Association Between Neutrophil-Lymphocyte Ratio and All-Cause Mortality in Critically Ill Patients with Chronic Obstructive Pulmonary Disease: A Retrospective Cohort Study

Authors' Contribution:
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Background: Neutrophil-lymphocyte ratio (NLR) is related to increased mortality risk in many diseases. However, there is limited research on critically ill patients with chronic obstructive pulmonary disease (COPD). A retrospective cohort study was performed to investigate whether NLR can be used as a biomarker to predict the mortality of critically ill COPD patients.

Material/Methods: In the research, the data were gathered from the database of the Medical Information Mart for Intensive Care-IV. The 28-day mortality was defined as the primary outcome, while the secondary outcomes were in-hospital and 90-day mortality. Through the application of the Kaplan-Meier curves and the multivariate Cox regression analysis, the potential association between NLR and mortality for critically ill patients with COPD was evaluated. For subgroup analysis, age, sex, ethnicity, mean blood pressure, and comorbidities were considered.

Results: We extracted data on 2650 patients, of which 53.7% were male. A higher level of NLR was correlated with higher 28-day mortality risk. Compared to the lower quartile (NLR<4.56), HR (95% CI) of the upper quartile (NLR>16.86) was 1.75 (1.21-2.52) in the multivariate Cox regression model when adjusted for confounders (P=0.003). A similar tendency was found in the 90-day mortality (HR=1.59, 95% CI=1.16-2.19, P=0.004) and the in-hospital mortality (HR=1.71, 95% CI=1.22-2.42, P=0.002). Subgroup analyses showed that the correlation between NLR and 28-day mortality was stable.

Conclusions: The higher level of NLR is likely to be correlated with the increase of the all-cause mortality risk in critically ill patients with COPD, but this needs to be validated in future prospective research.

Keywords: COPD, Severe Early-Onset • Mortality

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Background

Chronic obstructive pulmonary disease (COPD) is a lung disease with persistent respiratory symptoms and airflow restriction; it is preventable, common, and treatable [1]. Many epidemiological studies and the Burden of Obstructive Lung Diseases show that a total of 391.9 million cases of COPD were found among individuals aged 30-79 years in 2019, with a worldwide prevalence of 10.3% (95% CI=8.2-12.8) [2]. The World Health Organization has reported that COPD is currently among the 3 major causes of death globally, causing around 3 million deaths each year, and also has substantial social and economic costs worldwide [3]. In the United States, it is estimated that the 20-year (2019-2038) direct medical cost for COPD is $800.9 billion [4]. In the coming decades, the COPD burden is expected to rise greatly all over the world due to the aging population in wealthy countries and the rising prevalence of smoking in developing countries [5].

It is well-known that inflammation plays an important role in the progression of COPD [6,7], and several biomarkers, including Interleukin-6 (IL-6) [8,9], C-reactive protein (CRP) [10,11], and Procalcitonin (PCT) [12], have been reported to be related to increased mortality in patients with COPD. However, high costs and technical issues prevent the clinical use of these inflammation biomarkers [13]. Neutrophil-lymphocyte ratio (NLR) is a cost-effective and rapid index that is easily obtained in clinical practice from routine laboratory tests [14]. Over the last 10 years, more studies have reported that NLR may be a new marker of systemic inflammation to assess the prognosis of many diseases, including acute coronary syndrome [15], stroke [16], inflammatory bowel disease [17], sepsis [18], and neoplastic disease [19]. Furthermore, a meta-analysis found that NLR levels had a good predictive value for disease severity and mortality among COVID-19 patients [20]. Recently, it was shown that NLR has is associated with COPD exacerbation and severity [21-24]. However, the sample size used in earlier research was limited, and most studies focused on the association between NLR and prognosis in the acute exacerbation of patients with COPD, and few studies that have focused on critically ill COPD patients.

In view of this, the present research aimed to analyze the relationship between NLR and mortality in critically ill COPD patients using the MIMIC-IV database. Our research hypothesis was that higher NLR is associated with higher mortality risk of critically ill COPD patients.

Material and Methods

Data source

All data were extracted from the Medical Information Mart for Intensive Care Database IV, which is considered the largest open-source and freely accessible clinical database in critical care. Based on the electronic medical records of patients hospitalized in the intensive care units (ICUs) of Beth Israel Deaconess Medical Center, the MIMIC database involves data on basic demographics, laboratory results, ICU monitoring records, and therapy prescriptions. The latest version of MIMIC-IV was available on the official website of Physionet (https://physionet.org/content/mimiciv/2.2/) [25,26], which contains approximately 250 000 electronic hospitalization records from 2008 to 2019. Shujie Hao completed the data research training program of the Collaborative Institutional Training Initiative (record ID 50152135) and gained access to the database. This database use was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (Cambridge, MA) and the Beth Israel Deaconess Medical Center (Boston, MA). All patient identification data were recorded, and all personally identifiable information was concealed.

Population Selection Criteria

All critically ill patients with COPD as the primary diagnosis were enrolled using the Tenth Revision of International Classification of Diseases (ICD-10) in the MIMIC-IV database. Only the first ICU admission was taken into account when a patient had multiple ICU admissions. Patients were excluded if: (1) their ICU stay was less than 24 h, (2) their NLR data were incomplete or unavailable within 24 h after ICU admission, or (3) their record had more than 20% missing individual data.

