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ORIGINAL RESEARCH

# Peripheral Blood NMLR Can Predict 5-Year All-Cause Mortality in Patients with Chronic Obstructive Pulmonary Disease

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**Background:** Chronic obstructive pulmonary disease (COPD) is characterized by pulmonary and systemic inflammation. The peripheral blood (neutrophil + monocyte)/lymphocyte ratio (NMLR) can predict the clinical outcomes of several inflammatory diseases. However, its prognostic value in COPD remains unknown.

**Methods:** This retrospective study included 870 patients with COPD due to acute exacerbation, and the 5-year all-cause mortality of these patients was recorded. The Kaplan-Meier method was used to compare the mortality risk of these patients according to their NMLR value. Multivariable COX hazard regression and restricted cubic spline model were used to assess the relationship between the NMLR and 5-year all-cause mortality of patients with COPD.

**Results:** The NMLR values of non-surviving patients with COPD were significantly increased compared to the survivors [3.88 (2.53–7.17) vs 2.95 (2.08–4.89), P=0.000]. The area under the NMLR receiver operating characteristic curve for predicting the 5-year all-cause mortality of COPD patients was 0.63. Kaplan-Meier survival curves showed that the 5-year all-cause mortality of COPD patients was significantly increased when the admission peripheral blood NMLR was ≥ 5.90 (27.3% vs 12.4%, P=0.000). The COX regression model showed that NMLR was an independent predictor of 5-year all-cause mortality in COPD patients (hazard ratio=1.84, 95% confidence interval: 1.28–2.64, P=0.001). Moreover, the restricted cubic spline model showed a non-linear relationship between NMLR and COPD death risk ($P_{non\text{-}linear} < 0.05$).

**Conclusion:** The admission peripheral blood NMLR is a significant predictor of 5-year all-cause mortality in patients with COPD, and high NMLR values may indicate a poor clinical prognosis.

**Keywords:** chronic obstructive pulmonary disease, neutrophil, monocyte, lymphocyte, inflammation, prognosis

## Introduction

Chronic obstructive pulmonary disease (COPD) is a worldwide disease characterized by irreversible airflow limitation and persistent respiratory symptoms.[1] It is a major public health problem that causes significant economic, social and medical burdens.[2,3] Approximately 3 million patients were estimated to have died due to COPD in 2015, ranking third among the global age-standardized mortality rates.[4] Therefore, the early identification of COPD patients who are at a high risk of mortality is a critical clinical problem.

COPD is a chronic inflammatory airway disease associated with the inhalation of cigarette smoke or other harmful particles, resulting in innate and adaptive inflammatory immune responses.[5,6] The inflammatory response in COPD is characterized by increased numbers of neutrophils, lymphocytes and macrophages in the airway lumen, which secrete a variety of pro-inflammatory mediators that trigger a nonspecific inflammatory response.[7] Notably, this response is reflected not only in pulmonary manifestations, but also in systemic manifestations.[8] Of the patients with COPD, 16%

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were reported to have persistent systemic inflammation, and these patients had significantly increased all-cause mortality rates during 3-year follow-up compared with the patients without persistent inflammation.[9] Several studies have shown that the levels of inflammatory biomarkers, such as C reactive protein (CRP), cystatin C, fibrinogen and cyclophilin A, can predict the prognosis of COPD patients.[10–13]

It has been well-known that blood cell counts and their ratios are valuable biological indicators of systemic inflammation. And (neutrophil + monocyte)/lymphocyte ratio (NMLR) is another blood cell count-derived inflammatory biomarker that can be used to predict the prognosis of several inflammatory diseases.[14] It has been reported that NMLR was associated with 30-day mortality in patients with sepsis.[15] Another study demonstrated that the elevated NMLR at admission might be a risk factor for in-hospital death in patients with heart failure.[16] However, whether the NMLR can be used as an inflammatory biomarker to predict the mortality risk of COPD patients is unknown. Therefore, our present study aimed to investigate the relationship between NMLR values and clinical outcomes in patients with COPD.

# Methods

## Subjects

This retrospective study was conducted in the Department of Respiratory and Critical Care Medicine, the Second Affiliated Hospital of Xi'an Jiaotong University. It included 4499 patients with COPD who were admitted to our department due to acute exacerbation between June 2009 and June 2018. When patients required more than one admission during the inclusion period, only the data from the first admission were recorded. Patients aged < 20 years or ≥ 80 years were excluded from this study. Patients accompanying with active tuberculosis, asthma, bronchiectasis, malignancy, connective tissue disease, liver failure or renal failure were excluded. After screening all medical records, 1055 COPD patients were followed up by telephone after their discharge from the hospital. After a 5-year follow-up, 870 patients were finally enrolled in this study. COPD was defined as a postbronchodilator forced expiratory volume in 1 s ($FEV_1$)/ forced vital capacity (FVC) less than 0.70.[17]

## Pulmonary Function and Blood Gas Analysis

Spirometry was performed to assess pulmonary function when the patients were stable enough to use the spirometer maneuver before leaving the hospital. A reversibility assessment was conducted in the patients with a short-acting beta-2 agonist (SABA). Arterial blood samples were collected immediately and analyzed when COPD patients were admitted to the hospital.

## Clinical and Biochemical Examinations

The demographic and clinical information of all participants were recorded in detail. Smoking history, history of disease, and survival time were also collected. Fasting venous blood samples of all patients have been collected at the beginning of hospitalization, and routine blood test, liver function as well as renal function were determined.

## Statistical Analysis

All data were examined using the Kolmogorov–Smirnov test for normal distribution. Quantitative variables with normal distribution are presented as mean ± standard deviation (SD), and differences were identified using the Student's *t*-test. Non-normally distributed data are presented as median (range), and differences were identified using the Mann–Whitney *U*-test. Categorical variables are presented as percentages and compared using the Chi-square test. Statistical significance was set at $P<0.05$.

