Neutrophil-to-Lymphocyte Ratio on Admission Predicts In-hospital Mortality in Patients with COVID-19

Jin Hu

Huazhong University of Science and Technology <https://orcid.org/0000-0002-7773-9191>

Jun Zhou

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Fang Dong

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Jie Tan

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Shuntao Wang

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Zhi Li

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Ximeng Zhang

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Huiqiong Zhang

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Jie Ming

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology

Tao Huang (✉ huangtaowh@163.com)

Department of Breast and Thyroid Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology <https://orcid.org/0000-0003-2130-8621>

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Abstract

Background: A novel coronavirus caused an outbreak of acute infectious pneumonia are spreading over the globe. However, studies predicting prognosis are limited. We predicted outcomes of patients with coronavirus disease 2019 (COVID-19) using the neutrophil-to-lymphocyte ratio (NLR) on admission.

Methods: We retrospectively analyzed the characteristics of COVID-19 patients diagnosed from February 6 to March 1. The outcomes, including the occurrence of in-hospital mortality, acute kidney injury (AKI), and endotracheal intubation (ETI), were recorded. The relationships of neutrophils, lymphocytes, C-reactive protein, lactate dehydrogenase, and NLR with outcomes were assessed using multivariate regression model. *P*-values for trends across quartiles of NLR was examined.

Results: A total of 182 patients were included. 37 (20.3%) patients died during the hospitalization, 41 (22.5%) developed AKI, and 36 (19.8%) received ETI. The NLR had a superior predictive performance than others. Using an NLR cutoff of 11.4, the area under the curves (AUC) were 0.766 for in-hospital mortality, 0.755 for AKI, and 0.733 for ETI. In multivariate analysis, NLR >11.4 was further identified as an independent prognostic factor. Following stratification with quartiles of NLR, a positive trend between the increasing quartiles of NLR and the three outcomes were observed (*p*-values for trends across quartiles were 0.043, <0.001, and 0.041, respectively). The multivariate adjusted odds ratio (OR) in the highest quartile vs. the lowest quartile were 5.738 for mortality, 25.307 for AKI, and 5.136 for ETI.

Conclusions: Increasing NLR obtained on admission is a powerful predictor for inpatient mortality, AKI, and ETI in COVID-19 patients.

Background

In December 2019, the coronavirus disease 2019 (COVID-19), previously known as the 2019-nCoV, caused an outbreak of an acute infectious pneumonia. [1] The World Health Organization (WHO) reported that the novel coronavirus are spreading over the globe, with more than 15 million confirmed patients and 600,000 deaths as of July 23, 2020.[2]

The primary aims of clinicians according to the guidelines for the diagnosis and treatment of COVID-19 [3] include strengthening the early diagnosis and treatment of the disease, improving the cure rate, and reducing mortality. These guidelines also define the characteristics of clinical indicators that may be used to predict the early stages of infection, as follows: 1) lymphocyte levels that increase progressively; 2) inflammatory factor (interleukin 6, C-reactive protein [CRP]) levels that increase progressively; 3) serum lactic acid levels that increase progressively; 4) lung lesions that progress rapidly in the short term. In addition, another rapid advice guideline [4] states that close attention should be paid to cases where the absolute level of lymphocytes is under $0.8 \times 10^9/L$.

COVID-19 patients have been reported to have a high incidence of organ dysfunction [5, 6], endotracheal intubation (ETI) [7–10], and in-hospital mortality [11]. Wang et al. [7] found that patients admitted to the

intensive care unit (ICU) had a higher level of the white blood cells (WBC), neutrophils, and lactate dehydrogenase (LDH), as well as lower levels of lymphocytes, compared with those not admitted to ICU. The neutrophil-to-lymphocyte ratio (NLR) is commonly used to explore the involvement of viruses (such as the hepatitis B virus [12], and AIV-H7N9 [13]) in the prognosis of infected patients. However, to date, prognosis prediction has limited study of the disease. The use of a simple and easily available parameter on admission is essential to obtain a rapid prediction of disease prognosis.

The purpose of this study was to explore the effectiveness of the NLR taken within 24 h after admission to predict the outcomes of COVID-19 patients, including in-hospital mortality, acute kidney failure (AKI), and ETI.