Data Extraction

PostgreSQL and a structured query language were used to extract data [27]. The baseline characteristics, including clinical severity scales, laboratory parameters, clinical parameters, and demographic parameters, were all collected 1 day after admission to the ICU. Demographic parameters were race, sex, and age. Clinical parameters were respiratory rate, heart rate, temperature, mean blood pressure (MBP), diastolic blood pressure (DBP), systolic blood pressure (SBP), percutaneous oxygen saturation (SPO$_2$), and multiple comorbidities. Laboratory parameters were blood urea nitrogen (BUN), white blood cell (WBC) count, serum lactate, platelet count, hemoglobin, anion gap, hematocrit, serum bicarbonate, serum sodium, serum chloride, serum glucose, serum creatinine, serum potassium, neutrophil count, and lymphocyte count. The scoring systems included the Simplified Acute Physiology Score II (SAPS II) [28] and the Sequential Organ Failure Assessment (SOFA) [29].

The primary outcome in this study was 28-day mortality, with 90-day mortality and in-hospital mortality as secondary outcomes. NLR referred to the ratio of neutrophil count to lymphocyte count.

Statistical Analysis

Patients were classified into quartiles according to NLR levels. Categorical variables were expressed as frequency (percentage), and continuous variables as mean±standard deviation. Different NLR quartile groups were compared by the Kruskal-Wallis test (non-normal distribution), one-way variance analysis (normal distribution), and chi-square test (categorical variables). The Kaplan-Meier (KM) survival analysis and the Cox proportional hazard regression model were used to determine the relationship between different categories of NLR and mortality. Three models were created: Model I, which was unadjusted; Model II, where covariates were adjusted for race, age, and sex; and Model III, which was further adjusted for model II plus some additional variables (*P*<0.1) by use of univariate analysis or changes within an effect estimate of more than 10% (MBP, temperature, heart rate, respiratory rate, platelet, WBC, SPO_2, BUN, creatinine, potassium, lactate, glucose, anion gap, chloride, bicarbonate, SOFA, SAPS II, diabetes, liver disease, hypertension, renal disease, and malignant cancer). Subgroup analysis and interaction rested with sex, age (<75 and ≥75), race, MBP (<75 and ≥75 mmHg), malignant cancer, liver disease, renal disease, congestive heart failure, diabetes, and hypertension.

In this study, multiple multivariate imputations were used to impute missing values for continuous variables. The statistical software packages R 3.3.2 and free statistical software version 1.6 were used for statistical analysis. All of the tests were two-sided, and the statistical significance was set at *P*<0.05.

Results

Baseline Characteristics of the Included Participants

A total of 2650 subjects were selected who fulfilled the inclusion criteria from the MIMIC-IV database in this study (**Figure 1**). **Table 1** shows the detailed characteristics across NLR quartiles. Most patients (71.3%) were White. The patients had an average age of 71.8±11.4 years, and 53.7% were male. The overall mean NLR was 14.6±19.6. Participants in the highest NLR quartile group tended to be old and White, and to have a history of malignant cancer, congestive heart failure, or renal disease. As the NLR increased, heart rate, respiratory rate, platelet count, WBC count, anion gap, creatinine, glucose, and BUN levels increased, whereas SPO_2, chloride, and sodium levels decreased. Additionally, patients with higher NLR had higher SAPS and SOFA scores.

Relationship Between NLR and Mortality

Of the 2650 critically ill COPD patients enrolled, 28-day mortality was 14.1%, while 90-day mortality and in-hospital mortality
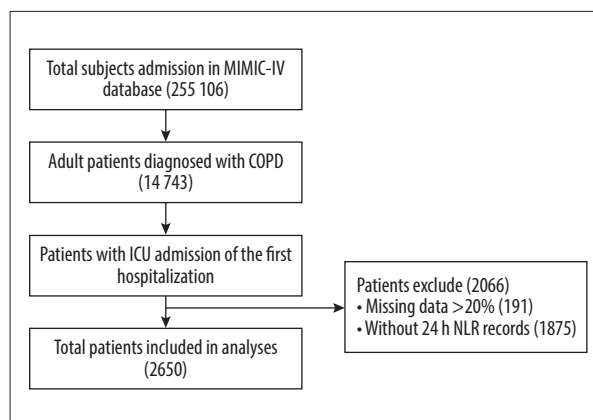
Figure 1. Flow chart of the population included in the study. MIMIC-IV – Medical Information Mart for Intensive Care-IV; COPD – chronic obstructive pulmonary disease; ICU – Intensive Care Unit; NLR – neutrophil-lymphocyte ratio.

were 17.1% and 15.2%, respectively. Kaplan-Meier survival curves showed significant differences in survival probability between groups. In addition, the survival probability was consistently observed to be markedly lower in the highest NLR quartile group (*P*<0.0001) (**Figure 2**). The independent effect of NLR on all-cause mortality in critically ill patients with COPD was decided through a further construction of the 3 different Cox regression models, as shown in **Table 2**. With the increase of NLR, HR value showed an upward trend in all 3 models. After controlling for potential confounders in Cox regression analysis, patients in the upper quartile group (NLR>16.86) saw a significantly higher risk of 28-day (HR=1.75, 95% CI=1.21-2.52, P=0.003), in-hospital (HR=1.71, 95% CI=1.22-2.42, P=0.002), and 90-day (HR=1.59, 95% CI=1.16-2.19, P=0.004) mortality than patients in the lower quartile group (NLR<4.56).

