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Prediction of adverse clinical outcomes in patients with coronavirus disease 2019

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Abstract

Objective: This study aims to investigate blood and biochemical laboratory findings in patients with coronavirus disease (COVID-19) and analyze the potential predictors of poor outcome in patients with COVID-19.

Methods: The clinical, laboratory, and outcome data of 87 patients with COVID-19 were collected and retrospectively analyzed. Only data collected at the time of admission were used in the analysis for predictors of poor outcome. These patients were divided into two groups: the adverse prognosis group (36 patients) and the non-adverse prognosis group (51 patients). The adverse prognosis of COVID-19 patients was defined as admission to the intensive care unit or death.

Results: On the univariate analysis, age, white blood cell (WBC) count, neutrophil counts, lymphocytes count, neutrophils-to-lymphocytes ratio (NLR), interleukin-6, albumin-to-globulin ratio (AGR), albumin, lactate dehydrogenase, glutamyl transpeptidase, and blood glucose were found to be the significant predictors. On the multivariate analysis, the predictors of poor outcome of patients with COVID-19 were NLR (OR = 2.741, [95% CI = 1.02 ~ 7.35], $P = .045$) and IL-6 (OR = 1.405, [95% CI = 1.04 ~ 1.89, $P = .025$]). The receiver operating characteristic (ROC) curve revealed that the AUC of NLR, interleukin-6, pneumonia severity index (PSI) score, and Confusion-Urea-Respiratory Rate-Blood pressure-65 (CURB-65) score were 0.883, 0.852, 0.824, and 0.782, respectively.

Conclusion: High interleukin-6 (6 pg/mL, cuff value) and NLR (4.48, cuff value) can be used to predict poor outcomes in patients with COVID-19 on admission, thus can serve as a beneficial tool for timely identifying COVID-19 patients prone to poor outcome and reduce patient mortality through early intervention.

KEYWORDS

Confusion-Urea-Respiratory Rate-Blood pressure-65, coronavirus disease-2019, interleukin-6, neutrophil-to-lymphocyte ratio, prognosis factors

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus (SARS-CoV-2), which belongs to a unique clade of the sarbecovirus subgenus of the Orthocoronavirinae subfamily, was identified as the pathogen of coronavirus disease-2019 (COVID-19) in January 2020.[1] As of the end of August 30, 2020, there were 24 854 140 cases reported, with 838 924 deaths (3.3%) worldwide. Severe and critical patients with COVID-19 present high mortality rate, and occurrence of acute respiratory distress syndrome (ARDS) or multi-organ dysfunction (MODS) significantly increasing its mortality risk.[2] It has been reported that the rate of ARDS in severe patients with COVID-19 was 15.9 to 29%.[1] The more critical the condition of the infected individual, the greater the chances of complications from SARS and multiple organ failure, or even death.

Previous studies have shown that many laboratory biomarkers, such as lymphocyte count, interleukin-6 (IL-6), ratio of albumin to globulin (AGR), neutrophil count, hypersensitivity, C-reactive protein (CRP), creatine kinase, blood urea, thrombocytopenia, lactate dehydrogenase (LDH), and D-dimer, are out of normal ranges in patients with COVID-19.[3-5] These laboratory biomarkers are routine and are the most available in clinics. However, available markers for predicting the progression of patients with COVID-19 are limited. Reverse transcription-polymerase chain reaction (RT–PCR) is one of the golden standards in the clinical diagnosis of COVID-19.[6] Nevertheless, blood and biochemical laboratory findings could also be used for early detection, prognosis, and prediction of disease progression. Thus, there is a need to look for indicators to predict the severity of COVID-19 and its adverse clinical outcomes.

The present study aimed to determine whether the blood and biochemical indexes could differentiate between COVID-19-infected patients with or without adverse prognosis. The investigators attempted to establish an early risk factor stratification based on adverse prognostic factors, in order to reduce patient mortality and alleviate the shortage of medical resources.

