

## RESEARCH ARTICLE

# Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study

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## Abstract

This retrospective study was designed to explore whether neutrophil to lymphocyte ratio (NLR) is a prognostic factor in patients with coronavirus disease 2019 (COVID-19). A cohort of patients with COVID-19 admitted to the Tongren Hospital of Wuhan University from 11 January 2020 to 3 March 2020 was retrospectively analyzed. Patients with hematologic malignancy were excluded. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. NLR values were measured at the time of admission. The primary outcome was all-cause in-hospital mortality. A multivariate logistic analysis was performed. A total of 1004 patients with COVID-19 were included in this study. The mortality rate was 4.0% (40 cases). The median age of nonsurvivors (68 years) was significantly older than survivors (62 years). Male sex was more predominant in nonsurvival group (27; 67.5%) than in the survival group (466; 48.3%). NLR value of nonsurvival group (median: 49.06; interquartile range [IQR]: 25.71-69.70) was higher than that of survival group (median: 4.11; IQR: 2.44-8.12;  $P < .001$ ). In multivariate logistic regression analysis, after adjusting for confounding factors, NLR more than 11.75 was significantly correlated with all-cause in-hospital mortality (odds ratio = 44.351; 95%

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confidence interval = 4.627-425.088). These results suggest that the NLR at hospital admission is associated with in-hospital mortality among patients with COVID-19. Therefore, the NLR appears to be a significant prognostic biomarker of outcomes in critically ill patients with COVID-19. However, further investigation is needed to validate this relationship with data collected prospectively.

#### KEYWORDS

lymphopenia, neutrophils, pneumonia, prognostic, SARS-CoV-2

## 1 | INTRODUCTION

Since December 2019, a cluster of acute respiratory illness, now known as novel coronavirus-infected pneumonia (NCIP), and has spread throughout China and now to 195 other countries and territories.<sup>1-4</sup> On 7 January 2020, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; previously known as 2019-nCoV), was identified in samples of bronchoalveolar lavage fluid from a patient in Wuhan and was confirmed as the cause of the NCIP.<sup>5</sup> Studies have shown that the disease caused by SARS-CoV-2, recently named as coronavirus disease 2019 (COVID-19) by World Health Organization (WHO), could induce symptoms including fever, dry cough, dyspnea, fatigue, and lymphopenia in infected patients. In more severe cases, infections causing viral pneumonia may lead to severe acute respiratory syndrome (SARS) and even death.<sup>2,3,6</sup> Most of the initial cases of COVID-19, the disease caused by SARS-CoV-2, were all related to Huanan Seafood Wholesale Market, which sells aquatic products, live poultries, and wild animals.<sup>2</sup> The first batch of cases identified later showed no exposure or even no relation to Huanan Wholesale Market, and the human-to-human transmission was confirmed; moreover, nosocomial infections were reported in some health care workers.<sup>3,7</sup> The number of fatalities due to COVID-19 is escalating. However, at this time, there are no specific vaccines or treatments for COVID-19. Most therapy consists of empirical antibiotics, antiviral therapy (oseltamivir), and systemic corticosteroids, which may have a limited effect on a fatal outcome. Evidence is now accumulating that the condition of some patients with COVID-19 deteriorates rapidly. As of 20 May 2020, WHO's online COVID-19 situation dashboard reveals there have been 4 801 202 confirmed cases of COVID-19, including 318 935 deaths. Thus, identifying the prognostic predictors of mortality in patients with COVID-19 might be useful for assessing the disease severity and making optimal treatment decisions. The neutrophil to lymphocyte ratio (NLR) has been suggested as a simple marker of the systemic inflammatory response in critical care patients.<sup>8,9</sup> It has also been reported as an independent prognostic factor for noninfectious diseases, such as acute myocardial infarction, stroke, and several types of cancers.<sup>10-12</sup> In addition, NLR has been shown to be an independent indicator of both short-term and long-term mortality in critically ill patients.<sup>13</sup> Therefore, the NLR is a systemic inflammatory marker and a potential predictor of clinical risk and outcome in many diseases. To our knowledge, the utility of NLR to predict mortality in patients with COVID-19 has not been studied yet. Based on the previous studies, we hypothesized that NLR might relate to the disease severity

and mortality in patients with COVID-19. In the current study, we sought to investigate whether NLR is a prognostic factor in patients with COVID-19.

