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The clinical course and prognostic factors of severe COVID-19 in Wuhan, China

A retrospective case-control study

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Abstract

With the surge of newly diagnosed and severe cases of coronavirus disease 2019 (COVID-19), the death toll is mounting, this study is aimed to explore the prognostic factors of severe COVID-19. This retrospective study included 122 inpatients diagnosed with COVID-19 from January 13 to February 25, 2020. Univariate and multivariate analysis were used to identity the risk factors, receiver operating characteristics curve (ROC) analysis was used for risk stratification. The baseline neutrophil-to-lymphocyte ratio (NLR) (OR = 1.171, 95%CI = 1.049–1.306, $P = .005$) and Lactate dehydrogenase (LDH) (OR = 1.007, 95%CI = 1.002–1.011, $P = .004$) were identified as the independent risk factors for severe COVID-19 conditions, and the NLR-LDH grading system was developed to perform risk stratification. The baseline C-reactive protein (CRP) (OR = 1.019, 95%CI = 1.004–1.306, $P = .016$) and B-type natriuretic peptide (BNP) (OR = 1.018, 95%CI = 1.004–1.035, $P = .007$) were identified as the independent predictors for disease progression of severe patients. Accordingly, The NLR-LDH grading system was a useful prognostic tool for the early detection of severe COVID-19. And in the severe patients, CRP and BNP seemed to be helpful for predicting the disease progression or death.

Abbreviations: CI = confidence interval, CK = creatine kinase, COVID-19 = coronavirus disease 2019, CRP = C-reactive protein, CT = computed tomography, IL-6 = interleukin-6, IQR = interquartile range, LDH = lactate dehydrogenase, PCT = procalcitonin, ROC = receiver operating characteristics curve, RT-PCR = real-time reverse-transcriptase–polymerase-chain-reaction, SAA = serum amyloid A, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: biomarkers, classification, coronavirus disease 2019, prognosis, survival

1. Introduction

According to national official statistics, up to May 2, 2020, more than 2 million people have been reported to be infected and more than 200 thousand of them died worldwide.[1,2] Right now, people in the whole world are facing a huge public health and medical challenge.[3–10]

Most patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were actually mild cases,[11,12] and deaths mostly occurred in severe and critical patients.[13,14] Therefore, current research should focus on finding risk factors for severe outcomes (including death) and disease progression, so that we can early identify severe patients or those with potential disease progression and perform risk stratification and corresponding management.[15,16] Consequently, we would be able to take early intervention in potentially severe patients and reduce the CFR as much as possible. By doing this, on the other hand, we can accordingly allocate medical resources more reasonably, alleviate the shortage of medical resources and hopefully will reduce the public health and medical burdens, especially in Wuhan.

Thus, we have enrolled a group of common, severe, and critical patients infected with SARS-CoV-2, compared the clinical characteristics of common group and severe group (including severe and critical type), explored the risk factors for severe conditions. We recorded the complete course of disease in all patients in detail after the illness onset, analyzed risk factors for disease progression (clinical type worsened or death) in severe patients. In addition, due to the long time of observation in all patients, we also depicted the trend of their various laboratory indices during the course of disease and summarized some characteristics which indicated the need for early clinical intervention.

2. Materials and methods

2.1. Patients

This retrospective, one-center study was reviewed and approved by the Medical Ethical Committee of Jinyintan Hospital, and written informed consent was obtained from all patients.

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JL, CT, MZ, WL, and BX contributed equally to this article.

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

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In this study, we collected the clinical data of 122 inpatients diagnosed with COVID-19 in Wuhan Jinyintan Hospital from January 13, 2020 to February 25, 2020. In order to explore the factors for poor prognosis in severe patients, subjects were selected especially from 1 intensive care unit (ICU) ward and 2 general wards, and as a result the proportion of severe conditions and deaths were rather large.

According to the World Health Organization interim guidance,[17] the diagnosis of COVID-19 is based on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test. Throat swab samples were extracted from suspected patients for detection, and positive test results for 2 target genes were considered as laboratory-confirmed infection. All the patients in our study were monitored and the complete course of disease after the onset of illness were recorded as well as the final clinical outcome of each individual.

2.2. Data collection

Detailed medical history, clinical symptoms, signs, and laboratory indices of all patients were accessed from electronic medical records, chest computed tomography (CT) scan results were retrieved from picture archiving and communication system (PACS). Each patient had underwent chest CT scan and laboratory tests at least twice. Laboratory tests included complete blood cell analysis, blood biochemistry, coagulation function, liver and kidney function, electrolytes, especially C-reactive protein (CRP), lactate dehydrogenase (LDH), serum amyloid A (SAA), erythrocyte sedimentation rate, ferritin, creatine kinase (CK), procalcitonin (PCT), interleukin-6 (IL-6).