2 | MATERIALS AND METHODS

2.1 | Study subjects

The present study was approved by the Medical Ethics Committee of Tongji Affiliated Hospital of Huazhong University of Science and Technology and conforms to the principles of the Helsinki declaration. All patients with COVID-19 were diagnosed and confirmed by real-time reverse transcription-polymerase chain reaction (RT–PCR) at Union Hospital of Tongji Medical College of Huazhong University of Science and Technology from January 31, 2020, to March 29, 2020.

Patients with COVID-19 were divided into adverse prognosis group and non-adverse prognosis group. Each patient with COVID-19 was followed up for at least one month. An adverse prognosis was considered as the admission to the intensive care unit (ICU) or death. The criterion for admission to the ICU was either (a) respiratory failure occurrence that requires mechanical ventilation; (b) shock occurrence; or (c) combined with other organ failure requiring ICU monitoring and treatment.[4] The independent prognosis predictors were determined by comparing the clinical and applied biochemical indexes between the adverse prognosis group and non-adverse prognosis group. Pneumonia severity index (PSI) and Confusion-Urea-Respiratory Rate-Blood pressure-65 (CURB-65) (defined as an Abbreviated Mental Test Score of 8 or less, blood urea nitrogen level >7 mmol/L [19 mg/dL], respiratory rate of ≥30 breaths/min, systolic blood pressure <90 mm Hg, diastolic blood pressure ≤60 mm Hg, age ≥65 years older]) were used to assess severity indices of COVID-19. In this article, we attempt to combine the PSI and CURB-65 scores to predict the severity of patients with COVID-19 and its adverse clinical outcomes.

2.2 | Statistical processing

The age and days were presented in median (range), and the classification variables were presented in number (%). Furthermore, normally distributed measurement data were presented as Mean ± standard deviation (SD), the comparison of two sample means was performed by *t* test, and the comparison of more than two sample means was performed using the variance test. Non-normally distributed measurement data were presented in median [interquartile range (IQR)] and analyzed by Mann-Whitney test. The measurement data were analyzed by chi-square or Fisher's accurate test, and the logistic regression analysis screened out the independent risk factors that influenced the prognosis of patients with severe pneumonia. Receiver operating characteristic (ROC) was used to determine and compare the different cutoffs of independent risk factors of COVID-19 in predicting adverse clinical outcome of patients with COVID-19. The SPSS 26.0 software was used for the statistical analysis.

3 | RESULTS

3.1 | Clinical features

3.1.1 | General information

Among the 87 patients with COVID-19 infection included in the present study, 51 (58.6%) patients were assigned to the non-adverse prognosis group and 36 (41.4%) patients were assigned to the adverse prognosis group. The age of 87 patients was confirmed to be within 22-88 years old (median: 60 years old). Among these 87 patients, 49 (56.3%) patients were male and 38 (43.7%) patients were female. Five patients (5.7%) among the study population had a history of exposure to the Wuhan South China Seafood Market, while 44 (50.6%) patients had a history of underlying diseases, including cardiovascular disease (n = 30; 34.5%), endocrine disease (n = 18; 20.7%), respiratory disease (n = 10; 11.4%), and malignant tumor

(n = 2; 2.3%) (Table 1). At the time of admission, most patients had fever, cough and fatigue, and one-third of these patients had difficulty in breathing. The other symptoms included muscle soreness, headache, nasal congestion, runny nose, sore throat, and diarrhea. The median time from admission to severe pneumonia in the poor outcome group was 5.5 days, with a minimum of one day and a maximum of 14 days.

3.2 | Analysis of blood test results

Among the 87 confirmed patients, the lymphocyte count decreased in 36 cases (41.3%), but there was no significant change in hemoglobin count and platelet count. (Table 2) Other biochemical abnormalities seen in the patients were elevated serum LDH levels (n = 31; 35.6%), increased glutamyl transpeptidase levels (n = 23; 26.4%), decreased albumin levels (n = 39; 44.8%), decreased AGR (n = 77; 88.5%), increased blood glucose levels (n = 37; 42.5%), increased blood calcium (n = 45; 51.7%), and increased IL-6 levels (n = 47; 54.0%). Patients with COVID-19 in the adverse prognosis group had lower lymphocyte counts than patients with COVID-19 in the non-adverse prognosis group ($P < .001$), lower albumin levels ($P < .001$), a reversal of the AGR ($P < .001$), higher white blood cell (WBC) count, ($P = .049$), higher neutrophils count ($P < .001$), higher NLR ($P < .001$), higher glutamyl transpeptidase levels ($P = .004$), higher LDH levels ($P < .001$), higher IL-6 levels ($P < .001$), and higher blood glucose levels ($P = .003$). Other laboratory measures did not differ significantly between the two groups.

