



Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19

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SUMMARY

Background: Several studies have described the clinical characteristics of patients with novel coronavirus (SARS-CoV-2) infected pneumonia (COVID-19), indicating severe patients tended to have higher neutrophil to lymphocyte ratio (NLR). Whether baseline NLR could be an independent predictor of in-hospital death in Chinese COVID-19 patients remains to be investigated.

Methods: A cohort of patients with COVID-19 admitted to the Zhongnan Hospital of Wuhan University from January 1 to February 29 was retrospectively analyzed. The baseline data of laboratory examinations, including NLR, were collected. Univariate and multivariate logistic regression models were developed to assess the independent relationship between the baseline NLR and in-hospital all-cause death. A sensitivity analysis was performed by converting NLR from a continuous variable to a categorical variable according to tertile. Interaction and stratified analyses were conducted as well.

Results: 245 COVID-19 patients were included in the final analyses, and the in-hospital mortality was 13.47%. Multivariate analysis demonstrated that there was 8% higher risk of in-hospital mortality for each unit increase in NLR (Odds ratio [OR]=1.08; 95% confidence interval [95% CI], 1.01 to 1.14; $P=0.0147$). Compared with patients in the lowest tertile, the NLR of patients in the highest tertile had a 15.04-fold higher risk of death (OR=16.04; 95% CI, 1.14 to 224.95; $P=0.0395$) after adjustment for potential confounders. Notably, the fully adjusted OR for mortality was 1.10 in males for each unit increase of NLR (OR=1.10; 95% CI, 1.02 to 1.19; $P=0.016$).

Conclusions: NLR is an independent risk factor of the in-hospital mortality for COVID-19 patients especially for male. Assessment of NLR may help identify high risk individuals with COVID-19.

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Introduction

The novel coronavirus, named as SARS-CoV-2, was first recognized in Wuhan, China, in December 2019. Considering the rapid outbreak in China and fast worldwide spread of the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, this infectious disease has aroused emerging global concerns. As of March 29, 2020, 82419 people have been diagnosed as COVID-19 in China, among them 3306 ended up with death. Moreover, 582131 people worldwide were infected, and the mortality rate was 4.7%. As there are

currently no standardized treatments and medications available, it is crucial to identify risk factors of severe prognosis for COVID-19 patients.

The neutrophil to lymphocyte ratio (NLR), easily calculated from a routinely blood test by dividing absolute neutrophil count by absolute lymphocyte count, has been reported of having great value in indicating a patient's overall inflammatory status.¹ Increasing NLR is a risk factor of mortality not only in infectious diseases but also in malignancy, acute coronary syndrome, intracerebral hemorrhage, polymyositis and dermatomyositis.^{2–5} A recent research has exhibited that severe cases of COVID-19 tended to have higher NLR.⁶ Whether NLR could be an independent predictor of mortality in hospitalized COVID-19 patients needs to be further elucidated.

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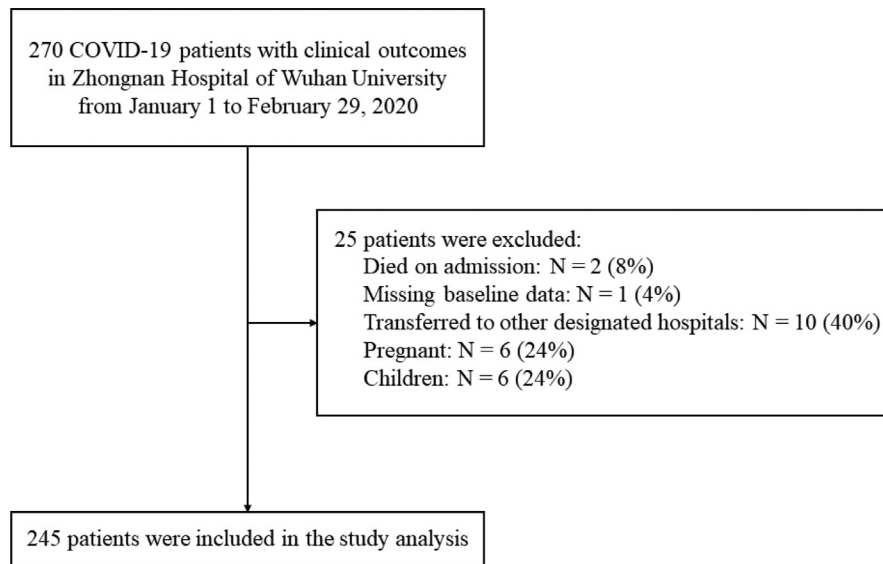


Fig. 1. Study Population.