Results of Subgroup Analysis

The potential clinical heterogeneity was analyzed using interaction and stratified analyses. The NLR and all-cause mortality correlation was evaluated in different subgroups (**Table 3**). In the subgroup analysis of 28-day mortality, stratified and interaction analyses were not found in sex, age (<75 and ≥75), race, MBP (<75 and ≥75 mmHg), malignant cancer, liver disease, renal disease, congestive heart failure, diabetes, and hypertension.

In the subgroup analysis of in-hospital mortality, women with COPD (second quartile: HR=2.32, 95% CI=1.28, 4.22; third quartile: HR=2.07, 95% CI=1.15, 3.73; upper quartile: HR=2.78, 95% CI=1.57, 4.91; *P*=0.045), and patients with MBP ≥75 mmHg (second quartile: HR=2.56, 95% CI=1.41, 4.66; third quartile: HR=3.61, 95% CI=1.99, 6.54; upper quartile: HR=3.55, 95% CI=1.93, 6.55; *P*=0.045) had a higher mortality risk. COPD

Table 1. Baseline characteristics of the study population.

Characteristics	All patients	Neutrophil-lymphocyte ratio				p value
		Q1 (<4.56)	Q2 (4.56-8.40)	Q3 (8.40-16.86)	Q4 (>16.86)	
Number	2650	663	662	662	663	
NLR	14.6±19.6	2.9±1.1	6.3±1.1	12.0±2.5	37.2±28.3	<0.001
Age, year	71.8±11.4	70.5±11.5	71.5±11.4	72.1±11.4	73.0±11.0	0.001
Gender, n (%)						0.537
Female	1227 (46.3)	308 (46.5)	308 (46.5)	292 (44.1)	319 (48.1)	
Male	1423 (53.7)	355 (53.5)	354 (53.5)	370 (55.9)	344 (51.9)	
Race, n (%)						<0.001
White	1889 (71.3)	452 (68.2)	467 (70.5)	480 (72.5)	490 (73.9)	
Non-white	433 (16.3)	157 (23.7)	112 (16.9)	91 (13.7)	73 (11)	
Unknown	328 (12.4)	54 (8.1)	83 (12.5)	91 (13.7)	100 (15.1)	
Vital signs						
SBP, mmHg	116.8±16.1	117.1±15.2	118.8±17.0	116.1±16.9	114.9±14.9	<0.001
DBP, mmHg	63.2±10.9	63.5±11.2	63.9±11.1	62.7±10.6	62.8±10.4	0.123
MBP, mmHg	77.9±10.6	78.4±10.6	79.1±11.0	77.4±10.5	76.9±10.2	<0.001
Heart rate, beats/min	86.0±15.6	82.9±14.2	84.4±15.3	87.0±15.2	89.6±16.7	<0.001
Respiratory rate, beats/min	20.2±3.7	19.4±3.3	19.9±3.6	20.4±3.8	21.0±3.8	<0.001
Temperature,°C	36.8±0.4	36.8±0.4	36.8±0.4	36.9±0.4	36.9±0.5	0.001
SPO_2, %	95.9±2.9	96.2±3.2	96.1±2.3	95.7±2.7	95.5±3.1	<0.001
Laboratory parameters						
Hematocrit, %	32.4±6.5	32.7±6.3	32.3±6.8	32.4±6.5	32.2±6.5	0.539
Hemoglobin, g/dl	10.3±2.1	10.4±2.0	10.2±2.2	10.3±2.2	10.1±2.1	0.109
Platelet count, 10^9/l	208.2±104.2	190.6±98.3	205.4±94.7	216.6±106.9	220.3±113.5	<0.001
WBC count, 10^9/l	13.3±10.3	11.0±15.2	11.8±7.3	13.5±6.3	16.7±9.0	<0.001
Anion gap, mmol/l	15.3±4.1	14.4±3.6	14.9±3.9	15.6±4.2	16.4±4.5	<0.001
Bicarbonate, mmol/l	23.9±5.3	24.1±4.7	24.5±5.5	23.6±5.3	23.4±5.7	<0.001
Chloride, mmol/l	100.9±6.5	102.3±6.1	100.9±6.8	100.8±6.5	99.9±6.4	<0.001
Sodium, mmol/l	138.2±5.2	138.7±4.7	138.2±5.1	138.0±5.2	137.8±5.5	0.012
Potassium, mmol/l	4.5±0.7	4.5±0.7	4.5±0.7	4.5±0.7	4.5±0.7	0.987
Creatinine, mmol/l	1.5±1.4	1.4±1.3	1.5±1.3	1.6±1.5	1.7±1.3	<0.001
Lactate, mmol/l	2.4±1.6	2.4±1.4	2.3±1.4	2.4±1.7	2.5±1.8	0.479
Glucose, mg/dl	147.5±50.1	141.1±48.6	142.4±45.6	150.4±49.4	156.0±54.8	<0.001
BUN, mg/dL	31.0±23.8	26.1±20.6	30.0±24.3	31.6±23.1	36.5±25.8	<0.001

Table 1 continued. Baseline characteristics of the study population.