Methods

Study population

We retrospectively analyzed 252 consecutive patients from the Wuhan Union Hospital, which was converted to a designated hospital for COVID-19 patients. All the patients were diagnosed with laboratory-confirmed COVID-19 and admitted to the hospital from February 6th to March 1st. Patients were excluded when their outcome records, neutrophils count and leucocytes count on admission, or body mass index (BMI) were not available. (Fig. 1)

Demographic and clinical features

The demographic parameters included age, sex, BMI. Symptoms and signs of patients on admission included fever, dry cough, dyspnea, chest tightness/chest pain, respiratory rate, fatigue, headache, diarrhea, and heart rate. The comorbidities included hypertension, chronic heart disease (CHD), and diabetes. Hospital laboratory values at admission included WBC ($\times 10^9/L$), neutrophils ($\times 10^9/L$), leucocytes ($\times 10^9/L$), hemoglobin (HGB, g/L), CRP (mg/dL), serum albumin (ALB, g/L), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), LDH (U/L), blood urea nitrogen (BUN, mmol/L), serum creatinine (SCr, $\mu\text{mol/L}$). The primary clinical outcome for the series was in-hospital mortality, and the secondary outcomes were AKI and ETI.

Statistical analysis

Continuous data were presented as means and standard derivation (SD). Categorical variables were reported as frequency. Mann-Whitney U test and student's t-test were used to evaluate the differences of baseline characteristics between groups. Multiple group comparisons were performed using the Chi-square test for categorical variables and the Kruskal-Wallis test for continuous data.

The diagnostic performance of NLR, neutrophil, lymphocyte, CRP, and LDH were evaluated by receiver operating characteristic (ROC) curves. The area under the curve (AUC) was then estimated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Univariable and age-, BMI-, and sex-adjusted were conducted using a logistic regression model. To eliminate confounding factors, multivariate analysis was performed. Odds ratios (OR) were showed with a 95% confidence interval (CI). All statistical analyses were performed utilizing SPSS statistical software (version 22.0; IBM Corporation, Armonk, NY, USA), and $P < 0.05$ was statistically significant.

The NLR of cut-off point with the maximum Youden Index was used as the optimal value. Neutrophilia was defined as a more than $7.0 \times 10^9/L$ count. Lymphocytopenia was defined as a less than $1.0 \times 10^9/L$ count. Quartiles of NLR: $Q1 \leq 2.60$; $2.6 < Q2 \leq 5.7$; $5.7 < Q3 \leq 13.2$; and $Q4, > 13.2$. In the regression model, we used the quartile rank as a continuous parameter to test linear risk trends. The estimated log-survival graph was utilized to proportional to OR.

Results

Patient characteristics

We included 182 patients with a median age of 65 years. 54.9% (100/182) of the patients were male. In-hospital mortality was 20.3% in this cohort. The mean hospital duration was 24.39 days. The incidence of organ dysfunction was 1.1% for an acute gastrointestinal bleeding (GIB), 22.5% for AKI, and 58.8% for an acute liver injury.

The level of NLR, neutrophil, lymphocyte, CRP, and LDH on admission

The mean NLR, neutrophil, lymphocyte, CRP, and LDH in deceased patients were 16.71 ± 11.94 , 8.69 ± 3.95 , 1.24 ± 0.43 , 83.48 ± 50.41 , and 1295.44 ± 4749.47 ; and in surviving patients were 9.13 ± 18.26 , 5.91 ± 4.66 , 1.49 ± 0.50 , 43.17 ± 46.19 , and 308.29 ± 181.07 , respectively (all $P < 0.02$). Patients who developed AKI showed higher levels of NLR ($P = 0.017$), neutrophils ($P = 0.019$), CRP ($P = 0.035$), and LDH ($P = 0.035$), and lower lymphocytes ($P = 0.005$) than that of patients without AKI. Compared to patients not receiving ETI, patients receiving ETI showed significant differences in neutrophils ($P < 0.001$), lymphocytes ($P = 0.004$), CRP ($P < 0.001$), and LDH ($P = 0.013$), but not NLR ($P = 0.058$).

Predictive value of NLR, neutrophil, lymphocyte, CRP, and LDH

ROC analysis was performed to assess the diagnostic performance of NLR, neutrophil, lymphocyte, CRP, and LDH (Fig. 2) NLR had the largest AUC, while they had similar predictive powers for in-hospital mortality (AUC 0.766 vs. AUC 0.728 vs. AUC 0.720 vs. AUC 0.738 vs. AUC 0.752; $P > 0.05$) and ETI (AUC 0.733 vs. AUC 0.738 vs. AUC 0.704 vs. AUC 0.778 vs. AUC 0.751, $P > 0.05$). However, NLR (AUC 0.755) was found to have a better predictive power in AKI than those exhibited by neutrophils (AUC 0.676), lymphocytes (AUC 0.685), CRP (AUC 0.637), and LDH (AUC 0.682) ($P < 0.05$).