2.3. Definition

The clinical classification of patients is mainly based on novel coronavirus pneumonia diagnosis and treatment plan (trial version 7) developed by the National Health Committee of the People's Republic of China.[9] Classifications are summarized as follows:

1. mild type, mild clinical symptoms with no sign of pneumonia in imaging features;
2. common type, complicated with fever, respiratory symptoms, and imaging findings of pneumonia;
3. severe type, complicated with any of the following:
   a. respiratory distress, respiratory rate $\geq$ 30 beats/minutes;
   b. in the resting state, means oxygen saturation $\leq$93%;
   c. the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) $\leq$ 300 mm Hg (1 mm Hg = 0.133 kPa);
4. critical type, complicated with any of the following:
   d. respiratory failure and mechanical ventilation required;
   e. shock;
   f. organ dysfunction and ICU admission required. In our research, we divided severe type and critical type both into severe group.

In addition, disease recovered was defined as the disappearance of previous clinical symptoms and imaging findings of pneumonia with throat swab samples RT-PCR test negative at least twice. Disease progression was defined as the clinical type worsened or death.

2.4. Statistical analysis

Quantitative variables are presented as median (interquartile range [IQR]) and compared using Kolmogorov–Smirnov test, and categorical variables are reported as frequency (percentages) and compared by means of corrected Chi-Squared or two-tailed Fisher exact test. Multivariate logistic regression with forward stepwise selection based on likelihood ratio was used to identify the risk factors for severe group and disease progression, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The receiver operating characteristics (ROC) curve and the area under the curve were constructed and the cutoff value was calculated based on the maximum Youden index. Survival is determined using the Kaplan–Meier analysis and compared using the log-rank test. All significance tests were two-sided and P values $<.05$ were considered to be significant. Data processing and analyses were performed by using IBM SPSS statistics version 25.0 (IBM, Inc., Chicago, IL) and we used GraphPad Prism version 8 for drawing figures.

3. Results

3.1. Baseline characteristics, treatments, and outcomes

Demographic and clinical characteristics of the patients were displayed in Table 1. A total of 122 patients were divided into common group (common type, n = 43) and severe group (severe and critical type, n = 79), the median age of which were respectively 55 (IQR, 38–66) and 65 (IQR, 54–71). Of all the patients, 2 (1.6%) were complicated with COPD, 50 (41.0%) with hypertension and 15 (12.3%) with diabetes. The most common symptom was fever, which was the case for 90.2% of all patients, followed by cough (77.0%), shortness of breath (62.3%), sputum production (13.1%), diarrhea (7.4%), and headache (1.6%). Among them, shortness of breath was more common in severe group.

Abnormalities of chest CT were found in all 122 patients, and 110 (90.2%) patients had more than 3 lobes affected. The frequency distribution of abnormal and normal laboratory indices were shown in Figure 1. Among all data available, the laboratory indices that more than half of the patients had gone abnormal were as follows: SAA, ferritin, lymphocyte count, erythrocyte sedimentation rate, albumin, CRP, D-dimer, LDH, IL-6, globulin, and fibrinogen concentration.

A total 56.6% of the patients received antivirus treatment and 88.5% of them received antibiotics treatment. Compared to common group, more patients in severe group received glucocorticoid therapy (53.2% vs 18.6%) and intravenous immunoglobulin (60.8% vs 11.6%). Of all the patients, 18.0% received invasive mechanical ventilation, and 19.7% received non-invasive mechanical ventilation. In addition, extracorporeal membrane oxygenation (ECMO) was performed in 4 (3.3%) patients.

The final clinical outcome of each individual was recorded. Specifically, 41 (95.3%) patients recovered, 2 (4.7%) worsened and no one died in common group. However, 40 (50.6%) patients recovered but 39 (49.4%) of them worsened (including 35 deaths) in severe group.

3.2. Prognostic factors in severe group

Logistic regression analysis showed that the baseline neutrophil-to-lymphocyte ratio (NLR) (OR = 1.171, 95%CI = 1.049–1.306, P = .005) and LDH (OR = 1.007, 95%CI = 1.002–1.011, P = .004) were independent predictors for severe conditions (Table 2). After ROC analysis, based on the calculation of

Table 1

Baseline characteristics, treatments, and outcomes of patients with COVID-19.