Characteristics	All patients	Neutrophil-lymphocyte ratio				p value
		Q1 (<4.56)	Q2 (4.56-8.40)	Q3 (8.40-16.86)	Q4 (>16.86)	
Comorbidities, n (%)						
Congestive heart failure	1401 (52.9)	298 (44.9)	377 (56.9)	351 (53)	375 (56.6)	<0.001
Malignant cancer	393 (14.8)	77 (11.6)	80 (12.1)	107 (16.2)	129 (19.5)	<0.001
Renal disease	847 (32.0)	186 (28.1)	206 (31.1)	216 (32.6)	239 (36)	0.018
Liver disease	327 (12.3)	82 (12.4)	80 (12.1)	74 (11.2)	91 (13.7)	0.564
Hypertension	841 (31.7)	228 (34.4)	207 (31.3)	207 (31.3)	199 (30)	0.363
Diabetes	1024 (38.6)	268 (40.4)	269 (40.6)	258 (39)	229 (34.5)	0.081
Death, n (%)						
28-day	374 (14.1)	45 (6.8)	77 (11.6)	103 (15.6)	149 (22.5)	<0.001
In-hospital	402 (15.2)	51 (7.7)	81 (12.2)	109 (16.5)	161 (24.3)	<0.001
90-day	453 (17.1)	63 (9.5)	87 (13.1)	126 (19)	177 (26.7)	<0.001
Score systems						
SOFA	5.8±3.9	5.2±3.5	5.4±3.6	5.9±4.0	6.6±4.1	<0.001
SAPS II	39.9±13.0	37.7±12.7	37.9±11.4	40.8±13.3	43.3±13.8	<0.001

NLR – neutrophil-lymphocyte ratio; SBP – systolic blood pressure; DBP – diastolic blood pressure; MBP – mean blood pressure; SPO_2 – percutaneous oxygen saturation; WBC – white blood cell; BUN – blood urea nitrogen; SOFA – Sequential Organ Failure Assessment; SAPS II – Simplified Acute Physiology Score II. Continuous variables are presented as means (SDs) or medians (quartiles), while categorical variables are presented as absolute numbers (percentages).

patients with liver disease (second quartile: HR=1.22, 95% CI=0.52, 2.83; third quartile: HR=1.47, 95% CI=0.64, 3.39; upper quartile: HR=1.15, 95% CI=0.5, 2.64; P=0.029) had a lower risk of mortality.

Similar findings were found in patients with 90-day mortality of MBP ≥75 mmHg (second quartile: HR=2.07, 95% CI=1.2, 3.58; third quartile: HR=3.17, 95% CI=1.86, 5.41; upper quartile: HR=3.12, 95% CI=1.79, 5.42; P=0.027) and patients with liver disease (second quartile: HR=0.98, 95% CI=0.44, 2.18; third quartile: HR=1.24, 95% CI=0.57, 2.69; upper quartile: HR=0.98, 95% CI=0.45, 2.14; P=0.021). COPD patients with hypertension (second quartile: HR=3.4, 95% CI=1.44, 8.04; third quartile: HR=2.84, 95% CI=1.18, 6.85; upper quartile: HR=4.81, 95% CI=2.06, 11.2; P=0.019) had a higher 90-day mortality risk. There was no statistically significant correlation in the other subgroups.

Discussion

This research explored the NLR and mortality correlation in COPD patients admitted to the ICU. The main finding is that

higher NLR values have an independent relationship with an increased risk of 28-day, in-hospital, and 90-day mortality after controlling for important covariates.