The primary clinical outcome in this entire cohort was in-hospital mortality. The best cutoff values for in-hospital mortality were 11.4, 49 mg/dL, and 480 U/L for NLR, CRP and LDH, respectively. Using a cutoff value of 11.4, the sensitivity of NLR for the prediction of in-hospital mortality was 70.3%, the specificity was 79.3%, the PPV was 46.4%, and the NPV was 91.3%. For patients with AKI, the sensitivity was 65.9%, the specificity was 79.4%, the PPV was 48.2%, and the NPV was 88.9%. For patients requiring ETI, the sensitivity, specificity, PPV, and NPV were 69.4%, 78.8%, 44.6%, and 91.3%, respectively.

Association between NLR, neutrophil, lymphocyte, CRP, and LDH and outcomes

Demographic and clinical characteristics of patients according to NLR levels have been shown in Table 1. The case group (NLR > 11.4) had more male patients than the control group (NLR ≤ 11.4; $P = 0.001$). There were no difference in age and BMI between groups. The significant difference was seen in comorbidities (only hypertension, but not in CHD or diabetes). In addition, patients with NLR > 11.4 had higher levels of CRP, ALB, LDH, and BUN. The incidence of in-hospital mortality, AKI, and ETI were 46.4%, 48.2%, and 44.6% in the case group, and 8.7%, 11.2%, and 8.7% in the control group, respectively (all $P < 0.001$).

Table 1
Clinical characteristics of patients according to NLR (cutoff value: 11.4).

Variables	NLR ≤ 11.4	NLR > 11.4	P
Age, years	62.37 ± 14.89	65.13 ± 12.25	0.227
Sex (male, %)	59 (46.8)	41 (73.2)	0.001
BMI	23.62 ± 2.79	23.68 ± 3.47	0.904
Symptoms and signs			
Fever	102 (81.0)	49 (87.5)	0.278
Dry cough	87 (69.0)	37 (66.1)	0.691
Dyspnea	58 (46.0)	35 (62.5)	0.040
Chest tightness / chest pain	46 (36.8)	21 (37.5)	0.928
Respiratory rate ≥ 30 bpm	36 (28.6)	18 (32.1)	0.626
SpO2	96.37 ± 3.01	92.48 ± 16.31	< 0.001
Fatigue	69 (54.8)	35 (62.5)	0.330
Headache	11 (8.7)	3 (5.4)	0.431
Diarrhea	22 (17.5)	5 (8.9)	0.135
Heart rate, beats per min	90.64 ± 16.31	92.82 ± 18.85	0.428
MAP, mmHg	97.63 ± 13.51	97.22 ± 12.79	0.850
In-hospital mortality (n, %)	11 (8.7)	26 (46.4)	< 0.001
ETI (n, %)	11 (8.7)	25 (44.6)	< 0.001
Duration in hospital	23.75 ± 9.38	25.65 ± 9.39	0.235
Acute organ injury (n, %)			
Acute GIB	1 (0.8)	1 (1.8)	0.522 [#]
AKI	14 (11.2)	27 (48.2)	< 0.001
Acute liver injury	64 (50.8)	43 (76.8)	0.001
Past medical history (n, %)			
Hypertension	49 (38.9)	30 (53.6)	0.046
CHD	17 (13.5)	11 (19.6)	0.199
Diabetes	23 (18.3)	8 (14.3)	0.334