## 2 | METHODS

### 2.1 | Study design and participants

All adult (age >18 years old) patients who were diagnosed with COVID-19 according to WHO interim guidance were screened, and those who died or were discharged between 11 January 2020 and 3 March 2020 were included in our study. Data were collected from patients who were cured and discharged, or who died without a cure. Confirmation of COVID-19 enrolled in this study was diagnosed according to the Guidance for Corona Virus Disease 2019 (6th edition) released by the National Health Commission of China.<sup>14</sup> This study complied to the ethical guidelines of the Declaration of Helsinki. The study was performed in accordance with the Research Ethics Commission of Wuhan Third Hospital & Tongren Hospital of Wuhan University (KY-2020-010) and the requirement for informed consent was waived by the Ethics Commission.

### 2.2 | RT-PCR assay for COVID-19

Throat swab samples were collected for extracting 2019-nCoV RNA from patients suspected of having the 2019-nCoV infection. The reverse transcription-polymerase chain reaction assay was performed according to the manufacturer's protocol using a 2019-nCoV nucleic acid detection kit (Shanghai Bio-germ Medical Biotechnology). Two target genes, including open reading frame 1ab (ORF1ab) and nucleocapsid protein (N), were amplified and tested. The primers used were as follows: Target 1 (ORF1ab): forward primer, CCCTGTGGGTTTTACA-CTTAA; reverse primer, ACGATTGTGCATCAGCTGA; and the probe, 5'-FAM-CCGTCTGCGGTATGTGGAA-AGGTTATGG-BHQ1-3'. Target 2 (N): forward primer, GGGGAACCTCTCTGCTAGAAT; reverse primer, CAGACATTTTGTCTCAAGCTG; and the probe, 5'-FAM-TTGCTGCTGC-TT GACAGATT-TAMRA-3'. These diagnostic criteria are based on the recommendations of the National Institute for Viral Disease Control and Prevention (China). Routine blood examinations were complete blood count, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes

and myocardial enzymes. Chest radiographs or computed tomography scan were also done for all inpatients.<sup>15</sup>

### 2.3 | Inclusion and exclusion criteria

All patients age more than 18 years, and having neutrophil and lymphocyte counts results within 24 hours after admission, were included in this study. Patients who missed the neutrophil and lymphocyte records or with chronic hematological disorder were excluded.

### 2.4 | Data collection

The electronic medical records of the patients were reviewed by a trained research team of physicians in Wuhan Third Hospital & Tongren Hospital of Wuhan University. Epidemiological, clinical, laboratory, treatment, and outcome data were analyzed. Patient data included demographics, medical history, exposure history, comorbidities, symptoms, signs, laboratory findings, and treatment (antiviral, antibiotic, and corticosteroid therapies, and respiratory support). All data were checked by two physicians (HC and JS) and a third researcher (SN) adjudicated any difference in interpretation between the two primary reviewers.

### 2.5 | Statistical analysis

Baseline characteristics were presented as median with interquartile range (IQR) for continuous variables and as number with percentage for categorical variables. Comparisons between continuous variables were analyzed by the Student *t* and Mann-Whitney *U* test based on variable distribution, and categorical variables were analyzed by the  $\chi^2$  test. The data were tested to the Kolmogorov-Smirnov normality test for homogeneity of variance. To assess the relationship between the NLR and in-hospital mortality, we did the receiver operating characteristics (ROC) curve and reported area under the ROC curve. Next, we grouped the patients based on the cut-off value of NLR during hospitalization. In addition, to adjust potential confounding with variables, we did a multivariate regression analysis. The following variables were considered for multivariable adjustment: age, gender, smoking status, laboratory data, comorbidities, and intensive care unit (ICU) length of stay. The results were reported as hazard ratio and 95% confidence interval (95% CI). All statistical processes were performed with the Statistical Package for the Social Sciences 20.0 (SPSS Inc, Chicago, IL). A two-sided *P* value less than .05 was considered statistically significant.