The average age of the nine patients who died was 65 years old (range: 56-74 years old). Among these patients, seven patients (77.7%) had a basic medical history, three patients (33.3%) had a diabetes history, and four patients (44.4%) had hypertension. In addition, in COVID-19 dead patients, CRP and AGR were increased in all nine cases (100%). Furthermore, a decrease in albumin levels (n = 8; 88.9%), lymphocyte count (n = 7; 77.7%) and increase in NLR, IL-6, blood glucose, and LDH (n = 7; 77.8%) was observed. The imaging changes, which were mainly ground-glass opacity (GGO) shadows and consolidation, were observed in all dead patients.

The X-ray or computed tomography (CT) revealed that 44 patients (50.6%) had multiple or bilateral lung lobes. The most common CT manifestations were GGOs, crazy paving-like changes (GGO with interlobular septal and interlobular septal thickening), and consolidation, without mediastinal lymph node lesions. This mainly occurred in the subpleural part of the lower lobe.

3.3 | Prognostic factors of poor outcome

The numbers for age ($P = .001$), white blood cell (WBC) count ($P = .049$), neutrophils count ($P = .001$), and lymphocyte count ($P = .001$), and the NLR ($P = .001$), IL-6 ($P = .001$), LDH ($P = .001$), blood glucose ($P = .003$), glutamyl transpeptidase ($P = .004$), AGR

TABLE 1 Demographics and characteristics of patients infected with coronavirus disease-2019

	All patients (n = 87)	Non-adverse prognosis group (n = 51)	Adverse prognosis group (n = 36)
Characteristics			
Age, years	60 (22-88)	58 (22-82)	66 (39-88)
Gender			
Male	49 (56.3%)	27 (52.9%)	22 (61.1%)
Female	38 (43.7%)	24 (47.1%)	14 (38.90%)
Exposure to Huanan seafood market	5 (5.7%)	2 (3.9%)	3 (8.3%)
Long-term exposure history	2 (2.3%)	1 (2.0%)	1 (2.8%)
Short-term exposure history	3 (3.4%)	2 (3.9%)	1 (2.7%)
Chronic medical illness	44 (50.6%)	20 (39.2%)	24 (66.7%)
Cardiovascular and cerebrovascular diseases	30 (34.5%)	13 (25.5%)	17 (47.2%)
Respiratory system disease	10 (11.5%)	4 (7.8%)	6 (16.7%)
Endocrine system disease	18 (20.7%)	6 (11.8%)	12 (33.3%)
Malignant tumor	2 (2.3%)	0	2 (5.6%)
Kidney disease	1 (1.8%)	0	1 (2.8%)
Disease type			
Mild or moderate	51 (58.6%)	51 (100%)	0
Severe	19 (21.8%)	0	19 (52.8%)
Critical	17 (19.5%)	0	17 (47.2%)

Note: The data are presented in median (range), n (%), or median (interquartile range).

TABLE 2 Univariate analysis of the association between the blood and laboratory variables and poor outcome of patients with coronavirus disease-2019