So far researches of COVID-19 are focused on the epidemiology and clinical features of the patients,⁷⁻⁹ information regarding risk factors of mortality is scarce. In the present study, we aim to investigate whether the NLR can serve as a valuable predictor of in-hospital mortality.

Methods

Study design and participants

For this retrospective cohort study, COVID-19 patients who were admitted to Zhongnan Hospital of Wuhan University from January 1 to February 29, 2020 were consecutively included. The clinical outcomes, discharge from hospital or death, were recorded up to February 29, 2020. Zhongnan Hospital of Wuhan University, located in Wuhan, Hubei Province, is one of the major hospitals responsible for the COVID-19 treatment assigned by the government. The diagnosis of COVID-19 was based on the World Health Organization interim guidance.¹⁰ The clinical data of 270 patients have been obtained, and a flow diagram is showed in Fig. 1. Patients whose age were under 18 years old, being pregnant, died on admission, having missing baseline data or being transferred to other designated hospitals during hospitalization were excluded. Therefore, 245 patients were included in the final analyses.

This study was approved by the Medical Ethics Committee of Zhongnan Hospital of Wuhan University (Approval Number 2020054) and complied with the Declaration of Helsinki. The data used in the study were anonymous, so the requirement for informed consent was waived.

Data collection

Information included demographic data, comorbidities, symptoms and signs, laboratory findings and chest computed tomographic (CT) scans were reviewed. All data were collected with a customized form from the electronic hospital information system. The medical records of the patients were reviewed by three investigators (JC, XD and YJ) independently to verify data accuracy.

Peripheral venous blood samples were assessed at the central laboratory of Zhongnan hospital following standard operative procedures. The routine blood tests (including white blood cell count [WBC], leukocyte subtypes, hemoglobin count and platelet count)

were measured with XN-9000 multi-function automatic blood analyzer of fluid (Sysmex Corporation, Kobe, Japan). The ARCHITCT ci16200 automatic biochemistry analyzer (Abbott Laboratories, Illinois, United States) was used to measure the biochemical parameters. Blood coagulation tests including plasma D-dimer, prothrombin time (PT), international normalized ratio (INR), activated partial prothrombin time (APTT), thrombin time (TT) were measured by ACL TOP 700 system (Instrumentation Laboratory, Milan, Italy).

Identifying of SARS-CoV-2: the throat swab samples were tested for SARS-CoV-2 with the Chinese Center for Disease Control and Prevention (CDC) recommended Kit (BioGerm, Shanghai, China) following WHO guidelines for qRT-PCR.^{11,12}

Statistical analysis

Summary statistics of the demographic and clinical characteristics of all patients stratified by NLR tertiles were expressed as frequencies and proportions for categorical variables, mean \pm SD or median and interquartile for continuous variables. The differences among groups were assessed using the chi-squared test for categorical variables, the one-way ANOVA for normally distributed continuous variables, and the Kruskal-Wallis test for skewed continuous variables.

We first examined the relationship of the NLR as a continuous variable with the outcome of in-hospital death, and then we evaluated this relationship when NLR was treated as variable categorized into tertiles. Univariate and multivariate logistic regression models were used to evaluate these relationships, then unadjusted and adjusted odds ratio (ORs) and 95% confidence intervals (CIs) were calculated. In the multivariate adjusted models, age, gender, body mass index (BMI), hypertension, chronic liver diseases, HIV infection, chronic obstructive pulmonary disease (COPD), smoking status (never smoked and smokers), respiratory rate (< 30 and ≥ 30 bpm), creatinine, Alanine aminotransferase, PT and d-dimer were included. These adjusted features included the ones that, when added to this model, changed the odds ratio by at least 10 percent. The lowest tertile was the reference for NLR.