First, the correlations between NMLR and several pulmonary function parameters were analyzed using the Spearman correlation test. The receiver operating characteristic (ROC) curve was used to determine the optimal cutoff for NMLR. Survival curves were plotted using the Kaplan-Meier method to compare the 5-year all-cause mortality rates between the NMLR-elevated and non-elevated groups. Finally, the association between NMLR and 5-year all-cause mortality in patients with COPD was analyzed using the COX regression and restricted cubic spline (RCS) models. All variables

detected in the univariate analysis (with a P-value of less than 0.05) were included in the multivariate analysis. Statistical analyses were conducted with SPSS version 17.0 software and R studio version 4.3.1 (SPSS Inc., Chicago, IL, USA).

# Results

## Baseline Characteristics of the Study Population

This retrospective study consisted of 870 COPD patients with available survival data. Of them, 135 (15.5%) died during the 5-year follow-up (Figure 1). The median age of the study cohort was 65 years, of which 77.4% were men. The baseline characteristics of the COPD patients are shown in Table 1 according to survival status. COPD patients in the non-survivor group were older and had a lower body mass index (BMI) and longer smoking history than those in the survivor group (all P<0.05). The non-survivor group had more severe airflow obstruction and diffusion impairment than the survivor group (all P<0.05). The NMLR was significantly increased in the non-survivor group compared with the survivor group [3.88 (2.53–7.17) vs 2.95 (2.08–4.89), P<0.05]. Other peripheral blood parameters, including neutrophil count, lymphocyte count, NLR and MLR were all significantly different between the two groups (P<0.05). Non-survivors had significantly lower values of $PaO_2$, albumin and alanine aminotransferase, as well as higher values of $PaCO_2$ and cystatin C than those in the survivors (all P<0.05).

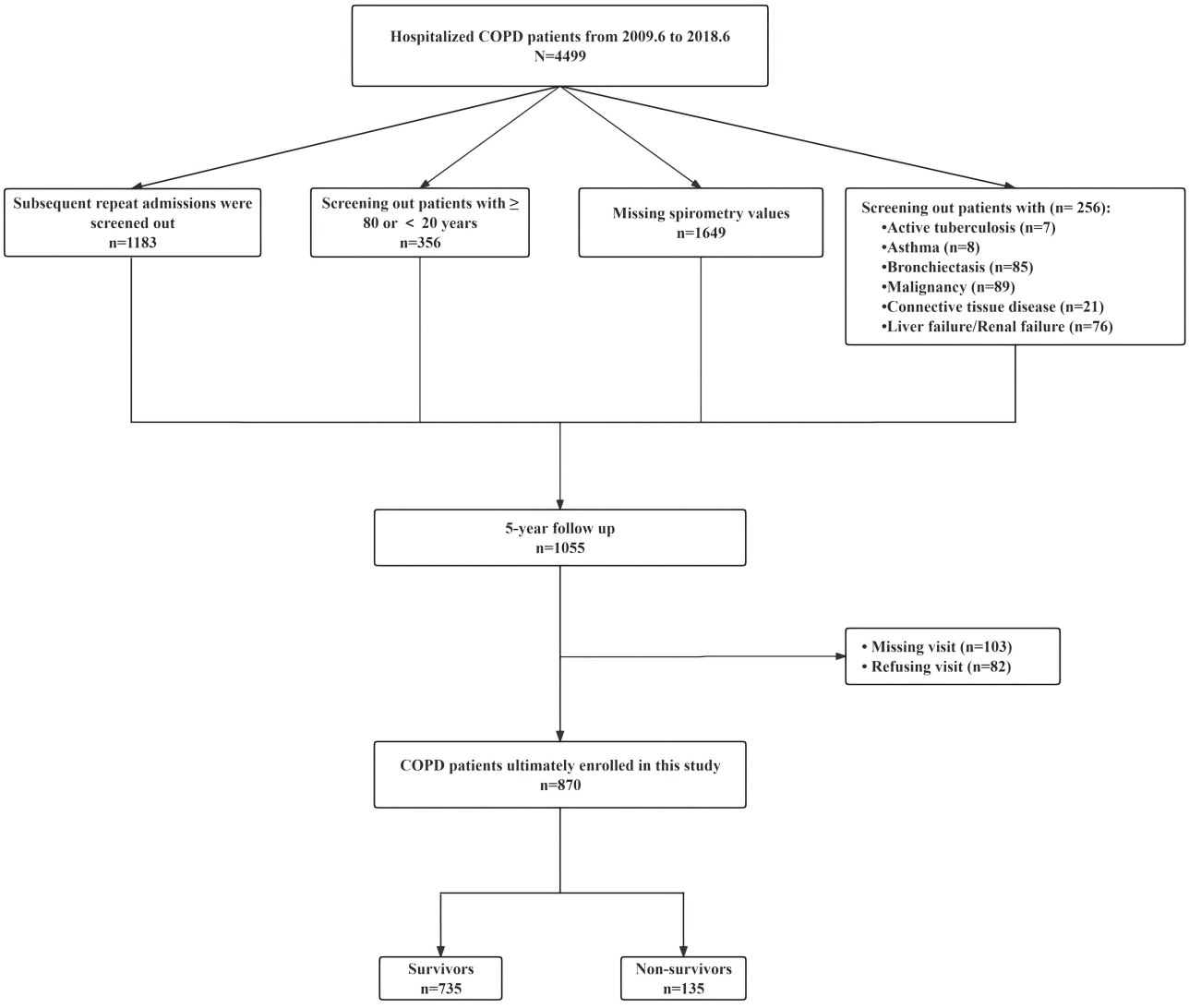


**Figure 1** Flow chart of study patients.

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**Table 1** Clinical and Physiological Characteristics of Study Patients

