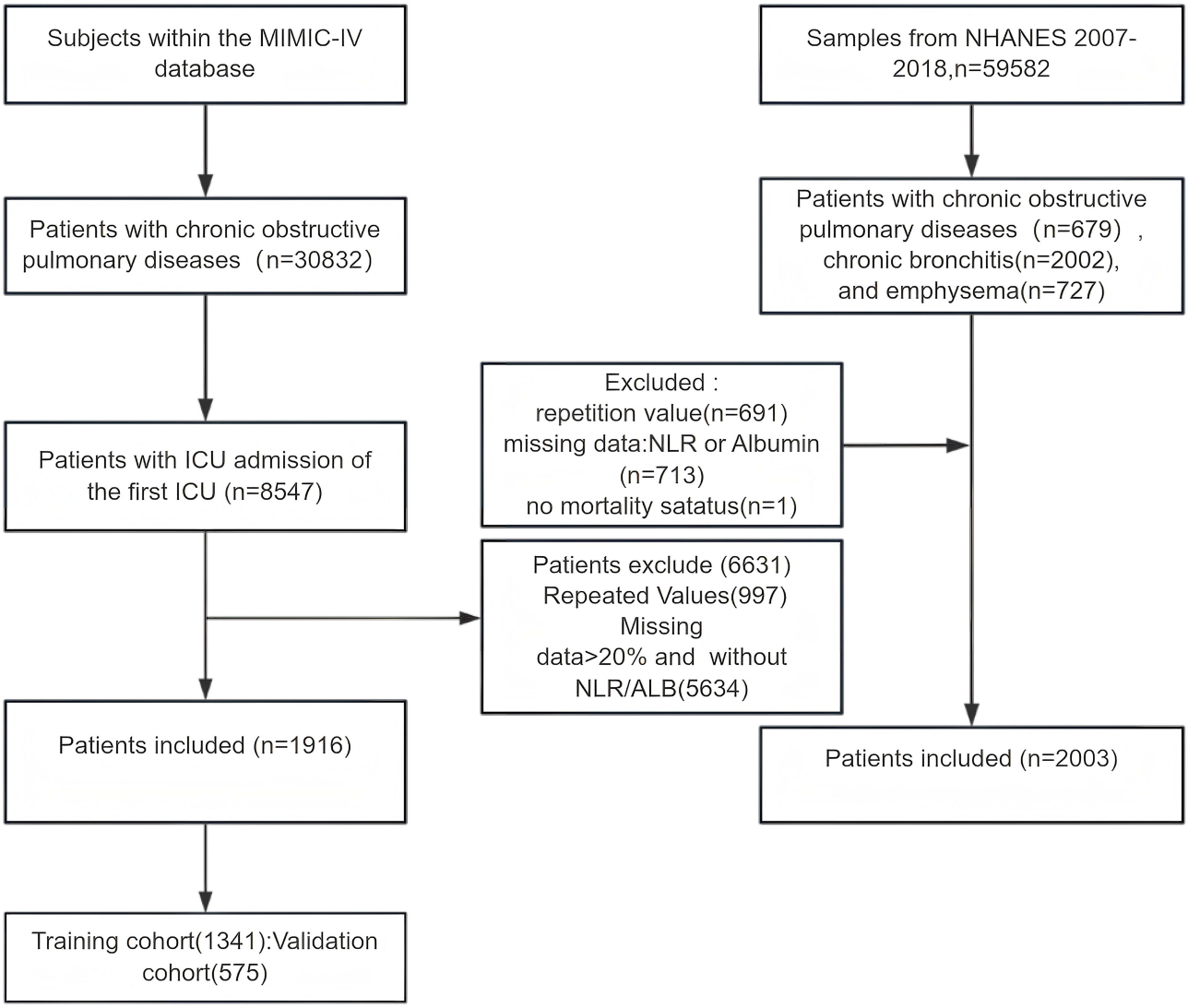

Figure 1 Flow chart of the population included in the study.
Abbreviations: MIMIC-IV – Medical Information Mart for Intensive Care-IV; COPD – chronic obstructive pulmonary disease; ICU – Intensive Care Unit; NLR /ALB– neutrophil to lymphocyte ratio/ serum albumin.

ROC and Predicting Mortality

We conducted a preliminary assessment of the potential prognostic value of NLR/ALB, NLR, MLR, and SII for 28-day, 90-day and in-hospital mortality among critically ill patients with COPD using ROC curve analysis (as illustrated in Figure 2). We discovered that the AUC for 28-day mortality in critically ill patients with COPD revealed the following results: for the NLR/ALB combination, the AUC was 0.662, with a 95% confidence interval (95% CI) spanning from 0.632 to 0.691. The AUC for the ALB was 0.644 (95% CI: 0.615 to 0.674).The AUC for the NLR was 0.637 (95% CI: 0.607 to 0.668), while the MLR yielded an AUC of 0.608 (95% CI: 0.577 to 0.639). The SII demonstrated an AUC of 0.588 (95% CI: 0.556 to 0.620), and the PLR had an AUC of 0.529 (95% CI: 0.497 to 0.560). For the 90-day mortality rates in critically ill COPD patients, the AUC results were as follows: NLR/ALB = 0.647 (95% CI: 0.620 to 0.674), NLR = 0.622 (95% CI: 0.595 to 0.649), ALB=0.647 (95% CI:0.622 to 0.674), MLR = 0.598 (95% CI: 0.570 to 0.626), SII = 0.584 (95% CI: 0.555 to 0.613) and PLR = 0.523 (95% CI: 0.494 to 0.551). Regarding in-hospital mortality, the observed AUC values were: NLR/ALB = 0.646 (95% CI: 0.614 to 0.678), ALB=0.644 (95% CI: 0.612 to 0.676), NLR = 0.621 (95% CI: 0.588 to 0.653), MLR = 0.588 (95% CI: 0.555 to 0.622), SII = 0.572 (95% CI: 0.537 to 0.607) and PLR = 0.515 (95% CI: 0.482 to 0.698). Except for the PLR metrics, the P-values for all other metrics were below 0.001; consequently, we have chosen not to include the PLR in

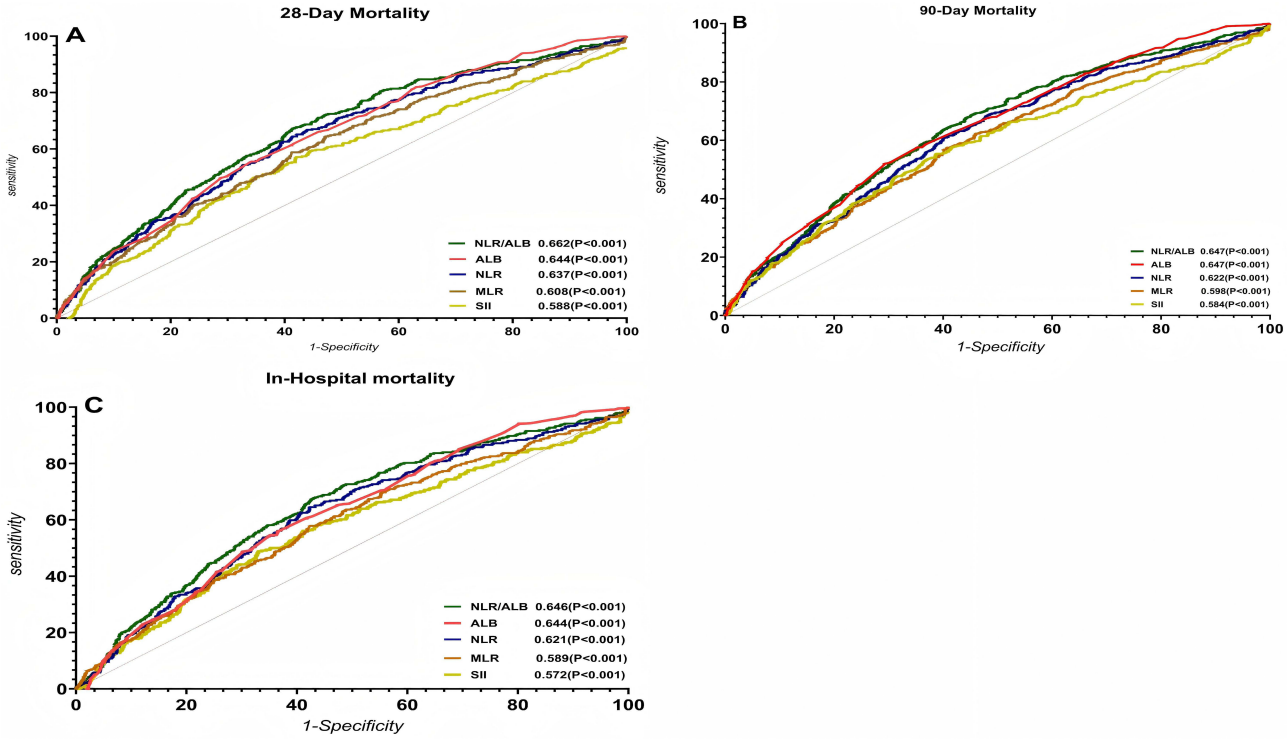

Figure 2 The analysis of receiver-operating characteristics curve for predicting mortality. (**A**) 28-day mortality; AUROC of NLR/ALB 0.662, 95% CI:0.632–0.691; AUROC of NLR 0.637, 95% CI: 0.607 −0.668; AUROC of ALB 0.644 95% CI: 0.615–0.674; AUROC of MLR 0.608 95% CI: 0.577–0.639; AUROC of SII 0.588 95% CI: 0.556–0.620. (**B**) 90-day mortality; AUROC of NLR/ALB 0.647, 95% CI: 0.620–0.676; AUROC of NLR 0.622, 95% CI: 0.595–0.649; AUROC of ALB 0.647, 95% CI: 0.615–0.676; AUROC of MLR 0.598 95% CI: 0.570–0.626; AUROC of SII 0.584 95% CI: 0.555–0.613. (**C**) In-hospital mortality; AUROC of NLR/ALB 0.646, 95% CI: 0.614–0.678; AUROC of NLR 0.621, 95% CI: 0.588–0.653; AUROC of ALB 0.644, 95% CI: 0.615–0.674; AUROC of MLR 0.588 95% CI: 0.555–0.622; AUROC of SII 0.572 95% CI: 0.537–0.607.

the graphical representations. In comparing the AUC for each metric, NLR/ALB demonstrated a relative superiority over the other metrics in terms of 28-day mortality, 90-day mortality and hospitalized mortality rate.