Interaction and stratified analyses were conducted according to gender, age (< 60 and ≥ 60 years), BMI (< 25 and ≥ 25 kg/m²) and hypertension at baseline. To evaluate the relationships between different blood cell types in the blood routine test and the in-hospital death, we repeated the multivariate logistic regression

models using continuous forms of the blood cell counts. All *P* values were calculated using two-tailed tests of statistical significance with a type I error rate of 5%. All statistical analyses were performed using Empower(R) (www.empowerstats.com, X&Y solutions, Inc., Boston, MA) and R (<http://www.R-project.org>).

Results

Of 245 patients included in the final analyses, the mean (standard deviation) age of the cohort was 53.95 (16.90) years, and 46.53% of the participants were male. The overall number of in-hospital death was 33 (13.47%). Table 1 compared the baseline demographic, clinical, and biochemical characteristics of included patients by tertiles of the NLR. Compared with subjects in the lowest tertile of the NLR, those in the highest tertile were older, more likely to be male. The most common symptoms on admission of patients in the highest tertile were fever and dry cough, followed by fatigue and poor appetite. Moreover, individuals in the highest tertile were more likely to have underlying comorbidities, including hypertension, diabetes, coronary heart disease, chronic liver disease and carcinoma. The incidence of in-hospital death significantly increased across NLR tertiles (2.44% vs. 6.17% vs. 31.71% for tertile 1 vs. tertile 2 vs. tertile 3, respectively).

Table 2 showed the univariate logistic regression models between baseline variables and death. The univariate analysis indicated that age (OR=1.09, 95% CI, 1.06–1.13, *P* < 0.0001), BMI (OR=1.15, 95% CI, 1.01–1.30, *P*=0.0328), Hypertension (OR=3.94, 95%CI, 1.82–8.53, *P*=0.0005), Diabetes (OR=3.30, 95% CI, 1.24–8.77, *P*=0.0168), CHD (OR=6.46, 95% CI, 2.33–17.90, *P*=0.0003), Respiratory rate \geq 30 bpm (OR=7.43, 95% CI, 1.76–31.38, *P*=0.0064), Neutrophil (OR=1.34, 95% CI, 1.19–1.50, *P* < 0.0001), ALT (OR=1.01, 95% CI, 1.00–1.02, *P*=0.0094), Creatinine (OR=1.01, 95% CI, 1.00–1.01, *P*=0.0177), PT (OR=1.30, 95% CI, 1.01–1.67, *P*=0.0448), C-reactive protein and Procalcitonin values were positively correlated with the risk of in-hospital death. The female (OR=0.23, 95% CI, 0.10–0.54, *P*=0.0007) and MAP (OR=0.96, 95% CI, 0.92–0.99, *P*=0.0245) was negatively correlated with the risk of death.

The results of univariate and multivariate logistic regression models assessing the relations of NLR and in-hospital mortality were shown in Table 3. In the unadjusted model, the ORs of death significantly augmented as the NLR increased and the tertiles of NLR upgraded. There was a 10% increase in risk of in-hospital mortality for per unit increase in NLR (OR=1.10; 95% CI, 1.05 to 1.14; *P* < 0.0001). The OR for tertile 3 was significantly higher than the OR for tertile 1 (OR=18.57; 95% CI, 4.24 to 81.44; *P* = 0.0001). Adjustment for demographic variables and comorbidities did not weaken the associations between the NLR and death. Further adjusting for the baseline levels of respiratory rate, alanine transaminase, creatinine, prothrombin time and D-dimer did not affect the relationships in the fully adjusted models. NLR as a continuous variable was associated with 8% increased risk of mortality in the fully adjusted models (OR=1.08; 95%CI, 1.01 to 1.14; *P*=0.0147). Meanwhile, elevated tertile of NLR exhibited an increase in risk of mortality for the third tertile (vs the first tertile) with OR of 16.04 (95% CI, 1.14 to 224.95; *P*=0.0395).