Variables	All patients (n = 122)	Common group (n = 43)	Severe group (n = 79)	*P* value
Age, years	62 (47–70)	55 (38–66)	65 (54–71)	.008
≥65	52 (42.6)	12 (27.9)	40 (50.6)	.021
Male gender	72 (59.0)	26 (60.5)	46 (58.2)	.849
Current smoking	5 (4.1)	2 (4.7)	3 (3.8)	1.000
Drinking	4 (3.3)	1 (2.3)	3 (3.8)	1.000
Comorbidity				
COPD	2 (1.6)	0	2 (2.5)	.540
Hypertension	50 (41.0)	13 (30.2)	37 (46.8)	.086
Diabetes	15 (12.3)	2 (4.7)	13 (16.5)	.082
Cerebrovascular disease	10 (8.2)	4 (9.3)	6 (7.6)	1.000
Cardiovascular disease	2 (1.6)	0	2 (2.5)	.540
Chronic liver disease	3 (2.5)	1 (2.3)	2 (2.5)	.551
Cancer	1 (0.8)	0	1 (1.3)	1.000
Signs and symptoms				
Fever	110 (90.2)	37 (86.0)	73 (92.4)	.341
Cough	94 (77.0)	36 (83.7)	58 (73.4)	.261
Shortness of breath	76 (62.3)	20 (46.5)	56 (70.9)	.011
Sputum production	16 (13.1)	9 (20.9)	7 (8.9)	.090
Fatigue	8 (6.6)	5 (11.6)	3 (3.8)	.128
Diarrhea	9 (7.4)	2 (4.7)	7 (8.9)	.491
Headache	2 (1.6)	1 (2.3)	1 (1.3)	1.000
Days from symptom onset to admission	12 (8–15)	14 (10–18)	11 (7–14)	<.001
Days in hospital	12 (9–20)	11 (9–18)	12 (9–20)	.374
Laboratory parameters				
PaO_2, mmHg	10.03 (7.42–13.52)	12.75 (9.94–22.94)	9.41 (7.05–12.49)	.013
$PaCO_2$,mmHg	4.53 (4.08–5.10)	5.09 (4.71–5.39)	4.36 (3.98–4.88)	.002
SaO_2, %	96 (92–98)	98 (96–99)	95 (91–97)	.056
Blood leukocyte count, $\times 10^9$/L	6.23 (4.55–8.64)	5.30 (4.05–6.70)	6.63 (5.06–9.37)	.007
Neutrophil count, $\times 10^9$/L	4.85 (3.22–7.81)	3.51 (2.46–4.96)	5.59 (3.61–8.54)	<.001
Lymphocyte count, $\times 10^9$/L	0.77 (0.55–1.22)	1.13 (0.74–1.47)	0.67 (0.49–0.99)	<.001
NLR	5.68 (2.91–11.89)	3.11 (1.96–5.00)	8.83 (4.20–15.53)	<.001
C-reactive protein, mg/L	47.4 (17.0–150.3)	18.6 (2.9–63.2)	80.7 (31.7–160.0)	<.001
Serum amyloid A, mg/L	196.5 (146.3–242.8)	174.3 (7.5–242.8)	199.4 (163.2–246.1)	.033
Procalcitonin, ng/ml	0.05 (0.05–0.16)	0.05 (0.05–0.05)	0.06 (0.05–0.19)	<.001
Ferritin, ng/ml	873.5 (454.1–1330.4)	527.2 (234.3–1056.4)	938.2 (594.5–1351.3)	.003
Interleukin-6, pg/ml	9.02 (6.32–13.52)	7.78 (5.34–14.28)	9.41 (6.56–13.38)	.396
Erythrocyte sedimentation rate, mm/h	48.0 (30.7–67.5)	49.0 (30.2–63.0)	48.0 (29.0–68.5)	.971
D-dimer, ug/mL	0.86 (0.53–3.08)	0.59 (0.32–1.19)	1.06 (0.62–4.25)	.011
Prothrombin time, s	11.5 (10.5–12.3)	10.9 (10.4–11.9)	11.7 (10.6–12.4)	.133
Activated partial thromboplastin time, s	27.6 (24.4–33.2)	28.4 (23.9–31.4)	27.4 (24.6–34.1)	.467
International normalized ratio	0.99 (0.90–1.04)	0.93 (0.89–1.02)	0.99 (0.92–1.07)	.041
Fibrinogen concentration, g/L	4.6 (3.4–5.8)	4.2 (2.9–5.3)	4.7 (3.4–6.4)	.146
Total bilirubin, mmol/L	11.9 (9.6–16.2)	11.0 (8.4–14.3)	12.2 (10.5–19.4)	.030
Direct bilirubin, mmol/L	3.8 (3.0–6.0)	3.4 (2.4–4.8)	4.0 (3.2–6.6)	.009
Alanine aminotransferase, U/L)	33 (20–55)	29 (15–52)	37 (23–57)	.292
Aspartate aminotransferase, U/L	38 (28–56)	28 (23–49)	40 (32–66)	<.001
Lactate dehydrogenase, U/L	346.0 (243.5–451.0)	238.0 (197.0–320.0)	408.0 (305.5–493.3)	<.001
Albumin, g/L	31.0 (27.6–34.1)	33.2 (30.8–35.5)	29.7 (26.9–31.9)	<.001
Globulin, g/L	31.9 (28.7–36.9)	32.1 (28.3–36.8)	31.8 (29.0–37.1)	.813
Blood urea nitrogen, mmol/L	4.95 (3.68–6.28)	3.85 (2.80–5.37)	5.30 (4.10–6.90)	.002
Creatinine, μmol/L	71.8 (58.4–86.2)	70.0 (56.7–83.0)	72.3 (58.4–88.6)	.425
Creatine kinase, U/L	93 (56–194)	90 (54–149)	103 (57–212)	.569
Creatine kinase-MB, U/L	14 (11–18)	11 (7–15)	16 (12–20)	.005
Myoglobin, ng/ml	62.7 (38.6–129.7)	44.8 (27.1–78.6)	86.3 (50.1–161.1)	.004
Troponin, pg/ml	7.9 (2.6–18.6)	2.7 (0.6–9.9)	10.3 (3.5–23.1)	.004
B-type natriuretic peptide, pg/mL	62.00 (27.53–94.23)	32.30 (17.95–73.05)	67.20 (30.70–120.40)	.151
Chest CT scan				<.001
1 lobe affected	3 (2.5)	3 (7.0)	0	
2 lobes affected	5 (4.1)	5 (11.6)	0	
3 lobes affected	4 (3.3)	4 (9.3)	0	
>3 lobes affected	110 (90.2)	31 (72.1)	79 (100)	
Fungal co-infection	14 (11.6)	0	14 (17.7)	.005

(*continued*)

Table 1

(continued).