## 3 | RESULTS

### 3.1 | Patient characteristics

From 11 January 2020 to 3 March 2020, a total of 1004 patients diagnosed with COVID-19 were admitted to Wuhan Third Hospital &

Tongren Hospital of Wuhan University. Of these, 40 of these patients had died of COVID-19. The median age of nonsurvivors was 68 (IQR: 58-79) years, which was significantly older than survivors (62 [50-70] years); male sex was more predominant in nonsurvivors (27; 67.5%) than in survivors (466; 48.3%). In the laboratory examination, the levels of white blood cell (WBC) count, neutrophil count, serum creatine kinase, creatine kinase isozyme, lactate dehydrogenase, blood urea nitrogen, serum creatinine, hydroxybutyrate-dehydrogenase, cTnI, D-dimer, NT-proBNP, alanine aminotransferase, aspartate aminotransferase, bilirubin, and hs-CRP were higher in nonsurvivors, but levels of platelets, lymphocyte, albumin, total cholesterol, high-density lipoprotein, low-density lipoprotein levels were lower (all *P* < .05). In addition, the number of comorbid diseases (diseases diagnosed at admission or related to previous medical history) in nonsurvivors was significantly higher than that in survivors, especially renal insufficiency, respiratory failure, and cerebrovascular disease. One important finding is that the median NLR value was 49.06 (range: 25.71-69.70) in nonsurvivors and 4.11 (range: 2.44-8.12) in survivors, with a large difference between the two groups (*P* < .001). The baseline characteristics, medical history, and major laboratory findings of the two groups were shown in Table 1.

### 3.2 | Association between NLR and in-hospital mortality

Nonparametric ROC analysis showed that the cut-off value of the ROC curve as the optimal threshold for in-hospital mortality was 11.75, that is, when NLR was more than 11.75, the model had the strongest predictive ability, with an area under the curve of 0.945 and 95% CI of 0.917 to 0.973 (Figure 1), sensitivity of 97.5%, specificity of 78.1%, and Yoden index of 0.756. We further divided patients into two groups using NLR greater than or less than or equal to 11.75 as the criterion to compare the clinical characteristics of patients with a high NLR and those with a low NLR (Table 2).

### 3.3 | Risk factors for in-hospital mortality

After multivariate logistic regression analysis, high-NLR remained independently associated with in-hospital death. In addition, we found that higher levels of hs-CRP, NT-proBNP, and blood urea nitrogen, as well as history of hypertension, respiratory failure, digestive system diseases, and cerebrovascular diseases, were also independently associated with in-hospital mortality (Table 3).

## 4 | DISCUSSION

In this study, we found there was an association between NLR and the clinical outcomes in patients with COVID-19. Following SARS-CoV-2 infection, most of the patients presented lymphopenia and elevated levels of infection-related biomarkers, more interestingly, a higher