To evaluate the consistency of the relationship between NLR and risk of all-cause mortality during hospitalization, stratified analyses were performed (Fig. 2). For each unit increase of NLR, the adjusted OR for mortality was 1.10 in males (*P*=0.016) and 1.00 in females (*P*=0.972), and the difference for interaction was not statistically significant (*P* interaction=0.240). There was a borderline significant association for mortality risk in patients less than 60 years (adjusted OR=1.09; 95% CI, 1.00 to 1.19; *P*=0.053) in comparison with patients 60 years or older (*P* interaction=0.786). The

adjusted OR for patients with normal body mass index (defined as BMI < 25 kg/m²) was 1.06 (*P*=0.107), while in those with an elevated BMI the OR was 1.11 (*P*=0.091). The difference of interaction was not significant between two groups (*P* interaction=0.473). Moreover, increasing NLR still was a risk factor for death in patients with or without hypertension, and no evidence of interaction effect was found between groups (*P* interaction=0.604).

The associations between different blood cell counts and in-hospital mortality were measured and shown in Table 4. The risk for mortality increased as the level of baseline neutrophil elevated in the adjusted model (OR=1.30; 95% CI, 1.05 to 1.60; *P*=0.0139 in model 2). There was a significant association between baseline monocyte count and mortality in the unadjusted model (OR=6.92; 95% CI, 2.01 to 23.84; *P*=0.0022), however, the significance faded when considering the cofounders in the adjusted models. Additionally, baseline lymphocyte, red blood cells and platelet counts were not associated with in-hospital death both in unadjusted or fully adjusted models.

Discussion

This retrospective cohort study included 245 COVID-19 patients, and the total in-hospital mortality was 13.47%. We found that higher NLR significantly associated with an increased risk of all-cause death during hospitalization. Older age and high level of D-dimer are considered independent predictors of in-hospital death.¹³ We adjusted age, D-dimer concentrations and other covariates to minimize the potential impact of confounding. Moreover, features that, when added to the model, changed the odds ratio by at least 10 percent have been added to the multiple logistic regression models. Compared with crude regression analyses, this association still persisted when adjusting for demographic and clinical variables in the multivariable regression analyses. According to the stratified analysis, the risk of mortality tended to be higher as NLR increased in male patients.

Several studies have addressed the difference of baseline leukocyte counts between the clinical stages in COVID-19 patients. Qin C et al.⁶ reported that severe cases of COVID-19 were likely to have higher neutrophil count but lower lymphocyte count compared with non-severe patients, thus the NLR tended to be higher in severe infection patients. Mo P et al.¹⁴ investigated 155 patients with COVID-19 and found that refractory patients had higher level of neutrophils in comparison with general patients. Moreover, some researchers evaluated the clinical characteristics of the SARS-CoV-2 reactivation. The study included 5 reactivated patients, among which one patient had progressive lymphopenia and progressive neutrophilia indicating the potential value of leukocyte counts on COVID-19 reactivation.¹⁵ Limited by the number of patients, difference of clinical outcome and lack of follow-up, the specific risk factors for in-hospital mortality remain to be identified.

In this study, we found that patients with increased NLR had a higher risk for mortality during hospitalization after adjustment for other cofounders, meanwhile, the male had a more significant association with the risk of mortality than the female. This finding is consistent with the results concluded by Mo P et al.¹⁴ that male patients have a higher incidence of disease refractoriness. Further research should be conducted to confirm this result and determine the differences in the pathophysiological mechanisms between male and female with COVID-19.

NLR has taken both the levels of neutrophils and lymphocytes into account, and been proposed as a new biomarker for systemic inflammation. The high NLR results from increased neutrophil count and decreased lymphocyte count. The inflammatory response could stimulate the production of neutrophils and speed up the apoptosis of lymphocytes. Dysregulated immune cell

Table 1
Baseline characteristics of COVID-19 patients and all-cause death during hospital according to the tertiles of neutrophil-lymphocyte ratio (NLR) (n = 245).