| Characteristic | Total | Survivors | Non-survivors | P-value |
|---|---|---|---|---|
| Number | 870 | 735 | 135 | |
| Age (yr.) | 65.00 (59.00–71.00) | 65.00 (59.00–71.00) | 69.00 (62.00–74.00) | 0.000 |
| Male (%) | 77.4 | 76.3 | 83.0 | 0.090 |
| Body mass index (kg/m$^2$) | 23.66±3.93 | 23.97±3.86 | 22.02±3.89 | 0.000 |
| Smoking index (pack-yr.) | 20.00 (0.00–40.00) | 20.00 (0.00–40.00) | 30.00 (0.00–45.00) | 0.007 |
| Smoking status | | | | |
| Never (%) | 38.2 | 39.6 | 30.4 | |
| Former (%) | 29.8 | 29.2 | 33.3 | |
| Current (%) | 32.0 | 31.2 | 36.3 | |
| Comorbidity | | | | |
| Hypertension (%) | 29.5 | 28.0 | 37.0 | 0.035 |
| Diabetes (%) | 7.6 | 7.2 | 8.9 | 0.496 |
| Coronary heart disease (%) | 21.3 | 20.3 | 25.9 | 0.139 |
| Inhalation therapy | | | | |
| SABD (%) | 2.8 | 2.7 | 3.0 | 0.875 |
| ICS/LABA (%) | 26.3 | 27.5 | 20.0 | 0.070 |
| ICS/LABA+LAMA (%) | 29.3 | 30.5 | 23.0 | 0.078 |
| LAMA (%) | 22.4 | 21.8 | 25.9 | 0.287 |
| $FEV_1$ (L) | 1.17 (0.83–1.56) | 1.21 (0.87–1.61) | 0.95 (0.71–1.25) | 0.000 |
| $FEV_1$ (%pred) | 46.80 (32.70–63.90) | 48.70 (35.10–66.10) | 35.50 (27.10–53.10) | 0.000 |
| FVC (L) | 2.52 (2.04–3.09) | 2.58 (2.09–3.17) | 2.30 (1.86–2.74) | 0.000 |
| FVC (%pred) | 80.20±21.02 | 81.39±20.78 | 73.72±21.23 | 0.000 |
| $FEV_1$/FVC (%) | 47.24 (38.04–58.16) | 48.56 (39.11–58.52) | 41.39 (32.89–56.17) | 0.000 |
| VA (L) | 4.90±1.08 | 4.95±1.09 | 4.67±1.00 | 0.004 |
| VA (%pred) | 86.51±14.70 | 87.33±14.50 | 82.07±15.03 | 0.000 |
| $DL_{CO}$ (mmol/min/kPa) | 5.84 (4.39–7.35) | 6.11 (4.71–7.64) | 4.15 (3.27–5.54) | 0.000 |
| $DL_{CO}$ (%pred) | 75.38±27.52 | 78.76±26.63 | 56.96±24.98 | 0.000 |
| $DL_{CO}$/VA (mmol/min/kPa/L) | 1.23±0.48 | 1.29±0.47 | 0.94±0.39 | 0.000 |
| pH | 7.43±0.03 | 7.43±0.03 | 7.42±0.04 | 0.746 |
| $PaO_2$ (mmHg) | 71.24±13.10 | 72.05±12.66 | 66.86±14.55 | 0.000 |
| $PaCO_2$ (mmHg) | 38.80 (35.60–42.40) | 38.60 (35.40–41.90) | 39.90 (36.10–46.50) | 0.002 |
| $PO_2$(A-a) (mmHg) | 27.10 (19.98–34.23) | 26.80 (19.70–33.80) | 27.70 (21.00–38.60) | 0.030 |
| Leukocyte count (×10$^9$/L) | 6.51 (5.19–8.29) | 6.40 (5.16–8.30) | 6.73 (5.41–8.29) | 0.353 |
| Neutrophil count (×10$^9$/L) | 4.24 (3.16–5.98) | 4.19 (3.11–5.87) | 4.49 (3.44–6.38) | 0.043 |
| Monocyte count (×10$^9$/L) | 0.41 (0.27–0.55) | 0.39 (0.27–0.55) | 0.42 (0.28–0.59) | 0.136 |
| Lymphocyte count (×10$^9$/L) | 1.50 (1.03–1.97) | 1.53 (1.08–1.99) | 1.21 (0.84–1.84) | 0.000 |
| NMLR | 3.06 (2.14–5.23) | 2.95 (2.08–4.89) | 3.88 (2.53–7.17) | 0.000 |
| NLR | 2.79 (1.92–4.92) | 2.64 (1.85–4.54) | 3.51 (2.21–6.43) | 0.000 |
| MLR | 0.25 (0.17–0.38) | 0.25 (0.16–0.36) | 0.31 (0.21–0.51) | 0.000 |
| Platelet count (×10$^9$/L) | 179.50 (142.00–227.00) | 182.00 (144.00–229.00) | 168.00 (136.00–213.00) | 0.060 |
| Hemoglobin (g/L) | 136.26±17.12 | 136.66±16.62 | 134.07±19.55 | 0.146 |
| Albumin (g/L) | 39.50 (36.90–42.23) | 39.80 (37.20–42.50) | 38.00 (35.60–40.80) | 0.000 |
| Globulin (g/L) | 24.92±4.49 | 24.84±4.39 | 25.37±4.95 | 0.119 |
| ALT (IU/L) | 17.00 (12.00–26.00) | 17.00 (12.00–26.00) | 15.16 (11.00–22.00) | 0.019 |
| AST (IU/L) | 19.00 (16.00–25.00) | 19.00 (16.00–25.00) | 20.00 (16.00–26.00) | 0.519 |
| DBIL (μmol/L) | 4.32 (3.12–5.91) | 4.29 (3.10–5.78) | 4.60 (3.20–6.35) | 0.069 |
| IBIL (μmol/L) | 6.90 (4.88–9.56) | 6.90 (4.90–9.50) | 6.79 (4.75–9.90) | 0.887 |
| Creatinine (μmol/L) | 70.03±16.88 | 69.93±16.96 | 70.56±16.46 | 0.558 |
| BUN (mmol/L) | 5.08 (4.10–6.16) | 5.06 (4.06–6.11) | 5.16 (4.23–6.35) | 0.204 |
| Cystatin C (mg/L) | 1.00 (0.86–1.14) | 0.99 (0.86–1.13) | 1.05 (0.89–1.21) | 0.010 |