NLR is a combination of lymphocyte and neutrophil counts that can predict the prognosis of patients. In recent years, NLR, as an emerging indicator of systemic inflammation, has been applied in COPD patients. Teng et al [22] discovered that the increased NLR is an independent risk factor for 28-day mortality (OR=1.067; 95% CI=1.039-1.095), ICU occupancy (OR=1.046; 95% CI=1.023-1.068), and invasive mechanical ventilation (OR=1.042; 95% CI=1.019-1.066) in a retrospective study of 698 patients with acute COPD exacerbation. In a 10-year prospective study of 386 patients with moderate to severe COPD, it was found that NLR was associated with long-term mortality in COPD patients (HR=1.090, 95% CI=1.036, 1.148) [30]. Emami et al [31] indicated that the mortality rate of patients with NLR≥6.9 is higher than those with NLR<6.9. There was an independent association between NLR and in-hospital mortality among patients with acute exacerbation of COPD. Our results agree with prior research findings in terms of the relationship between NLR and mortality among COPD patients. However, the sample size of previous studies was limited and
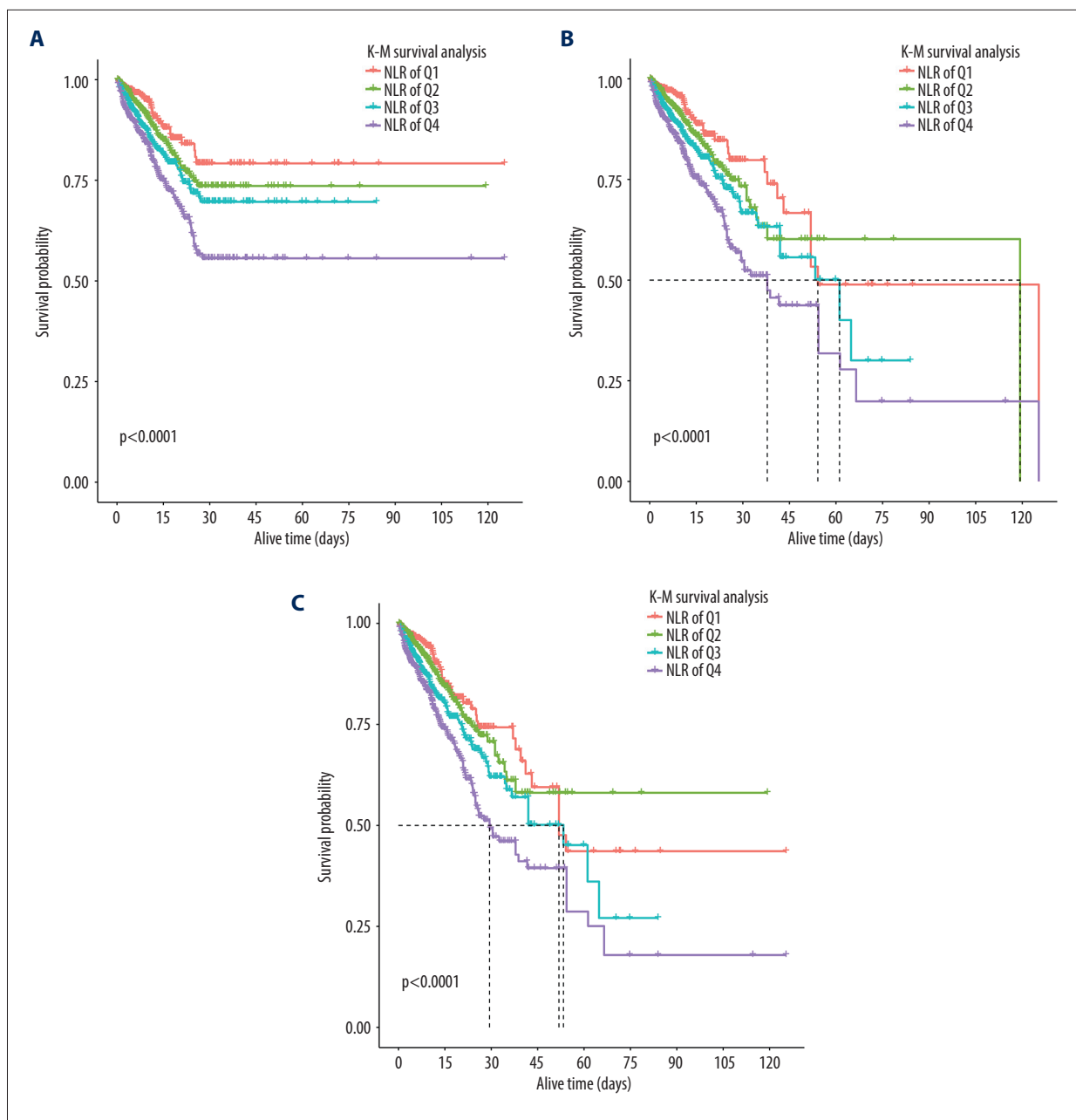
Figure 2. Kaplan-Meier survival curves showing the association between NLR and all-cause mortality. Image software: R 3.3.2, MathSoft. (**A**) 28-day mortality; (**B**) In-hospital mortality; (**C**) 90-day mortality.

potential confounders were not controlled for. Furthermore, they focused on the NLR and mortality correlation within the acute exacerbation of COPD patients.

The inflammatory process of COPD can be used to show the correlation between NLR and mortality. It has long been recognized that airway and systemic inflammation in COPD are related to disease progression, exacerbation, and mortality [32,33]. Neutrophils play a significant role in airway inflammation [34]. Several previous studies [35,36] have discovered

that lung inflammation is maintained after smoking cessation and may progressively increase over time, indicating that neutrophil recruitment and activation could be caused by the continuous inflammatory response in the lungs [37]. When activated, human neutrophil lipocalin, myeloperoxidase (MPO), matrix metalloproteinase MMP-8 and MMP-9, cathepsin G, proteinase-3, and neutrophil elastase were released, contributing to the development and progression of COPD and emphysema [38]. Additionally, systemic inflammatory reactions are common in critically ill patients. Previous findings indicated

Table 2. HRs (95% CIs) for mortality across groups of neutrophil-lymphocyte ratio.