Variable	Tertile 1 (0.54-2.21; n=82)	Tertile 2 (2.21-4.82; n=81)	Tertile 3 (4.85-88.09; n=82)	P value
Demographic				
Age, years	47.74 ± 15.83	52.68 ± 17.07	61.41 ± 15.01	<0.001
Sex				<0.001
Male	24 (29.27%)	40 (49.38%)	50 (60.98%)	
Female	58 (70.73%)	41 (50.62%)	32 (39.02%)	
BMI (kg/m ²)	22.66 ± 2.93	24.41 ± 3.23	23.99 ± 3.65	0.003
Smoking	1 (1.22%)	4 (4.94%)	5 (6.10%)	0.257
Symptoms and signs				
Fever	61 (74.39%)	62 (76.54%)	75 (91.46%)	0.010
Dry cough	39 (47.56%)	49 (60.49%)	52 (63.41%)	0.092
Fatigue	36 (43.90%)	36 (44.44%)	45 (54.88%)	0.285
Anorexia	14 (17.07%)	15 (18.52%)	27 (32.93%)	0.028
Myalgia	24 (29.27%)	27 (33.33%)	24 (29.27%)	0.810
Dyspnea	8 (9.76%)	10 (12.35%)	27 (32.93%)	<0.001
Sputum	15 (18.29%)	24 (29.63%)	28 (34.15%)	0.064
Pharyngalgia	9 (10.98%)	7 (8.64%)	1 (1.22%)	0.026
Diarrhea	6 (7.32%)	8 (9.88%)	4 (4.88%)	0.438
Nausea	3 (3.66%)	8 (9.88%)	6 (7.32%)	0.278
Dizziness	3 (3.66%)	2 (2.47%)	5 (6.10%)	0.490
Headache	5 (6.10%)	5 (6.17%)	2 (2.44%)	0.449
Vomiting	2 (2.44%)	5 (6.17%)	3 (3.66%)	0.440
Abdominal pain	3 (3.66%)	0 (0.00%)	0 (0.00%)	0.049
Respiratory rate ≥ 30 bpm	0 (0.00%)	0 (0.00%)	8 (9.88%)	<0.001
Heart rate, beats per min	81.23 ± 12.01	87.14 ± 13.23	91.40 ± 18.49	<0.001
MAP, mmHg	88.48 ± 7.87	93.78 ± 10.77	90.34 ± 10.34	0.002
Comorbidities				
COPD	2 (2.44%)	4 (4.94%)	2 (2.44%)	0.585
Hypertension	11 (13.41%)	14 (17.28%)	27 (32.93%)	0.005
Diabetes	5 (6.10%)	6 (7.41%)	12 (14.63%)	0.131
CHD	5 (6.10%)	3 (3.70%)	10 (12.20%)	0.100
Carcinoma	2 (2.44%)	1 (1.23%)	6 (7.32%)	0.091
CLD	0 (0.00%)	3 (3.70%)	4 (4.88%)	0.135
HIV infection	1 (1.22%)	0 (0.00%)	1 (1.22%)	0.608
Laboratory findings				
White blood cells, 10 ⁹ /L	3.86 ± 1.58	4.23 ± 1.36	8.49 ± 5.69	<0.001
Neutrophil, 10 ⁹ /L	2.03 ± 0.90	2.83 ± 1.00	7.38 ± 5.37	<0.001
Lymphocyte, 10 ⁹ /L	1.39 ± 0.67	0.92 ± 0.31	0.62 ± 0.35	<0.001
Red blood cells, 10 ¹² /L	4.09 ± 0.52	4.22 ± 0.56	4.04 ± 0.79	0.161
Hemoglobin, G/L	127.89 ± 15.59	130.39 ± 13.73	124.33 ± 24.79	0.117
Platelet, 10 ⁹ /L	178.39 ± 47.57	174.70 ± 66.60	191.49 ± 89.23	0.274
ALT, U/L	23.93 ± 18.08	26.77 ± 17.79	40.56 ± 42.19	<0.001
AST, U/L	27.65 ± 12.91	36.16 ± 27.33	52.10 ± 57.68	<0.001
Glucose, mmol/L	5.84 ± 1.47	6.81 ± 3.30	8.22 ± 3.85	<0.001
Blood urea nitrogen, mmol/L	4.20 ± 1.60	4.69 ± 2.34	8.06 ± 8.31	<0.001
Creatinine, μmol/L	65.60 ± 20.48	75.06 ± 37.49	118.18 ± 180.33	<0.001
D-dimer, ng/mL	303.63 ± 565.30	685.37 ± 3143.50	2287.51 ± 6052.35	<0.001
PT, sec	12.39 ± 0.90	12.81 ± 1.01	13.42 ± 1.73	<0.001
APTT, %	31.03 ± 2.32	31.33 ± 3.82	31.27 ± 5.35	0.410
TT, sec	14.82 ± 1.91	14.98 ± 1.49	15.55 ± 4.01	0.198
C-reactive protein, mg/L	14.18 ± 16.58	36.18 ± 36.18	94.63 ± 76.13	<0.001
Procalcitonin, ng/mL				<0.001
<0.1	72 (93.51%)	69 (90.79%)	38 (46.34%)	
≥ 0.1, <0.5	5 (6.49%)	4 (5.26%)	26 (31.71%)	
≥ 0.5, <1	0 (0.00%)	3 (3.95%)	7 (8.54%)	
≥ 1	0 (0.00%)	0 (0.00%)	11 (13.41%)	
Imaging features				
Consolidation or Ground-glass opacity	77 (95.06%)	78 (97.50%)	82 (100.00%)	0.108
All-cause death				
	2 (2.44%)	5 (6.17%)	26 (31.71%)	<0.001