**Note**: Data are expressed as means ± standard deviation or median (interquartile range) or percentage.

**Abbreviations**: SABD, short-acting bronchodilator; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonists; $FEV_1$, forced expiratory volume in 1s; FVC, forced vital capacity; VA, alveolar ventilation; $DL_{CO}$, diffusing lung capacity for carbon monoxide; $PaO_2$, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; $PO_2$(A-a), alveolar-arterial oxygen gradient; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; NMLR, (neutrophil + monocyte)/lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBIL, direct bilirubin; IBIL, indirect bilirubin; BUN, blood urea nitrogen.

## Correlations Between NMLR and Pulmonary Function Parameters

To evaluate the correlations between the NMLR and pulmonary function parameters, correlation coefficients were calculated by Spearman analysis, and the results are shown in Figure 2. We found that the NMLR was significantly negatively correlated with $FEV_1$ %pred, $FEV_1$/FVC, diffusing lung capacity for carbon monoxide ($DL_{CO}$) %pred, and $DL_{CO}$/alveolar ventilation (VA) ($FEV_1$ %pred: r=−0.185, P=0.000; $FEV_1$/FVC: r=−0.174, P=0.000; $DL_{CO}$ %pred: r=−0.140, P=0.000; $DL_{CO}$/VA: r=−0.135, P=0.000).

## Analysis of the NMLR ROC Curve in Predicting 5-Year All-Cause Mortality

The ROC curve was used to assess the diagnostic effectiveness of NMLR and other related blood parameters in predicting the 5-year all-cause mortality of COPD patients (Figure 3). The AUC for NMLR was the largest at 0.63, with a threshold of 5.90 (P<0.0001). The AUC of neutrophil counts for predicting mortality risk of COPD patients was 0.55, and the best cutoff value was 3.88 $\times 10^9$/L (P=0.0425). The AUC for lymphocyte counts was 0.61, with the best cutoff value of 1.04 $\times 10^9$/L (P<0.0001). In addition, NLR and MLR also had diagnostic value in predicting the risk of death of COPD patients (NLR: AUC=0.62, cutoff value 5.30; MLR: AUC=0.61, cutoff value 0.37) (both P<0.0001). However, monocyte counts had no diagnostic value for 5-year all-cause mortality in the patients with COPD (P=0.1361).