Variables	All patients (n = 122)	Common group (n = 43)	Severe group (n = 79)	*P* value
Bacterial co-infection	7 (5.8)	1 (2.4)	6 (7.6)	.419
In-patient treatment				
Antivirus	69 (56.6)	23 (53.5)	46 (58.2)	.703
Antibiotics	108 (88.5)	35 (81.4)	73 (92.4)	.081
Glucocorticoid therapy	50 (41.0)	8 (18.6)	42 (53.2)	<.001
Intravenous immunoglobulin	53 (43.4)	5 (11.6)	48 (60.8)	<.001
Albumin infusion	17 (13.9)	2 (4.7)	15 (19.0)	.052
Oxygen therapy	104 (85.2)	34 (79.1)	70 (88.6)	.185
2–5L/min	43 (35.2)	23 (53.5)	20 (25.3)	.003
>5L/min	51 (41.8)	11 (25.6)	40 (50.6)	.012
High-flow nasal ventilation	38 (31.1)	1 (2.3)	37 (46.8)	<.001
Mechanical ventilation				
Invasive	22 (18.0)	2 (4.7)	20 (25.3)	.006
Non-invasive	24 (19.7)	0	24 (30.4)	<.001
ECMO	4 (3.3)	2 (4.7)	2 (2.5)	.613
Clinical outcomes				
Recovered	85 (69.7)	41 (95.3)	40 (50.6)	<.001
Progressive	41 (33.6)	2 (4.7)	39 (49.4)	<.001
Transfer to ICU	24 (19.7)	0	24 (30.4)	<.001
Death	35 (28.7)	0	35 (44.3)	<.001

COPD = chronic obstructive pulmonary disease, CT = computed tomography, ECMO = extracorporeal membrane oxygenation, IL-6 = interleukin-6, NLR = neutrophil-to-lymphocyte ratio.

maximum Youden index, the cutoff value of NLR and LDH were 5.865 and 390 U/L respectively (Fig. 2A).

According to the cutoff value of NLR and LDH, we developed the NLR-LDH grading system to divide patients into 3 grades: Grade 1, NLR < 5.87 and LDH < 390U/L; Grade 2, NLR ≥ 5.87 and LDH < 390U/L, or NLR < 5.87 and LDH ≥3 90U/L; Grade 3, NLR ≥ 5.87 and LDH ≥ 390U/L.

All 122 patients were divided into 3 groups based on the NLR-LDH grading system: Grade 1 (n = 53), Grade 2 (n = 33) and Grade 3 (n = 36). During the course of disease, 1 (1.9%) patient died in the Grade 1 group, 10 (30.3%) died in Grade 2 group, and 24 (66.7%) died in Grade 3 group. As is shown by the Kaplan–Meier analysis, the cumulative survival rates of the 3 groups of patients were respectively 98.1% ± 1.9%, 60.3 ± 9.9%, and