	All patients (n = 87) M = 49 (56.3%) F = 38 (43.7%)	Non-adverse prognosis group (n = 51) M = 27 (52.9%) F = 24 (47.1%)	Adverse prognosis group (n = 36) M = 22 (61.1%) F = 14 (38.9%)	*P* value
White blood cell count (35-95 G/L)	5.49 (4.11-7.02)	5.05 (4.06-6.48)	5.72 (4.29-8.26)	.049
Increased	10 (11.5%)	2 (3.9%)	8 (22.2%)	.041
Decreased	10 (11.5%)	6 (11.8)	4 (11.1%)	
Neutrophil count (18-63 G/L)	3.3 (2.20-4.09)	3.32 (2.2-4.09)	5.08 (3.37-7.64)	<.001
Increased	14 (16.1%)	1 (2.0%)	13 (36.1%)	
Lymphocytes (11-32 G/L)	1.21 ± 0.60	1.44 ± 0.44)	0.88 ± 0.65	<.001
Decreased	36 (41.3%)	12 (23.5%)	24 (66.7%)	
Monocyte count (0.1-0.6 G/L)	0.35 (0.25-0.50)	0.36 (0.34-0.45)	0.28 (0.15-0.61)	.990
Increased	11 (13%)	3 (5.8%)	8 (22.2%)	
NLR	2.87 (1.95-5.73)	2.2 (1.56-2.87)	6.78 (3.79-11.85)	<.001
Platelet count (1250-3500 G/L)	207 (152-259)	203 (155-236)	219.5 (141.25-312.75)	.727
Blood biochemistry glutamyl transpeptidase (100-600 U/L)	30.0 (22.0-68.0)	26 (21-43)	50 (24.5-113.5)	.004
Increased	23 (26.4%)	6 (11.7%)	17 (47.2%)	
LDH (1090-2450 U/L)	204 (164.0-281.0)	179 (156-225)	270 (189.5-441.0)	<.001
Increased	31 (35.6%)	9 (17.6%)	22 (61.1%)	
Albumin (330-550 g/L)	33.4 ± 6.1	36.2 ± 5.1	29.3 ± 5.1	<.001
Decreased	39 (44.8%)	11 (21.6%)	28 (77.8%)	
AGR (150%-250%)	1.10 ± 0.29	1.24 ± 0.23	0.91 ± 0.25	<.001
Decreased	77 (88.5%)	41 (80.4%)	36 (100%)	
Blood urea nitrogen (2.9-8.2 mmol/L)	4.78 (3.98-6.60)	4.56 (3.92-5.42)	5.33 (4.05-7.42)	.05
Serum creatinine (570-1110 μmol/L)	67.9 (55.5-78.2)	67.3 (54.4-80.8)	68.8 (58.5-77.7)	.549

(Continues)

TABLE 2 (Continued)

	All patients (n = 87) M = 49 (56.3%) F = 38 (43.7%)	Non-adverse prognosis group (n = 51) M = 27 (52.9%) F = 24 (47.1%)	Adverse prognosis group (n = 36) M = 22 (61.1%) F = 14 (38.9%)	*P* value
Increased	3 (3.4%)	0	3 (8.3%)	
Decreased	24 (27.6%)	16 (31.4%)	8 (22.2%)	
Glucose (3.9-6.1 mmol/L)	5.87 (5.27-7.45)	5.64 (5.10-6.5)	6.48 (5.36-10.47)	.003
Increased	37 (42.5%)	15 (29.4%)	22 (61.1%)	
Interleukin-2 (0.10-4.10 pg/mL)	4.39 ± 0.61	4.32 ± 0.64	4.49 ± 0.55	.209
Interleukin-4 (0.10-3.20 pg/mL)	4.40 ± 1.22	4.23 ± 1.22	4.49 ± 0.53	.104
Increased	83 (95.4%)	41 (80.4%)	32 (88.9%)	
Interleukin-6 (<7 pg/mL)	7.0 (4.87-11.2)	5.20 (3.7-7.0)	10.0 (10.1-29.0)	<.001
Increased	47 (54.0%)	17 (33.3%)	31 (86.1%)	
Interleukin-8 (0.10-5.90 pg/mL)	5.53 ± 1.32	5.34 ± 1.39	5.79 ± 1.26	.131
Increased	22 (25.3%)	13 (25.6%)	9 (25.0%)	
Tumor necrosis factor-alpha (0.10-23 pg/mL)	4.05 (2.69-5.16)	3.68 (2.59-5.16)	4.08 (2.80-4.90)	.315
Interferon-γ (0.10-18.00 pg/mL)	3.98 (3.50-4.66)	3.98 (3.50-4.62)	3.98 (3.52-4.92)	.353

Note: The data are presented in median (range), n (%). Normally distributed measurement data were presented as Mean ± standard deviation (SD). Non-normally distributed measurement data were presented in median (interquartile range [IQR]). SI conversion factors: To convert lactate dehydrogenase level to μkat/L, multiply by 0.0167. The *P*-values that compared the adverse prognosis group and non-adverse prognosis group were obtained from the chi-square test, *t* test or Mann-Whitney test.