Variables	Survivors (N = 964)	Nonsurvivors (N = 40)	P value
Age, y	62 (50-70)	68 (58-79)	.007
Male, n (%)	466 (48.3)	27 (67.5)	.018
Smoking, n (%)	440 (45.6)	22 (55)	.245
Hemoglobin, g/dL	128 (118-138)*	133 (123-146)	.069
WBC, 10 × 9/L	6.05 (4.70-7.80)	14.85 (11.73-18.68)	<.001
Platelet, 10 × 9/L	180 (139-228)*	119 (82-186)	<.001
Albumin, g/L	35.3 (31.2-39.3)	26.8 (24.9-31.5)	<.001
Neutrophil, 10 × 9/L	4.196 (3.000-6.150)	13.305 (10.550-17.593)	<.001
Lymphocyte, 10 × 9/L	0.97 (0.65-1.41)	0.33 (0.16-0.47)	<.001
NLR	4.11 (2.44-8.12)	49.06 (25.71-69.70)	<.001
High sensitivity CRP, ng/mL	18.89 (3.68-66.91)*	208.46 (117.47-284.78)	<.001
Creatinine, mol/L	69.25 (56.60-89.08)	143.95 (91.20-355.70)	<.001
CK, IU/L	75.00 (48.00-139.75)	274.00 (107.50-643)	<.001
CK-MB, IU/L	11 (8-16)	28.00 (14.25-43.75)	<.001
LDH, IU/L	227 (177-317)*	568.50 (352.00-823.25)	<.001
cTnl, ng/L	0.002 (0.000-0.011)*	0.478 (0.106-1.205)	<.001
HBDH, U/L	193 (153-264)*	435 (250-662)	<.001
NT-proBNP pmol/L	29.53 (12.75-70.96)*	251.56 (102.27-471.65)	<.001
Blood urea nitrogen, mmol/L	4.9 (3.9-6.8)*	21.6 (6.5-36.9)	<.001
ALT, U/L	33 (20-61)	51 (23-96)	.048
AST, U/L	31 (22-49)	79 (38-133)	<.001
D-Dimer, ng/mL	0.73 (0.35-2.16)*	6.12 (3.40-21.27)	<.001
Triglyceride, mmol/L	1.54 (1.11-2.26)	1.85 (1.29-2.63)	.124
Total bilirubin, μmol/L	10.4 (7.7-13.7)*	15.6 (7.6-22.7)	.01
Total cholesterol, mmol/L	4.34 (3.72-5.09)*	3.70 (3.03-4.37)	<.001
HDL, mmol/L	0.88 (0.72-1.06)*	0.63 (0.50-0.89)	<.001
LDL, mmol/L	2.69 (2.23-3.23)*	2.20 (1.68-2.78)	<.001
ICU history	40 (4.1)	26 (65)	<.001
ICU length of stay	14 (9-17)	10.5 (5.25-17.75)	.052
Diabetes	97 (10.1)	10 (25)	.003
Hypertension	215 (22.3)	20 (50)	<.001
CHD	65 (6.7)	10 (25)	<.001
Hyperlipemia	19 (2)	1 (2.5)	.814
COPD	8 (0.8)	0 (0)	.563
Other lung diseases	126 (13.1)	21 (52.5)	<.001
Respiratory failure	48 (5)	25 (62.5)	<.001
Acute renal failure	3 (0.3)	0 (0)	.724
Other kidney diseases	91 (9.4)	8 (20)	.028
Livercirrhosis	8 (0.8)	0 (0)	.563
Other liver diseases	68 (7.1)	7 (17.5)	.014

**TABLE 1** Baseline characteristics of survivors and nonsurvivors

Variables	Survivors (N = 964)	Nonsurvivors (N = 40)	P value
Digestive system disease	19 (2)	2 (5)	.19
Tumour	11 (1.1)	1 (2.5)	.438
Cerebrovascular disease	21 (2.2)	9 (22.5)	<.001

TABLE 1 (Continued)

Note: Data are presented as median with IQR for continuous variables and as number with percentage for categorical variables.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, serum creatine kinase; CK-MB, creatine kinase-MB; COPD, chronic obstructive pulmonary disease; HBDH, hydroxybutyrate-dehydrogenase; HDL, high-density lipoprotein; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NLR, neutrophil to lymphocyte ratio; WBC, white blood cell.

\* $P < .05$ .

number of neutrophils and a lower number of lymphocytes, that is, the increase of NLR, were found in nonsurvivors with COVID-19 compared to survivors. NLR has been shown to be a simple, stand-alone method for evaluating systemic inflammation. Neutrophils play a central role in the innate immune response, resulting in multiple organ failure and lethality of severely injured patients. In contrast, lymphocytes play a major role in the inflammatory response. Therefore, a high NLR indicates an imbalance of the inflammatory response and may be a surrogate marker of disease severity in infectious diseases, such as sepsis and bacteremia.<sup>16</sup> Based on the ROC curve analysis, the NLR showed the significant performance to predict in-hospital mortality. The cut-off level for the NLR was 11.75 (Figure 1). Our study supports that a high NLR is a strong predictor for in-hospital mortality in patients with COVID-19. NLR is a convenient marker of systemic

