An increased pretreatment neutrophil-to-lymphocyte ratio predicts severe novel coronavirus-infected pneumonia

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Abstract

Objective The aim of this study was to identify early warning signs for severe novel coronavirus-infected pneumonia (COVID-19).

Methods We retrospectively analyzed the clinical data of 90 patients with COVID-19 at the *Guanggu District* of Hubei Women and Children Medical and Healthcare Center comprising 60 mild cases and 30 severe cases. The demographic data, underlying diseases, clinical manifestations and laboratory blood test results were compared between the two groups. Logistic regression analysis was performed to identify the independent risk factors that predicted severe COVID-19. The receiver-operating characteristic (ROC) curve of independent risk factors was calculated, and the area under the curve (AUC) was used to evaluate the efficiency of the prediction of severe COVID-19.

Results The patients with mild and severe COVID-19 showed significant differences in terms of cancer incidence, age, pretreatment neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP) and the serum albumin (ALB) level ($P<0.05$). The severity of COVID-19 was correlated positively with the comorbidity of cancer, age, NLR, and CRP but was negatively correlated with the ALB level ($P<0.05$). Multivariate logistic regression analysis showed that the NLR and ALB level were independent risk factors for severe COVID-19 (OR=1.319, 95% CI: 1.043-1.669, P=0.021; OR=0.739, 95% CI: 0.616-0.886, P=0.001), with AUCs of 0.851 and 0.128, respectively. An NLR of 4.939 corresponded to the maximum joint sensitivity and specificity according to the ROC curve (0.700 and 0.917, respectively).

Conclusion An increased NLR can serve as an early warning sign of severe COVID-19.

1. Introduction

The outbreak of novel coronavirus (SARS-CoV-2)-induced pneumonia (COVID-19) is currently ongoing in many areas of the world (1-3) because of its strong infectivity and familial aggregation (4, 5). The World Health Organization (WHO) has declared the ongoing outbreak a global public health emergency. On 20 April 2020, data reported by the WHO showed that 2314621 cases were confirmed novel coronavirus infections, and 157847 individuals died in total (6). COVID-19 was divided into 4 types: mild, moderate, severe and critical, among which severe and critical cases have higher mortality, longer hospitalization time and more difficulty in clinical treatment. Early identification of warning signs of severe COVID-19 and timely intervention may help to reduce mortality, improve the cure rate and shorten the hospital stay duration.

It has been widely reported that the lymphocyte count is decreased in the early stage of this disease (7-9). We proposed that a blood lymphocyte-related index may be a potential predictor of prognosis. The neutrophil-to-lymphocyte ratio (NLR) is a widely used marker for the assessment of the prognosis of patients with pneumonia and cancer (10-12). An increase in the NLR indicates poor clinical prognosis. Whether the NLR is associated with the severity of COVID-19 is of considerable research interest. In this

study, we aimed to explore the independent risk factors for severe COVID-19 and confirm whether the pretreatment NLR could be an early warning sign for severe COVID-19.

2. Materials And Methods

2.1 Study design and patients

A retrospective study of 90 patients in our ward diagnosed with COVID-19 between February 10, 2020 and March 20, 2020 was designed and performed. Diagnosis and classification of COVID-19 was performed according to the new coronavirus pneumonia diagnosis and treatment plan (trial version 5) developed by the National Health Committee of the People's Republic of China (13). COVID-19 is divided into mild, moderate, severe and critical types. In our ward, COVID-19 cases mainly consist of moderate and severe type cases, while mild type and critical type cases are relatively few. Therefore, in our research, we defined mild and moderate as the mild group and severe and critical as the severe group. This study was approved by the Ethics Committee of *Guanggu District* of Hubei Women and Children Medical and Healthcare Center and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent before enrollment in this study. A total of 118 COVID-19 patients were initially enrolled in this retrospective study, 10 patients were excluded because their absolute lymphocyte count before treatment was not available, and 18 patients were excluded for lack of pretreatment coagulation markers. Pretreatment data were extracted from the medical records of patients from hospital computerized databases or from clinical charts by means of a questionnaire. The following information was included: demographics (age and sex); past history and clinical manifestations; pretreatment laboratory blood test results (such as white blood cell count, neutrophil count, lymphocyte count, coagulation markers, renal and liver function tests); vital signs; chest CT; and nucleic acid detection of novel coronavirus (nCov-19).