Abbreviations: AGR, the albumin to globulin ratio; F, Female;G, $\times 10^9$ cells; LDH, Lactate dehydrogenase; M, Male; NLR, The neutrophil-to-lymphocyte ratio; T: $\times 10^9$ cells.

($P = .001$), and albumin ($P = .001$) levels in the single-factor analysis were correlated with the poor outcome of the disease ($P < .01$) (Table 1). The difference of other blood and biochemical indexes between the two groups was not statistically significant ($P > .05$). On the multivariate analysis, the predictors of poor outcome of patients with COVID-19 were NLR (OR = 2.741, [95% CI = 1.02 ~ 7.35], $P = .045$) and IL-6 (OR = 1.405, [95% CI = 1.04 ~ 1.89, $P = .025$]) (Table 3).

3.3.1 | ROC curve analysis

Receiver operating characteristic curve analysis suggested that various parameters could be used to assist the prediction of poor outcome of patients with COVID-19, with areas under the curve of 0.883 for NLR, 0.852 for IL-6, 0.782 for PSI and 0.695 for CURB-65. (Table 4) The specificity of predicting the poor outcome of patients with COVID-19 based on NLR >4.48 was 75.0%, and the sensitivity was 96.1%. For IL-6 >6 pg/mL, the specificity was 91.6% and the sensitivity was 74.5%. For PSI score >70, the specificity was 88.9% and the sensitivity was 62.8%. For CURB-65 score >1, the specificity was 69.4% and the sensitivity was 70.6%. High IL-6 and NLR can be used to predict poor outcomes in patients with COVID-19, which had greater predictive power, when compared to either the CURB-65 or PSI scores. The combination of IL-6 level and NLR was superior to individual factors as predictors of COVID-19-infected patients, with an AUC of 0.966. The AUC of combination of the IL-6 level, NLR, and PSI scores was 0.973. The AUC of the combination of the IL-6 level, NLR, and CURB-65 scores was 0.969. For the prediction of poor outcome of patients with COVID-19, lymphocyte count, albumin, AGR, LDH, and age were promising indicators with AUCs of 0.833, 0.828, 0.824, 0.772, and 0.692, respectively. Among patients without independent risk factors, there were almost no poor outcome patients. However, 28 patients had two independent risk factors among the 36 poor outcome patients.

4 | DISCUSSION

In this retrospective study, 87 patients with COVID-19 infection were included in the present study, and 9 (10.3%) of whom died. 36 (41.4%) patients had as adverse prognosis. The worldwide mortality rate of COVID-19 is currently reported to be only 3.8%; however, the mortality rate of severely affected patients in Wuhan is 10%-40%. At present, the supportive management is applied for the treatment of COVID-19, and ARDS-induced respiratory failure accounts the

TABLE 3 Results of the binary regression analysis to predict poor outcome of patients with coronavirus disease-2019

							95% CI for OR	
	B	SE	Wald	DF	*P* Value	OR	Lower	Upper
Age/y	0.027	0.074	0.134	1	.714	1.028	0.888	1.188
Lymphocytes (11-32 G/L)	−1.286	1.505	0.729	1	.393	0.277	0.014	5.284
LDH (109-245 U/L)	0.008	0.007	1.077	1	.299	1.008	0.993	1.022
Glutamyl transpeptidase (100-600 U/L)	−0.032	0.020	2.672	1	.102	0.968	0.932	1.006
Albumin (33-55 g/L)	0.060	0.162	0.137	1	.711	1.062	0.773	1.460
AGR (150%-250%)	−4.300	3.572	1.449	1	.229	0.014	0.000	14.886
Glucose (3.9-6.1 mmol/L)	−0.305	0.304	1.010	1	.315	0.737	0.406	1.337
NLR	1.008	0.504	4.002	1	.045	2.741	1.021	7.359
Interleukin-6 (<7 pg/mL)	0.340	0.152	5.015	1	.025	1.405	1.043	1.893
Blood urea nitrogen (2.9-8.2 mmol/L)	−0.037	0.382	0.009	1	.923	0.964	0.456	2.038
White blood cell count (3.5-9.5 G/L)	0.224	0.368	0.371	1	.542	1.251	0.608	2.575
Constant	−4.635	7.939	0.341	1	.559	0.010		