Variables	NLR ≤ 11.4	NLR > 11.4	P
Laboratory test results			
WBC, ×10 ⁹ /L	8.39 ± 13.77	10.71 ± 3.80	0.271
HGB, g/L	116.67 ± 22.45	111.57 ± 23.34	0.164
CRP, mg/dL	38.87 ± 42.18	79.68 ± 53.84	< 0.001
Total protein, g/L	63.04 ± 6.43	61.46 ± 9.21	0.185
ALB, g/L	31.93 ± 6.00	26.32 ± 5.36	< 0.001
AST, U/L	35.71 ± 20.19	348.30 ± 2109.85	0.097
ALT, U/L	47.14 ± 38.46	231.07 ± 1222.32	0.092
LDH, U/L	294.72 ± 179.15	985.51 ± 3849.13	0.045
BUN, mmol/L	6.93 ± 8.47	11.12 ± 8.60	0.002
SCr, umol/L	86.32 ± 159.24	110.26 ± 135.79	0.330
NLR = neutrophil to lymphocyte ratio; BMI = body mass index; MAP = mean arterial pressure; SpO ₂ = oxygen saturation; ETI = endotracheal intubation; GIB = gastrointestinal bleeding; AKI = acute kidney injury; CHD = chronic heart disease; WBC = white blood cell; HGB = hemoglobin; CRP = C reactive protein; ALB = serum albumin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; BUN = blood urea nitrogen; SCr = serum creatinine. # = Fisher Test.			

Table 2 shows the OR and 95% CI for outcomes according to the NLR (cutoff: 11.4), neutrophilia, lymphocytopenia, CRP (cutoff: 49 mg/dL), and LDH (cutoff: 480 U/L). In the univariate analysis, all variables were significantly related to outcomes. These differences remained significant after adjustment for age, BMI, and sex. In multivariate analyses, for patients with NLR > 11.4, the differences remained statistically significant for in-hospital mortality (OR 6.576, 95% CI 2.184–19.794; $P = 0.001$), AKI (OR 5.411, 95% CI, 2.381–12.294; $P < 0.001$), and ETI (OR 3.959, 95% CI, 1.454–10.780; $P = 0.007$). However, neutrophil and lymphocyte counts were not associated with clinical outcomes. CRP and LDH continued to have some predictive power for the incidence of the in-hospital mortality.

Table 2
Risk of in-hospital mortality, AKI, ETI by NLR > 11.4, neutrophilia, lymphocytopenia, CRP, LDH.

Variables	In-hospital mortality	P	AKI	P	ETI	P
NLR > 11.4 (presence vs absence)						
Unadjusted OR (95% CI)	9.061 (4.025–20.397)	< 0.001	7.382 (3.438–15.848)	< 0.001	8.431 (3.741–19.000)	< 0.001
Age-, BMI-, and sex-adjusted OR (95% CI)	7.366 (3.193–16.995)	< 0.001	7.382 (3.438–15.848)	< 0.001	8.431 (3.741–19.000)	< 0.001
Multivariate-adjusted OR (95% CI)*	6.576 (2.184–19.794)	0.001	5.411 (2.381–12.294)	< 0.001	3.959 (1.454–10.780)	0.007
Neutrophilia (presence vs absence)						
Unadjusted OR (95% CI)	3.990 (1.875–8.492)	< 0.001	2.612 (1.283–5.319)	0.008	4.746 (2.166–10.401)	< 0.001
Age-, BMI-, and sex-adjusted OR (95% CI)	3.000 (1.343–6.702)	0.007	2.491 (1.167–5.321)	0.018	4.421 (1.917–10.196)	< 0.001
Multivariate-adjusted OR (95% CI)*	1.832 (0.460–7.301)	0.391	2.323 (0.724–7.452)	0.156	3.842 (1.308–11.289)	0.014
Lymphocytopenia (presence vs absence)						
Unadjusted OR (95% CI)	2.943 (1.297–6.675)	0.010	3.013 (1.373–6.612)	0.006	3.358 (1.435–7.861)	0.005
Age-, BMI-, and sex-adjusted OR (95% CI)	2.810 (1.194–6.612)	0.018	2.988 (1.338–6.674)	0.008	3.744 (1.538–9.115)	0.004
Multivariate-adjusted OR (95% CI)*	1.400 (0.380–5.157)	0.613	3.074 (1.081–8.744)	0.035	2.387 (0.705–8.085)	0.162
CRP > 49 mg/dl (presence vs absence)						