Relationship Between NLR/ALB and Mortality

The study cohort described in the article was derived from the MIMIC-IV database. The observed 28-day mortality rate in this population was found to be 22.18%, while the mortality rates at 90 days and during hospitalization were recorded at 17.95% and 30.32%, respectively. KM survival analyses revealed notable statistical differences in survival

Table 1 Baseline Characteristics of 1916 Subjects

Characteristics	All Patients	NLR/ALB				p value
		Q1 (<1.108)	Q2 (1.108–2.095)	Q3 (2.095–4.221)	Q4 (>4.221)	
Number	1916	479	479	479	479	
NLR/ALB	3.78±5.36	0.74±0.24	1.50±0.29	2.99±0.59	9.83±7.93	<0.001
Age	71.56±11.39	70.03±11.65	71.87±11.16	71.86±11.45	72.50±11.17	0.001
Gender, n (%)						0.670
Female	879(45.88)	224 (46.76)	224(46.76)	208(43.42)	223 (46.56)	
Male	1037(54.12)	255 (53.24)	255(53.24)	271(56.58)	256(53.44)	

(*Continued*)

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Table 1 (Continued).

Characteristics	All Patients	NLR/ALB				p value
		Q1 (<1.108)	Q2 (1.108–2.095)	Q3 (2.095–4.221)	Q4 (>4.221)	
Race, n (%)						<0.001
White	1367(71.35)	353(73.70)	354(73.90)	349(72.86)	311(64.93)	
Non-White	271(14.14)	99 (20.67)	66(13.78)	60(12.53)	46(9.60)	
Unknown	278(14.51)	27(5.63)	59(12.32)	70(14.61)	122(25.47)	
Vital signs						
SBP, mmHg	116.18±16.06	117.36±16.13	118.11±16.68	115.85±15.82	113.40±15.21	<0.001
DBP, mmHg	61.51±10.81	62.29±10.78	62.27±11.18	60.97±10.64	60.53±10.54	0.016
MBP, mmHg	76.50±10.49	77.47±10.72	77.54±10.92	75.86±10.02	75.15±10.10	<0.001
Respiratory rate/min	20.00±3.78	19.38±3.67	19.69±3.72	20.04±3.79	20.88±3.80	<0.001
Heart rate/min	86.96±15.81	84.37±15.12	84.86±15.38	87.99±15.75	90.60±16.20	<0.001
Temperature/°C	36.81±0.52	36.80±0.49	36.78±0.44	36.87±0.47	36.78±0.64	0.086
SPO2%	96.09±2.72	96.15±2.36	96.15±3.23	96.19±2.34	95.86±2.84	0.313
Laboratory parameters						
RDW%	15.68±2.42	15.34±2.35	15.70±2.63	15.73±2.34	15.92±2.32	<0.001
Hematocrit%	32.68±5.95	33.10±5.81	33.11±6.18	32.15±5.80	32.37±5.97	0.006
Hemoglobin, g/dL	10.62±2.02	10.86±2.00	10.75±2.08	10.40±1.98	10.46±1.98	<0.001
Platelet count,10^9/L	208.37±107.01	189.39±94.85	205.50±103.04	221.56±111.87	217.03±114.60	<0.001
Creatinine, mmol/L	1.44±1.18	1.34±1.16	1.35±1.03	1.51±1.22	1.54±1.29	0.016
BUN, mg/dL	29.91±20.96	25.72±17.53	27.99±20.64	30.93±21.00	35.01±23.21	<0.001
Glucose, mg/dL	142.09±56.01	137.12±52.07	142.36±58.21	140.68±57.08	148.18±56.09	<0.001
Potassium, mmol/L	4.28±0.57	4.30±0.50	4.26±0.58	4.25±0.58	4.30±0.61	0.162
Sodium, mmol/L	138.17±4.95	137.92±4.36	138.31±5.32	138.16±4.63	138.30±5.40	0.647
Monocytes,10^9/L	30.03±44.94	26.83±27.63	28.53±30.45	33.53±64.08	31.24±47.63	0.148
Albumin,10^9/L	3.23±0.62	3.57±0.54	3.36±0.59	3.12±0.56	2.87±0.58	<0.001
Bicarbonate, mmol/L	24.54±5.20	24.45±5.34	24.75±5.34	24.23±5.11	24.74±5.01	0.343
Chloride, mmol/L	102.38±6.18	102.23±5.63	102.10±6.35	102.42±5.96	102.77±6.71	0.515
Comorbidities, n (%)						
Congestive heart failure, n (%)	874(45.62)	199(41.54)	228(47.60)	226(47.18)	221(46.14)	0.214
Malignant cancer, n (%)	339(17.69)	89 (18.58)	76(15.87)	88(18.37)	86(17.95)	0.675
Renal disease, n (%)	523 (27.30)	108(22.55)	135(28.18)	151(31.59)	129(26.93)	0.019
Liver disease, n (%)	297(15.50)	83(17.33)	81(16.91)	60(12.53)	73 (15.24)	0.157

(*Continued*)

Table 1 (Continued).

Characteristics	All Patients	NLR/ALB				p value
		Q1 (<1.108)	Q2 (1.108–2.095)	Q3 (2.095–4.221)	Q4 (>4.221)	
Hypertension, n (%)	763 (39.82)	204(42.59)	204(42.59)	170(35.49)	185(38.62)	0.069
Diabetes, n (%)	662(34.55)	184 (38.41)	173 (36.12)	166(34.66)	139 (29.02)	0.017
Clinical outcomes, n (%)						
28-day all-cause mortality	425(22.18)	53(11.06)	80 (16.70)	120(25.05)	172(35.91)	<0.001
In-hospital all-cause mortality	344(17.95)	46(9.60)	61(12.73)	102(21.29)	135(28.18)	<0.001
90-day all-cause mortality	581(30.32)	81(16.91)	119 (24.84)	164(34.23)	217(45.30)	<0.001
All-cause mortality	987(51.51)	186(38.83)	235(49.06)	263(54.90)	303(63.25)	<0.001
Length of hospital stay, day	12.39±10.78	12.43±12.19	11.67±8.90	12.90±10.55	12.56±11.23	0.346
Length of ICU stay, day	4.50±6.14	3.74±5.34	3.91±5.31	4.75±5.78	12.56±11.23	<0.001
Scoring systems						
SOFA	6.26±4.00	5.61±3.77	5.73±3.80	6.30±3.83	7.38±4.34	<0.001
Sapsii	41.32±13.76	38.01±12.59	39.90±13.39	40.90±12.69	46.49±14.83	<0.001
Charlson	7.64±2.56	7.33±2.40	7.73±2.56	7.89±2.73	7.60±2.52	0.011

Abbreviations: NLR/ALB, combination of neutrophil-to-lymphocyte ratio and albumin concentration; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SPO2, percutaneous oxygen saturation; WBC, white blood cell; BUN, blood urea nitrogen; SOFA, Sequential Organ Failure Assessment; Sapsii, Simplified Acute Physiology Score II; Charlson-Charlson Comorbidity Index.

probabilities among different groups (Figure 3). To identify the independent factor influencing NLR/ALB in relation to all-cause mortality in critically ill COPD patients, three distinct Cox regression models were meticulously constructed, the results of which are detailed in Table 2. As the NLR/ALB increased, the HR values across all three models exhibited an upward trend. In Model I, a higher NLR/ALB ratio was found to correlate with an increased incidence of 28-day, 90-day and in-hospital mortality among patients with COPD in ICU. Similarly, in Model II, a higher NLR/ALB ratio was linked to a heightened risk of 28-day, 90-day and in-hospital mortality in COPD patients in the ICU when compared to the first quartile, following adjustments for age, sex and race. In the study, we conducted univariate and multivariate Cox regression analyses on critically ill patients with COPD to identify risk factors associated with 28-day, 90-day and in-hospital mortality. We selected variables with a p-value of less than 0.05 in the univariate analysis and incorporated them into the multivariate Cox regression analysis to determine independent risk factors. In model III, the NLR/ALB emerged as an independent predictor for 28-day, 90-day and in-hospital mortality in this population, even after adjusting for additional confounding variables (adjusted hazard ratios and 95% CI: Q1 2.27 (1.63–3.16), Q2 2.06 (1.56–2.71) and Q3 1.93 (1.35–2.77), with p-values less than 0.01). These findings imply that elevated levels of NLR/ALB in ICU patients with COPD are independently associated with 28-day, 90-day and in-hospital mortality, making it a significant risk factor.