inflammation and infection, outperforms the predictive ability of absolute leukocyte, lymphocyte or neutrophil counts, and has been demonstrated to be a useful biomarker for predicting bacterial infection, included pneumonia.<sup>9,13,17</sup> Furthermore, NLR is shown to predict outcomes in patients with cardiovascular disease<sup>18</sup> as well as solid tumor malignancy.<sup>19</sup> In addition, higher NLR has been reported to be associated with worse prognosis in patients with acute pancreatitis and was identified as a significant predictor of ICU admission and a longer length of stay.<sup>20</sup> Increasing clinical data suggest that the NLR might be a powerful predictive and prognostic indicator for severe COVID-19.<sup>6,21,22</sup> Consistent with previous findings that several patients infected with SARS-CoV-2 had a high neutrophil count and a low lymphocyte count during the severe phase,<sup>6</sup> the increased mortality rate in patients with NLR found in our study, indicated a serious disturbance in the internal environment and potential critical condition in severe infected cases.<sup>23</sup> In general, increased NLR was common among patients with COVID-19, which become more pronounced in severe cases. On the basis of these, we suggested that COVID-19 might damage lymphocytes, and the immune system was impaired during the course of the disease. Consistent with the findings from Chen et al,<sup>24</sup> we observed that the overall fatality rate for confirmed COVID-19 cases was higher in male than in female patients, with the risk of death rising with age for both sexes. Furthermore, we observed that 92.5% of patients had at least one underlying disorder (ie, renal insufficiency, respiratory failure, and cerebrovascular disease), and a higher percentage of hypertension and cardiovascular disease in nonsurvivors than survivors, in consistent with those reports.<sup>2,6</sup> These findings suggested that COVID-19 is more likely to infected those elder men with chronic comorbidities due to weaker immune functions. Older patients often present with atypical signs and symptoms and have multiple comorbid conditions, which often leads to delayed diagnosis and treatment and even death. Indeed, these patients are at higher risk of COVID-19, hospital admission, ICU admission, and in-hospital death than are young adults.<sup>16,25</sup> Physicians may find it time-consuming and difficult to completely assess older patients. However, NLR is a biomarker that integrates two WBC subtypes representing two inversely and related immune pathways. It represents an easily accessible objective parameter, can be readily calculated from differential WBC counts, more stable for measurement than the individual

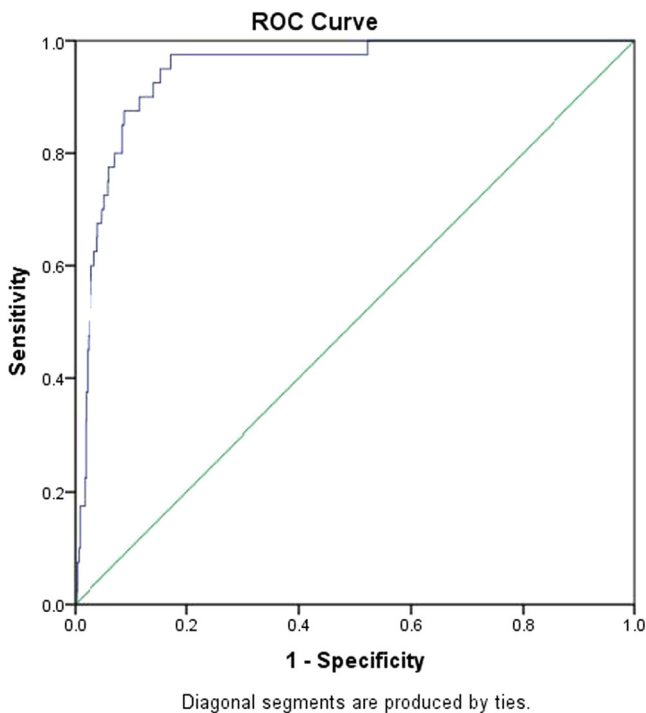


FIGURE 1 Receiver operating characteristic (ROC) curves for in-hospital mortality