2.2 Statistical analysis

The NLR was calculated as the neutrophil count divided by the lymphocyte count. Normally distributed data were expressed as the mean ± standard deviation, and nonnormally distributed data were expressed as the median (interquartile range). Differences between two groups were evaluated using t-tests, chi-square tests or Mann-Whitney U tests. Correlation analysis of risk factors with severe COVID-19 was evaluated by Pearson correlation analysis or Spearman correlation analysis, as appropriate. Logistic regression was used to select independent risk factors. The selection of cutoff values of NLR was determined by receiver operating characteristic (ROC) curve analysis. All data were statistically analyzed using a commercially available statistical software package (SPSS 24.0; IBM Corp., Armonk, NY, USA). All tests were bilateral, and a *P*-value < 0.05 was considered statistically significant.

3. Results

3.1 Clinical characteristics

A total of 90 COVID-19 patients were enrolled in this retrospective study; 60 were diagnosed as mild or moderate (mild group), and 30 were diagnosed as severe or critical (severe group) on admission. The median age of the two groups was significantly different: the mild group was 63 years old, and the severe group was 75.5 years old (P=0.000). As shown in Table 1, there was no significant difference in gender or clinical symptoms between the two groups (P>0.05). No significant differences in hypertension, diabetes, or coronary heart disease were found between the two groups (P>0.05), but there were more patients with cancer in the severe group than in the mild group (P=0.008). The NLR and C-reactive protein in the severe group were significantly higher than those in the mild group, while albumin was significantly lower (Table 2).

3.2 Correlation analysis of risk factors with severe COVID-19

The correlation analysis of risk factors showed that age, cancer, NLR, CRP, and albumin were significantly correlated with severe COVID-19. Cancer, age, NLR and CRP were positively correlated with severe COVID-19, while albumin was negatively correlated with severe COVID-19 (Table 3).

3.3 Regression analysis of risk factors for severe COVID-19

As shown in Table 4, multivariate logistic regression analysis concluded that NLR and albumin were both independent risk factors for severe COVID-19 (Table 5).

3.4 ROC curve analysis of independent risk factors

ROC curve analysis established 4.939 as the cutoff point of NLR for severe COVID-19 with an area under the curve (AUC) of 0.851 (CI=0.762-0.940, P= 0.000) (Figure 1). The NLR of 4.939 corresponded to the maximum joint sensitivity and specificity on the ROC curve (70.0% sensitivity and 91.7% specificity). The AUC of albumin under the ROC curve was 0.128, suggesting poor discrimination of the model. Based on these results, we selected NLR > 4.939 as an early warning sign for severe COVID-19.

4. Discussion

COVID-19 has been prevalent in many countries in the world, and the number of deaths is rising daily. Identification of early warning signs for severe COVID-19 and timely intervention may become urgent issues.

The results of the present study showed that there were significant differences in age, cancer incidence, NLR, CRP and albumin between the severe COVID-19 patients and mild COVID-19 patients, and there was a positive correlation between age, cancer, NLR, CRP and severe COVID-19 (P < 0.05) and a negative correlation between albumin and severe COVID-19 (P < 0.05). In the multivariate analysis logistic regression model, significant independent predictors for severe COVID-19 included a high NLR (OR=1.319, 95% CI: 1.043-1.699, P = 0.021) and albumin level (OR=0.739, 95% CI: 0.616-0.886, P = 0.001), which was in accordance with previous studies (14-16). NLR and albumin, associated with inflammation and tumor burden, were also revealed to be significantly related to survival in previous studies (16-18). The AUC

calculated from the ROC curve was 0.851 (95% CI: 0.762-0.940), and the corresponding best cutoff value of NLR was 4.939, sensitivity was 0.700, and specificity was 0.917, which indicates high predictive value.