Data are mean ± SD, median (interquartile range), or percentage. P values comparing groups are from a χ^2 test for categorical variables, and ANOVA for continuous variables. BMI=Body mass index. MAP=mean arterial pressure. COPD=chronic obstructive pulmonary disease. CHD=coronary heart disease; CLD=chronic liver disease. ALT=alanine transaminase. AST=aspartate transaminase. PT=prothrombin time. APTT=activated partial thromboplastin time. TT=thrombin time.

responses and consequently immunologic abnormality are believed to play remarkable roles in the severity of virus-induced disease.¹⁶ When immune response is dysregulated, it would result in an excessive inflammation, even death. One of the most prominent factors associating with the severity and outcomes of the Middle East respiratory syndrome coronavirus (MERS-CoV) disease is the hematological change in leukocyte populations.¹⁷

leukocytosis characterized by increased neutrophils and monocytes was primarily observed in several MERS-CoV patients, and all the deceased patients showed rapid drops of lymphocyte counts.^{18,19} Recent studies showed that higher levels of inflammatory cytokines, chemokines and NLR in infected patients were correlated with the severity of the disease than did those non-severe patients, suggesting the involvement of cytokine storm in disease

Table 2

The unadjusted association between baseline variables and all-cause death during hospitalization (n = 245).

Variable	Statistics	Odds ratio (95% CIs)	P value
Age, years	53.95 ± 16.90	1.09 (1.06, 1.13)	<0.0001
Sex			
Male	114 (46.53%)	1.0	
Female	131 (53.47%)	0.23 (0.10, 0.54)	0.0007
BMI (kg/m ²)	23.67 ± 3.34	1.15 (1.01, 1.30)	0.0328
COPD			
No	237 (96.73%)	1.0	
Yes	8 (3.27%)	4.14 (0.94, 18.22)	0.0602
Hypertension			
No	193 (78.78%)	1.0	
Yes	52 (21.22%)	3.94 (1.82, 8.53)	0.0005
Diabetes			
No	222 (90.61%)	1.0	
Yes	23 (9.39%)	3.30 (1.24, 8.77)	0.0168
CHD			
No	227 (92.65%)	1.0	
Yes	18 (7.35%)	6.46 (2.33, 17.90)	0.0003
Carcinoma			
No	236 (96.33%)	1.0	
Yes	9 (3.67%)	1.89 (0.38, 9.51)	0.4404
CLD			
No	238 (97.14%)	1.0	
Yes	7 (2.86%)	2.67 (0.50, 14.37)	0.2525
HIV infection			
No	243 (99.18%)	1.0	
Yes	2 (0.82%)	-*	0.9894
Smoking			
No	235 (95.92%)	1.0	
Yes	10 (4.08%)	2.93 (0.72, 11.94)	0.1341
Heart rate, bpm	86.59 ± 15.37	1.01 (0.99, 1.03)	0.3044
MAP, mmHg	90.86 ± 9.94	0.96 (0.92, 0.99)	0.0245
Respiratory rate, bpm			
< 30	236 (96.72%)	1.0	
≥ 30	8 (3.28%)	7.43 (1.76, 31.38)	0.0064
Neutrophil, 10 ⁹ /L	4.09 ± 3.97	1.34 (1.19, 1.50)	<0.0001
Lymphocyte, 10 ⁹ /L	0.98 ± 0.57	0.58 (0.26, 1.32)	0.1979
Hemoglobin, G/L	127.52 ± 18.78	0.98 (0.96, 1.00)	0.0504
Platelet, 10 ⁹ /L	181.56 ± 70.01	0.99 (0.99, 1.00)	0.0507
ALT, U/L	30.48 ± 29.33	1.01 (1.00, 1.02)	0.0094
Creatinine, μmol/L	86.46 ± 109.60	1.01 (1.00, 1.01)	0.0177
PT, sec	12.88 ± 1.34	1.30 (1.01, 1.67)	0.0448
D-dimer, ng/mL	1102.17 ± 4050.14	1.00 (1.00, 1.00)	0.1123
C-reactive protein, mg/L	45.77 ± 57.85	1.02 (1.01, 1.03)	<0.0001
Procalcitonin, ng/mL			
<0.1	179 (76.17%)	1.0	
≥ 0.1, <0.5	35 (14.89%)	66.37 (14.14, 311.53)	<0.0001
≥ 0.5, <1	10 (4.26%)	206.50 (29.61, 1440.03)	<0.0001
≥ 1	11 (4.68%)	398.25 (50.19, 3160.05)	<0.0001