Variables	In-hospital mortality	P	AKI	P	ETI	P
Unadjusted OR (95% CI)	7.102 (3.020–16.700)	< 0.001	2.317 (1.141–4.709)	0.020	5.588 (2.443–12.784)	< 0.001
Age, BMI, and sex-adjusted OR (95% CI)	6.787 (2.771–16.626)	< 0.001	2.153 (1.044–4.443)	0.038	4.934 (2.129–11.436)	< 0.001
Multivariate-adjusted OR (95% CI)*	3.970 (1.071–13.989)	0.039	0.880 (0.326–2.375)	0.800	2.211 (0.709–6.900)	0.172
LDH > 480 U/L (presence vs absence)						
Unadjusted OR (95% CI)	9.412 (4.106–21.574)	< 0.001	3.068 (1.404–6.706)	0.005	4.227 (1.883–9.489)	< 0.001
Age, BMI, and sex-adjusted OR (95% CI)	8.183 (3.381–19.807)	< 0.001	2.782 (1.236–6.262)	0.013	3.565 (1.537–8.267)	0.003
Multivariate-adjusted OR (95% CI)*	5.799 (1.592–21.123)	0.008	1.288 (0.424–3.918)	0.655	1.101 (0.352–3.446)	0.869
Cox proportional hazard models were used to assess OR and 95% CI.						
*Multivariate analysis: adjustment for age, sex, BMI, HGB, Total protein, ALB, AST, ALT, BUN, SCr, hypertension, CHD, diabetes, AKI, ETI, acute liver injury.						
CI = confidence interval; OR = odds ratio; NLR = neutrophil to lymphocyte ratio; AKI = acute kidney injury; ETI = endotracheal intubation; BMI = body mass index; ETI = endotracheal intubation; GIB = gastrointestinal bleeding; CHD = chronic heart disease; WBC = white blood cell; HGB = hemoglobin; CRP = C reactive protein; ALB = serum albumin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; BUN = blood urea nitrogen; SCr = serum creatinine.						

Table 3. Clinical features of patients by quartiles of NLR.

Variables	Quartiles of NLR				P
	Q1 (≤ 2.60)	Q2 (2.6–5.7)	Q3 (5.7–13.2)	Q4 (> 13.2)	
Age, years	58.78 ± 14.45	63.89 ± 15.10	64.57 ± 13.71	65.60 ± 12.71	0.100
sex (male, %)	22 (48.9)	22 (47.8)	24 (52.2)	32 (71.1)	0.090
BMI	24.01 ± 2.62	23.78 ± 3.01	23.06 ± 2.70	23.73 ± 3.61	0.468

Variables	In-hospital mortality	P	AKI	P	ETI	P
Symptoms and signs						
Fever	37 (82.2)	36 (78.3)	39 (84.8)	39 (86.7)	0.731	
Dry cough	36 (80.0)	29 (63.0)	31 (67.4)	28 (62.2)	0.240	
Dyspnea	16 (35.6)	23 (50.0)	26 (56.5)	28 (62.2)	0.067	
Chest tightness/chest pain	15 (33.3)	15 (32.6)	17 (37.0)	20 (44.4)	0.662	
Respiratory rate $\geq$ 30 bpm	8 (17.8)	14 (30.4)	18 (39.1)	14 (31.1)	0.166	
SpO2	96.87 $\pm$ 2.19	96.11 $\pm$ 3.20	94.15 $\pm$ 7.62	93.58 $\pm$ 5.71	0.007	
Fatigue	20 (44.4)	27 (58.7)	30 (65.2)	27 (60.0)	0.223	
Headache	4 (8.9)	4 (8.7)	5 (10.9)	1 (2.2)	0.493	
Diarrhea	7 (15.6)	9 (19.6)	6 (13.0)	5 (11.1)	0.695	
Heart rate, beats per min	92.96 $\pm$ 14.95	89.98 $\pm$ 17.84	88.44 $\pm$ 15.64	93.96 $\pm$ 19.61	0.383	
MAP, mmHg	94.16 $\pm$ 11.14	99.71 $\pm$ 14.90	99.15 $\pm$ 12.89	96.92 $\pm$ 13.51	0.176	
In-hospital mortality (n, %)	3 (6.7)	5 (10.9)	9 (19.6)	20 (44.4)	< 0.001	
ETI (n, %)	4 (8.9)	4 (8.7)	10 (21.7)	18 (40.0)	< 0.001	
Duration in hospital	19.81 $\pm$ 9.00	24.13 $\pm$ 9.59	26.61 $\pm$ 8.79	26.55 $\pm$ 8.95	0.004	
Acute organ injury (n, %)						
Acute GIB	0	0	1 (2.2)	1 (2.2)	0.568 [#]	
AKI	3 (6.7)	7 (15.2)	10 (22.2)	21 (46.7)	< 0.001	
Acute liver injury	20 (44.4)	23 (50.0)	31 (67.4)	33 (73.3)	0.014	
Past medical history (n, %)						
Hypertension	15 (33.3)	17 (37.0)	22 (47.8)	25 (55.6)	0.127	
CHD	4 (8.9)	8 (17.4)	6 (13.0)	10 (22.2)	0.333	