Prognostic Performance of Laboratory Parameters

We utilized a multifactorial model specifically designed to assess all-cause mortality in critically ill patients with COPD. The MIMIC-IV dataset was split into a training set and a validation set in a 7:3 ratio. Based on the training set, a multifactorial Cox model was developed and then directly applied to the validation set, revealing similar results: elevated NLR/ALB values were positively associated with 28-day mortality, 90-day mortality and in-hospital mortality among critically ill patients diagnosed with COPD. In the training cohort, the HR and 95% CI for the four groups were 1.46 (0.97–2.21), 2.15 (1.45–3.18), and 3.56 (2.46–5.14); the adjusted HR and 95% CI were 2.27 (1.63–3.16), 2.06

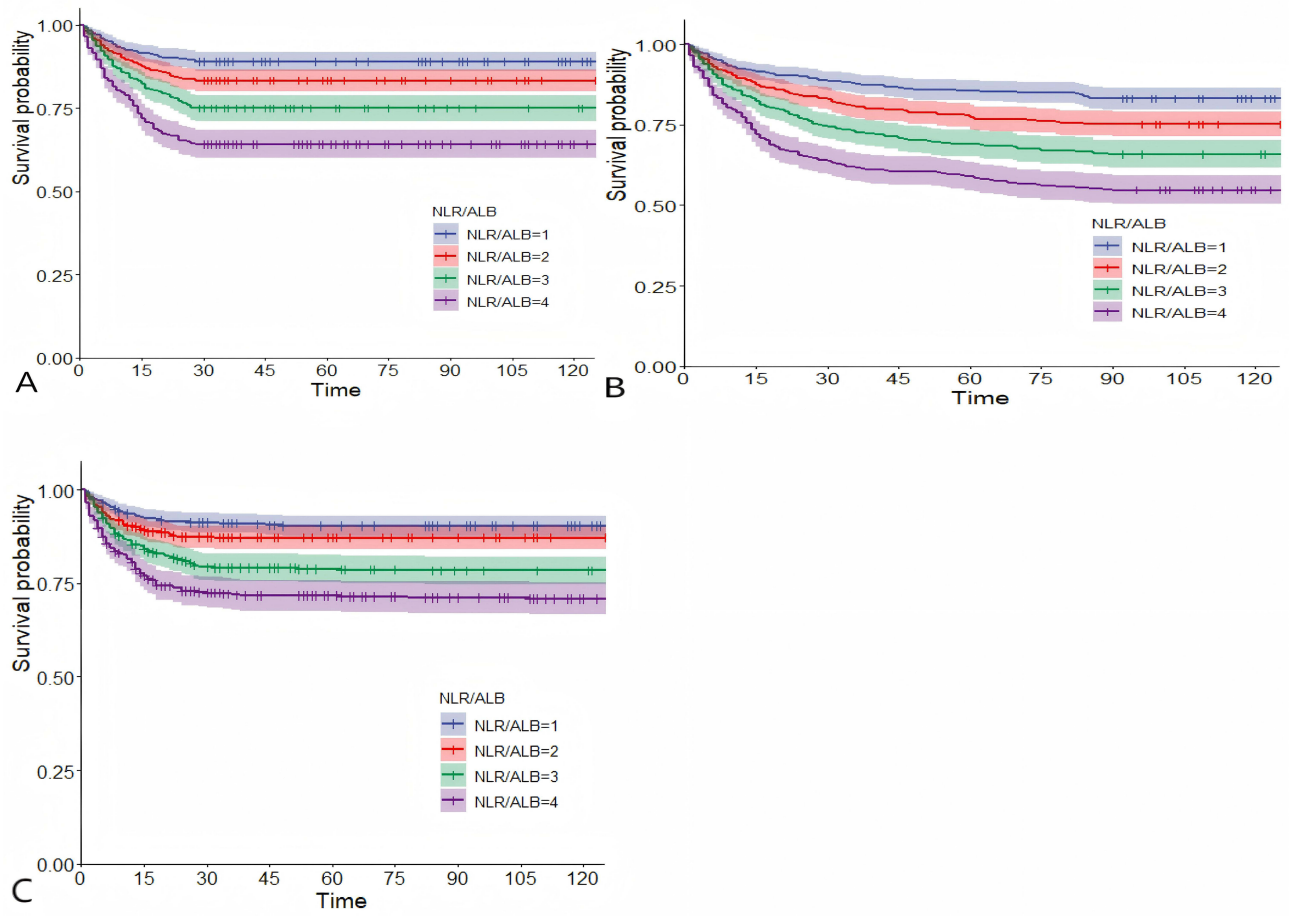

Figure 3 Kaplan-Meier survival curves showing the association between NLR/ALB and 28-day, 90-day and in-hospital mortality. Image software: R 3.3.2, MathSoft. (**A**) 28-day mortality; (**B**) In-hospital mortality; (**C**) 90-day mortality.

(1.56–2.71) and 1.93 (1.35–2.77), respectively, with all p-values less than 0.01. In the validation cohort, the HR and 95% CI were 1.81 (0.96–3.42), 3.12 (1.76–5.54), and 4.24 (2.42–7.43); the adjusted HR and 95% CI were 1.25 (0.65–2.38), 2.04 (1.12–3.70), and 2.45 (1.35–4.44), respectively (Table 3). Statistically significant factors from the multifactorial Cox regression analysis were incorporated into the development of a nomogram prediction model using the training set, with

Table 2 HRs (95% CIs) for Mortality Across Groups of Neutrophil-to-Lymphocyte Ratio/Serum Albumin Ratio in the MIMIC IV Database

	Model I(Not Adjusted)			**Model II**			**Model III**		
	HR (95% CI)	**P value**	**P**	**HR (95% CI)**	**P value**	**P**	**HR (95% CI)**	**P value**	**P**
28-day all-cause mortality									
Quartiles			<0.001			<0.001			<0.001
Q1	1 (Ref)			1 (Ref)			1 (Ref)		
Q2	1.56 (1.10~2.20)	0.012		1.45 (1.03~2.06)	0.035		1.28 (0.90~1.82)	0.164	
Q3	2.43 (1.76~3.35)	<0.001		2.27 (1.64~3.14)	<0.001		1.76 (1.26~2.47)	0.001	
Q4	3.76 (2.77~5.12)	<0.001		3.33 (2.43~4.56)	<0.001		2.27 (1.63~3.16)	<0.001	

(*Continued*)

Table 2 (Continued).

	Model I(Not Adjusted)			Model II			Model III		
	HR (95% CI)	**P value**	**P**	**HR (95% CI)**	**P value**	**P**	**HR (95% CI)**	**P value**	**P**
In-hospital mortality									
Quartiles			<0.001			<0.001			<0.001
Q1	1 (Ref)			1 (Ref)			1 (Ref)		
Q2	1.36 (0.93~2.00)	0.110		1.27 (0.86~1.86)	0.225		1.10 (0.75~1.62)	0.640	
Q3	2.36 (1.67~3.35)	<0.001		2.18 (1.54~3.10)	<0.001		1.65 (1.15~2.37)	0.006	
Q4	3.37 (2.41~4.70)	<0.001		2.89 (2.05~4.07)	<0.001		1.93 (1.35~2.77)	<0.001	
90-day all-cause mortality									
Quartiles			<0.001			<0.001		<0.001	
Q1	1 (Ref)			1 (Ref)			1 (Ref)		
Q2	1.54 (1.16~2.05)	0.003		1.44 (1.09~1.91)	0.050		1.28(0.96~1.70)	0.090	
Q3	2.25 (1.73~2.94)	<0.001		2.11 (1.61~2.76)	<0.001		1.69 (1.28~2.23)	<0.001	
Q4	3.30 (2.56~4.26)	<0.001		2.94 (2.26~3.82)	<0.001		2.06 (1.56~2.71)	<0.001	

Table 3 HRs (95% CIs) for Training Cohort and Validation Cohort 28-Day All-Cause Mortality Across Groups of NLR/ALB in the MIMIC IV

(Training Cohort) 28-Day All-Cause Mortality						
	Univariate Models			**Multivariate Models**		
	HR (95% CI)	**P value**	**P trend**	**HR (95% CI)**	**P value**	**P trend**
Quartiles			<0.001			<0.001
Q1	1 (Ref)			1 (Ref)		
Q2	1.46 (0.97~2.21)	0.073		2.27 (1.63~3.16)	0.082	
Q3	2.15 (1.45~3.18)	<0.001		2.06 (1.56~2.71)	0.007	
Q4	3.56 (2.46~5.14)	<0.001		1.93 (1.35~2.77)	<0.001	
(Validation cohort) 28-Day all-cause mortality						
Quartiles			<0.001			0.005
Q1	1 (Ref)			1 (Ref)		
Q2	1.81 (0.96~3.42)	0.069		1.25 (0.65~2.38)	0.387	
Q3	3.12 (1.76~5.54)	<0.001		2.04 (1.12~3.70)	0.012	
Q4	4.24 (2.42~7.43)	<0.001		2.45 (1.35~4.44)	0.002	

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results presented in Figure 4. For critical care patients with COPD, NLR/ALB as the 4th group, age 70 years max, RDW, bun, albumin and glucose at the upper limit of normal values, no liver disease or cancer, and a score of about 165, it can be seen that the 1-year survival rate of the patients is 60%. The column line graph has predictive effect. The estimated model demonstrated robust discriminatory power, as indicated by a C-statistic of 0.781 (95% CI: 0.763–0.799) in the training set and 0.701 (95% CI: 0.684–0.718) in the validation set. Furthermore, the AUROC was calculated to be 0.758 (95% CI: 0.709–0.806) for the training set, while the AUROC for the validation set was 0.734 (95% CI: 0.653–0.815) (Figure 5); the clinical DCA demonstrated showed that the model had a favorable clinical application (Figure 6); and the predicted probabilities in the calibration curve graphs were in high-level agreement with the actual values (Figure 7).