Data are mean ± SD, n (%), n/N (%), or median (IQR).

BMI = Body mass index. COPD = chronic obstructive pulmonary disease. CHD = coronary heart disease; CLD = chronic liver disease. MAP = mean arterial pressure. ALT = alanine transaminase. PT = prothrombin time.

* The model failed because of the small sample size.

Table 3

Risk association between baseline NLR and in-hospital death.

	Unadjusted Odds ratio (95% CIs)	P value	Model 1 ^a Odds ratio (95% CIs)	P value	Model 2 ^b Odds ratio (95% CIs)	P value
NLR	1.10 (1.05, 1.14)	<0.0001	1.09 (1.03, 1.14)	0.0013	1.08 (1.01, 1.14)	0.0147
Tertiles NLR						
Tertile 1	1.0		1.0		1.0	
Tertile 2	2.63 (0.50, 13.97)	0.2560	1.71 (0.14, 21.38)	0.6768	1.52 (0.09, 25.08)	0.7700
Tertile 3	18.57 (4.24, 81.44)	0.0001	16.61 (1.58, 174.66)	0.0192	16.04 (1.14, 224.95)	0.0395

^a Model 1 was adjusted for age, sex, body mass index, history of Hypertension, history of chronic liver disease, history of HIV infection, history of chronic obstructive pulmonary disease, smoking status.^b Model 2 was adjusted for age, sex, body mass index, history of Hypertension, history of chronic liver disease, history of HIV infection, history of chronic obstructive pulmonary disease, smoking status, respiratory rate, alanine transaminase, creatinine, prothrombin time, D-dimer.

Table 4

Associations between baseline blood cell counts in the blood routine test and the in-hospital death.

	Unadjusted Odds ratio (95% CIs)	P value	Model 1 ^a Odds ratio (95% CIs)	P value	Model 2 ^b Odds ratio (95% CIs)	P value
Neutrophil, 10 ⁹ /L	1.34 (1.19, 1.50)	<0.0001	1.26 (1.08, 1.47)	0.0030	1.30 (1.05, 1.60)	0.0139
Lymphocyte, 10 ⁹ /L	0.58 (0.26, 1.32)	0.1979	0.81 (0.37, 1.78)	0.6009	0.86 (0.34, 2.15)	0.7431
Monocyte, 10 ⁹ /L	6.92 (2.01, 23.84)	0.0022	2.55 (0.47, 13.80)	0.2788	0.78 (0.04, 13.47)	0.8617
Red blood cells, 10 ¹² /L	0.60 (0.34, 1.06)	0.0800	0.84 (0.28, 2.50)	0.7553	0.48 (0.14, 1.70)	0.2576
Platelet, 10 ⁹ /L	0.99 (0.99, 1.00)	0.0507	0.99 (0.98, 1.00)	0.0428	0.99 (0.98, 1.00)	0.1609

^a Model 1 was adjusted for age, sex, body mass index, history of Hypertension, history of chronic liver disease, history of HIV infection, history of chronic obstructive pulmonary disease, smoking status.