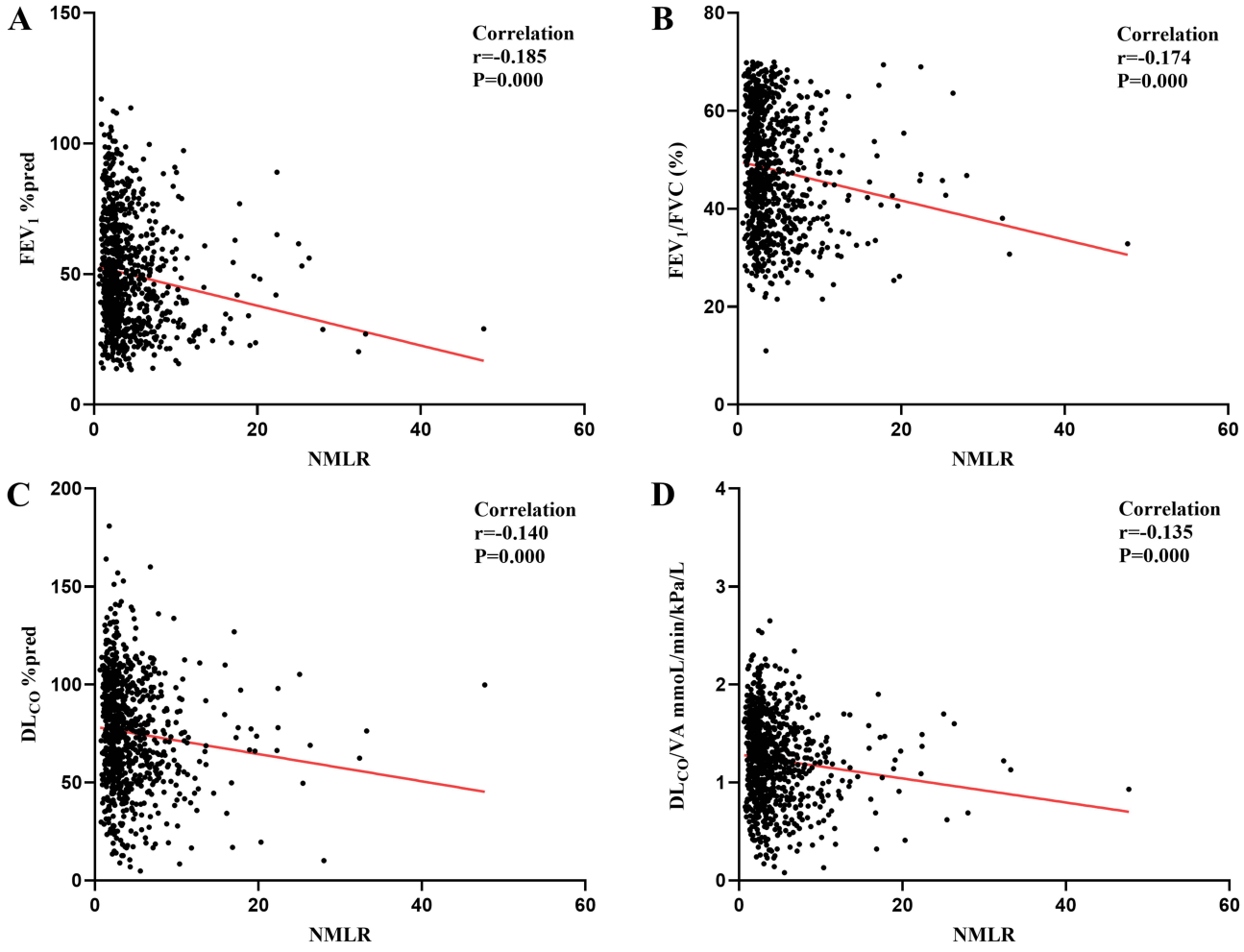


**Figure 2** Correlations of the peripheral blood NMLR with pulmonary function parameters. (**A**) Correlations of the $FEV_1$ %pred with NMLR; (**B**) Correlations of the $FEV_1$ /FVC with NMLR; (**C**) Correlations of the $DL_{CO}$ %pred with NMLR; (**D**) Correlations of the $DL_{CO}$/VA with NMLR.

**Abbreviations**: NMLR, (neutrophil + monocyte)/lymphocyte ratio; $FEV_1$, forced expiratory volume in 1s; FVC, forced vital capacity; $DL_{CO}$, diffusing lung capacity for carbon monoxide; VA, alveolar ventilation.


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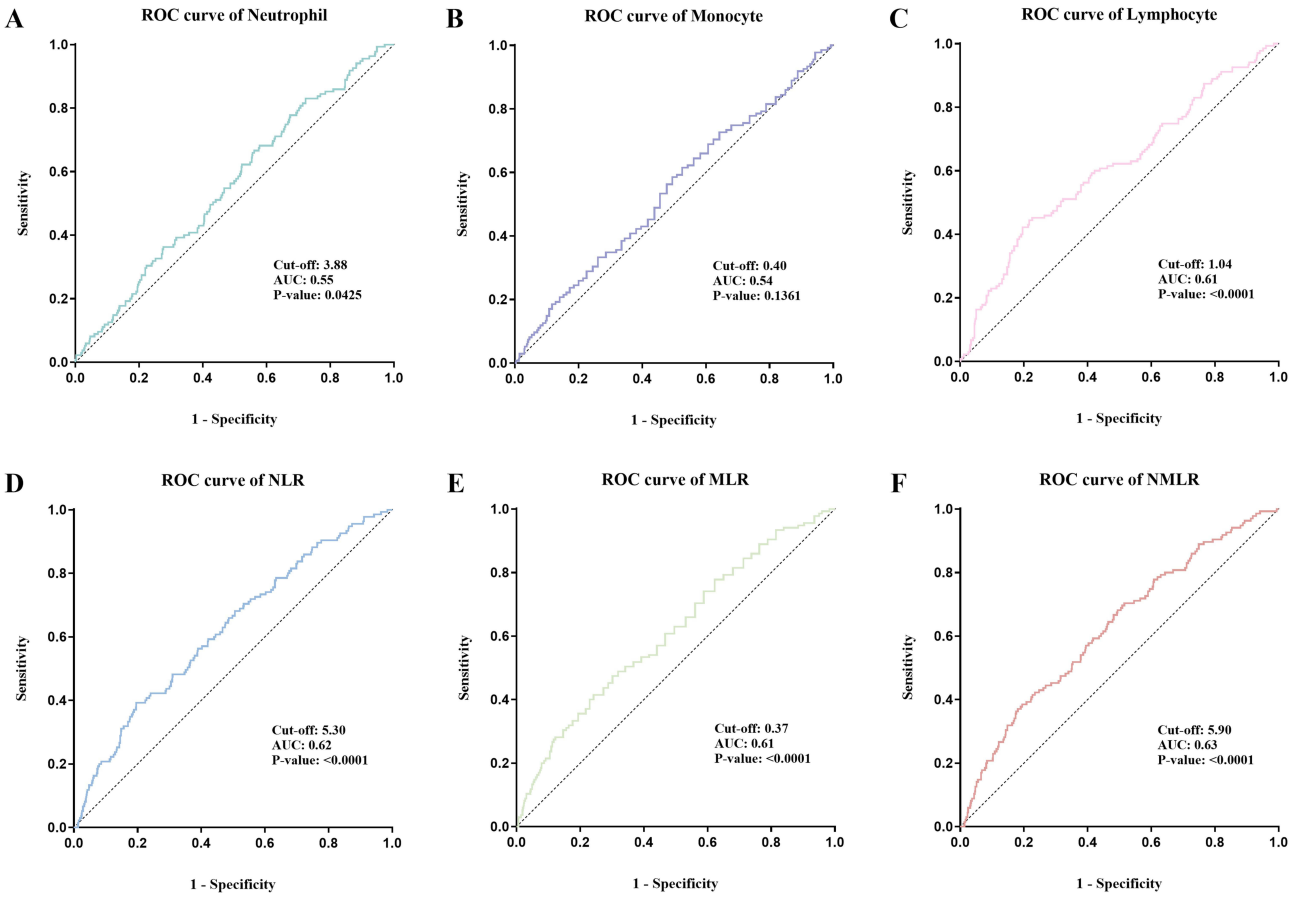


**Figure 3** ROC curves of the peripheral blood parameters for 5-year all-cause mortality in patients with COPD. ROC curves for neutrophil (**A**), monocyte (**B**), lymphocyte (**C**), NLR (**D**), MLR (**E**) and NMLR (**F**) as related to 5-year all-cause mortality of COPD patients.
**Abbreviations**: ROC, receiver operating characteristic; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; NMLR, (neutrophil + monocyte)/ lymphocyte ratio.