Note: The column entitled "Wald" provides the results of the Wald test, indicating the significance of the association with disease severity; The "Constant" represents the intercept of the regression model. SI conversion factors: To convert lactate dehydrogenase level to μkat/L, multiply by 0.0167.

Abbreviations: AGR, the albumin to globulin ratio; B, regression coefficient; CI, confidence interval; DF, degree of freedom; G, $\times 10^9$ cells; LDH, Lactate dehydrogenase; NLR, The neutrophil-to-lymphocyte ratio; OR, odds ratio; SE, standard error; T, $\times 10^9$ cells.

TABLE 4 The ROC curve comparison of various prognostic indicators for the prediction of patients with coronavirus disease-2019

	AUC (95% CI)	*P*	SEN (95% CI)	SPE (95% CI)	PPV (95% CI)	NPV (95% CI)	Cutoff
NLR	0.883 (0.796-0.942)	$P < .001$	0.750 (0.578-0.879)	0.961 (0.865-0.995)	0.931 (0.768-0.992)	0.845 (0.726-0.927)	>4.48
Interleukin-6 (<7 pg/mL)	0.852 (0.759-0.919)	$P < .001$	0.916 (0.775-0.982)	0.745 (0.501-0.776)	0.647 (0.499-0.777)	0.917 (0.775-0.982)	>6
Lymphocytes (11-32 G/L)	0.833 (0.738-0.904)	$P < .001$	0.472 (0.435-0.769)	0.902 (0.786-0.967)	0.815 (0.619-0.937)	0.767 (0.638-0.867)	≤1.01
Albumin (33-55 g/L)	0.828 (0.732-0.901)	$P < .001$	0.861 (0.705-0.953)	0.745 (0.604-0.857)	0.705 (0.546-0.834)	0.884 (0.747-0.962)	≤34.2
AGR (1.5-2.5)	0.824 (0.728-0.897)	$P < .001$	0.667 (0.490-0.814)	0.804 (0.669-0.902)	0.706 (0.522-0.851)	0.774 (0.638-0.877)	≤1
LDH level (109-245 U/L)	0.772 (0.670-0.855)	$P < .001$	0.611 (0.435-0.769)	0.882 (0.761-0.956)	0.786 (0.590-0.993)	0.763 (0.638-0.86.7)	>255
Age/y	0.692 (0.584-00.786)	$P < .001$	0.556 (0.381-0.721)	0.803 (0.889-0.902)	0.887 (0.466-0.830)	0.719 (0.585-0.830)	>64
Glutamyl transpeptidase (100-600 U/L)	0.670 (0.561-0.767)	$P < .001$	0.861 (0.304-0.645)	0.882 (0.761-0.956)	0.739 (0.516-0.898)	0.703 (0.576-0.811)	>51
PSI score	0.782 (0.680-0.863)	$P < .001$	0.889 (0.739-0.969)	0.628 (0.481-0.759)	0.627 (0.481-0.759)	0.889 (0.739-0.969)	>70
CURB-65 score	0.695 (0.587-0.789)	$P < .001$	0.694 (0.519-0.837)	0.706 (0.562-0.825)	0.625 (0.795-0.993)	0.766 (0.620-0.877)	>1
NLR-IL-6	0.966 (0.904-0.993)	$P < .001$	0.861 (0.705-0.953)	0.9608 (0.865-0.995)	0.939 (0.590-0.917)	0.907 (0.796-0.970)	
IL-6-NLR-CURB-65	0.969 (0.908-0.995)	$P < .001$	0.861 (0.705-0.953)	0.961 (0.865-0.995)	0.935 (0.795-0.993)	0.907 (0.796-0.970)	
IL-6-NLR-PSI	0.973 (0.913-0.996)	$P < .001$	0.944 (0.813-0.993)	0.811-0.978	0.895 (0.752-0.971)	0.959 (0.860-0.995)	

Note: SI conversion factors: To convert lactate dehydrogenase level to μkat/L, multiply by 0.0167.