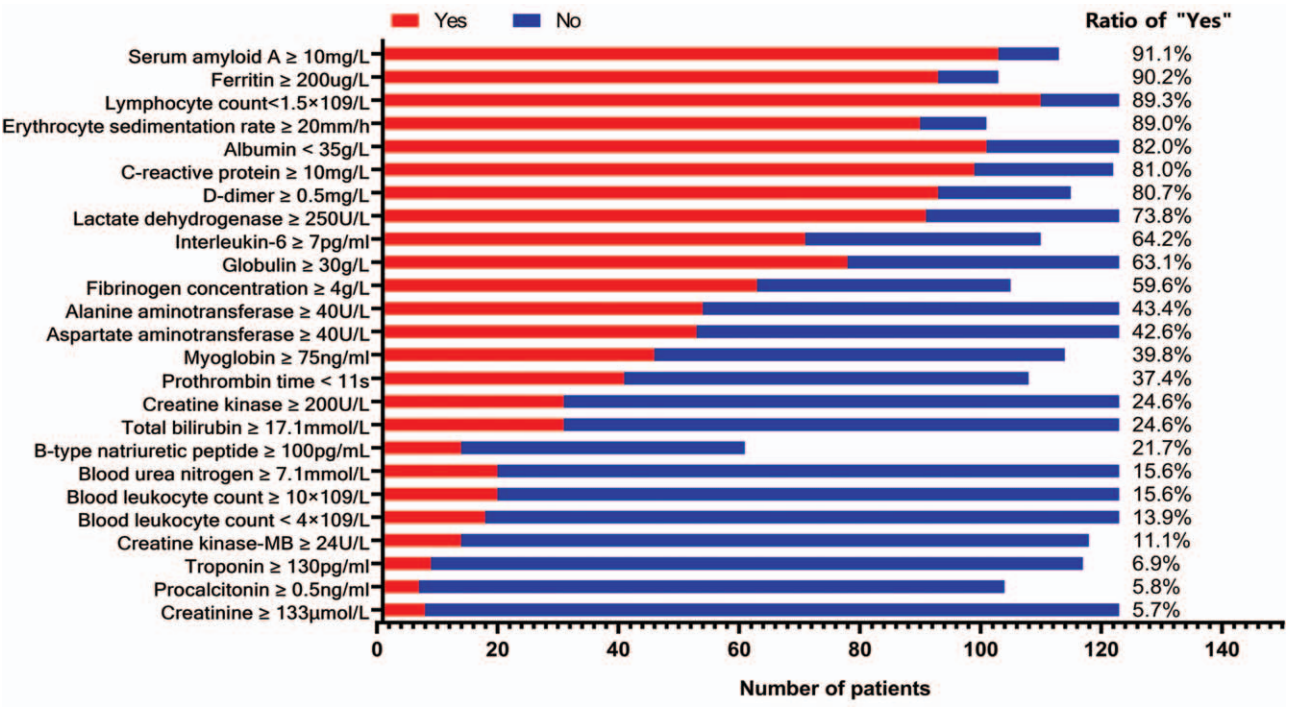

Figure 1. The stacked bar chart of abnormal and normal laboratory indices of all the patients.

Table 2

Univariate and multivariate analysis of factors associated with severe group.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* values	OR	95% CI	*P* values
Sex (Male vs. Female)	1.038	0.765–1.409	.849	–	–	–
Age (≥65 vs <65 years)	1.460	1.092–1.053	.021	–	–	–
C-reactive protein	1.014	1.006–1.021	< .001	–	–	–
Serum amyloid A	1.006	1.001–1.010	.021	–	–	–
Ferritin	1.001	1.000–1.002	.017	–	–	–
Lactate dehydrogenase	1.011	1.006–1.015	< .001	1.007	1.002–1.011	.004
Albumin	0.085	0.724–0.896	< .001	–	–	–
NLR	1.252	1.117–1.402	< .001	1.171	1.049–1.306	.005

24.9% ± 9.7%, which were in descending order (Log rank $P < .001$). In addition, there were significant differences between Grade 1 and Grade 2 group (Log rank $P < .001$), as well as between Grade 2 and Grade 3 group (Log rank $P = .013$) (Fig. 3).

3.3. Risk factors for disease progression in severe patients

Of all patients, only 4.7% in common group developed disease progression but no one died, and so we only analyzed the risk factors for disease progression in severe group rather than common group.

According to the different clinical outcomes, we divided the 79 patients in severe group into 2 subgroups: severe-recovered group (n = 40) and severe-progression group (n = 39). Univariate and multivariate logistic regression analysis showed that the baseline CRP (OR = 1.019, 95%CI = 1.004–1.306, $P = .016$) and B-type natriuretic peptide (BNP) (OR = 1.018, 95%CI = 1.004–1.035, $P = .007$) were the independent predictors for disease progression (Table 3). And the cutoff value of CRP and BNP were respectively 45.15 mg/L and 108.05 pg/ml calculated by ROC analysis (Fig. 2B).

3.4. Dynamic change of laboratory indices during the course of disease

The inflammatory indices of severe-progression group turned abnormal during the first week after the illness onset and reached its peak in the third week or so, thereafter it continued to be far above the reference line. In severe-recovered group and common group, these indices began to turn abnormal respectively from the first week and the second week after the illness onset. After that, they gradually restored below the reference line in common group, while in severe-recovered group they could not. The ascending period of lymphocyte count and descending period of globulin were approximately during 17 to 25 days after the illness onset. In addition, the SAA values in the 3 groups were all at the highest level in the first week after the illness onset, and then fell to the lowest in the third week or so. (Fig. 4).

The cardiac, liver, kidney and coagulation function indices in severe-progression group were all far beyond normal range, but in severe-recovered group and common group these indices were basically within the normal range (Fig. 5).