## Factors Associated with 5-Year All-Cause Mortality in COPD Patients

Kaplan-Meier survival curves showed that the 5-year cumulative survival rate for COPD patients was decreased when the NMLR was ≥5.90 (Log rank test $c^2 = 25.31$, $P < 0.0001$, Figure 4). COPD patients were further divided into two groups according to the NMLR threshold, and their baseline characteristics are shown in the supplementary data (Table S1). The 5-year all-cause mortality of COPD patients was significantly increased when the NMLR was ≥ 5.90 (27.3% vs 12.4%, P<0.001). Univariate and multivariate Cox proportional hazard analyses were used to explore the relationship between the NMLR and 5-year all-cause mortality of COPD patients (Table 2). The univariate Cox proportional hazard analysis showed that the NMLR was a high-risk factor for 5-year all-cause mortality of COPD patients [hazard ratio (HR)=2.46, 95% confidence interval (CI): 1.74–3.44, P<0.05]. Further multivariate analysis showed that it was still a significant predictive factor for 5-year all-cause mortality in patients with COPD (HR=1.84, 95% CI: 1.28–2.64, P=0.001). The 5-year all-cause mortality of COPD patients was also significantly influenced by age, BMI, coexistence with hypertension, $DL_{CO}$ %pred, $PaCO_2$ and albumin levels (all P<0.05).

In addition, the relationship between NMLR and 5-year all-cause mortality of COPD patients was also studied using a restricted cubic spline model, and the results are presented in Figure 5. The solid red line is the HR of NMLR as a constant variable in the adjusted model, and the red shaded area represents the 95% CI. There was a significant non-linear relationship between NMLR and 5-year all-cause mortality in COPD patients ($P_{non\text{-}linear} < 0.05$). The mortality risk of COPD gradually increased as the NMLR value elevated, and the highest risk was reached when NMLR was equal to 9.43. However, the death risk did not further increase when NMLR exceeded 9.43.

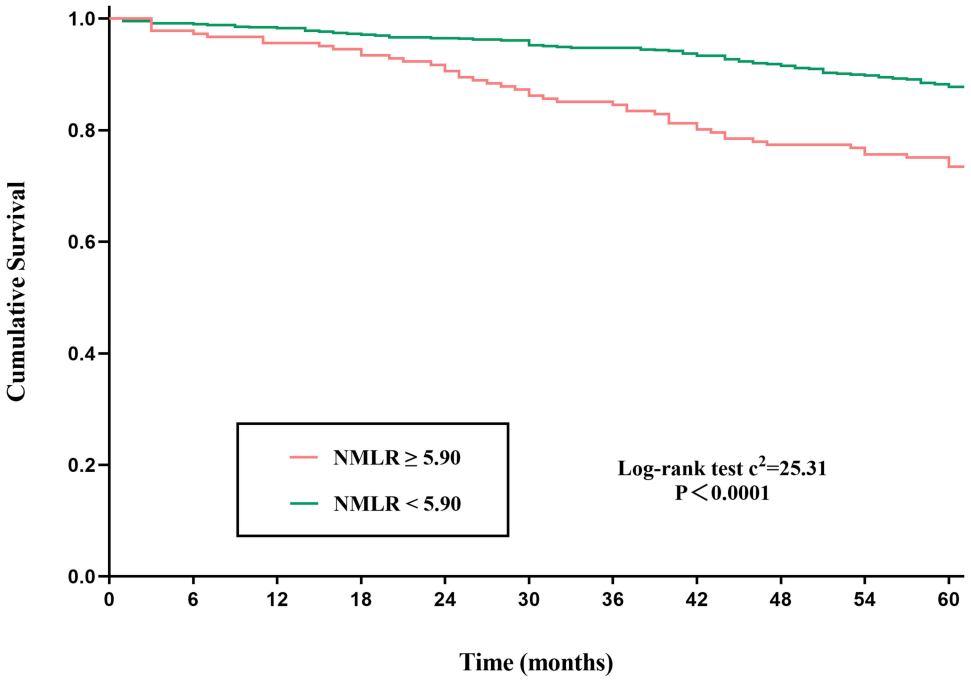


**Figure 4** Kaplan–Meier survival curves of COPD patients according to the cut-point of NMLR. Red line refers to NMLR ≥5.90, and green line refers to NMLR <5.90.
**Abbreviation**: NMLR, (neutrophil + monocyte)/lymphocyte ratio.