	Model I (non-adjusted)			Model II			Model III		
	HR (95% CI)	P value	P trend	HR (95% CI)	P value	P trend	HR (95% CI)	P value	P trend
28-day mortality									
Quartiles			<0.001			<0.001			0.003
Q1	1 (Ref)			1 (Ref)			1 (Ref)		
Q2	1.48 (1.02~2.14)	0.037		1.41 (0.98~2.04)	0.068		1.4 (0.95~2.04)	0.085	
Q3	1.94 (1.37~2.76)	<0.001		1.8 (1.27~2.57)	0.001		1.51 (1.04~2.18)	0.028	
Q4	2.79 (2~3.9)	<0.001		2.62 (1.87~3.67)	<0.001		1.75 (1.21~2.52)	0.003	
In-hospital mortality									
Quartiles			<0.001			<0.001			0.002
Q1	1 (Ref)			1 (Ref)			1 (Ref)		
Q2	1.44 (1.02~2.05)	0.04		1.36 (0.96~1.94)	0.085		1.36 (0.95~1.96)	0.094	
Q3	1.87 (1.34~2.61)	<0.001		1.72 (1.23~2.41)	0.001		1.49 (1.05~2.11)	<0.001	
Q4	2.69 (1.96~3.69)	<0.001		2.5 (1.82~3.43)	<0.001		1.71 (1.22~2.42)	0.002	
90-day mortality									
Quartiles			<0.001			<0.001			0.002
Q1	1 (Ref)			1 (Ref)			1 (Ref)		
Q2	1.23 (0.89~1.7)	0.219		1.17 (0.84~1.62)	0.35		1.19 (0.85~1.67)	0.302	
Q3	1.7 (1.26~2.31)	0.001		1.57 (1.16~2.14)	<0.001		1.42 (1.03~1.95)	<0.001	
Q4	2.36 (1.77~3.15)	<0.001		2.19 (1.64~2.93)	<0.001		1.59 (1.16~2.19)	0.004	

HR – hazard ratio; CI – confidence interval. Models were derived from Cox regression models. **Model I:** non-adjusted. **Model II** adjusted for: age; sex; race. **Model III** adjusted for: age; sex; race; diabetes; hypertension; liver disease; renal disease; malignant cancer; platelets; WBC; anion gap; bicarbonate; BUN; chloride; creatinine; potassium; lactate; heart rate; mbp; respiratory rate; temperature; spo2; glucose; sofa; sapsii.

that lymphopenia was related to high mortality rates in individuals with systemic inflammatory response syndrome, and lymphopenia could perpetuate harmful inflammation [39,40]. Lymphocyte count was negatively proportional to inflammation, and neutrophil count increased with the systemic inflammatory response, causing a higher NLR. Taken together, the level of NLR simultaneously provides information about 2 different immune pathways, indicating that the overall inflammatory state of the body has a higher predictive value of risk than alone [41], suggesting that the increase of NLR may be a crucial marker for monitoring the clinical prognosis of COPD.

In our subgroup analyses, taking 28-day mortality as an example, there were consistent findings within different subgroups by age (<75 and ≥75), sex, race, MBP (<75 and ≥75 mmHg), and COPD comorbidities, including malignancy, liver disease, renal disease, congestive heart failure, hypertension, and diabetes. However, critically ill COPD patients with MBP≥75 mmHg had a higher risk of 90-day and in-hospital mortality, and critically ill COPD patients with hypertension had a higher risk of 90-day mortality. The association between NLR and hypertension has been widely studied, and NLR is considered to be a reliable hypertension predictor [42-44]. Sun et al [45] found that a higher

Table 3. Subgroup analysis of the associations between mortality and the neutrophil-lymphocyte ratio.

| Characteristic | N | NLR of 28-day mortality | | | | P for interaction |
| | | Q 1 | Q 2 | Q 3 | Q4 | |
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Age						0.996
<75	1590	1 (Ref)	1.62 (0.93~2.81)	1.79 (1.04~3.1)	2.00 (1.15~3.47)	
≥75	1060	1 (Ref)	1.46 (0.86~2.48)	1.74 (1.05~2.91)	1.78 (1.07~2.95)	
Gender						0.055
Female	1227	1 (Ref)	2.26 (1.24~4.12)	1.81 (1~3.28)	2.71 (1.53~4.8)	
Male	1423	1 (Ref)	1.13 (0.68~1.87)	1.60 (0.99~2.59)	1.45 (0.88~2.38)	
Ethnicity						0.152
White	1889	1 (Ref)	1.32 (0.83~2.12)	1.51 (0.95~2.39)	1.58 (1~2.51)	
Non-white	433	1 (Ref)	2.54 (1.03~6.27)	3.40 (1.34~8.6)	2.24 (0.83~6.04)	
Other	328	1 (Ref)	1.10 (0.38~3.22)	1.66 (0.6~4.57)	3.16 (1.11~9)	
MBP						
<75	1172	1 (Ref)	1.15 (0.7~1.9)	1.10 (0.69~1.76)	1.50 (0.95~2.38)	0.103
≥75	1478	1 (Ref)	2.40 (1.3~4.45)	3.37 (1.83~6.2)	3.10 (1.66~5.81)	
Malignant cancer						0.4
Yes	393	1 (Ref)	0.57 (0.25~1.31)	0.91 (0.42~1.96)	0.83 (0.41~1.68)	
No	2257	1 (Ref)	1.89 (1.22~2.94)	2.29 (1.48~3.55)	2.63 (1.69~4.1)	
Congestive heart failure						0.741
Yes	1401	1 (Ref)	1.43 (0.86~2.36)	1.78 (1.08~2.93)	2.13 (1.31~3.45)	
No	1249	1 (Ref)	1.54 (0.86~2.76)	1.79 (1.03~3.1)	2.01 (1.14~3.54)	
Diabetes						0.173
Yes	1024	1 (Ref)	1.15 (0.65~2.02)	1.35 (0.81~2.27)	1.91 (1.11~3.29)	
No	1626	1 (Ref)	2.11 (1.24~3.59)	2.42 (1.42~4.13)	2.50 (1.47~4.26)	
Hypertension						0.235
Yes	841	1 (Ref)	2.86 (1.2~6.8)	2.37 (0.96~5.83)	3.79 (1.55~9.24)	
No	1809	1 (Ref)	1.25 (0.81~1.91)	1.55 (1.04~2.32)	1.62 (1.07~2.43)	
Renal disease						0.486
Yes	847	1 (Ref)	1.06 (0.57~1.98)	1.31 (0.72~2.38)	1.14 (0.63~2.06)	
No	1803	1 (Ref)	1.90 (1.17~3.07)	1.95 (1.21~3.12)	2.62 (1.62~4.23)	
Liver disease						0.056
Yes	327	1 (Ref)	1.28 (0.52~3.17)	1.57 (0.65~3.76)	1.27 (0.53~3.04)	
No	2323	1 (Ref)	1.71 (1.12~2.61)	1.88 (1.24~2.85)	2.41 (1.59~3.63)	