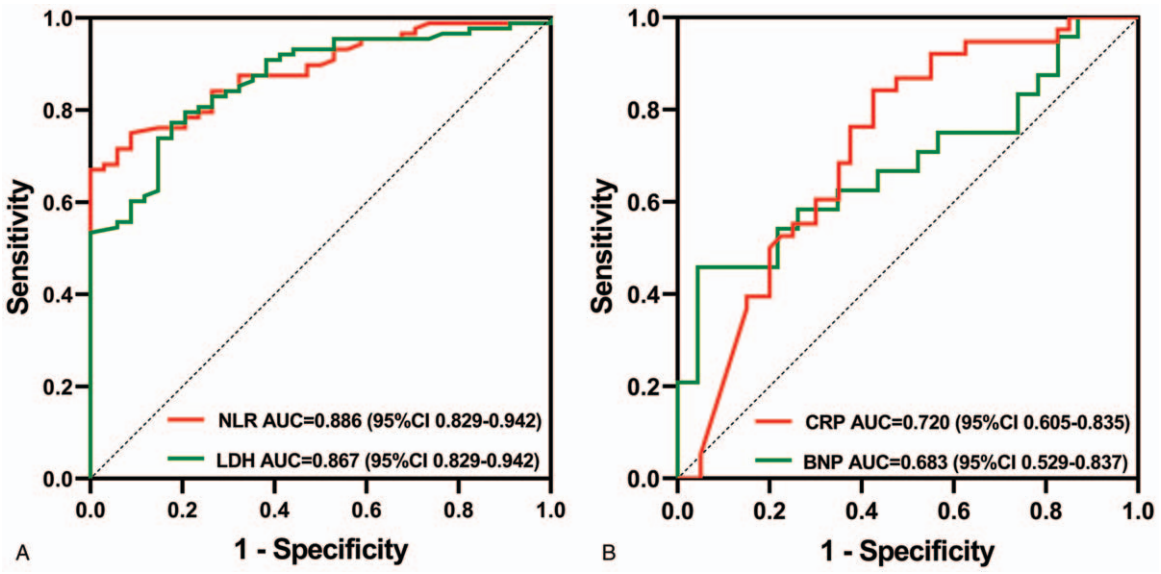

Figure 2. (A). The receiver operating characteristics (ROC) analysis of neutrophil-to-lymphocyte ratio (NLR) and lactate dehydrogenase (LDH) for prediction of severe conditions; (B). ROC analysis of C-reactive protein (CRP) and B-type natriuretic peptide (BNP) for prediction of disease progression in severe group.

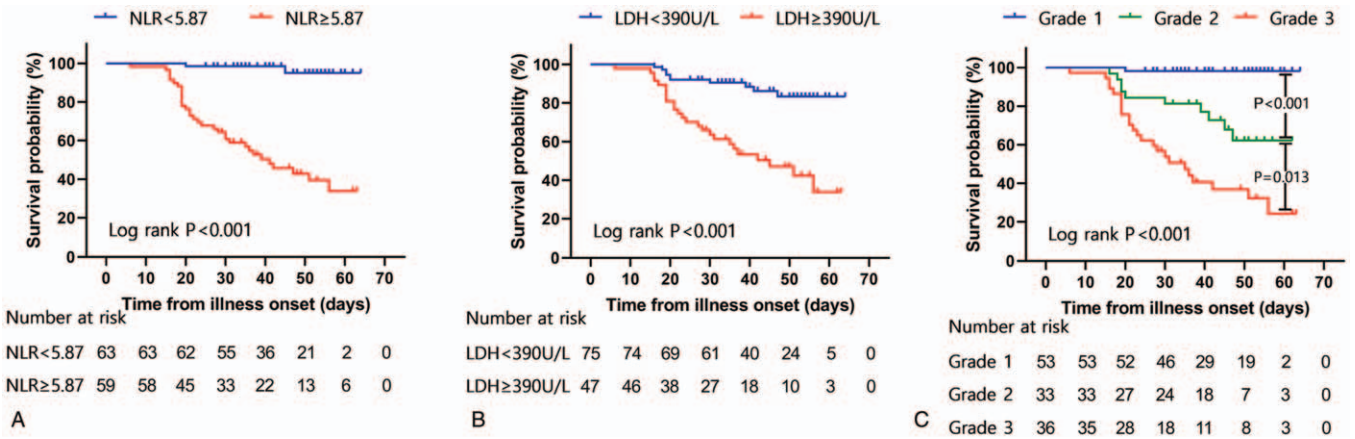

Figure 3. Kaplan–Meier curve of cumulative survival of patients with COVID-19 classified by the index of neutrophil-to-lymphocyte ratio (NLR) (A), lactate dehydrogenase (LDH) (B) and NLR-LDH grading system (C).

As is shown in Figures 4 and 5, the curves of severe-progression group and severe-recovered group were almost consistent for the first 7 to 9 days and then gradually went separate ways.

4. Discussion

Up to March 9, 2020, nearly 100 countries worldwide had people diagnosed with COVID-19. And with the surge of newly diagnosed and severe cases, humans are facing unprecedented challenges as to the effective management and control of the outbreak.[18]

All that enrolled in this study were COVID-19 inpatients diagnosed by RT-PCR test, the 79 (64.8%) of whom were severe cases, and all patients were monitored for a complete course of disease. Fever and cough were the major symptoms in all patients, and shortness of breath was more common in severe patients, together with 2 other patients having a headache, which might be associated with the neuroinvasive feature of SARS-CoV-2.[19] In severe patients, the lymphocyte count was lower and the neutrophil count was higher, and some inflammatory indices such as CRP, PCT and SAA were also found abnormal. Besides pulmonary function and inflammatory indices, the cardiac, liver and kidney functions of severe patients, such as indices like myoglobin, troponin, total bilirubin, aspartate aminotransferase, LDH, albumin, globulin, blood urea nitrogen, D-dimer, were also worse and worth concern.

As analyzed by a previous study including 1099 patients, compared to the mortality of 0.1% in nonsevere COVID-19 patients, the mortality in severe patients was 8.1%, which was 80 times higher.[20] Therefore, the early detection of severe patients and the management of risk stratification may play a significant role in reducing overall mortality.[21]

In our study, the prognostic factors in severe group found by univariate and multivariate analysis were NLR and LDH, and we developed a simple prognostic tool named NLR-LDH grading system, and divided the patients into Grade 1, Grade 2 and Grade 3. During the research, the cumulative survival rate of the 3 grades of patients was respectively 98.1% ± 1.9%, 60.3 ± 9.9%, and 24.9% ± 9.7%. Apparently, with the higher grades comes greater risk of death, and the Kaplan–Meier analysis indicated significant statistical differences between the 3 groups. As a result, we have reason to believe the NLR-LDH grading system is advantageous for the early detection of severe patients in clinical and further management.