**TABLE 2** Clinical characteristics between high NLR and low NLR

Variables	Low NLR $\leq 11.75$	High NLR $> 11.75$	P value
NLR	3.30 (2.22-5.44)	22.0 (14.49-44.80)	<.001
Number of death	1 (0.1)	39 (19)	<.001
ICU history	11 (1.4)	55 (26.8)	<.001
Length of stay	14 (8-16)	15 (9-23)	<.001
Age, y	62 (49-69)	63 (54-73)	.001
Male, n (%)	370 (46.3)	123 (60.0)	<.001
Smoking, n (%)	347 (43.4)	115 (56.1)	.001
Hemoglobin, g/dL	128 (118-137)*	132 (118-144)*	.049
WBC, $10 \times 9/L$	5.6 (4.4-6.9)	10.8 (7.8-14.8)	<.001
Platelet, $10 \times 9/L$	187 (148-237)*	145 (107-188)	<.001
Albumin, g/L	36.4 (32.7-39.8)	28.8 (26.9-32.5)	<.001
Neutrophil, $10 \times 9/L$	3.75 (2.83-5.94)	10.49 (7.27-13.52)	<.001
Lymphocyte, $10 \times 9/L$	1.09 (0.83-1.51)	0.42 (0.29-0.55)	<.001
High sensitivity CRP, ng/mL	12.7 (2.8-44.4)*	116.6 (64.2-200.0)	<.001
Creatinine, mol/L	67.2 (55.6-83.2)	90.6 (68.8-177.1)	<.001
CK, IU/L	67 (46-118)	178 (74-433)	<.001
CK-MB, IU/L	11 (8-15)	19 (11-31)	<.001
LDH, IU/L	214 (170-278)*	401 (274-620)	<.001
cTnl, ng/L	0.002 (0.000-0.006)*	0.022 (0.004-0.227)*	<.001
HBDH, U/L	181 (147-234)*	327 (225-495)	<.001
NT-proBNP pmol/L	25.88 (12.26-52.34)*	102.47 (30.94-265.24)*	<.001
Blood urea nitrogen, mmol/L	4.6 (3.7-5.9)*	9.1 (6.0-20.4)	<.001
ALT, U/L	30 (19-52)	54 (28-114)	<.001
AST, U/L	29 (21-43)	59 (33-101)	<.001
D-Dimer, ng/mL	0.64 (0.32-1.35)*	3.76 (0.83-6.44)*	<.001
Triglyceride, mmol/L	1.52 (1.09-2.22)	1.70 (1.26-2.45)	.004
Total bilirubin, $\mu\text{mol/L}$	9.7 (7.4-12.6)*	14 (10.3-21.1)	<.001
Total cholesterol, mmol/L	4.30 (3.70-5.04)*	4.28 (3.65-5.11)	.645
HDL, mmol/L	0.89 (0.74-1.09)*	0.79 (0.61-0.92)	<.001
LDL, mmol/L	2.68 (2.21-3.19)*	2.66 (2.17-3.38)	.96
Diabetes	78 (9.8)	29 (14.1)	.07
Hypertension	174 (21.8)	61 (29.8)	.016
CHD	43 (5.4)	32 (15.6)	<.001
Hyperlipemia	18 (2.3)	2 (1.0)	.243
COPD	7 (0.9)	1 (0.5)	.577
Other lung diseases	87 (10.9)	60 (29.3)	<.001
Respiratory failure	18 (2.3)	55 (26.8)	<.001
Acute renal failure	1 (0.1)	2 (1)	.047
Other kidney diseases	68 (8.5)	31 (15.1)	.005
Livercirrhosis	6 (0.8)	2 (1.0)	.747

Variables	Low NLR $\leq 11.75$	High NLR $> 11.75$	P value
Other liver diseases	46 (5.8)	29 (14.1)	<.001
Digestive system disease	15 (1.9)	6 (2.9)	.349
Tumour	8 (1.0)	4 (2.0)	.264
Cerebrovascular disease	15 (1.9)	15 (7.3)	<.001

TABLE 2 (Continued)

Note: Data are presented as median with IQR for continuous variables and as number with percentage for categorical variables.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, serum creatine kinase; CK-MB, creatine kinase-MB; COPD, chronic obstructive pulmonary disease; HBDH, hydroxybutyrate-dehydrogenase; HDL, high-density lipoprotein; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; NLR, neutrophil to lymphocyte ratio; WBC, white blood cell.

\* $P < .05$ .