Variables	In-hospital mortality	P	AKI	P	ETI	P
Diabetes	9 (20.0)	8 (17.4)	7 (15.2)	7 (15.6)	0.927	
Laboratory test results						
WBC, × 10 ⁹ /L	9.82 ± 22.11	7.26 ± 6.31	8.44 ± 3.09	10.96 ± 3.73	0.460	
HGB, g/L	121.31 ± 17.80	111.50 ± 26.02	118.61 ± 24.58	108.98 ± 20.11	0.030	
CRP, mg/dL	21.77 ± 36.97	44.46 ± 46.96	57.99 ± 40.95	81.24 ± 54.17	< 0.001	
Total protein, g/L	63.62 ± 6.42	63.12 ± 7.58	61.82 ± 6.38	61.66 ± 9.03	0.514	
ALB, g/L	34.81 ± 5.95	30.69 ± 5.51	28.92 ± 5.17	26.41 ± 5.82	< 0.001	
AST, U/L	31.62 ± 14.82	36.52 ± 24.80	64.96 ± 114.73	389.09 ± 2353.79	0.378	
ALT, U/L	41.07 ± 32.55	46.65 ± 37.32	65.76 ± 62.69	263.58 ± 1363.83	0.345	
LDH, U/L	275.02 ± 221.73	283.98 ± 164.21	397.39 ± 253.16	1082.25 ± 4303.20	0.228	
BUN, mmol/L	7.09 ± 9.22	5.58 ± 3.47	8.56 ± 3.47	11.70 ± 9.30	0.006	
SCr, umol/L	70.42 ± 33.55	78.47 ± 42.92	112.09 ± 258.74	113.70 ± 150.18	0.402	

NLR = neutrophil to lymphocyte ratio; BMI = body mass index; MAP = mean arterial pressure; SpO₂ = oxygen saturation; ETI = endotracheal intubation; AKI = acute kidney injury; CHD = chronic heart disease; WBC = white blood cell; HGB = hemoglobin; CRP = C reactive protein; ALB = serum albumin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; LDH = lactate dehydrogenase; BUN = blood urea nitrogen; SCr = serum creatinine. # = Fisher Test.

Table 4. OR for in-hospital mortality, AKI, and ETI by NLR quartile.

Variables	Quartiles of NLR				P value for trend
	Q1 (≤ 2.60)	Q2 (2.6–5.7)	Q3 (5.7–13.2)	Q4 (> 13.2)	
In-hospital mortality (n, %)	3 (6.7)	5 (10.9)	9 (19.6)	20 (44.4)	

Variables	In-hospital mortality	P	AKI	P	ETI	P
Unadjusted OR (95% CI)	1.00 (reference)	1.707 (0.383–7.611)	3.405 (0.857–13.527)	11.20 (3.02–41.53)	< 0.001	
P value		0.483	0.082	< 0.001		
Age-, BMI-, and sex-adjusted OR (95% CI)	1.00 (reference)	1.696 (0.365–7.874)	3.381 (0.812–14.083)	9.061 (2.335–35.171)	0.002	
P value		0.500	0.094	0.001		
Multivariate-adjusted OR (95% CI)*	1.00 (reference)	1.031 (0.196–5.418)	1.916 (0.387–9.494)	5.738 (1.190–27.666)	0.043	
P value		0.972	0.426	0.030		
Acute kidney injury (n, %)	3 (6.7)	7 (15.2)	10 (21.7)	21 (46.7)		
Unadjusted OR (95% CI)	1.00 (reference)	2.513 (0.607–10.406)	3.889 (0.993–15.225)	12.250 (3.307–45.380)	< 0.001	
P value		0.204	0.051	0.0002		
Age-, BMI-, and sex-adjusted OR (95% CI)	1.00 (reference)	2.592 (0.615–10.922)	4.251 (1.062–17.016)	11.746 (3.078–44.826)	< 0.001	
P value		0.194	0.041	< 0.001		
Multivariate-adjusted OR (95% CI)*	1.00 (reference)	3.576 (0.757–16.88)	4.287 (0.910–20.185)	25.307 (5.090–125.817)	< 0.001	
P value		0.108	0.066	< 0.001		
ETI (n, %)	8 (8.9)	4 (8.7)	10 (21.7)	18 (40.0)		
Unadjusted OR (95% CI)	1.00 (reference)	0.976 (0.229–4.166)	2.847 (0.822–9.868)	6.833 (2.084–22.402)	< 0.001	
P value		0.974	0.099	0.002		
Age-, BMI-, and sex-adjusted OR (95% CI)	1.00 (reference)	1.142 (0.260–5.016)	3.471 (0.955–12.607)	7.506 (2.154–26.157)	0.002	
P value		0.861	0.059	0.002		