Finally, the data were analyzed in subgroups with the aim of excluding other factors, using Models I and III, respectively, and then subgroups according to age, sex, ethnicity, blood pressure, and by presence or absence of disease (Table 4). No interaction was found for 28-day mortality across subgroups in either the univariate or multivariate models. However, subgroup analyses focusing on patients with COPD combined with malignancy or COPD alongside MBP ≥75 mmHg did demonstrate a significant interaction (P<0.05) for 90-day mortality. In the subgroup analysis of 90-day mortality, malignancy with COPD (Unadjusted model: Q2: HR = 1.40, 95% CI: 0.86 to 2.27; Q3: HR = 2.15, 95% CI: 1.38 to 3.35; Q4: HR = 1.77, 95% CI: 1.12 to 2.80, P=0.002. Adjusted model: Q2: HR = 1.13, 95% CI: 0.69 to 1.86; Q3: HR = 1.66, 95% CI: 1.04 to 2.65; Q4: HR = 1.22 and 95% CI: 0.74 to 2.03, P=0.022), and patients with MBP ≥75 mmHg (Unadjusted model: Q2: HR = 2.06, 95% CI: 1.34 to 3.18; Q3: HR = 2.57, 95% CI: 1.67 to 3.96; Q4: HR = 4.20, 95% CI: 2.78 to 6.34, P=0.045) had a higher mortality risk. Similar findings were found in patients with in-hospital mortality of MBP ≥75 mmHg (Unadjusted model: Q2: HR = 1.40, 95% CI: 0.71 to 2.74; Q3: HR = 2.23, 95% CI: 1.22 to 4.08; Q4: HR = 1.85, 95% CI: 0.99 to 3.46, P=0.037). There was no statistically significant correlation in the other subgroups.

At the same time, we also made an interesting discovery in the NHANES database: the NLR/ALB is related to the prognosis of COPD patients. We selected 2003 patients with COPD from the NHANES database who met the criteria. The AUC of the different parametric models was compared using ROC to compare the prognostic and diagnostic accuracy of the NLR, NLR/ALB, ALB, PLR and SII variables (Figure 8). In model III, NLR/ALB proved to be an independent predictor of all-cause mortality in the patients with COPD, after adjusting for additional confounders (unadjusted HR and 95% CI: Q2=1.28 (0.95~1.74), Q3=1.82 (1.37~2.43) and Q4=3.94 (3.03~5.12) compared to Q1; p-values < 0.01) (Table 5). Higher AUC values of NLR/ALB was found to have a high correlation with all-cause

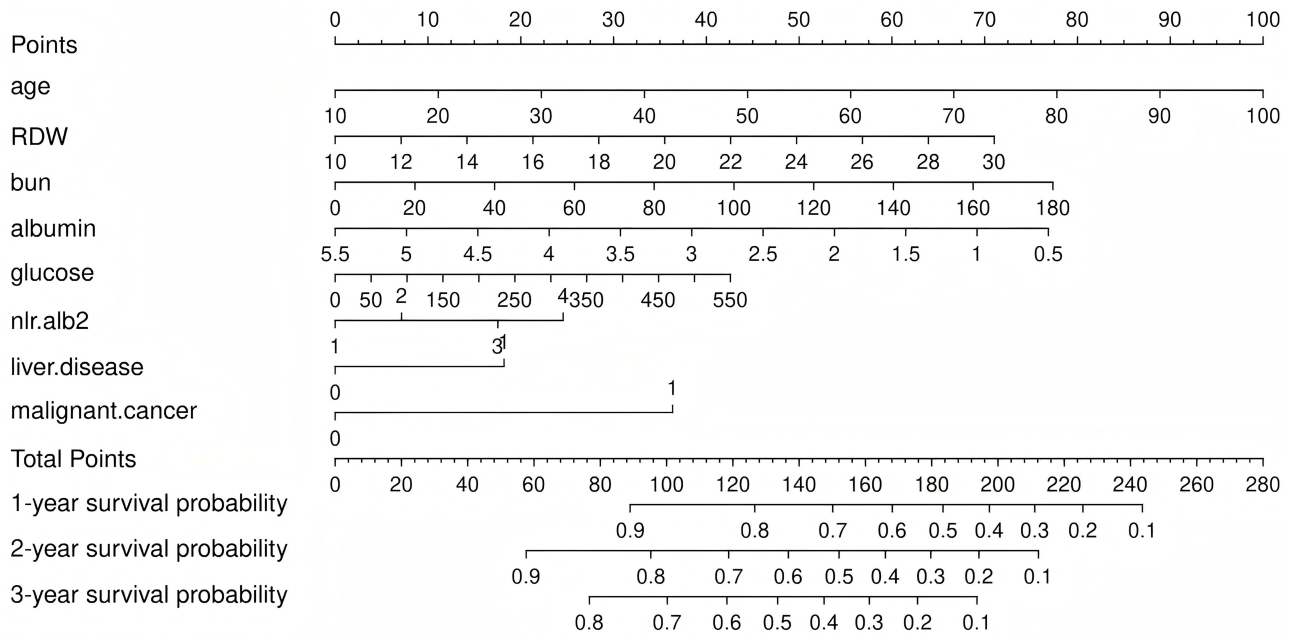

Figure 4 Nomograms predicting 1-year, 2-year, and 3-year OS in critically ill patients with COPD, OS Overall survival.

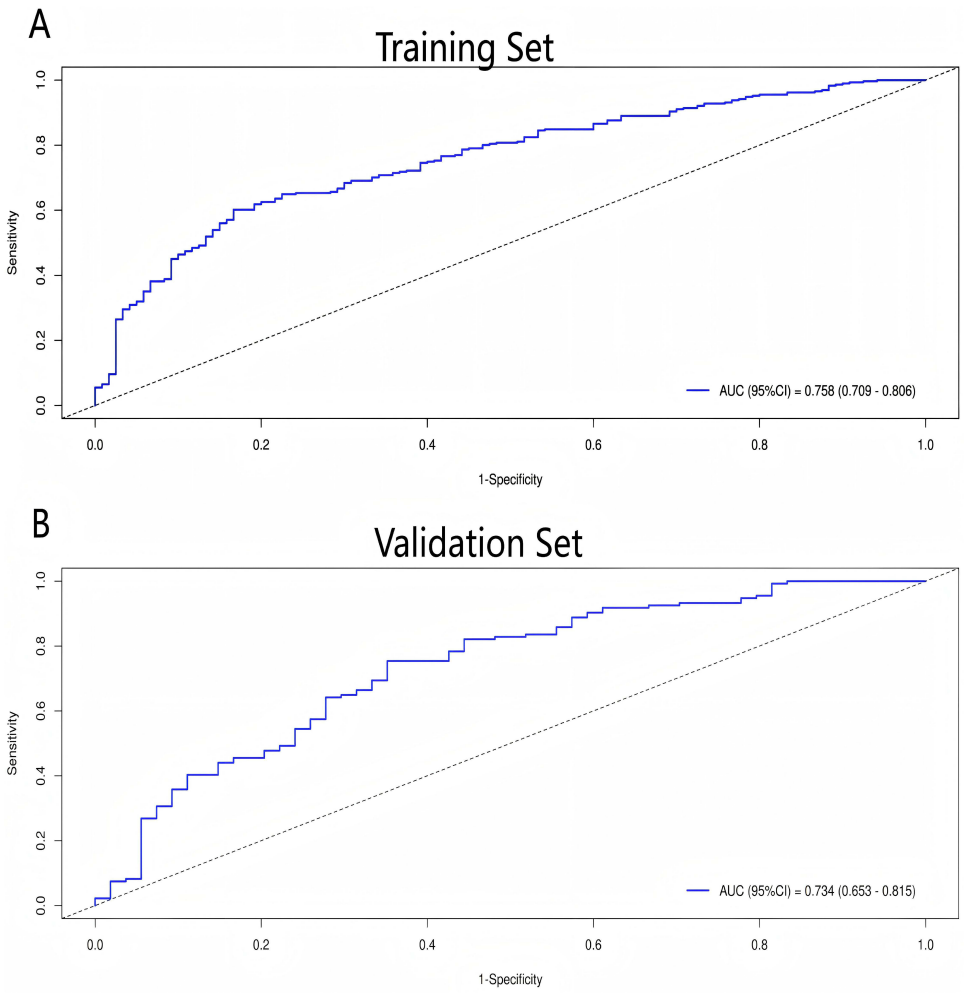

Figure 5 ROC curves of the training set and the validation set in the MIMIC-IV. Besides, the AUROC of training set reached 0.758 (95% CI: 0.709–0.806) (**A**); the AUROC of validation set reached 0.734 (95% CI: 0.653–0.815) (**B**).

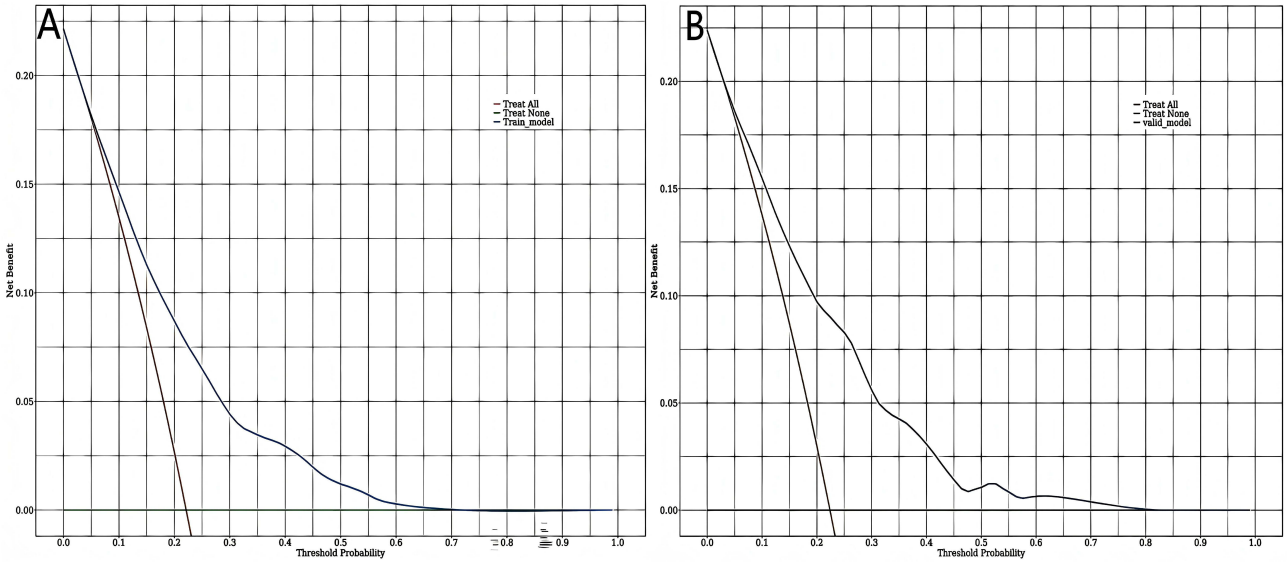

Figure 6 DCA of the different set: the Training Model(**A**), the Validation model(**B**). The horizontal line indicates no patients develop 28-day deaths, and the red line indicates all patients develop 28-day deaths. The blue line represents the admissions data of critically ill patients with COPD from MIMIC IV.