## Discussion

Patients with COPD have persistent systemic inflammation, which can be confirmed by increased blood levels of CRP, fibrinogen, leukocytes and TNF-a,[18] and persistent systemic inflammation increases the mortality rate.[9] Therefore,

**Table 2** Univariate and Multivariate Cox Proportional Hazard Analysis with 5-Year All-Cause Mortality of COPD

| Variable | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age (yr.) | 1.04 (1.02–1.07) | 0.000 | 1.03 (1.01–1.06) | 0.006 |
| Sex (male vs female) | 0.69 (0.44–1.08) | 0.102 | | |
| Body mass index (kg/m$^2$) | 0.88 (0.84–0.92) | 0.000 | 0.93 (0.88–0.98) | 0.005 |
| Smoking index (pack-yr.) | 1.01 (1.00–1.01) | 0.035 | 1.00 (0.99–1.01) | 0.429 |
| Hypertension (yes vs no) | 1.48 (1.04–2.09) | 0.029 | 1.67 (1.15–2.43) | 0.007 |
| $FEV_1$ (%pred) | 0.98 (0.97–0.98) | 0.000 | 0.99 (0.98–1.02) | 0.862 |
| FVC (%pred) | 0.98 (0.97–0.99) | 0.000 | 0.99 (0.98–1.01) | 0.685 |
| VA (%pred) | 0.97 (0.96–0.98) | 0.000 | 1.00 (0.98–1.01) | 0.790 |
| $DL_{CO}$ (%pred) (≥60% vs<60%) | 4.28 (3.02–6.05) | 0.000 | 2.67 (1.80–3.96) | 0.000 |
| $PaO_2$ (≥60 vs<60 mmHg) | 2.41 (1.66–3.51) | 0.000 | 1.16 (0.75–1.79) | 0.503 |
| $PaCO_2$ (≥50 vs<50 mmHg) | 3.08 (1.93–4.90) | 0.000 | 2.68 (1.60–4.50) | 0.000 |
| $PO_2$(A-a) (mmHg) | 1.02 (1.01–1.03) | 0.001 | 1.01 (1.00–1.02) | 0.050 |
| NMLR (≥5.90 vs<5.90) | 2.46 (1.74–3.44) | 0.000 | 1.84 (1.28–2.64) | 0.001 |
| Albumin (g/L) | 0.92 (0.89–0.95) | 0.000 | 0.95 (0.91–0.99) | 0.008 |
| ALT (IU/L) | 0.99 (0.98–1.01) | 0.646 | | |
| Cystatin C (mg/L) | 1.22 (0.93–1.60) | 0.143 | | |

**Abbreviations**: $FEV_1$, forced expiratory volume in 1s; FVC, forced vital capacity; VA, alveolar ventilation; $DL_{CO}$, diffusing lung capacity for carbon monoxide; $PaO_2$, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; $PO_2$(A-a), alveolar-arterial oxygen gradient; NMLR, (neutrophil + monocyte)/lymphocyte ratio; ALT, alanine aminotransferase.


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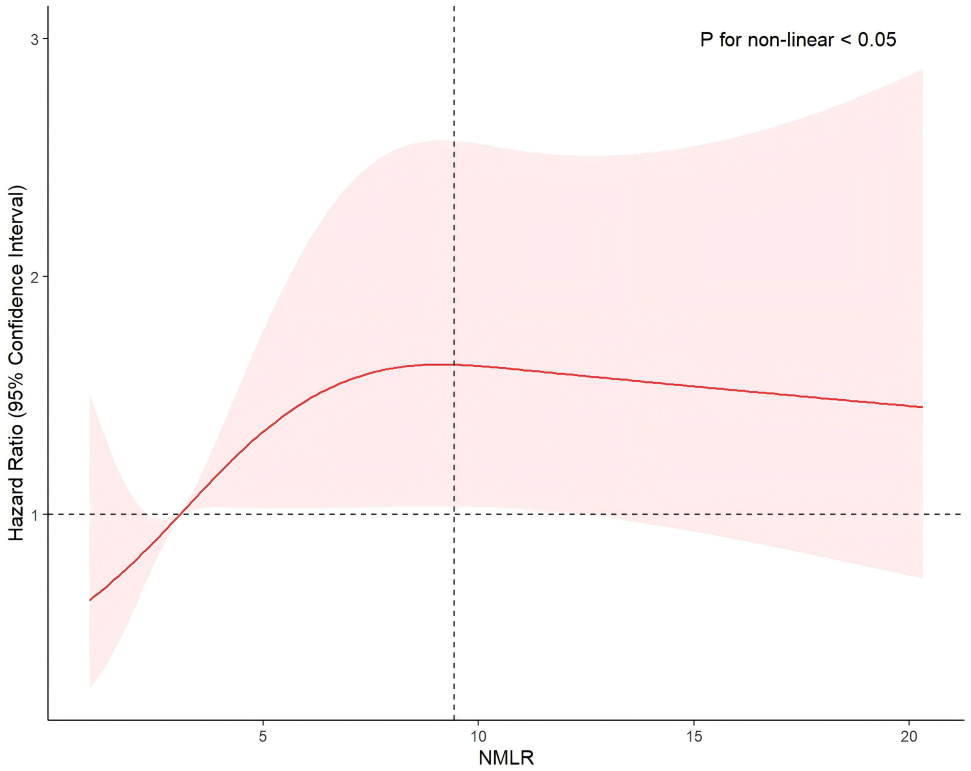


**Figure 5** RCS analysis on the association between NMLR and 5-year all-cause mortality in COPD patients. Adjustment for age, sex, BMI, coexistence of hypertension, $DL_{CO}$ %pred (≥60% vs<60%), $PaCO_2$ (≥50 vs<50 mmHg), and albumin.
**Abbreviations**: RCS, restricted cubic spline; NMLR, (neutrophil + monocyte)/lymphocyte ratio; BMI, body mass index; $DL_{CO}$, diffusing lung capacity for carbon monoxide; $PaCO_2$, partial pressure of carbon dioxide in arterial blood.

identifying an accessible, economical and valuable systemic inflammatory indicator that can identify COPD patients early with poor clinical outcomes is of great clinical significance.