Abbreviations: AGR: the albumin to globulin ratio; AUC, area under curve; CURB-65, Confusion-Urea-Respiratory Rate-Blood pressure-65; G, $\times 10^9$ cells; Lactate dehydrogenase; LDH; NLR, The neutrophil-to-lymphocyte ratio; NPV, negative predictive value; PPV, positive predictive value; PSI, pneumonia severity index; SEN, sensitivity; SPE, specificity; T, $\times 10^9$ cells.

most important cause leading to mortality.[7] A case study published by Li et al enrolled the first 425 confirmed patients in Wuhan,[8] with the age of 15-89 (median, 59) years. There was no significant difference in gender (56% males). In addition, epidemiological and clinical information of the 72 314 cases were collected by the Chinese CDC which for the first time illustrated the epidemiological curve of COVID-19 outbreak in China.[9] 62% of the above cases were finally confirmed with COVID-19, resulting in an overall CFR of 2.3%. Noteworthily, those deadly patients were mostly those with an old age, especially for those aged ≥80 years (approximately 15%). Nearly 1/2 (49.0%) critically ill cases and those with underlying diseases (like neoplasm, chronic respiratory disorder, diabetes, and cardiovascular disease) died. In our study, the average age of these nine dead patients was 65 years old. Among these patients, seven dead patients (77.7%) had a basic medical history, three dead patients (33.3%) had a diabetes history, and four dead patients (44.4%) had hypertension.

The neutrophil-to-lymphocyte ratio (NLR) integrates information on both the innate and adaptive compartments of the immunity and represents a reliable measure of the inflammatory burden.[10] The NLR has been proposed as an easy parameter to assess the individual inflammatory status.[11] It has proven its accuracy in predicting the outcome of patients with major cardiac events,[12] ischemic stroke,[13] cancers,[14] sepsis, and infectious pathologies.[15] It can be used as a reliable and simple index to determine the increase in inflammation in chronic obstructive pulmonary diseases patients.[16] It is a common index to evaluate the severity of bacterial infection and prognosis of patients with pneumonia and tumors.[17] In this study, we found that the neutrophil count in most patients (84.00%) was within the normal range, but poor outcome patients with COVID-19 had a continuous increase in neutrophils. This is because respiratory viruses can suppress the innate immune response and evade the host's innate immunity, while neutrophils are the main natural immune cells that regulate the innate immune response against viral lung infections.[18] Our study explored the relationship between NLR and COVID-19 and found that patients with NLR >4.48 were more likely to develop poor prognosis of patients with COVID-19.

A previous study reported that out of 1099 COVID-19-infected cases, 83.2% had lymphocytopenia.[19] The CD3+/CD4+/CD8+/

CD19+ T cell counts are reported to decline significantly in the early SARS-CoV infection period.[20] The virus molecules transmit across respiratory mucosa to infect more cells, which thus results in the cytokine storm, produces various immune reactions, and leads to alterations of WBC count and immunocytes including lymphocytes in the peripheral blood.[21] It was found that the continuous decrease in lymphocyte count was correlated to the progress and prognosis of patients with COVID-19, and the lymphocyte-related indexes may be a potential predictor.[22] In terms of laboratory tests, the lymphocyte count decreased in 36 cases (41.3%), the absolute value of lymphocytes in most patients was reduced. Adverse prognosis of patients with COVID-19 had lower lymphocyte counts ($P < .001$). Furthermore, it was found that the lymphocyte-related inflammatory factors were abnormal in dead patients.