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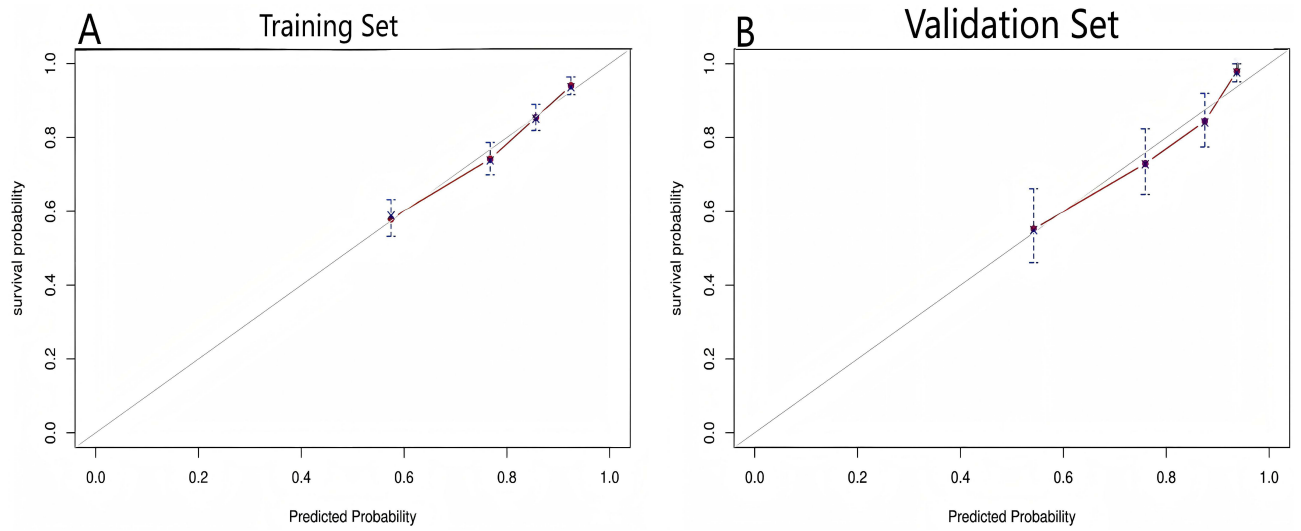

Figure 7 Calibration curves of the training set (**A**), internal validation set (**B**). The x-axis represents the predicted probability calculated, and the y-axis is the observed actual probability of the 28-day survival probability. The clinodiagonal represents a perfect prediction by an ideal model.

mortality in patients with COPD. The NLR/ALB ratio was categorized into quartiles, and COX regression-adjusted analyses revealed that patients with COPD in the highest quartile (Q4) exhibited a significantly higher risk of all-cause mortality when compared to those in the lowest quartile (Q1) in the Table 5. Table 5. This finding based on the results indicates that the NLR/ALB is not only a predictor of mortality in critically ill COPD patients but also holds relevance for mortality outcomes in the COPD population. Consequently, it can be inferred that the NLR/ALB may serve as a more reliable indicator than other hematologic inflammatory markers for assessing the mortality in individuals with COPD. To further investigate whether NLR/ALB remained a risk factor for all-cause mortality in certain disease subgroups, an exploratory subgroup analysis was performed on the original cohort. The Forest plot expressed that high NLR/ALB was a risk factor for all-cause mortality in patients with COPD (Figure 9).

Discussion

This study focused on investigating whether the values of NLR/ALB can serve as the predictor for adverse outcomes in critically ill patients diagnosed with COPD. Following adjustments for various confounding factors and multiple variables, both the Cox regression analysis and subgroup evaluations indicated that elevated NLR/ALB values were significantly correlated with an increased risk of all-cause mortality in critically ill patients with COPD. We performed subgroup analyses of clinical indicators and comorbidities and then found no interaction between subgroups in 28-day mortality, which simultaneously supports the above conclusion. However, critically ill patients with COPD with MBP ≥75 mmHg and those with comorbid malignancies were at higher risk of death in both 90-day and in-hospital mortality. It has been shown that NLR and ALB reflect chronic inflammation and are predictive of poor outcome in cancer patients.[20–23] There is also additional evidence that NLR is also positively correlated with hypertension[24–27] and that ALB values indicate a negative correlation with the blood pressure values in hypertensive patients.[28,29] Our study has demonstrated that a higher NLR/ALB ratio is associated with a poorer prognosis in patients with MBP≥75 mmHg. However, this finding requires further validation.

COPD is a heterogeneous rather than a monolithic disease,[30] characterised by progressively worsening airflow limitation due to bronchitis and emphysema. The progression of emphysema and bronchiectasis is not similar. Since one disease may lead to the development of the other, in the NHANES database we collected patients with bronchitis, emphysema and COPD and we found that NLR/ALB was linked to death risk in bronchitis, emphysema and COPD patients, and outperformed other inflammatory biomarkers in predicting all-cause mortality in COPD patients.

The morbidity and mortality rates of COPD patients in developing countries are high.[31,32] 22%-40% of patients with COPD have at least one or more acute exacerbations per year and are admitted to the intensive care unit.[33] Taking

Table 4 Subgroup Analysis of the Associations Between All-Cause Mortality and the NLR/ALB

	NLR/ALB of 28-Day Mortality									
	Univariate Models					Multivariate Models				
	Q 1	Q 2	Q 3	Q4	P for interaction	Q 1	Q 2	Q 3	Q4	P for interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Age, year	0.269					0.422				
<70	1 (Ref)	2.09 (1.16~3.77)	2.87 (1.64~5.02)	4.27 (2.50~7.30)		1 (Ref)	1.85 (1.02~3.36)	2.61 (1.46~4.65)	3.26 (1.83~5.80)	
≥70	1 (Ref)	1.21 (0.79~1.86)	2.03 (1.36~3.01)	3.20 (2.20~4.67)		1 (Ref)	1.04 (0.67~1.60)	1.42 (0.94~2.15)	1.88 (1.25~2.82)	
Gender	0.242					0.322				
Male	1 (Ref)	1.27 (0.79~2.04)	2.49 (1.63~3.81)	3.29 (2.17~4.98)		1 (Ref)	1.14 (0.70~1.85)	1.96 (1.26~3.06)	2.22 (1.41~3.49)	
Female	1 (Ref)	1.95 (1.17~3.24)	2.30 (1.39~3.79)	4.40 (2.77~6.97)		1 (Ref)	1.53 (0.91~2.55)	1.60 (0.95~2.66)	2.56 (1.57~4.17)	
Race	0.673					0.66				
White	1 (Ref)	1.51 (1.01~2.25)	2.17 (1.49~3.18)	3.25 (2.25~4.69)		1 (Ref)	1.26 (0.84~1.90)	1.53 (1.03~2.27)	1.93 (1.31~2.85)	
Unknown	1 (Ref)	0.90 (0.31~2.63)	1.66 (0.63~4.40)	2.93 (1.17~7.32)		1 (Ref)	0.88 (0.30~2.62)	1.19 (0.44~3.26)	1.92 (0.73~5.06)	
Non-white	1 (Ref)	2.21 (0.89~5.49)	4.10 (1.78~9.42)	4.40 (1.85~10.50)		1 (Ref)	1.52 (0.59~3.94)	3.31 (1.35~8.10)	2.87 (1.03~8.00)	
MBP	0.183					0.409				
<75	1 (Ref)	1.14 (0.72~1.82)	2.00 (1.34~3.00)	3.00 (2.04~4.41)		1 (Ref)	0.92 (0.58~1.47)	1.43 (0.94~2.16)	1.65 (1.09~2.50)	
≥75	1 (Ref)	2.30 (1.34~3.95)	2.92 (1.71~5.00)	4.70 (2.81~7.86)		1 (Ref)	2.04 (1.18~3.53)	2.42 (1.38~4.25)	3.53 (2.04~6.10)	
Medical History										
Malignant cancer	0.056					0.201				
Yes	1 (Ref)	1.59 (0.86~2.95)	2.56 (1.47~4.47)	2.45 (1.40~4.31)		1 (Ref)	1.30 (0.70~2.42)	1.99 (1.11~3.56)	1.69 (0.91~3.12)	
No	1 (Ref)	1.62 (1.06~2.47)	2.41 (1.62~3.59)	4.43 (3.05~6.42)		1 (Ref)	1.24 (0.81~1.90)	1.61 (1.06~2.43)	2.42 (1.62~3.61)	

(*Continued*)

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Table 4 (Continued).