Table 3 continued. Subgroup analysis of the associations between mortality and the neutrophil-lymphocyte ratio.

Characteristic	N	NLR of in-hospital mortality				P for interaction
		Q 1	Q 2	Q 3	Q4	
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Age						0.945
<75	1590	1 (Ref)	1.63 (0.97~2.73)	1.84 (1.11~3.05)	1.99 (1.21~3.29)	
≥75	1060	1 (Ref)	1.26 (0.75~2.12)	1.57 (0.95~2.58)	1.57 (0.96~2.57)	
Gender						0.045
Female	1227	1 (Ref)	2.32 (1.28~4.22)	2.07 (1.15~3.73)	2.78 (1.57~4.91)	
Male	1423	1 (Ref)	1.05 (0.65~1.68)	1.42 (0.91~2.21)	1.31 (0.84~2.05)	
Ethnicity						0.316
White	1889	1 (Ref)	1.15 (0.73~1.8)	1.39 (0.9~2.15)	1.46 (0.96~2.23)	
Non-white	433	1 (Ref)	2.92 (1.19~7.11)	2.83 (1.09~7.35)	1.99 (0.75~5.26)	
Other	328	1 (Ref)	1.31 (0.49~3.47)	1.92 (0.75~4.9)	2.85 (1.07~7.62)	
MBP						0.045
<75	1172	1 (Ref)	1.07 (0.66~1.72)	1.04 (0.67~1.63)	1.39 (0.91~2.12)	
≥75	1478	1 (Ref)	2.56 (1.41~4.66)	3.61 (1.99~6.54)	3.55 (1.93~6.55)	
Malignant cancer						0.082
Yes	393	1 (Ref)	0.45 (0.2~1.01)	1.22 (0.61~2.45)	0.86 (0.46~1.62)	
No	2257	1 (Ref)	2.17 (1.39~3.39)	2.55 (1.64~3.98)	3.14 (2.01~4.9)	
Congestive heart failure						0.617
Yes	1401	1 (Ref)	1.37 (0.85~2.21)	1.59 (0.99~2.56)	2.01 (1.27~3.17)	
No	1249	1 (Ref)	1.61 (0.91~2.85)	2.00 (1.17~3.43)	2.21 (1.27~3.84)	
Diabetes						0.118
Yes	1024	1 (Ref)	1.08 (0.63~1.85)	1.21 (0.73~1.99)	1.9 (1.13~3.18)	
No	1626	1 (Ref)	1.95 (1.17~3.24)	2.19 (1.33~3.63)	2.18 (1.33~3.57)	
Hypertension						0.098
Yes	841	1 (Ref)	3.36 (1.4~8.04)	2.74 (1.12~6.7)	4.43 (1.87~10.5)	
No	1809	1 (Ref)	1.23 (0.82~1.84)	1.55 (1.05~2.28)	1.61 (1.1~2.37)	
Renal disease						0.481
Yes	847	1 (Ref)	1.04 (0.56~1.96)	1.37 (0.76~2.49)	1.22 (0.68~2.19)	
No	1803	1 (Ref)	1.79 (1.14~2.81)	1.75 (1.13~2.72)	2.31 (1.5~3.56)	
Liver disease						0.029
Yes	327	1 (Ref)	1.22 (0.52~2.83)	1.47 (0.64~3.39)	1.15 (0.5~2.64)	
No	2323	1 (Ref)	1.69 (1.12~2.54)	1.84 (1.24~2.73)	2.26 (1.54~3.32)	

Table 3 continued. Subgroup analysis of the associations between mortality and the neutrophil-lymphocyte ratio.