In this study, 47 cases (54.0%) had increased IL-6 level, and the vast majority of these were poor outcome cases (86.1%). In multivariable regression analysis, we showed that patients had poor prognosis when IL-6 greater than 6 pg/mL. A number of literature reports have confirmed that the level of IL-6 in serum is related to the severity of patients with COVID-19.[4,23] The involvement of IL-6 signal transduction would have immeasurable value in infection, inflammation, regeneration, cancer, and other diseases.[24] Relevant research results have shown that blocking IL-6 signaling is useful in the treatment of autoimmune and inflammatory diseases, such as inflammatory bowel disease, diabetes, multiple sclerosis, asthma, and rheumatoid arthritis, as well as inflammatory-related cancer experimental models.[24,25] Therefore, the anti-IL-6 strategy has become a new approach to treat human inflammatory diseases. At the time of coronavirus-19 infecting the upper as well as lower respiratory tract, both acute and mild respiratory syndromes may occur, and later the pro-inflammatory factors, such as interleukin IL-6 or IL-1β, will be released.[26]

In the present study, 77 cases (88.5%) had decreased AGR. Most of the patients with COVID-19 had low albumin levels. Serum albumin level is an indicator of human nutrition. Hypoalbuminemia in serum reflects malnutrition and weakens a patient's cellular and humoral immunity, phagocytosis, and other defense mechanisms. Besides, it has been reported that albumin levels might be reduced due to inflammation or the development of malignant tumors, and low albumin levels are known to be predictors of poor prognosis in patients with malignant tumors.[5,27,28] Patients with the COVID-19 had high levels of LDH but were non-specific. Fan CB et al reported that SARS-CoV-2 led to bile duct cell dysfunction and systemic inflammatory response to liver damage,[29] which is supported by the first autopsy pathological analysis of a patient with COVID-19 showing moderate microvesicular steatosis and mild lobular and portal activity in the liver tissue.[30] This high-level may reflect the degree of tissue necrosis and the severity of pneumonia, providing a basis for future treatment and prognostic evaluation.[31] In the present study, 31 patients (35.6%) had increased serum LDH levels. Higher LDH levels were found in the dead patients.

ROC curve analysis suggested that various parameters could be used to assist the prediction of poor outcome of patients with COVID-19, with areas under the curve of 0.883 for NLR, 0.852 for IL-6, 0.782 for PSI, and 0.695 for CURB-65. Our results showed a higher predictive validity than did the usual pneumonia severity scores of PSI and CURB-65. One reason is that early-onset COVID-19 pneumonia patients were not severe, with an incubation period of 7-10 days. Another issue to consider is that the current severity tool that relies on. Actually, Guo et al suggested that the CURB-65 score was not creditable enough to predict the mortality of virus pneumonia.[32] After NLR or IL-6 was incorporated into PSI and CURB-65 models respectively, it was found that the prediction effect of the improved model was significantly better than that of the original model. The AUC of a combination of the IL-6 level, NLR, and PSI score was 0.973. The combined prediction value of these three parameters is better than that of a single factor, and it is of great predictive value in predicting the poor outcome of patients with COVID-19, thus can serve as a beneficial tool for timely identifying patients with COVID-19 prone to poor outcome and reduce patient mortality through early intervention.

Lymphocyte count, albumin, AGR, LDH, and age were promising indicators to assist the prediction of poor outcome of patients with COVID-19 with AUCs of 0.833, 0.828, 0.824, 0.772, and 0.692, respectively. NRL and IL-6 were independent risk factors for prognosis of patients with COVID-19, and these had a certain reference value for prognosis evaluation. Among patients without independent risk factors, there were almost no poor outcome patients. However, 28 patients had two independent risk factors among the 36 poor outcome patients. For patients with two independent risk factors, these patients were often critical patients, who were prone to severe pneumonia, respiratory failure, and death, suggesting poor prognosis. These patients should be quickly treated in the intensive care unit.

The present study has several limitations. The sample size (87 samples) was relatively small. Further studies with a larger sample size are needed to confirm these results. Furthermore, the investigators intend to further improve the study in the future.

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ETHICAL APPROVAL

The present study was approved by the Medical Ethics Committee of Tongji Affiliated Hospital of Huazhong University of Science and Technology and conforms to the principles of Helsinki declaration.

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