Not only capable of causing pneumonia, COVID-19 may also cause damage to other organs such as the heart, the liver, and the kidneys.[22–25] Our results showed that the cardiac, liver, kidney, and coagulation function indices in severe-progression group were worse than other groups. Therefore, for severe patients, we ought to pay additional attention to other organ functions besides pulmonary function, especially cardiac function.[26,27] As described in novel coronavirus pneumonia diagnosis and treatment plan (trial version 7) developed by the National Health Committee of the People's Republic of China,[9] the cardiomyocytes of patients with COVID-19 showed pathological changes of degeneration and necrosis, indicating that SARS-CoV-2 may cause direct damage to

Table 3

Risk factors for disease progression in patients with severe or critical COVID-19.

	Univariate analysis			Multivariate analysis		
Variables	**OR**	**95% CI**	***P* values**	**OR**	**95% CI**	***P* values**
Sex (Male vs. Female)	1.500	0.873–2.577	.173	–	–	–
Age (≥65 vs. <65 years)	1.402	0.884–2.223	.179	–	–	–
C-reactive protein	1.103	1.005–1.021	.002	1.019	1.004–1.035	.016
Procalcitonin	14.235	0.622–325.707	.096	–	–	–
BNP	1.009	1.001–1.018	.033	1.018	1.005–1.031	.007
Globulin	1.090	1.004–1.184	.039	–	–	–
NLR	1.091	1.026–1.161	.006	–	–	–

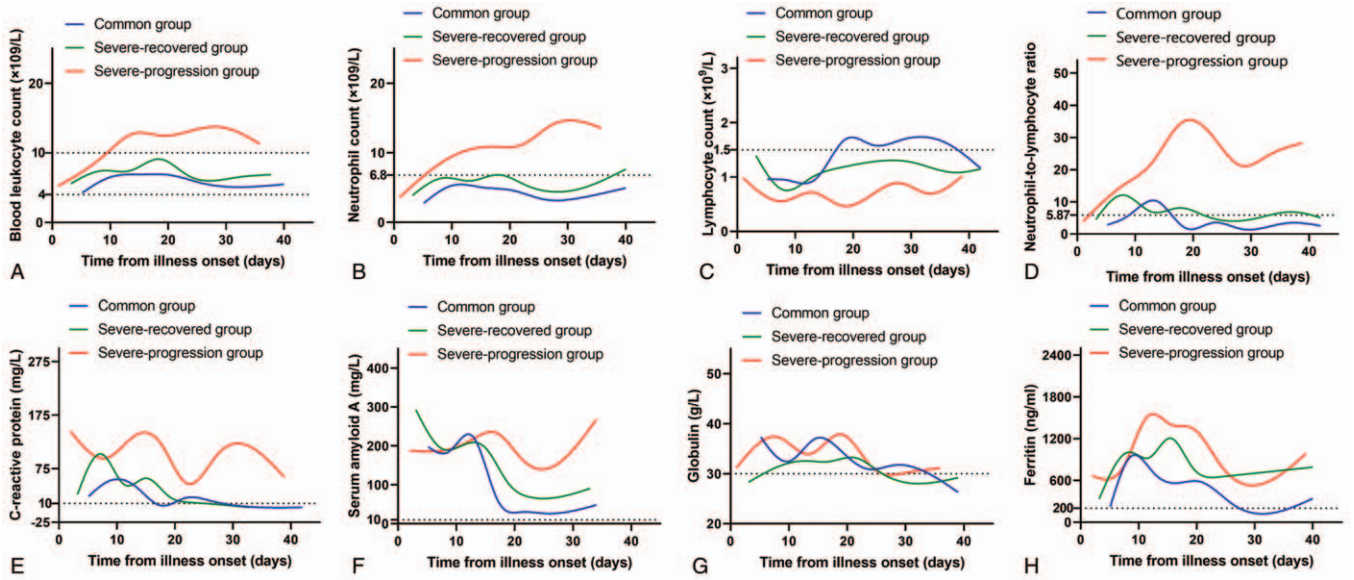

Figure 4. The dynamic trends of inflammatory indices. (A), blood leukocyte count; (B), neutrophil count; (C), Lymphocyte count; (D), neutrophil-to-lymphocyte ratio (NLR); (E), C-reactive protein; (F), serum amyloid A; (G), globulin; (H), ferritin.

cardiomyocytes, but other researchers found not.[28] Besides that, after a long time under the condition of hypoxia, the myocardium is prone to major injury and electrophysiological disorder due to ischemia and hypoxia, which is also one of the most common causes of death in some patients. In this study, we found the CK, myoglobin and troponin value in severe group were significantly higher than those in common group as well. Then we subdivided the patients in severe group into severe-recovered group and severe-progression group, and the multivariate analysis demonstrated that the independent risk factors for disease progression in severe patients were CRP and BNP, whose cutoff value were respectively 45.15 mg/L and 108.05 pg/ml. The BNP value could be linked to right ventricle dysfunction, due to lung vascular distress, some research showed that vascular disease process was contributing factor in COVID-19 pathogenesis and pulmonary shunting is consistent with intense vasodilation and endothelial dysfunction.[29,30] For severe patients, consequently, in addition to diminishing inflammation, we should also look out for their hearts. When cardiac function indices such as CK, myoglobin, troponin and BNP are found abnormal, especially when BNP exceeds 108.05 pg/ml, it is high time that we raised an early warning and took timely measures, and hopefully will reduce the case-fatality rate. Of course, we should never neglect other organ functions such as liver and kidney functions.