| Characteristic | N | NLR of 90-day mortality | | | | P for interaction |
| | | Q 1 | Q 2 | Q 3 | Q4 | |
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Age						0.943
<75	1590	1 (Ref)	1.37 (0.86~2.2)	1.65 (1.04~2.62)	1.84 (1.16~2.9)	
≥75	1060	1 (Ref)	1.14 (0.71~1.85)	1.57 (1~2.46)	1.50 (0.96~2.35)	
Gender						0.189
Female	1227	1 (Ref)	1.68 (1.01~2.79)	1.52 (0.92~2.51)	1.96 (1.21~3.18)	
Male	1423	1 (Ref)	0.99 (0.63~1.55)	1.58 (1.04~2.4)	1.49 (0.97~2.27)	
Ethnicity						0.196
White	1889	1 (Ref)	1.01 (0.66~1.52)	1.43 (0.96~2.11)	1.42 (0.97~2.09)	
Non-white	433	1 (Ref)	2.13 (0.98~4.62)	2.42 (1.07~5.47)	2.04 (0.85~4.88)	
Other	328	1 (Ref)	1.22 (0.46~3.23)	1.79 (0.71~4.56)	2.69 (1.01~7.13)	
MBP						0.027
<75	1172	1 (Ref)	0.96 (0.62~1.5)	1.01 (0.68~1.52)	1.32 (0.9~1.95)	
≥75	1478	1 (Ref)	2.07 (1.2~3.58)	3.17 (1.86~5.41)	3.12 (1.79~5.42)	
Malignant cancer						0.493
Yes	393	1 (Ref)	0.62 (0.3~1.32)	1.38 (0.71~2.69)	0.94 (0.51~1.75)	
No	2257	1 (Ref)	1.61 (1.09~2.39)	2.11 (1.43~3.1)	2.54 (1.72~3.74)	
Congestive heart failure						0.468
Yes	1401	1 (Ref)	1.1 (0.72~1.69)	1.38 (0.91~2.1)	1.74 (1.17~2.6)	
No	1249	1 (Ref)	1.55 (0.89~2.67)	2.12 (1.27~3.53)	2.23 (1.31~3.78)	
Diabetes						0.181
Yes	1024	1 (Ref)	1.02 (0.62~1.69)	1.19 (0.75~1.89)	1.81 (1.12~2.93)	
No	1626	1 (Ref)	1.58 (1~2.5)	2.02 (1.29~3.15)	1.98 (1.27~3.08)	
Hypertension						0.019
Yes	841	1 (Ref)	3.4 (1.44~8.04)	2.84 (1.18~6.85)	4.81 (2.06~11.2)	
No	1809	1 (Ref)	1.03 (0.71~1.5)	1.46 (1.03~2.06)	1.47 (1.04~2.1)	
Renal disease						0.112
Yes	847	1 (Ref)	0.75 (0.43~1.3)	1.08 (0.65~1.8)	0.93 (0.56~1.55)	
No	1803	1 (Ref)	1.8 (1.17~2.77)	1.91 (1.25~2.9)	2.5 (1.65~3.78)	
Liver disease						0.021
Yes	327	1 (Ref)	0.98 (0.44~2.18)	1.24 (0.57~2.69)	0.98 (0.45~2.14)	
No	2323	1 (Ref)	1.46 (1.01~2.12)	1.75 (1.23~2.49)	2.14 (1.51~3.03)	

HRs were adjusted for age; sex; race; diabetes; hypertension; liver disease; renal disease; malignant cancer; platelets; WBC; anion gap; bicarbonate; BUN; chloride; creatinine; potassium; lactate; heart rate; mbp; respiratory rate; temperature; spo2; glucose; sofa; sapsii.

quartile of NLR is an independent predictor of all-cause 3-month mortality in patients with hypertension who are more than 80 years old (RR=16.451, 95% CI=2.137, 66.643). Several studies have shown that higher NLR is associated with a worse prognosis of hypertension [46-49], but this needs to be further confirmed. Interestingly, this study showed that COPD patients with a history of liver disease had a lower risk of in-hospital and 90-day mortality, with a higher NLR. However, the sample size of participants in the study was quite limited. A previous systematic review [50] found that NLR was a predictor for prognosis of patients with cirrhosis, but was not significantly associated with liver fibrosis in patients with chronic hepatitis C infection. Therefore, the potential mechanism underlying the association the outcome of COPD and these factors needs further research.

There are several limitations to the present study. Firstly, it was a retrospective and observational study, and causal inferences cannot be made. Secondly, there are still some unmeasured variables influencing results after adjusting for confounders as much as possible. This is because the MIMIC-IV databases do not record all of the variables, such as income, place of residence, insurance status, and educational attainment, which are likely to be relevant to mortality. Thirdly, attention was paid to the NLR value obtained within 24 h after ICU admission, but the impact of NLR changes on outcomes during the ICU stay is unknown. Finally, although this study had a relatively large sample size, multicenter prospective studies are needed to verify these findings in the future.

Conclusions

High NLR is associated with a higher risk of 28-day, in-hospital, and 90-day mortality in COPD patients admitted to the ICU. The level of NLR is likely to reliably predict the mortality risk in critically ill COPD patients, but this needs to be considered and confirmed in future prospective research.

Acknowledgments

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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