Variables	In-hospital mortality	P	AKI	P	ETI	P
Multivariate-adjusted OR (95% CI)*	1.00 (reference)	0.762 (0.141–4.129)	2.366 (0.526–10.655)	5.136 (1.115–23.654)	0.041	
P value		0.752	0.262	0.036		
Cox proportional hazard models were used to assess OR and 95% CI. *Multivariate analysis: adjustment for age, sex, BMI, HGB, Total protein, ALB, AST, ALT, BUN, SCr, hypertension, CHD, diabetes, AKI, ETI, acute liver injury. CI = confidence interval; OR = odds ratio; NLR = neutrophil to lymphocyte ratio; BMI = body mass index; AKI = acute kidney injury; ETI = endotracheal intubation; HGB = hemoglobin; ALB = serum albumin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; SCr = serum creatinine; CHD = chronic heart disease.						

As shown in **Table 3**, the clinical characteristics of 182 patients were analyzed according to the quartiles of NLR. The duration of hospital stay, the frequency of acute liver injury, and the CRP and BUN was significantly associated with increasing NLR quartiles. In contrast, the level of HGB and ALB was related to decreasing NLR quartiles. Of note, the incidence of in-hospital mortality ($P < 0.001$), AKI ($P < 0.001$), and ETI ($P < 0.001$) increased significantly with the increase of quartile.

Table 4 shows the OR and 95% CI for outcomes according to the quartiles of NLR (Q1 as reference). There appears to be a trend for an increasing incidence of in-hospital mortality, AKI and ETI with advancing NLR quartiles. The p -values for all the trends was $P < 0.01$. The difference remained significant after adjustment for age, BMI, and sex. In multivariable analysis, the p -value for the trends remained significant ($P = 0.043$ in in-hospital mortality, $P < 0.001$ in AKI, and $P = 0.041$ in ETI) after adjusting for confounding factors. For NLR (cutoff: 11.4), multivariate adjusted OR compared to Q4 and Q1 was 5.738 (95% CI 1.190-27.666; $P = 0.030$) for in-hospital mortality, 25.307 (95% CI 5.090-125.817; $P < 0.001$) for AKI, and 5.136 (95% CI 1.115–23.654; $P = 0.036$) for ETI, respectively.

Discussion

In the present study, we analyzed the involvement of NLR on admission with the incidence of in-hospital mortality, AKI, and ETI in patients with COVID-19. The results showed that higher NLR on admission was significantly associated with all poor outcomes present in this study, even after adjustment for potential confounding factors.

Huang et al. [14] was the first research group to report COVID-19 and found that COVID-19 was related to ICU admission with high mortality. Chen et al. [11] reported a relatively high mortality for COVID-19 of up to 14.1%, which was higher than that reported in previous studies [7, 15, 16]. However, by July 23, 2020, over 15 million cases of COVID-19 had been reported by WHO, from almost every country in the world. The number of deaths was over 600,000 with mortality as high as 4.1%. In our study, the total number of

deaths was 37, and the mortality was as high as 20.3%, which was higher than that of any research reported thus far. This was likely due to the large proportion of serious or critical patients admitted to Wuhan Union Hospital and the limitation of medical resources during the start of a disease outbreak.