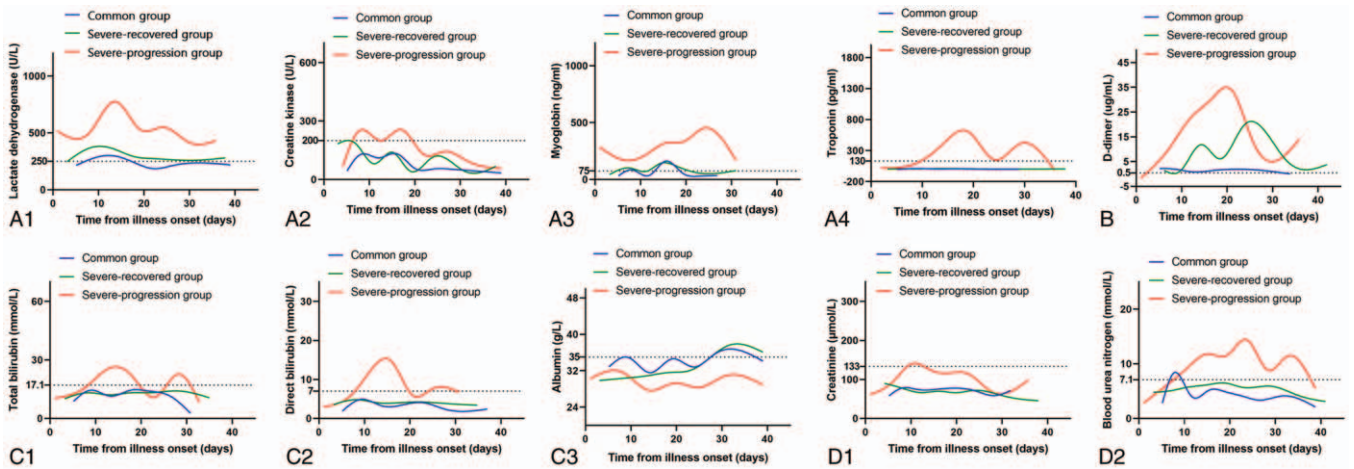

Figure 5. The dynamic trends of organ function indices. (A), Cardiac function indices including Lactate dehydrogenase (A1), creatine kinase (A2), myoglobin (A3) and troponin (A4). (B), Coagulation function indices including D-dimer. (C), Liver function indices including total bilirubin (C1), direct bilirubin (C2) and albumin (C3). (D), Kidney function indices including creatinine (D1) and blood urea nitrogen (D2).

After monitoring the laboratory indices throughout the entire course of disease in all patients (Figures 4 and 5), we discovered that the time point when laboratory indices became abnormal in severe group usually appeared earlier than that in common group. But the recovery period of severe-recovered group and common group appeared almost simultaneously, which was around the second week of illness onset and this was parallel to imaging findings.[31,32] By contrast, the indices of common group could often restore to normal while those of severe-recovered group could not. For patients in severe-progression group, those indices would continue to rise till the third week of illness onset and remain at a high level. In severe patients, as a result, if certain inflammatory and organ function indices reach far above reference line and continue to rise more than 2 weeks after illness onset, that may be the signal for disease progression or death and would require emphasized attention. Another interesting point is that the curves of severe-progression group and severe-recovered group were almost consistent for the first 7 to 9 days and then gradually went separate ways, which indicated that this period of time might be a critical turning point for poor prognosis. The ascending period of lymphocyte count and descending period of globulin were approximately during 17 to 25 days after the illness onset, which might mark the process of viral shedding.

Furthermore, it is worth mentioning that for both common and severe patients, the SAA values were at the highest level since the onset of illness, and then fell to the lowest level during the third week. But numerically speaking, SAA values of severe patients still remained above reference line. SAA is a pentraxin that activates the classic complement system via C1q and reinforces the production of the primary cytokines, IL-β1 and TNF, contributing to the cytokine storm.[33] The result showed that SAA seemed to be a sensitive index that could be used for the early detection of COVID-19, and its certain changing trends might also help identify patients with poor prognosis. As for IL-6, which was previously suspected to be higher in severe patients, we did not find evidence for this assumption in our study. In addition, the peak value of D-dimer far exceeds the reference line in severe-progression group, which might suggest later embolization, and so anticoagulation therapy might be considered at this time.[34,35]

Finally, we have to admit some limitations in this study. First, it was a single-center retrospective study with a small sample size; second, the NLR-LDH grading system that we proposed lacked an external validation cohort and so we still have much work to do to validate this in the future. Last but not least, the selection of patients based on RT-PCR, not including patients diagnosed on TDM.

5. Conclusion

The NLR-LDH grading system was a useful prognostic tool for the early detection of severe COVID-19. And in the severe patients, CRP, and BNP seemed to be helpful for predicting the disease progression or death.

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