WBC counts, and less affected by conditions that could change the individual cell counts.<sup>26</sup> The NLR is beneficial for clinicians to inform their understanding of the severity of COVID-19. A high calculated NLR may, therefore, aid in determining outcome risk, need for close clinical monitoring, and urgent effective treatment. Samaras et al<sup>27</sup> proposed a targeted approach for high-risk patients.<sup>25</sup> Our results may also help in the early identification of older patients at higher risk of COVID-19.

Our results show a significant increase in mortality with increasing quartile of baseline NLR in patients with COVID-19. The main reason for this difference may be due to an insufficient number of patients with low NLR in our study. Another reason is that part of patients in our study included had a diagnosis of sepsis in patients with COVID-19, which may suggest a more severe inflammation in patients in our study.

Systemic inflammation is associated with the development and progression of COVID-19, recent studies have shown increased levels of inflammatory biomarkers were associated with poor outcomes in COVID-19.<sup>21</sup> NLR may serve as an additional inflammatory biomarker mainly because it reflects the systemic inflammatory and stress responses with neutrophils rising and lymphocytes apoptosis.<sup>28,29</sup>

**TABLE 3** Multivariate regression analysis of predictors of in-hospital mortality

Variable	OR	95% CI	P value
NLR $> 11.75$	44.351	4.627-425.088	.001
High sensitivity CRP, ng/mL	1.009	1.004-1.015	.001
NT-proBNP pmol/L	1.001	1.000-1.002	.054
Blood urea nitrogen, mmol/L	1.015	0.991-1.039	.218
Hypertension	2.606	0.988-6.870	.053
Respiratory failure	4.207	1.626-10.881	.003
Digestive system disease	39.463	3.851-404.357	.002
Cerebrovascular disease	13.534	3.162-57.940	<.001

Abbreviations: CI, confidence interval; NLR, neutrophil to lymphocyte ratio; OR, odds ratio.

A study of patients with trauma and systemic inflammatory response syndrome showed lymphopenia was associated with high mortality, the lymphocytes were important in the regulation of an appropriate inflammatory response and low circulating lymphocytes may perpetuate a harmful inflammatory status.<sup>30</sup> High NLR in patients is associated with high levels of inflammation. de Jager et al<sup>31</sup> showed that NLR predicts bacteremia was better than conventional inflammation markers like C-reactive protein, WBC count, and neutrophil count. A recent study showed that NLR, as well as other inflammatory factors like lymphopenia and plasma calprotectin, are independent predictors of increased all-cause mortality in moderate to severe chronic obstructive pulmonary disease in stable phase and not in treatment with systemic glucocorticoids.<sup>32</sup> Thus, we supposed increased NLR values could predict the poor outcome in COVID-19 patients on the evidence of the association between NLR-related inflammation and disease severity.

This study has some important limitations to consider. First, it was a single-center and retrospective observational study, subject selection bias could not be avoided and the causal relationship between NLR and mortality could not be drawn. Therefore, our findings need to be confirmed in a prospective multicenter study. Second, our primary outcome was all-cause in-hospital mortality, so we could not analyze the cause of specific mortalities. The exact mechanisms underlying the association between NLR and mortalities in elderly individuals are not certain. Third, NLR value is influenced by comorbidities and medications that affect the neutrophil and lymphocyte count. Fourth, systemic inflammation may cause mortality, but further studies are needed to identify the exact mechanisms. We only analyzed NLR at admission; however, there may be a specific pattern in serial NLR examination. If there is an association between serial NLR and mortality, then this association could have more specificity in predicting mortality. As previously discussed, our study only shows an association, so there is a limitation of the clinical implications. Thus, more studies are needed to identify the associations between NLR and cause-specific mortality in elderly individuals.

In summary, we found high NLR was associated with poor outcome in critically ill patients with COVID-19. NLR was an

independent risk factor for predicting all-cause in-hospital mortality in COVID-19 patients. Thus, the NLR at admission may represent a surrogate marker of disease severity. However, we need more external validation to use the NLR in the clinical decision-making process.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTION

XY and FL conceived the project. Data collection and analyses were performed by FL, FZ, SF, YD, HW, RC, ZY, YL, JS, LZ, JZ, CG, HC, WG, XH, and YZ. The manuscript was written by XY and WZ, and revised by DL and SN. All authors read and approved the final manuscript.

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