Guan et al. [17] reported that, lymphocytopenia was present in over 80% of the patients on admission. In addition, Chen et al. [11] reported that compared with the recovered patients, non-survivors had a persistent and more severe lymphopenia. The WBC and neutrophil counts were also higher in non-survivors. [7] In our study, neutrophils and lymphocytes were associated with a prognosis in the primary outcome even after adjustment for age, BMI, and sex. However, these significant differences did not exist in the multivariable analysis. Although several guidelines suggest that lymphopenia may be associated with critical disease and even death. [3, 4]

Neutrophilia may be associated with cytokine storm caused by a viral invasion. [7] Lymphocytopenia is a significant feature of COVID-19 in critical patients. In 2005, Gu et al. [18] reported that it was the result of the destruction of lymphocytes caused by the destruction of cytoplasmic components after the targeted invasion of viral particles. Lymphocytopenia was also reported in critical patients infected with the MERS-CoV, which may be the result of the apoptosis of lymphocytes. [19, 20] A previous study suggested that the severity of lymphopenia reflects the severity of COVID-19. [6, 21] Organ dysfunction, including an acute renal injury, may be related to the direct effect of virus, hypoxia, and shock. The reason for this phenomenon could be that neutrophilia and lymphopenia were related to severe COVID-19 patients [22], but further study need to be performed.

In recent decades, several studies have reported on large differences in hematological components due to the systemic inflammatory response, which were subsequently used to predict the disease severity and outcomes. NLR, a simple, easily calculated and readily available parameter has been investigated for its use in some diseased states, including inflammatory conditions, cardiovascular disease, and carcinomas. [23–25] In recent years, several studies have reported that the use of NLR to evaluate associations between a viral [12, 13] involvement and prognosis of infected patients. There is reason to believe that it is reasonable to predict the prognosis of patients with novel coronavirus by NLR.

A recent study has implicated that NLR was an independent risk factor of the in-hospital mortality for COVID-19 patients.[26] Of note, the value of all variables were the baseline data of laboratory examinations. It is possible that therapeutic manipulations may rapidly influence the value of NLR. For COVID-19 patients with a high mortality, it is very important to predict the prognosis using commonly obtained laboratory data on admission within 24 h.

Our study has certain limitations. First, this study design was that of a retrospective study, such that more detailed therapeutic responses will be needed. Several patients developed disorders of consciousness upon admission, which may have resulted in the involuntary omission of patients information (in particular, a detailed medical history). Missing data can lead to a bias in results. Second, the lack of effective antivirals [27] and corticosteroid [28] use may have also contributed to the poor clinical outcomes observed in certain patients. Moreover, the case fatality ratio reported in our study is not

representative of the true mortality of COVID-19 patients, due to the large number of critically ill patients found in the Wuhan Union Hospital. Lastly, the interpretation of our findings may also be limited by the sample size.

Our research provides a preliminary insight into the identification of variables for the prediction of COVID-19 patient outcomes and serves as a basis for further detailed clinical and pathophysiological studies, which will also be necessary.

Conclusion

In conclusion, a higher NLR on admission is an ideal independent prognostic predictor for disease outcomes in COVID-19 patients. This study addresses the gaps in current knowledge of COVID-19 and contributes to improving the patients' outcomes and lowering the mortality.

Abbreviations

COVID-19 = Coronavirus disease 2019; WHO = World Health Organization; CRP = C reactive protein; ETI = endotracheal intubation; ICU = intensive care unit; WBC = white blood cell; LDH = lactate dehydrogenase; NLR = neutrophil to lymphocyte ratio; AKI = acute kidney injury; BMI = body mass index; CHD = chronic heart disease; HGB = hemoglobin; ALB = serum albumin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; BUN = blood urea nitrogen; SCr = serum creatinine; ROC = receiver operating characteristic; AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value; OR = odds ratios; CI = confidence interval; GIB = gastrointestinal bleeding.

Declarations

Ethics approval and consent to participate

Informed consent for individual patient was not obtained since all data were retrieved retrospectively from the laboratory test information system without additional blood samples or laboratory analysis. The study was approved by Union hospital Tongji Medical College, Huazhong University of Science and Technology Ethics Committee.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None

Authors' contributions

JH and TH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: TH and JM. Acquisition, analysis, or interpretation of data: FD, JT, STW, ZL, XMZ, and HQZ. Drafting of the manuscript: JH and JZ. Critical revision of the manuscript for important intellectual content: All authors. Supervision: TH and JM. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow diagram illustrating the selection of patients. COVID-19= coronavirus disease 2019; NLR= neutrophil to lymphocyte ratio; BMI= body mass index.

Figure 2

Receiver operated characteristic curve of NLR, Neutrophil, Lymphocyte, CRP, and LDH for the diagnosis of in-hospital mortality (A), AKI (B), and ETI (C). NLR= neu-trophil to lymphocyte ratio; CRP= C reactive protein; LDH= lactate dehydrogenase; AKI= acute kidney injury; ETI= endotracheal intubation.