Neutrophils, important immune cells of the body, play the role of host defense and immune regulation when the body is invaded by infective agents (19). When neutrophils decrease significantly, the risk of infection increases significantly (20). Lymphocytes, the main effector cells of the human immune response, are closely related to the immunity and defense of the body; accordingly, there is a negative correlation between the number of lymphocytes and the degree of inflammation (21, 22). The NLR, the ratio of neutrophils to lymphocytes, is considered an important marker of the systemic inflammatory response, and more accurately reflects the balanced relationship between the severity of inflammatory reactions and the immune state (23, 24). It is believed that the inflammatory cytokine storm may be related to the progression of the disease (25-28). We speculate that there may be a significant correlation between the NLR and severe COVID-19. Huang et al. (8) reported that ICU patients had higher plasma levels of inflammatory cytokines such as IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1A and TNF-α than non-ICU patients, which reflected the obvious inflammatory reaction in severe and critical patients and was consistent with our results. An ambispective cohort study by Li et al. indicated that high cytokine levels, such as IL-2R, IL-6, IL-10, and TNF-α, were significantly associated with severe COVID-19 on admission (29).

At present, the reported risk factors for the severity of COVID-19 include older age, a longer wait for access to medical care, comorbidities, elevated proinflammatory cytokine levels, high LDH levels, and high procalcitonin and D-dimer levels (26, 29, 30). Most of the risk factors are not widely used because of their low sensitivity and difficulty in rapid evaluation. Therefore, there is an urgent need for simple and convenient predictive indicators to guide clinical practice. It is convenient in routine blood draws to obtain NLR, which has higher specificity and sensitivity for the early diagnosis of severe COVID-19.

In conclusion, the NLR at diagnosis was an independent risk factor for severe COVID-19 and may be an early warning sign for severe COVID-19 during clinical care. Further prospective studies with a large number of participants are necessary to validate the predictive role of the NLR in COVID-19 patients.

Declarations

Author Contributions

H Liao and B Shi developed the idea. X Wang contributed to the literature search and writing the manuscript. X Chen, C Zhou, D Jiao, P Fan, and Q Cui contributed to data collection. X Wang, D Jiang and H Huang contributed toward data analysis and revising the paper.

Compliance with ethical standards

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Conflict of Interest: The authors declare no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. .

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Tables

Table 1. Baseline characteristics of patients with 2019 novel coronavirus pneumonia

Variables	Mild group n = 60	Severe group n = 30	χ^2/Z	P
Age, years	63.000(46.000-71.000)	75.500(69.000-84.500)	-4.328	0.000
Gender				
Male	30	18	0.804	0.370
Female	30	12		
Comorbidities				
Hypertension	16	10	0.433	0.511
Diabetes	12	7	0.133	0.715
Coronary heart disease	3	6	3.472	0.062
Cancer	1	6	6.990	0.008
Clinical symptoms				
Fever	27	16	0.557	0.456
Cough	25	14	0.204	0.652
Chest tightness	10	10	3.214	0.073
Fatigue	11	7	0.313	0.576

Table 2. Comparison of blood test results of patients with 2019 novel coronavirus pneumonia

Blood tests	Mild group n = 60	Severe group n = 30	*t/Z*	*P*
NLR	2.322(1.812-3.565)	7.078(3.499-	-5.409	0.000
Hb, g/L	129.000(120.250-137.750)	14.178)	-1.439	0.150
Plt, $\times 10^9$/L	214.500(150.750-243.750)	124.500(101.	1.120	0.266
AST, U/L	17.800(12.850-32.725)	250-134.250)	-0.693	0.490
Scr, μmol/L	63.700(57.100-78.850)	191.500(116.	-0.417	0.677
CRP, mg/L	1.670(0.550-4.238)	000-224.750)	-5.732	0.000
Fib, g/L	3.420(2.800-4.180)	19.500(14.70	-1.907	0.067
D-Dimer,	0.290(0.208-0.568)	0-41.700)	-1.694	0.103
mg/L	37.860±3.876	64.150(55.62	-7.264	0.000
ALB, g/L		5-97.175)		
		77.820(38.49		
		5-103.630)		
		4.305(2.913-		
		5.570)		
		1.515(0.925-		
		3.588)		
		31.337±4.28		
		7		

Abbreviations: NLR neutrophil-lymphocyte ratio; Hb hemoglobin; Plt platelet; AST aspartate transaminase; Scr serum chlorine; CRP C-reactive protein; Fib fibrinogen; ALB albumin.