	NLR/ALB of 28-Day Mortality									
	Univariate Models					Multivariate Models				
	Q 1	Q 2	Q 3	Q4	P for interaction	Q 1	Q 2	Q 3	Q4	P for interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Congestive heart failure	0.342					0.510				
Yes	1 (Ref)	1.17 (0.70~1.97)	2.24 (1.41~3.58)	3.64 (2.33~5.68)		1 (Ref)	1.06 (0.63~1.80)	1.64 (1.02~2.99)	2.35 (1.47~3.78)	
No	1 (Ref)	1.96 (1.23~3.13)	2.56 (1.64~4.01)	3.82 (2.50~5.86)		1 (Ref)	1.50 (0.93~2.42)	1.88 (1.18~2.67)	2.15 (1.35~3.44)	
Diabetes	0.458					0.678				
Yes	1 (Ref)	1.64 (0.88~3.03)	3.19 (1.83~5.58)	3.90 (2.23~6.83)		1 (Ref)	1.10 (0.59~2.07)	1.78 (0.99~3.21)	1.96 (1.07~3.59)	
No	1 (Ref)	1.50 (0.99~2.29)	2.08 (1.40~3.10)	3.60 (2.49~5.21)		1 (Ref)	1.39 (0.91~2.13)	1.73 (1.15~2.61)	2.31 (1.55~3.43)	
Hypertension	0.093					0.139				
Yes	1 (Ref)	2.52 (1.35~4.72)	3.56 (1.93~6.57)	6.57 (3.70~11.68)		1 (Ref)	2.19 (1.16~ 4.13)	2.70 (1.44~ 5.06)	3.81 (2.07~ 7.03)	
No	1 (Ref)	1.21 (0.79~1.85)	1.97 (1.34~2.88)	2.77 (1.92~4.01)		1 (Ref)	1.00 (0.65~1.54)	1.45 (0.97~2.16)	1.77 (1.19~2.63)	
Renal disease	0.453					0.629				
Yes	1 (Ref)	1.43 (0.78~2.59)	1.84 (1.05~3.24)	2.74 (1.58~4.77)		1 (Ref)	1.13 (0.61~2.08)	1.26 (0.70~2.29)	1.79 (0.99~2.25)	
No	1 (Ref)	1.57 (1.02~2.40)	2.65 (1.79~3.94)	4.23 (2.91~6.12)		1 (Ref)	1.40 (0.91~2.16)	2.04 (1.36~3.07)	2.45 (1.64~3.66)	
Liver disease	0.463					0.849				
Yes	1 (Ref)	1.32 (0.64~2.71)	2.80 (1.42~5.53)	2.94 (1.54~5.62)		1 (Ref)	1.35 (0.65~2.82)	2.64 (1.29~5.42)	2.77 (1.34~5.73)	
No	1 (Ref)	1.63 (1.10~2.43)	2.44 (1.69~3.53)	4.04 (2.84~5.74)		1 (Ref)	1.28 (0.86~1.91)	1.63 (1.12~2.38)	2.12 (1.46~3.10)	

Age, y	0.611					0.810				
<70	1 (Ref)	1.86 (1.17~2.98)	2.38 (1.52~3.74)	3.61 (2.36~5.53)		1 (Ref)	1.59 (0.99~2.56)	2.11 (1.32~3.37)	2.65 (1.67~4.22)	
≥70	1 (Ref)	1.11 (0.69~1.18)	1.98 (1.29~3.03)	2.95 (1.95~4.44)		1 (Ref)	1.11 (0.78~1.59)	1.48 (1.05~2.09)	1.79 (1.27~2.53)	
Gender	0.330					0.509				
Male	1 (Ref)	1.32 (0.89~1.97)	2.38 (1.66~3.41)	3.32 (2.34~4.70)		1 (Ref)	1.15 (0.77~1.73)	1.84 (1.26~2.68)	2.18 (1.49~3.20)	
Female	1 (Ref)	1.81 (1.21~2.70)	2.09 (1.40~3.11)	3.28 (2.26~4.77)		1 (Ref)	1.49 (0.99~2.23)	1.59 (1.05~2.39)	2.09 (1.40~3.11)	
Race	0.627					0.626				
White	1 (Ref)	1.53 (1.11~2.11)	2.03 (1.45~2.76)	2.82 (2.09~3.82)		1 (Ref)	1.29 (0.93~1.80)	1.47 (1.06~2.03)	1.72 (1.25~2.39)	
Unknown	1 (Ref)	1.06 (0.41~2.75)	1.99 (0.83~4.80)	3.19 (1.38~7.35)		1 (Ref)	1.12 (0.43~2.96)	1.58 (0.64~3.90)	2.36 (0.98~5.67)	
Non-white	1 (Ref)	1.75 (0.82~3.71)	3.23 (1.62~6.42)	3.87 (1.91~7.83)		1 (Ref)	1.19 (0.54~2.60)	2.36 (1.14~4.88)	2.39 (1.03~5.50)	
MBP	0.045					0.067				
<75	1 (Ref)	1.22 (0.84~1.78)	1.92 (1.37~2.69)	2.59 (1.87~3.58)		1 (Ref)	0.99 (0.68~1.45)	1.41 (0.99~1.99)	1.46 (1.02~2.08)	
≥75	1 (Ref)	2.06 (1.34~3.18)	2.57 (1.67~3.96)	4.20 (2.78~6.34)		1 (Ref)	1.85 (1.19~2.88)	2.23 (1.42~3.51)	3.35 (2.15~5.21)	
Medical History										
Malignant cancer	0.002					0.022				
Yes	1 (Ref)	1.40 (0.86~2.27)	2.15 (1.38~3.35)	1.77 (1.12~2.80)		1 (Ref)	1.13 (0.69~1.86)	1.66 (1.04~2.65)	1.22 (0.74~2.03)	
No	1 (Ref)	1.72 (1.21~2.44)	2.42 (1.73~3.38)	4.24 (3.10~5.81)		1 (Ref)	1.34 (0.94~1.90)	1.66 (1.17~2.34)	1.72 (1.73~3.40)	
Congestive heart failure	0.341					0.520				
Yes	1 (Ref)	1.20 (0.79~1.82)	2.04 (1.38~3.00)	3.11 (2.14~4.50)		1 (Ref)	1.08 (0.71~1.66)	1.53 (1.02~2.28)	2.09 (1.41~3.10)	
No	1 (Ref)	1.90 (1.30~2.78)	2.43 (1.68~3.51)	3.44 (2.42~4.89)		1 (Ref)	1.46 (0.99~2.15)	1.85 (1.26~2.72)	2.00 (1.36~2.96)	

(*Continued*)

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Table 4 (Continued).

	NLR/ALB of 28-Day Mortality									
	Univariate Models					Multivariate Models				
	Q 1	Q 2	Q 3	Q4	P for interaction	Q 1	Q 2	Q 3	Q4	P for interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Diabetes	0.334					0.759				
Yes	1 (Ref)	1.92 (1.15~3.21)	3.12 (1.92~5.07)	3.71 (2.27~6.04)		1 (Ref)	1.29 (0.76~2.18)	1.75 (1.05~2.91)	1.82 (1.07~3.09)	
No	1 (Ref)	1.38 (0.99~1.94)	1.90 (1.38~2.62)	3.04 (2.25~4.10)		1 (Ref)	1.26 (0.90~1.77)	1.62 (1.16~2.26)	2.06 (1.49~2.84)	
Hypertension	0.093					0.163				
Yes	1 (Ref)	2.12 (1.29~3.51)	2.82 (1.72~4.64)	5.08 (3.20~8.06)		1 (Ref)	1.79 (1.08~ 2.98)	2.17 (1.30~ 3.63)	2.95 (1.79~ 4.85)	
No	1 (Ref)	1.30 (0.93~1.84)	1.95 (1.42~2.67)	2.58 (1.90~3.52)		1 (Ref)	1.09 (0.77~1.55)	1.51 (1.08~2.09)	1.72 (1.23~2.40)	
Renal disease	0.546					0.862				
Yes	1 (Ref)	1.52 (0.91~2.53)	2.15 (1.33~3.47)	2.68 (1.66~4.34)		1 (Ref)	1.20 (0.71~ 2.02)	1.53 (0.93~2.53)	1.78 (1.06~2.98)	
No	1 (Ref)	1.51 (1.07~2.12)	2.20 (1.60~3.04)	3.53 (2.61~4.77)		1 (Ref)	1.36 (0.97~1.92)	1.75 (1.26~2.45)	2.14 (1.54~2.97)	
Liver disease	0.802					0.964				
Yes	1 (Ref)	1.35 (0.76~2.38)	2.24 (1.27~3.94)	2.76 (1.63~4.67)		1 (Ref)	1.25 (0.70~2.25)	2.00 (1.10~3.65)	2.49 (1.38~4.51)	
No	1 (Ref)	1.61 (1.16~2.23)	2.36 (1.75~3.20)	3.52 (2.63~4.72)		1 (Ref)	1.30 (0.93~1.80)	1.65 (1.21~2.26)	1.95 (1.42~2.68)	
Age, y	0.665					0.846				
<70	1 (Ref)	1.71 (0.89~3.27)	2.81 (1.55~5.09)	3.60 (2.01~6.43)		1 (Ref)	1.50 (0.78~2.89)	2.69 (1.45~4.98)	2.92 (1.56~5.45)	
≥70	1 (Ref)	1.21 (0.79~1.86)	2.03 (1.36~3.01)	3.20 (2.20~4.67)		1 (Ref)	0.91 (0.56~1.47)	1.28 (0.82~2.00)	1.54 (0.99~2.40)	
Gender	0.230					0.286				
Male	1 (Ref)	1.04 (0.61~1.78)	2.44 (1.55~3.85)	3.03 (1.93~4.76)		1 (Ref)	0.91 (0.53~1.57)	1.86 (1.15~3.00)	1.96 (1.20~3.21)	
Female	1 (Ref)	1.81 (1.04~3.14)	2.23 (1.30~3.82)	3.81 (2.31~6.28)		1 (Ref)	1.39 (0.80~2.43)	1.45 (0.83~2.52)	2.03 (1.20~3.47)	