^b Model 2 was adjusted for age, sex, body mass index, history of Hypertension, history of chronic liver disease, history of HIV infection, history of chronic obstructive pulmonary disease, smoking status, respiratory rate, alanine transaminase, creatinine, prothrombin time, D-dimer.

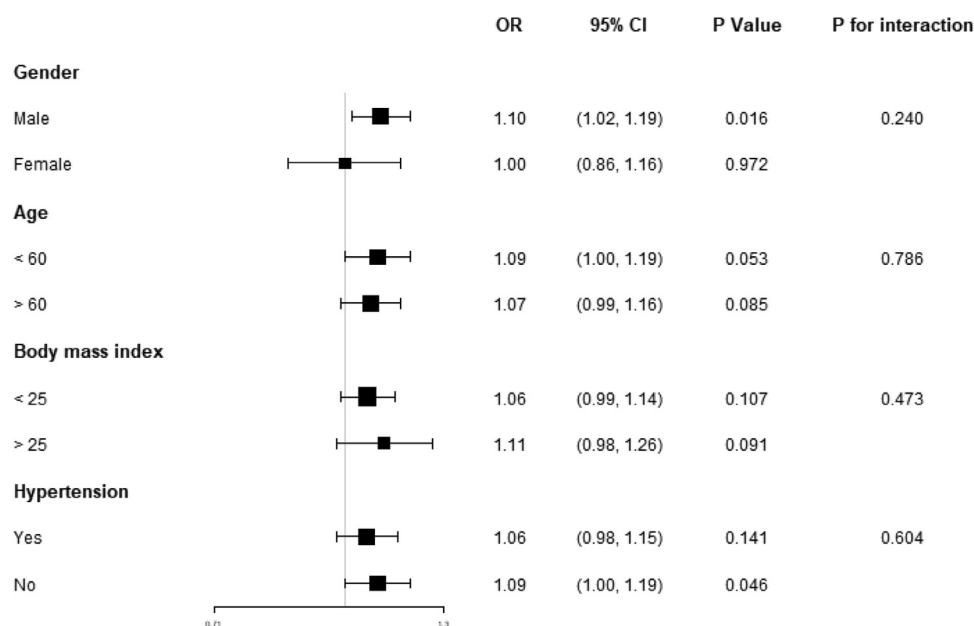


Fig. 2. Risk associations between NLR as a continuous variable and in-hospital death in subgroups of gender, age, body mass index and history of hypertension. Data were adjusted for age, sex, body mass index, history of Hypertension, history of chronic liver disease, history of HIV infection, history of chronic obstructive pulmonary disease, smoking status, respiratory rate, alanine transaminase, creatinine, prothrombin time, D-dimer.

severity.^{6,20} These findings are consistent with our results. Furthermore, patients with severe virus infection are more likely to co-infected with bacteria due to low immune functions, which would be another possible reason to explain the increased level of neutrophils, C-reactive protein and procalcitonin shown in our study.

The results of this study have several clinical implications and strengths. Since NLR could be quickly calculated based on a blood routine test on admission, clinicians may identify high risk COVID-19 patients at an early stage. Thus, treatments can be modified accordingly to reduce the in-hospital death. As this is an observational study and susceptible to various confounders. We adopted strict methods of statistical adjustment to minimize potential confounding. In addition, we tested the robustness of the results by repeating the analyses with tertiles of the NLR and in different subgroups of gender, age, body mass index and history of hypertension.

There are some limitations that should be noted meanwhile. First, the number of observed events is to some extent small which limits the statistical power of this explorative study. However, the sample size of this research is sufficient to draw a conclusion. Statistical analyses with tertiles of the NLR and in subgroups have ensured the reliability of the results. Second, since all subjects in our study were hospitalized Chinese patients diagnosed with

COVID-19, results of this study might not directly be applied to other ethnicities. Third, although we have adjusted for multiple potential confounders, residual and unmeasured confounding might not be fully considered.

In conclusion, this retrospective cohort study performed in the Chinese population revealed that the NLR is an independent risk factor for the in-hospital mortality. Further researches are needed to confirm our findings in other cohorts and to compare the predictive ability of baseline NLR and the change in NLR under treatments.

Declaration of Competing Interest

The authors state that they have no conflicts of interest to disclosure.

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