A high blood neutrophil count may be a useful indicator of mortality risk in COPD patients,[19] and low lymphocyte numbers in the blood are related to worse clinical outcomes.[20] A previous retrospective study showed that blood monocyte levels were associated with an increased risk of acute exacerbations in patients with COPD.[21] It should be noted that peripheral blood neutrophils and lymphocytes are influenced by multiple factors, and cannot fully address the clinical problems in COPD. The combined NMLR parameter is more stable than neutrophil or lymphocyte numbers alone, and it can be used as an inflammatory and prognostic biomarker for several diseases. For example, the NMLR at admission could predict the prognosis of patients after cardiopulmonary resuscitation, and high NMLR levels were associated with a significantly poor clinical outcome.[22] NMLR was also reported to be associated with cardiovascular mortality in elderly patients with acute myocardial infarction,[23] and positively correlated with the prevalence and all-cause mortality of psoriasis patients.[24] Our present study found that the peripheral blood NMLR was significantly increased in non-survivors, suggesting that it might may be a useful biomarker for predicting the prognosis of COPD patients.

Persistent systemic inflammation has been reported to be associated with pulmonary function impairment in COPD.[25] Our present study showed that the potential inflammatory parameter NMLR was negatively correlated with $FEV_1$ %pred, $FEV_1$/FVC, $DL_{CO}$ %pred and $DL_{CO}$/VA, suggesting that elevated NMLR levels may be associated with impaired lung function in patients with COPD. Later we used the ROC curve model to further assess the predictive value of NMLR for 5-year all-cause mortality in patients with COPD. The AUC of NMLR for predicting 5-year all-cause mortality in COPD patients was 0.63, which was the largest among the six peripheral blood indices, indicating that NMLR may have a greater predictive value than the NLR or MLR. Based on the NMLR threshold, COPD mortality was significantly increased when the NMLR value was ≥ 5.90, which was also reflected in the survival curves, suggesting that the peripheral blood NMLR can predict the mortality risk of COPD.

The relationship between the NMLR and 5-year all-cause mortality in patients with COPD was further studied using COX regression analysis. Univariate and multivariate COX regression analyses showed that NMLR of ≥ 5.90 was a significant factor for 5-year all-cause mortality in patients with COPD, identifying it as a new predictive biomarker. As a comprehensive parameter including neutrophil, monocyte and lymphocyte counts, NMLR may not only represent systemic inflammation but also reflect the degree of pulmonary inflammation in COPD. Circulating monocytes can differentiate into macrophages within the lung, neutrophils migrate towards the airways guided by macrophage-secreted chemokines, and lymphocytes regulate lung immunity, finally inducing alveolar wall destruction, mucus hypersecretion and airflow obstruction in COPD.[26–28] Thus, the NMLR may predict the long-term mortality of patient with COPD by regulating systemic and pulmonary inflammation.

Consistent with previous findings, we also found that BMI values,[29] albumin levels[30] and hypertension comorbidity[31] can provide valuable information for predicting the prognosis of COPD patients. Our study showed that $DL_{CO}$ was also a strong predictor for all-cause mortality in COPD patients as previously reported.[32] In addition, hypoxemia decreases the quality of life and is associated with a poor prognosis in patients with COPD.[33] However, our present multivariate analysis showed that hypoxemia was not a significant variable for 5-year all-cause mortality in COPD patients, possibly because the hypoxemia data were derived from the acute exacerbation of COPD rather than the stable phase.

The relationship between dynamic changes in the NMLR and COPD death risk was analyzed using the RCS curve. The 5-year mortality risk of COPD patients gradually increased with increasing NMLR values, indicating that elevated NMLR levels represent a poor prognosis. However, the death risk reached a maximum when the NMLR was equal to 9.43, and the death risk of COPD did not increase when the NMLR was more than 9.43. The reason for these results may be related to the presence of severe bacterial infections in some patients with COPD, resulting in the increases of neutrophil counts and NMLR values. These patients had a relatively better prognosis after effective antibiotic treatment. Therefore, more attention should be paid on the hospitalized COPD patients with NMLR value ≥ 5.90, as these patients may have a significantly higher risk of death in the ensuing five years. Given that NMLR can be readily, inexpensively and routinely detected in the clinic, our findings advocate for its utilization as one of the most potent predictors of death in the patients with COPD.

Several limitations of our present study should be addressed. First, there was a very high degree of heterogeneity in patients' medication use over a 5-year period, and the medical treatment data of enrolled patients during the inclusion period were absent. Therefore, the confounding factor of medical treatment over the 5-year period cannot be excluded from this study. Second, we cannot fully elucidate the predictive value of NMLR in the patients with COPD from a single measurement. We will conduct a prospective cohort study to investigate the changing trend of peripheral blood NMLR and its correlation with 5-year all-cause mortality in COPD. Except for 5-year all-cause mortality, the short-term mortality (1-year or 3-year), readmission rate and the frequency of acute exacerbation within one year will be set as the primary study endpoints in the future researches. Finally, the specific death causes of COPD patients cannot be accurately obtained due to the retrospective follow-up. In order to further explore the relationship between NMLR and various causes of death in COPD, we will record the causes of death in a timely manner through a prospective study.

In conclusion, the present study has demonstrated that the peripheral blood NMLR at admission is a significant predictor for 5-year all-cause mortality of COPD patients, and elevated NMLR levels may indicate a poor clinical prognosis. In clinical practice, the early recognition of elevated NMLR values and appropriate medical treatments may provide better prognosis in patients with COPD.

## Data Sharing Statement

The datasets and analysis of this study are available from the corresponding author on reasonable request.

## Ethical Approval

The study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Research Committee of Human Investigation of the Second Affiliated Hospital of Xi'an Jiaotong University. Informed consent was obtained from all participants before their inclusion in the study.

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## Disclosure

The authors declare that there are no conflicts of interest in this work.

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