Race	0.439					0.570				
White	1 (Ref)	1.19 (0.76~1.86)	2.05 (1.37~3.07)	2.49 (1.67~3.72)		1 (Ref)	0.96 (0.61~1.51)	1.35 (0.88~2.05)	1.36 (0.89~2.09)	
Unknown	1 (Ref)	0.81 (0.27~2.43)	1.50 (0.56~4.02)	2.60 (1.04~6.51)		1 (Ref)	0.81 (0.27~2.44)	1.15 (0.42~3.18)	1.93 (0.73~5.14)	
Non-white	1 (Ref)	3.20 (1.09~9.35)	5.03 (1.81~13.97)	6.94 (2.50~19.29)		1 (Ref)	2.07 (0.68~6.31)	4.25 (1.43~12.65)	4.47 (1.36~14.68)	
MBP	0.231					0.236				
<75	1 (Ref)	0.93 (0.57~1.53)	1.76 (1.16~2.68)	2.56 (1.72~3.81)		1 (Ref)	0.72 (0.44~1.20)	1.20 (0.78~1.85)	1.32 (0.86~2.04)	
≥75	1 (Ref)	2.47 (1.29~4.72)	3.57 (1.90~6.72)	4.70 (2.53~8.76)		1 (Ref)	2.20 (1.14~4.23)	3.02 (1.56~5.82)	3.65 (1.89~7.05)	
Medical History										
Malignant cancer	0.037					0.183				
Yes	1 (Ref)	1.40 (0.71~2.74)	2.23 (1.22~4.08)	1.85 (0.99~3.46)		1 (Ref)	1.12 (0.57~2.21)	1.72 (0.92~3.23)	1.29 (0.65~2.55)	
No	1 (Ref)	1.43 (0.89~2.27)	2.49 (1.62~3.81)	4.16 (2.78~6.24)		1 (Ref)	1.07 (0.67~1.72)	1.60 (1.03~2.50)	2.18 (1.41~3.38)	
Congestive heart failure	0.733					0.762				
Yes	1 (Ref)	1.18 (0.67~2.08)	2.34 (1.41~3.89)	3.49 (2.14~5.68)		1 (Ref)	1.05 (0.59~1.86)	1.70 (1.01~2.86)	2.21 (1.32~3.71)	
No	1 (Ref)	1.54 (0.91~2.58)	2.34 (1.45~3.79)	3.20 (2.02~5.08)		1 (Ref)	1.13 (0.66~1.91)	1.61 (0.97~2.66)	1.64 (0.98~2.73)	
Diabetes	0.355					0.522				
Yes	1 (Ref)	1.60 (0.84~3.03)	3.08 (1.73~5.49)	3.18 (1.76~5.76)		1 (Ref)	1.09 (0.57~2.09)	1.77 (0.96~3.27)	1.61 (0.84~3.06)	
No	1 (Ref)	1.25 (0.77~2.01)	2.02 (1.30~3.13)	3.37 (2.24~5.06)		1 (Ref)	1.12 (0.69~1.82)	1.61 (1.02~2.53)	2.05 (1.32~3.18)	
Hypertension	0.135					0.136				
Yes	1 (Ref)	2.66 (1.28~5.53)	4.13 (2.03~8.41)	5.93 (2.99~11.75)		1 (Ref)	2.29 (1.09~4.81)	2.94 (1.42~6.09)	3.16 (1.53~6.55)	
No	1 (Ref)	1.00 (0.63~1.59)	1.82 (1.22~2.72)	2.59 (1.76~3.82)		1 (Ref)	0.81 (0.50~1.29)	1.30 (0.85~1.98)	1.60 (1.06~2.44)	

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Table 4 (Continued).

	NLR/ALB of 28-Day Mortality									
	Univariate Models					Multivariate Models				
	Q 1	Q 2	Q 3	Q4	P for interaction	Q 1	Q 2	Q 3	Q4	P for interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Renal disease	0.850					0.911				
Yes	1 (Ref)	1.60 (0.79~3.21)	2.29 (1.19~4.40)	3.37 (1.77~6.39)		1 (Ref)	1.24 (0.61~2.52)	1.52 (0.77~3.02)	2.14 (1.08~4.25)	
No	1 (Ref)	1.24 (0.78~1.96)	2.33 (1.54~3.53)	3.32 (2.24~4.91)		1 (Ref)	1.07 (0.67~ 1.70)	1.70 (1.11~ 2.61)	1.79 (1.17~2.74)	
Liver disease	0.399					0.722				
Yes	1 (Ref)	1.10 (0.48~2.49)	2.84 (1.36~5.92)	2.55 (1.24~5.23)		1 (Ref)	1.20 (0.52~ 2.75)	2.96 (1.36~ 6.47)	2.82 (1.26~ 6.33)	
No	1 (Ref)	1.45 (0.94~2.24)	2.35 (1.58~3.49)	3.63 (2.48~5.30)		1 (Ref)	1.09 (0.71~1.69)	1.47 (0.98~ 2.22)	1.76 (1.17~2.64)	
Age, y	0.331					0.538				
<70	1 (Ref)	1.71 (0.89~3.27)	2.81 (1.55~5.09)	3.60 (2.01~6.43)		1 (Ref)	1.38 (1.01~1.91)	1.50 (1.09~2.07)	2.15 (1.56~2.96)	
≥70	1 (Ref)	1.18 (0.92~1.52)	1.61 (1.26~2.05)	1.92 (1.51~2.43)		1 (Ref)	1.04 (0.81~1.34)	1.35 (1.04~1.74)	1.40 (1.08~1.81)	
Gender	0.524					0.33				
Male	1 (Ref)	1.04 (0.61~1.78)	2.44 (1.55~3.85)	3.03 (1.93~4.76)		1 (Ref)	1.07 (0.81~1.41)	1.51 (1.15~1.98)	1.76 (1.33~2.33)	
Female	1 (Ref)	1.48 (1.12~1.97)	1.61 (1.21~2.13)	2.18 (1.67~2.85)		1 (Ref)	1.33 (1.00~1.77)	1.40 (1.04~1.88)	1.69 (1.27~2.26)	
Race	0.126					0.257				
White	1 (Ref)	1.21 (0.92~1.58)	1.71 (1.32~2.21)	2.21 (1.71~2.85)		1 (Ref)	1.25 (0.99~1.58)	1.41 (1.11~1.78)	1.54 (1.21~1.96)	
Unknown	1 (Ref)	1.00 (0.45~2.25)	1.84 (0.89~3.81)	2.99 (1.49~5.)		1 (Ref)	1.09 (0.48~2.47)	1.53 (0.71~3.29)	2.22 (1.06~4.67)	
Non-white	1 (Ref)	1.25 (0.79~1.96)	1.45 (0.92~2.28)	1.59 (0.99~2.57)		1 (Ref)	0.85 (0.3~1.36)	1.41 (0.88~2.27)	1.27 (0.74~2.19)	

MBP	0.310					0.396				
<75	1 (Ref)	1.18 (0.90~1.55)	1.55 (1.20~1.99)	1.86 (1.46~3.38)		1 (Ref)	1.05 (0.80~1.38)	1.29 (0.99~1.68)	1.35 (1.03~1.76)	
≥75	1 (Ref)	1.49 (1.13~1.97)	1.74 (1.32~2.31)	2.58 (1.95~3.41)		1 (Ref)	1.32 (0.99~1.76)	1.56 (1.16~2.11)	2.14 (1.58~2.90)	
Medical History										
Malignant cancer	0.147					0.431				
Yes	1 (Ref)	1.22 (0.84~1.77)	1.62 (1.14~2.29)	1.51 (1.05~2.17)		1 (Ref)	1.00 (0.68~1.46)	1.25 (0.85~1.82)	1.14 (0.76~1.71)	
No	1 (Ref)	1.44 (1.15~1.81)	1.78 (1.42~2.23)	2.50 (2.01~3.10)		1 (Ref)	1.20 (0.59~1.54)	1.47 (1.16~1.86)	1.76 (1.39~2.22)	
Congestive heart failure	0.275					0.878				
Yes	1 (Ref)	1.14 (0.87~1.49)	1.79 (1.37~2.34)	2.21 (1.70~2.87)		1 (Ref)	1.09 (0.83~1.44)	1.53 (1.15~2.03)	1.73 (1.30~2.96)	
No	1 (Ref)	1.56 (1.18~2.06)	1.74 (1.33~2.28)	2.33 (1.80~3.03)		1 (Ref)	1.23 (0.92~1.63)	1.46 (1.10~1.95)	1.68 (1.26~2.25)	
Diabetes	0.603					0.990				
Yes	1 (Ref)	1.49 (1.08~3.05)	2.04 (1.48~2.79)	2.35 (1.71~3.24)		1 (Ref)	1.19 (0.85~1.66)	1.48 (1.05~2.07)	1.69 (1.19~2.40)	
No	1 (Ref)	1.25 (0.77~2.01)	2.02 (1.30~3.13)	3.37 (2.24~5.06)		1 (Ref)	1.16 (0.90~1.48)	1.38 (1.07~1.77)	1.53 (1.20~1.96)	
Hypertension	0.215					0.375				
Yes	1 (Ref)	1.38 (1.00~1.91)	1.77 (1.28~2.44)	2.70 (2.00~3.65)		1 (Ref)	1.24 (0.89~1.73)	1.56 (1.11~2.20)	2.05 (1.48~2.86)	
No	1 (Ref)	1.28 (1.01~1.64)	1.58 (1.25~1.99)	1.90 (1.51~2.40)		1 (Ref)	1.09 (0.85~1.40)	1.35 (1.06~1.72)	1.43 (1.11~1.83)	
Renal disease	0.169					0.627				
Yes	1 (Ref)	1.42 (1.01~1.99)	1.64 (1.17~2.30)	1.77 (1.25~2.49)		1 (Ref)	1.14 (0.80~1.61)	1.33 (0.93~1.90)	1.34 (0.93~1.94)	
No	1 (Ref)	1.26 (0.99~1.59)	1.66 (1.32~2.08)	2.37 (1.91~2.94)		1 (Ref)	1.17 (0.92~1.49)	1.43 (1.12~1.81)	1.72 (1.36~2.19)	

(*Continued*)

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Table 4 (Continued).