Table 3 Correlation analysis of risk factors with severe COVID-19

Statistics	Age	Cancer	NLR	CRP	ALB
r	0.459	0.323	0.573	0.645	-0.607
P-value	0.000	0.002	0.000	0.000	0.000

Abbreviations: NLR neutrophil-lymphocyte ratio; CRP C-reactive protein; ALB albumin.

Table 4. Regression analysis of risk factors for severe COVID-19

Factor	B	SE	Wals	P	OR	OR(95% CI)	
						Lower limit	Upper limit
Age	-0.009	0.032	0.083	0.774	0.991	0.932	1.054
Cancer	1.437	1.769	0.660	0.416	0.238	0.007	7.609
NLR	0.277	0.120	5.334	0.021	1.319	1.043	1.669
ALB	-0.303	0.092	10.711	0.001	0.739	0.616	0.886
CRP	0.011	0.011	0.992	0.319	1.011	0.990	1.032

Abbreviations: NLR neutrophil-lymphocyte ratio; CRP C-reactive protein; ALB albumin.

The authors confirmed that Table 5, mentioned on page 6, was mentioned in error.

Figures

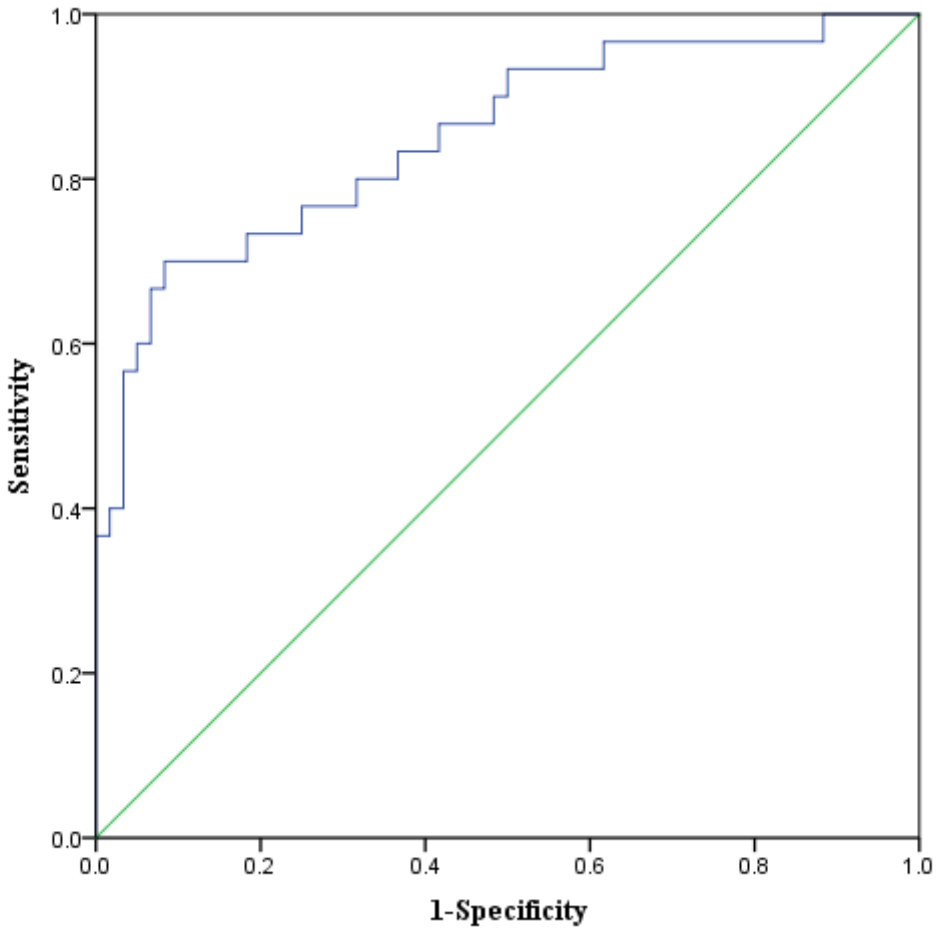

Figure 1

Receiver operating characteristic curve (ROC) and area under the curve (AUC) for the pretreatment NLR (AUC=0.851, P=0.000)