	NLR/ALB of 28-Day Mortality									
	Univariate Models					Multivariate Models				
	Q 1	Q 2	Q 3	Q4	P for interaction	Q 1	Q 2	Q 3	Q4	P for interaction
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Liver disease	0.706					0.886				
Yes	1 (Ref)	1.13 (0.73~1.74)	1.75 (1.14~2.67)	1.86 (1.25~2.78)		1 (Ref)	1.10 (0.70~ 1.72)	1.64 (1.04~ 2.58)	1.70 (1.08~ 2.70)	
No	1 (Ref)	1.36 (1.10~1.69)	1.71 (1.39~2.12)	2.29 (1.86~2.82)		1 (Ref)	1.15 (0.92~1.44)	1.38 (1.11~ 1.72)	1.62 (1.29~2.03)	

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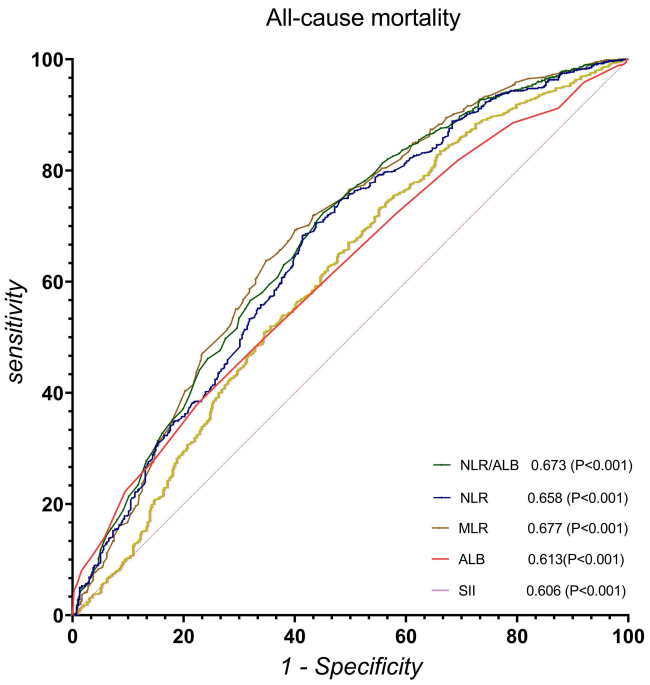

Figure 8 AUROC for prediction of all-cause mortality of patients with COPD in the NHANES database. AUROC of NLR/ALB 0.673, 95% CI:0.646–0.700; AUROC of MLR 0.677, 95% CI: 0.650 −0.705; AUROC of NLR 0.658 95% CI: 0.631–0.686; AUROC of ALB 0.613, 95% CI: 0.585–0.642; AUROC of SII 0.606 95% CI: 0.577–0.635.

a highly feasible approach to early diagnosis and intervention before adverse outcomes occur in critically ill COPD patients can undoubtedly prevent the disease from progressing to a more complicated state.[34] Thus, an effective marker is urgently needed to quickly identify high-risk COPD patients in critical condition, allowing for timely and appropriate treatment to enhance their prognosis.[35,36]

NLR as a prognostic marker predicts a wide range of diseases and studies have shown that this biomarker is significantly linked to hospitalization rates and mortality among patients with COPD.[37,38] And albumin reflects the nutritional status of an individual, a decrease in serum albumin has been associated with a deterioration in the clinical condition of COPD patients.[39–41] In order to accurately predict prognosis, we used a combination of NLR and Alb to study poor prognosis in critically ill patients with COPD. NLR/ALB is a composite inflammatory index that combines neutrophils, lymphocytes and albumin, but it has been relatively understudied. This index is less affected by individual biomarker values and better reflects adverse disease outcomes. NLR/ALB integrates three clinically validated biomarkers, making it a comprehensive, accessible, and cost-effective indicator. Current research suggest that NLR/ALB can

Table 5 HRs (95% CIs) for All-Cause Mortality Across Groups of NLR/ALB in the NHANES Database

(NHANES)All-Cause Mortality						
Univariate Models				**Multivariate Models**		
HR (95% CI		**P value**	**P trend**	**HR (95% CI)**	**P value**	**P trend**
Quartiles			<0.001			<0.001
Q1	1 (Ref)			1 (Ref)		
Q2	1.28 (0.95~1.74)	0.108		1.16 (0.85~1.57)	0.348	
Q3	1.82 (1.37~2.43)	<0.001		1.43 (1.07~1.91)	0.015	
Q4	3.94 (3.03~5.12)	<0.001		1.92 (1.45~2.55)	<0.001	

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Variable	Count	G1	G2	G3	G4	P.value	P.for.interaction	HR(95%CI)
Overall	2003	500	501	501	501	<0.001		1.63 (1.5-1.78)
age							<0.001	NA (NA-NA)
>=70	565	92(18.40)	113(22.55)	139(27.74)	221(44.11)	<0.001		1.26 (1.13-1.4)
<70	1438	408(81.60)	388(77.45)	362(72.26)	280(55.89)	<0.001		1.7 (1.5-1.93)
gender							0.025	NA (NA-NA)
male	824	175(0.35)	177(35.33)	223(44.51)	249(49.70)	<0.001		1.75 (1.55-1.97)
female	1179	325(0.65)	324(64.67)	278(55.49)	252(50.30)	<0.001		1.45 (1.28-1.63)
congestiveheartfailure							0.033	NA (NA-NA)
No	1743	456(91.20)	463(92.42)	446(89.02)	378(75.45)	<0.001		1.48 (1.34-1.62)
Yes	260	44(8.80)	38(7.58)	55(10.98)	123(24.55)	<0.001		1.8 (1.49-2.16)
MBP							0.46	NA (NA-NA)
>=75	1722	449(89.80)	441(88.02)	413(82.44)	419(83.63)	<0.001		1.65 (1.5-1.81)
<75	281	51(10.20)	60(11.98)	88(17.56)	82(16.37)	<0.001		1.5 (1.22-1.85)
cancer							0.639	NA (NA-NA)
No	1646	436(87.20)	400(79.84)	422(84.23)	388(77.45)	<0.001		1.63 (1.48-1.79)
Yes	357	64(12.80)	101(20.16)	79(15.77)	113(22.55)	<0.001		1.54 (1.31-1.81)
hypertension							0.637	NA (NA-NA)
No	884	236(47.20)	222(44.31)	234(46.71)	192(38.32)	<0.001		1.57 (1.35-1.83)
Yes	1119	264(52.80)	279(55.69)	267(53.29)	309(61.68)	<0.001		1.65 (1.49-1.82)
diabetes							0.444	NA (NA-NA)
No	1523	407(81.40)	400(79.84)	371(74.05)	345(68.86)	<0.001		1.58 (1.43-1.74)
Yes	480	93(18.60)	101(20.16)	130(25.95)	156(31.14)	<0.001		1.71 (1.46-2.01)
liverdisease							0.711	NA (NA-NA)
No	1813	439(87.80)	449(89.62)	456(91.02)	469(93.61)	<0.001		1.65 (1.51-1.8)
Yes	190	61(12.20)	52(10.38)	45(8.98)	32(6.39)	0.001		1.59 (1.22-2.07)
renal							0.983	NA (NA-NA)
No	1855	476(95.20)	473(94.41)	467(93.21)	439(87.62)	<0.001		1.61 (1.47-1.76)
Yes	148	24(4.80)	28(5.59)	34(6.78)	62(12.38)	<0.001		1.61 (1.25-2.07)

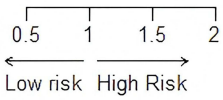

Figure 9 Subgroup analysis for the association between NLR/ALB and all-cause mortality of patients with COPD in the NHANES database.

predict poor prognosis in patients with gastrointestinal tumors, such as those after gastric cancer surgery and esophageal cancer surgery, as well as in patients with male alcoholic cirrhosis.[20,42,43] To our knowledge, no studies have yet discussed the link between NLR/ALB and clinical outcomes in critically ill COPD patients.

Furthermore, a certain amount of patients were included in this study, which would have made our findings more reliable. There are also several limitations in our study. Firstly, NLR/ALB is a dynamic biomarker that changes as a patient's disease status changes and the values will vary at different stages of disease progression. Therefore, the results of the study are subject to selection bias. Secondly, there are some imperfections in the variables in the MIMIC-IV database, which may cause errors in our results. Although the present article did not demonstrate an interaction between heart failure, myocardial infarction in subgroup analyses and patients with COPD, it has been demonstrated that comorbidities such as cardiovascular disease, osteoporosis, sarcopenia, and pulmonary vascular disease exacerbate the disease burden in patients suffering from COPD.[44] Thirdly, the findings were not supported by clinical data collection or local validation, as we did not conduct post-discharge follow-up. Despite the limitations in this study, NLR/ALB remains a valuable tool for predicting adverse outcomes in critical care patients with COPD.

Conclusion

Elevated NLR/ALB levels are associated with increased 28-day, 90-day all-cause mortality, as well as in-hospital mortality in critically ill patients with COPD.

Ethics Statement

The data were extracted from the MIMIC IV, which is considered the largest open-source and freely accessible clinical database in critical care. Yongli Liu completed the data research training program of the Collaborative Institutional Training Initiative (record ID 54640691) and gained access to the database. In this study, the MIT Institutional Review Board waived informed consent and approved the sharing of the research resource since it involved an analysis of public databases.

The NHANES database has undergone rigorous review and has been granted approval by the Research ERB of the NCHS. This approval ensures that the study complies with ethical standards and protects the rights and welfare of the participants. Furthermore, all participants provided their written informed consent before taking part in the research, which signifies their voluntary agreement to participate and their understanding of the study's purpose, procedures, potential risks, and benefits.

Ethical approval for this study was obtained from the Medical Research Ethics Committee of the Qilu Hospital of Shandong University (No. KYLL-202410-049).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. The scientific guarantor of this publication is Yiqing Qu.

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Disclosure

The authors report no conflicts of interest in this work.

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